ELECTRONIC SUPPORTING INFORMATION

Identification of ligand linkage vectors for the development of p300/CBP degraders

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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 or phosphomolybdic acid stain or potassium permanganate 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 wavelengths. 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. Purification by high-performance liquid chromatography (HPLC) was performed 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-HPLC 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. Enantiomeric excess was determined by chiral gas chromatography (GC) equipped with a flame ionization detector using a

Agilent J&W Cyclodex-B 10.5% β-cyclodextrin capillary column, 0.25 micron thickness, 30 m x 0.25 mm; GC parameters: injector temperature 250 °C; 100:1 split ratio; column oven temperature at 50 °C for 2 min, ramped by 10 °C/min to 250 °C and maintained for 18 min; flow rate: 1.0 mL/min; injection volume: 1 μL. Compound characterisation and purity were analysed by MS and nuclear magnetic resonance (NMR). ^{1}H NMR (400, 600 MHz), ^{13}C NMR (100, 151 MHz) and ^{19}F{1H} NMR (376 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6 at 298K or 383K 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

General Procedure for Preparation of Pomalidomide Linker (GP1)[1]

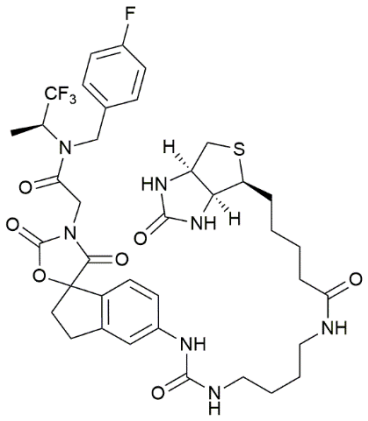
To a solution of 4-Fluorothalidomide (1.0 equiv.), mono-*N*-Boc protected diamine (1.1 equiv.) and DIPEA (3.0 equiv.) were dissolved in DMSO (0.2 M) and heated between 90 – 130 °C for 16 hours. After this time, the solvent was removed by Kugelrohr distillation at 40 °C and 0.1 Torr. The residue was purified by flash column chromatography over silica gel, eluting with EtOAc:hexanes (20 – 100 %).

General Procedure for Preparation of Urea Linked A-485-Pomalidomide Conjugates (GP2)

N-Boc protected pomalidomide linker **16** was dissolved in DCM (0.05 M) and TFA (50 eq.) was added dropwise to the stirring solution. The reaction was complete after one hour and volatiles were removed *in vacuo* to afford the Boc-deprotected pomalidomide linker TFA salt as a yellow film which was used immediately without further purification.

To a solution of aryl amine **15** (0.10 mmol, 1.0 eq.) in anhydrous DCM (4 mL) was added triethylamine (3.0 eq.) followed by triphosgene (0.50 eq.). The mixture was allowed to stir at room temperature for three hours, after which a solution of Boc-deprotected pomalidomide linker **17** (1.1 eq.) in DMF (1 mL) and DCM (2 mL) was added dropwise to the solution. The reaction was allowed to stir at room temperature for 16-24 hours and was then quenched with water and extracted thrice with EtOAc. The combined organic layers were then washed with brine, and dried over anhydrous sodium sulphate, then filtered, and reduced *in vacuo*. The crude residue was then adsorbed to silica gel and purified first by silica gel flash column chromatography (2 – 12% MeOH) followed by reverse phase C_{18} functionalised silica gel flask column chromatography (5% MeCN in water to 95% MeCN in water) to afford the desired conjugate.

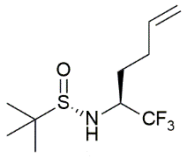
N-(4-(3-(3'-(2-((4-fluorobenzyl)((S)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-5-yl)ureido)butyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide (2)



To a separate flask, aryl amine **1**[2] (0.051 g, 0.11 mmol, 1.0 eq.) was added and dissolved in DCM (2.5 mL), and the mixture was cooled to 0 ^{o}C on an ice-water bath. DIPEA (0.090 mL, 0.52 mmol, 4.9 eq.) and triphosgene (0.016 g, 0.054 mmol, 0.49 eq.) were then added to the solution and after ten minutes the ice-water bath was removed and the solution was stirred at

room temperature for two hours, after which the solution was cooled to 0 °C on an ice-water bath. The crude residue of deprotected **13** was dissolved in DCM (2 mL) and DMF (1 mL) and added dropwise to the reaction mixture dropwise. After ten minutes, the ice-water bath was removed, and the solution was stirred at room temperature for 16 hours. The reaction was quenched with HCl (1.5 mL, 3 M) until pH was ~1 and was further diluted with brine (20 mL) and extracted with EtOAc (3 x 50 mL). The organics were dried over anhydrous sodium sulphate, filtered, then reduced *in vacuo* to give a crude residue. The residue was then adsorbed onto silica gel and purified by silica gel flash chromatography (2 – 15% MeOH in DCM) and then reverse phase C_{18} functionalized silica gel flash chromatography (95:5 – 5:95 H_2O:MeCN) to afford **2** (0.017g, 0.021 mmol, 19%) as a white solid; ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 8.32 (s, 1H), 7.51 (q, *J* = 1.2 Hz, 1H), 7.36 (s, 2H), 7.29 – 7.22 (m, 3H), 7.16 (t, *J* = 8.8 Hz, 2H), 6.02 (t, *J* = 5.8 Hz, 1H), 5.98 – 5.90 (m, 2H), 5.21 (s, 1H), 4.86 (dd, *J* = 17.6, 5.9 Hz, 1H), 4.75 – 4.56 (m, 2H), 4.34 – 4.31 (m, 1H), 4.17 (ddd, *J* = 7.4, 4.7, 2.1 Hz, 1H), 3.17 – 3.08 (m, 7H), 3.06 – 2.98 (m, 1H), 2.86 (dd, *J* = 12.4, 5.3 Hz, 1H), 2.72 – 2.61 (m, 2H), 2.49 – 2.44 (m, 1H), 2.09 (t, *J* = 7.4 Hz, 2H), 1.74 – 1.66 (m, 1H), 1.62 – 1.54 (m, 3H), 1.50 – 1.46 (m, 5H), 1.41 – 1.37 (m, 5H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.0, 171.3, 166.7, 162.0, 161.4 (d, *J* = 281.2 Hz), 154.6, 153.3, 145.5, 142.7, 132.8, 129.2, 127.7, 125.0 (q, *J* = 282.0 Hz), 123.5, 116.8, 114.6 (d, *J* = 23.8 Hz), 113.2, 93.5, 60.8, 59.0, 54.6, 51.0, 45.2, 41.1, 39.1, 38.5, 37.8, 34.8, 34.5, 29.3, 27.6, 27.5, 26.8, 26.2, 24.6, 11.0; ^{19}F NMR (376 MHz, DMSO) δ = -72.1, -115.8; HRMS (ESI) *m/z* calculated for $[C_{38}H_{45}F_4N_7O_7S+Na]^+$ = 842.2930, found 842.2936.

(S)-2-methyl-N-((S)-1,1,1-trifluorohex-5-en-2-yl)propane-2-sulfinamide (4)[3]



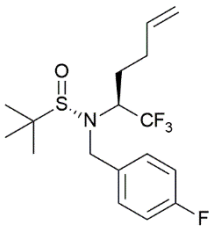
Following a known procedure,[3] a mixture of (S)-2-methylpropane-2-sulfinamide (2.174 g, 17.9 mmol, 1.1 eq.) in $Ti(OEt)_4$ (5.17 mL, 24.5 mmol, 1.5 eq.) was added 1-ethoxy-2,2,2-trifluoroethanol (1.92 mL, 16.3 mmol, 1.0 eq.) dropwise. The mixture was heated to 70 °C and the solution clarified and was then stirred at this temperature for 24 hours. The solution was then cooled to room temperature and diluted with EtOAc (50 mL) and brine (170 mL). This biphasic mixture was filtered over a pad of celite and washed with EtOAc (250 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulphate, filtered, and removed *in vacuo* to produce ***(S)-N-(1-ethoxy-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide*** (**3**) (3.98 g, 15.5 mmol, 88%) as a mixture of diastereomers. This intermediate was used without further purification.

To a flask containing magnesium turnings (0.933 g, 38.4 mmol, 3.1 eq.) anhydrous THF and 4-bromo-1-butene (0.94 mL, 9.3 mmol, 0.75 eq.) were added. As the exotherm began, additional 4-bromo-1-butene (2.3 mL, 22.7mmol, 1.8 eq.) was dissolved in anhydrous THF (22 mL) in a separate flask and was added to the Grignard mixture dropwise over 10 minutes, and the mixture was stirred for 1 hour at room temperature.

Sulfinamide **3** (3.059 g, 12.4 mmol, 1.0 eq.) was weighed in a separate flask and dissolved in anhydrous DCM (90 mL). This solution was then cooled to -45 °C using a chiller in an acetone bath. The prepared Grignard solution was then added dropwise to the mixture using a syringe pump at a rate of 1 mL/min. After addition of the Grignard, the solution was warmed to -40 °C and stirred for 2.5 hours. The solution was then warmed to -20 °C and stirred for 15 hours. The mixture was then slowly quenched with sat. aq. ammonium chloride (50 mL), diluted with water (50 mL), then extracted with DCM (2 x 100 mL). The combined organics were then dried over anhydrous sodium sulphate, filtered, and removed *in vacuo*. The crude residue was then

purified by silica gel flash column chromatography (20 – 45% EtOAc in hexanes) to afford **4** (2.65 g, 10.3 mmol, 83%) as a low melting white solid. Small portions of the solid were able to be crystallised from hot water to afford single crystals that were analysed by X-ray diffraction; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.75 (dddd, *J* = 17.4, 10.3, 7.3, 6.0 Hz, 1H), 5.13 – 4.98 (m, 2H), 3.65 (ddtd, *J* = 16.6, 9.4, 7.2, 3.7 Hz, 1H), 3.55 (d, *J* = 9.3 Hz, 1H), 2.32 (dd, *J* = 14.1, 7.6 Hz, 1H), 2.17 (dq, *J* = 15.2, 7.8 Hz, 1H), 1.89 (dtd, *J* = 14.4, 8.0, 3.7 Hz, 1H), 1.83 – 1.71 (m, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.5, 125.4 (q, *J* = 283.8 Hz), 116.6, 57.5 (q, *J* = 29.8 Hz), 57.2, 29.2, 28.6, 22.7; HRMS (ESI) *m/z* calculated for $[C_{10}H_{18}F_3NOS+H]^+$ = 258.1134, found 258.1129.

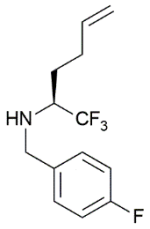
Preparation of (S)-N-(4-fluorobenzyl)-2-methyl-N-((S)-1,1,1-trifluorohex-5-en-2-yl)propane-2-sulfinamide (5)



A mixture of sulfinamide **4** (2.068 g, 8.0 mmol, 1.0 eq.) in anhydrous THF (20 mL) was cooled to 0 °C in an ice-water bath, and a solution of *n*-BuLi in hexanes (2.5 M, 3.6 mL, 9.0 mmol, 1.1 eq.) was added dropwise, and the solution turned from clear to a deep red colour. After 10 minutes 4-fluorobenzyl bromide (1.1 mL, 8.8 mmol, 1.1 eq.) was added dropwise to the solution. The solution was stirred for an additional 20 minutes and then quenched slowly with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were then dried over anhydrous sodium sulphate, filtered, and the solvent was removed *in vacuo*. The crude residue was then purified by silica gel flash column chromatography (2 – 20% EtOAc in hexanes) to afford **5** (2.57 g, 7.0 mmol, 88%) as a yellow oil; ^{1}H NMR (600 MHz,

$CDCl_3$) δ = 7.39 – 7.33 (m, 2H), 7.06 – 7.00 (m, 2H), 5.58 (ddt, *J* = 16.9, 10.2, 6.4 Hz, 1H), 4.98 – 4.88 (m, 2H), 4.44 (d, *J* = 14.6 Hz, 1H), 4.15 (d, *J* = 14.5 Hz, 1H), 3.48 (br s, 1H), 2.19 (dq, *J* = 13.8, 7.0, 6.5 Hz, 1H), 2.13 – 2.03 (m, 1H), 1.97 – 1.83 (m, 2H), 1.23 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.7 (d, *J* = 247.0 Hz), 161.9, 136.6, 131.8 (d, *J* = 8.1 Hz), 126.8 (q, *J* = 286.5 Hz), 116.1, 115.7 (d, *J* = 21.4 Hz), 59.8, 58.7, 49.4, 29.8, 26.1, 23.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -71.8, -114.1; HRMS (ESI) *m/z* calculated for $[C_{17}H_{23}F_4NOS+H]^+$ = 366.1509, found 366.1506.

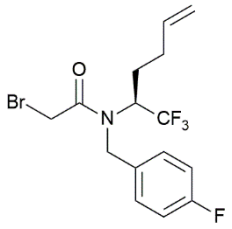
(S)-1,1,1-trifluoro-N-(4-fluorobenzyl)hex-5-en-2-amine (6)



Acetyl chloride (4.5 mL, 62.8 mmol, 15 eq.) was added dropwise via an addition funnel to a flask containing anhydrous EtOH (20 mL) at 0 °C. The mixture was stirred for 30 minutes then a solution of sulfinamide **5** (1.521 g, 4.2 mmol, 1.0 eq.) in anhydrous EtOH (5 mL) was added dropwise, and the mixture was stirred for an additional 24 hours. The reaction was then quenched with sat. aq. sodium bicarbonate (80 mL) and extracted with EtOAc (3 x 70 mL). The combined organics were dried over anhydrous sodium sulphate, filtered, and the solvents were removed *in vacuo*. The crude residue was purified by silica gel column chromatography (2 – 20% EtOAc in hexanes) to afford **6** (0.958 g, 3.6 mmol, 86%) as a colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.31 (dd, *J* = 8.2, 5.5 Hz, 2H), 7.01 (ddd, *J* = 8.7, 7.7, 1.2 Hz, 2H), 5.81 – 5.64 (m, 1H), 5.05 – 4.95 (m, 2H), 3.98 (d, *J* = 13.1 Hz, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.09 – 2.95 (m, 1H), 2.29 (dq, *J* = 13.9, 6.4 Hz, 1H), 2.13 (dq, *J* = 15.2, 7.8 Hz, 1H), 1.85 – 1.70 (m, 1H), 1.56 – 1.47 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 162.2 (d, *J* = 245.1 Hz), 137.4,

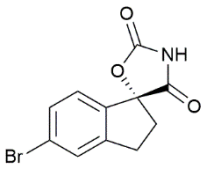
135.7 (d, *J* = 3.0 Hz), 129.9 (d, *J* = 8.0 Hz), 127.4 (q, *J* = 285.0 Hz), 115.9, 115.4, 115.3, 57.8 (q, *J* = 27.1 Hz), 51.2, 29.8, 28.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ = -74.5, -115.6; HRMS (ESI) *m/z* calculated for $[C_{13}H_{15}F_4N+H]^+$ = 262.1213, found 262.1214.

(S)-2-bromo-N-(4-fluorobenzyl)-N-(1,1,1-trifluorohex-5-en-2-yl)acetamide (7)



To a solution of **6** (0.917 g, 3.5 mmol, 1.0 eq.) in DCM (10 mL) was added bromoacetyl bromide (0.42 mL, 4.8 mmol, 1.4 eq.). The mixture was stirred at room temperature for 16 hours, cooled to 0 °C on an ice-water bath, and quenched with sat. aq. sodium bicarbonate (50 mL). The aqueous mixture was then extracted with EtOAc (3 x 50 mL), and the combined organic layers were dried over anhydrous sodium sulphate. The dried organics were then filtered, and the solvent was removed *in vacuo*. The crude residue was purified by silica gel flash column chromatography (2 – 15% EtOAc in hexanes) to afford **7** (1.132 g, 3.0 mmol, 84%) as a clear oil that was used without further purification; HRMS (ESI) *m/z* calculated for $[C_{15}H_{16}BrF_4NO+H]^+$ = 382.0424, found 382.0420.

(R)-5-bromo-2,3-dihydrospiro[indene-1,5'-oxazolidine]-2',4'-dione (8)[4]

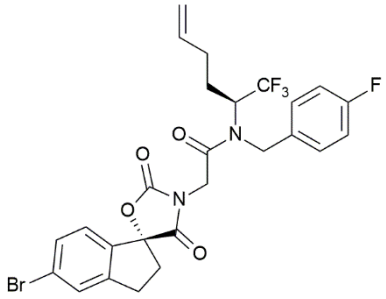


To a solution of silyl protected cyanohydrin **S1** (6.33 g, 20.4 mmol, 1.0 eq.) in anhydrous ethanol (70 mL) was added acetyl chloride (44 mL, 0.612 mol, 30 eq.) via a dropping funnel over 1 hour at 0 °C. The solution was then warmed to room temperature and allowed to stir for

2 days, after which volatiles were removed *in vacuo*. The crude residue was triturated with Et_2O (2 x 120 mL) to afford an off-white foam intermediate that was used immediately.

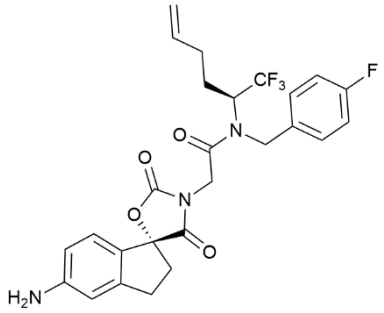
The crude intermediate was then dissolved in anhydrous THF (88 mL) and DIPEA was added (14 mL, 80.4 mmol, 3.9 eq.) and the mixture was cooled to 0 ℃ on an ice-water bath. Triphosgene (2.728 g, 9.2 mmol, 0.45 eq.) was weighed in a fumehood, then added to the mixture portionwise over 30 minutes. The solution was allowed to warm to room temperature and stirred for an additional 3 hours, after which the solution was cooled back to 0 °C using an ice-water bath, and 3 N HCl solution (25 mL) was added dropwise to a pH of ~1 and then allowed to stir at room temperature for an additional 2 hours. The solution was then diluted with EtOAc (100 mL) and washed with water (50 mL). The aqueous layer was then extracted with EtOAc (2 x 100 mL) and the combined organic layers were dried over anhydrous sodium sulphate, filtered, and volatiles were removed *in vacuo*. The crude residue was then purified silica gel flash column chromatography (2 – 20% EtOAc in DCM) to afford **8** as a brown solid (3.10 g, 11.0 mmol, 54%). The compound was then enantioenriched first by trituration of the material with toluene (4 x 80 mL). The combined toluene washes were evaporated to afford enantioenriched material that could then be directly recrystallised, while the precipitate from the trituration afforded racemic material. The enantioenriched material was then directly recrystallised from toluene twice to afford enantioenriched **8** (1.746 g, 6.2 mmol, 30%, 99% ee) as a white crystalline solid that was analysed with chiral GC and X-ray crystallography to confirm the ee and absolute configuration; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.67 (s, 1H), 7.54 – 7.49 (m, 1H), 7.47 – 7.40 (m, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 3.28 – 3.08 (m, 2H), 2.79 (ddd, *J* = 14.4, 8.4, 6.1 Hz, 1H), 2.56 (ddd, *J* = 14.2, 8.3, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.4, 153.6, 147.5, 135.9, 131.2, 128.9, 125.7, 125.0, 94.9, 35.7, 30.2; HRMS (ESI) *m/z* calculated for $[C_{11}H_8BrNO_3+Na]^+$ = 303.9580, found 303.9587.

2-((R)-5-bromo-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluorohex-5-en-2-yl)acetamide (9)



To a solution of spirocyclic imide **8** (0.702 g, 2.5 mmol, 1.0 eq.) and alkyl bromide **7** (0.967 g, 2.5 mmol, 1.0 eq.) in DMF (12 mL) was added potassium carbonate (0.807 g, 5.8 mmol, 2.3 eq.) and the reaction was stirred at 0 °C for 2 hours. The reaction was then quenched with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the volatiles were removed *in vacuo*. The crude residue was purified by silica gel flash column chromatography (10 – 45% EtOAc in hexanes) to afford **9** (1.34 g, 2.3 mmol, 92%) as a white foam; ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 7.63 (s, 1H), 7.52 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.23 – 7.09 (m, 2H), 5.76 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1H), 5.25 – 4.95 (m, 3H), 4.84 – 4.66 (m, 2H), 4.61 – 4.28 (m, 2H), 3.22 (ddd, *J* = 15.4, 8.3, 6.2 Hz, 1H), 3.12 (ddd, *J* = 16.7, 8.8, 4.6 Hz, 1H), 2.73 (ddd, *J* = 14.8, 8.7, 6.2 Hz, 1H), 2.56 (ddd, *J* = 14.0, 8.4, 4.6 Hz, 1H), 2.14 – 2.04 (m, *J* = 7.2 Hz, 2H), 2.00 (ddd, *J* = 16.7, 11.7, 7.2 Hz, 1H), 1.96 – 1.85 (m, 1H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 172.3, 167.1, 161.0 (d, *J* = 244.2 Hz), 153.1, 147.3, 136.3, 135.8, 132.2, 129.9, 128.0, 127.7, 124.6 (q, *J* = 285.1 Hz) 125.1, 115.4, 114.6 (d, *J* = 22.1 Hz), 92.6, 55.1, 45.7, 41.3, 34.2, 29.0, 28.2, 24.2; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -69.8, -115.4; HRMS (ESI) *m/z* calculated for $[C_{26}H_{23}BrF_4N_2O+H]^+$ = 583.0850, found 583.0862

2-((R)-5-amino-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluorohex-5-en-2-yl)acetamide (10)

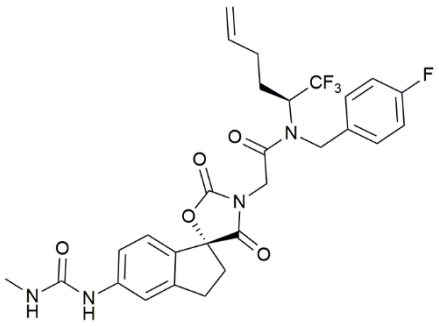


To a round-bottomed flask, aryl bromide **9** (1.35 g, 2.3 mmol, 1.0 eq.) was added, and the flask was placed inside an N_2 filled glovebox. To this flask was added $Pd(OAc)_2$ (0.040 g, 0.18 mmol, 0.08 eq.) and *rac*-BINAP (0.180 g, 0.29 mmol, 0.13 eq.). The flask was removed from the glovebox and caesium carbonate (1.446 g, 4.4 mmol, 1.9 eq.) was quickly added. The solids were then suspended in anhydrous toluene (20 mL) and diphenyl imine (0.62 mL, 3.7 mmol, 1.6 eq.) was added. The mixture was heated to 100 °C for 16 hours, then cooled to room temperature and volatiles were removed *in vacuo*. The crude residue was adsorbed to silica gel and purified by silica gel flash chromatography (5 – 45% EtOAc in hexanes) to afford **2-((*R*)-5-((diphenylmethylene)amino)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((*S*)-1,1,1-trifluorohex-5-en-2-yl)acetamide** (1.41 g, 2.1 mmol, 89%) as a light orange foam that was used without further purification; HRMS (ESI) *m/z* calculated for $[C_{39}H_{33}F_4N_3O_4+H]^+$ = 684.2480, found 684.2469

To a solution of **2-((*R*)-5-((diphenylmethylene)amino)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((*S*)-1,1,1-trifluorohex-5-en-2-yl)acetamide** (0.970 g, 1.4 mmol, 1.0 eq.) in THF (8 mL) was added 3 N HCl (2.0 mL, 6.0 mmol, 4.3 eq.) dropwise. The mixture was stirred at room temperature for 80 minutes, after which the reaction was quenched with sat. aq. sodium bicarbonate solution (40 mL) and

extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the solvent was removed *in vacuo*. The crude residue was then adsorbed to silica gel and purified by silica gel flash chromatography (2 – 45% EtOAc in hexanes) to afford **10** (0.592 g, 1.14 mmol, 80%) as a white solid; ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 7.46 – 7.32 (m, 1H), 7.22 – 7.10 (m, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.61 – 6.38 (m, 1H), 5.76 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.15 – 4.94 (m, 2H), 4.75 (s, 1H), 4.56 – 4.33 (m, 1H), 3.05 (dt, *J* = 15.5, 7.5 Hz, 1H), 2.95 – 2.84 (m, 1H), 2.64 (ddd, *J* = 15.1, 8.8, 6.7 Hz, 1H), 2.44 (ddd, *J* = 14.2, 8.3, 3.8 Hz, 1H), 2.08 (s, 1H), 1.99 (tt, *J* = 14.4, 7.3 Hz, 1H), 1.93 – 1.81 (m, 1H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.3, 167.3, 161.0 (d, *J* = 244.4 Hz), 153.4, 150.7, 146.1, 135.8, 131.3, 128.1, 124.6 (q, *J* = 282.6 Hz), 123.9, 115.4, 114.5, 113.1, 111.9, 109.8, 108.6, 94.3, 54.9, 45.6, 41.1, 34.7, 29.0, 28.2, 24.2; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -69.8, -115.4. HRMS (ESI) *m/z* calculated for $[C_{26}H_{25}F_4N_3O_4+H]^+$ = 542.1673, found 542.1675.

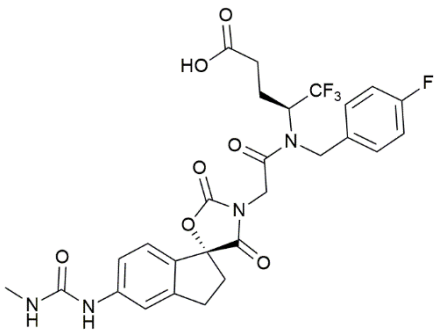
N-(4-fluorobenzyl)-2-((R)-5-(3-methylureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-((S)-1,1,1-trifluorohex-5-en-2-yl)acetamide (11)



To a solution of aryl amine **10** (0.075 g, 0.14 mmol, 1.0 eq.) and DIPEA (0.07 mL, 0.40 mmol, 2.9 eq.) in DCM (5 mL) was added triphosgene (0.020 g, 0.067 mmol, 0.48 eq.) in a single portion. The solution was stirred at 0 °C for 2 hours, then a 2 M solution of methylamine in THF (0.20 mL, 0.40 mmol, 2.9 eq.) was added and the solution was stirred at room temperature

for 18 hours. The solution was then diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and the volatiles were removed *in vacuo*. The crude residue was then purified over silica gel flash chromatography (40 – 100% EtOAc in hexanes) to afford **11** (0.077 g, 0.13 mmol, 92%) as a white solid; ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 8.34 (s, 1H), 7.52 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.30 – 7.23 (m, 2H), 7.21 – 7.11 (m, 2H), 5.90 (q, *J* = 4.7 Hz, 1H), 5.76 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1H), 5.07 – 4.98 (m, 2H), 4.83 – 4.67 (m, 2H), 4.59 – 4.37 (m, 2H), 3.19 – 3.11 (m, 1H), 3.07 – 2.99 (m, 1H), 2.74 – 2.64 (m, 4H), 2.54 – 2.46 (m, 2H), 2.15 – 2.04 (m, 2H), 2.04 – 1.95 (m, 1H), 1.95 – 1.86 (m, 1H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.0, 167.2, 161.0 (d, *J* = 244.1 Hz), 155.2, 153.3, 145.5, 142.7, 135.8, 132.3, 129.2, 128.1, 124.7 (q, *J* = 284.2 Hz), 123.4, 116.9, 115.4, 114.6 (d, *J* = 21.7 Hz), 113.3, 93.6, 55.0, 45.7, 41.2, 34.5, 29.2, 28.2, 25.5, 24.2; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -69.8, -115.5; HRMS (ESI) *m/z* calculated for $[C_{28}H_{28}F_4N_4O_5+Na]^+$ = 599.1888, found 599.1869.

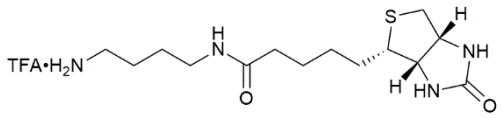
(S)-5,5,5-trifluoro-4-(N-(4-fluorobenzyl)-2-((R)-5-(3-methylureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)acetamido)pentanoic acid (12)



To a solution of alkene **11** (0.045 g, 0.078 mmol, 1.0 eq.) in a mixture of MeCN:CCl_4:H_2O (2:2:3 mL) was added $NaIO_4$ (103 mg, 0.48 mmol, 6.0 eq.) followed by $RuCl_3$•$3H_2O$ (6.2 mg, 0.011 mmol, 0.20 eq.). The mixture was stirred for 16 hours, then diluted with brine (50 mL)

and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the solvent was removed *in vacuo*. The crude residue was adsorbed onto silica gel and purified by silica gel flash column chromatography (5 – 20% MeOH in DCM) to afford **12** (0.014 g, 0.024 mmol, 31%) as a white solid; HRMS (ESI) *m/z* calculated for $[C_{27}H_{26}F_4N_4O_7+H]^+$ = 595.1810, found 595.1825.

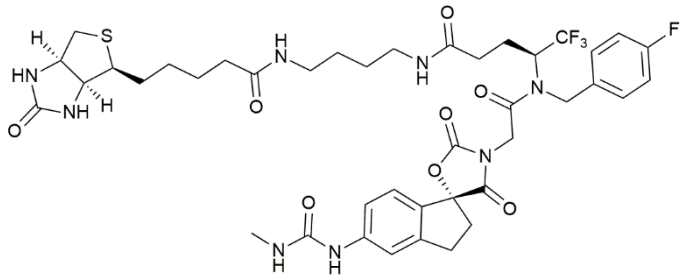
N-(4-aminobutyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide trifluoroacetate (13)



To a solution of tert-butyl (4-aminobutyl)carbamate (0.173 g, 0.91 mmol, 1.0 eq.) and DIPEA (0.8 mL, 4.5 mmol, 5.0 eq.) in DMF (16 mL) cooled to 0 °C on an ice-water bath was added biotin pentafluorophenyl ester (0.492 g, 1.2 mmol, 1.3 eq.). After 10 minutes the ice-water bath was removed and the reaction was stirred at room temperature for 20 hours. The volatiles were removed *in vacuo* and the crude residue was triturated in Et_2O (2 x 20 mL) to afford ***N*-boc-(4-aminobutyl)biotinamide** (0.320 g, 0.77 mmol, 85%) as a white powder. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.73 (t, *J* = 5.8 Hz, 1H), 6.76 (d, *J* = 6.1 Hz, 1H), 6.47 – 6.41 (m, 1H), 6.36 (s, 1H), 4.30 (t, *J* = 6.5 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.14 – 3.06 (m, 1H), 3.02 – 2.97 (m, 2H), 2.88 (q, *J* = 5.6 Hz, 2H), 2.85 – 2.76 (m, 1H), 2.57 (d, *J* = 12.4 Hz, 1H), 2.06 – 2.00 (m, 2H), 1.65 – 1.56 (m, 1H), 1.55 – 1.41 (m, 3H), 1.38 – 1.32 (m, 11H), 1.31 – 1.24 (m, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.8, 162.7, 155.6, 77.3, 61.0, 59.2, 55.4, 39.6, 38.2, 35.2, 28.3, 28.2, 28.0, 27.0, 26.6, 25.3; HRMS (ESI) *m/z* calculated for $[C_{19}H_{34}N_4O_4S+Na]^+$ = 437.2199, found 437.2193.

To a solution of ***N*-boc-(4-aminobutyl)biotinamide** (0.0108 g, 0.027 mmol, eq.) in DCM (3 mL) was added TFA (0.2 mL, 2.6 mmol, eq.). The solution was stirred at room temperature for 2 hours then volatiles were removed *in vacuo* to afford **13** which was then used immediately without further purification.

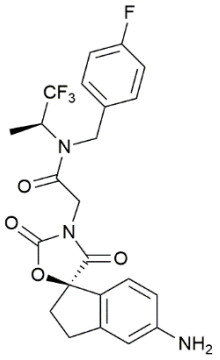
(S)-5,5,5-trifluoro-4-(N-(4-fluorobenzyl)-2-((R)-5-(3-methylureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)acetamido)-N-(4-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)butyl)pentanamide (14)



To a solution of **12** (0.038 g, 0.064 mmol, 1.0 eq.) in anhydrous DMF (1 mL) was added DIPEA (56 µL, 0.32 mmol, 5.0 eq.) and HATU (31 mg, 0.081 mmol, 1.3 eq.). The solution was stirred at room temperature for 30 minutes then a solution of **13** (0.082 mmol, 1.3 eq.) in anhydrous DMF (1 mL) was added dropwise and the reaction was stirred at room temperature for 16 hours, afterwards the volatiles were removed *in vacuo* and the crude material was adsorbed to silica gel and purified by silica gel flash column chromatography (2 – 20% MeOH in DCM) followed by C_{18} functionalized silica gel reverse phase flash column chromatography (5 – 95% MeCN in water) to afford **14** (24.1 mg, 0.027 mmol, 42%) as a white solid; ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 8.33 (s, 1H), 7.51 (s, 1H), 7.49 – 7.32 (m, 3H), 7.25 (d, *J* = 2.4 Hz, 3H), 7.14 (s, 2H), 6.02 – 5.85 (m, 3H), 5.25 – 4.92 (m, 1H), 4.81 – 4.65 (m, 2H), 4.52 (t, *J* = 15.2 Hz, 2H), 4.33 (dd, *J* = 7.6, 5.5 Hz, 1H), 4.17 (ddd, *J* = 7.3, 4.6, 2.0 Hz, 1H), 3.22 (s, 1H), 3.17 – 3.10 (m, 2H), 3.10 – 2.98 (m, 5H), 2.86 (dd, *J* = 12.4, 5.3 Hz, 1H), 2.73 – 2.61 (m, 5H), 2.54 – 2.45 (m, 1H), 2.19 (h, *J* = 8.1 Hz, 1H), 2.14 –

2.06 (m, 4H), 1.74 – 1.65 (m, 1H), 1.61 – 1.47 (m, 3H), 1.47 – 1.34 (m, 6H); ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ -69.8, -115.6; HRMS (MALDI) *m/z* calculated for [$C_{41}H_{50}F_4N_8O_8S$ +Na]$^+$ = 913.3301, found 913.3301.

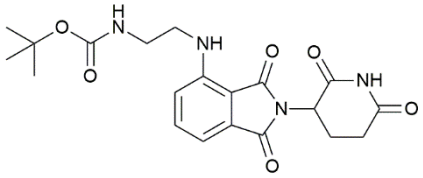
2-((R)-5-amino-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (15)



To a 3-necked flask containing *rac*-BINAP (0.109 g, 0.18 mmol, 0.14 eq.) and $Pd(OAc)_2$ (21 mg, 0.094 mmol, 0.07 eq.) was charged with caesium carbonate (0.738 g, 2.3 mmol, 1.8 eq.) followed by anhydrous toluene (8 mL). To a separate flask containing aryl bromide **S2** (0.724 g, 1.3 mmol, 1.0 eq.) was added anhydrous toluene (10 mL), followed by diphenyl imine (0.35 mL, 2.1 mmol, 1.6 eq.). The solution containing aryl bromide **S2** and diphenyl imine were added via syringe to the other flask, and the solution changed colour to a bright orange, then to a deep red, and the mixture was heated to 100 °C for 22 hours. Once cooled to room temperature, volatiles were removed *in vacuo* and the crude residue was adsorbed to silica gel and purified by silica gel flash column chromatography (20 – 60% EtOAc in hexanes) to ***afford 2-((R)-5-((diphenylmethylene)amino)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide*** (0.637 g, 0.99 mmol, 76%) as an orange foam that was used without further purification; HRMS (ESI) *m/z* calculated for [$C_{36}H_{29}F_4N_3O_4$+H]$^+$ = 644.2167, found 644.2151.

Intermediate diphenyl imine (0.600 g, 0.93 mmol, 1.0 eq.) was dissolved in THF (8 mL) and 3 N HCl solution (1.25 mL, 8.75 mmol, 4 eq.) was added dropwise. The solution was stirred for 80 minutes and then quenched with a solution of sat. aq. sodium bicarbonate (40 mL), and then the aqueous solution was then extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and reduced *in vacuo*. The crude residue was then purified over silica gel flash column chromatography (20 – 45% EtOAc in hexanes) to afford **15** (0.386 g, 0.81 mmol, 87%) as a white solid; ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 7.36 (dd, *J* = 8.3, 5.2 Hz, 2H), 7.16 (t, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.58 – 6.50 (m, 2H), 5.35 – 4.91 (m, 2H), 4.86 (d, *J* = 17.6 Hz, 1H), 4.74 – 4.49 (m, 2H), 4.38 (d, *J* = 16.7 Hz, 1H), 3.11 – 2.99 (m, 1H), 2.91 (ddd, *J* = 16.1, 8.8, 3.8 Hz, 1H), 2.63 (ddd, *J* = 14.3, 8.8, 6.7 Hz, 1H), 2.43 (ddd, *J* = 14.3, 8.3, 3.8 Hz, 1H), 1.39 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.4, 170.2, 166.7, 160.9 (d, *J* = 243.7 Hz, 153.4, 150.7, 146.1, 131.3, 127.7 (d, *J* = 8.3 Hz), 125.0 (q, *J* = 281.8 Hz), 123.9, 114.6 (d, *J* = 22.3 Hz), 113.1, 108.6, 94.2, 51.1, 45.2, 41.0, 34.7, 29.0, 10.9; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8; HRMS (ESI) *m/z* calculated for $[C_{23}H_{21}F_4N_3O_4+H]^+$ = 480.1541, found 480.1534.

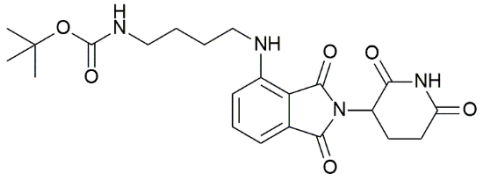
tert-butyl (2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)carbamate (16a)



Following GP1: compound **16a** was isolated as a yellow solid (0.118 g, 0.283 mmol, 64%); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.24 (br s, 1H), 7.50 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.39 (t, *J* = 6.1 Hz, 1H), 4.95 – 4.85 (m, 2H), 3.44 (q, *J* = 6.1 Hz, 2H), 3.36 (q, *J* = 6.1 Hz, 2H), 2.95 – 2.67 (m, 3H), 2.15 – 2.08 (m, 1H), 1.44 (s, 9H);

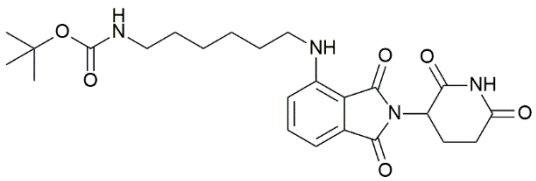
^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.2, 169.5, 168.5, 167.7, 156.2, 147.0, 136.4, 132.6, 116.8, 112.0, 110.4, 79.9, 49.0, 42.7, 40.3, 31.6, 28.5, 22.9; HRMS (ESI) *m/z* calculated for $[C_{20}H_{23}N_4O_6\text{-}H]^-$ = 415.1623, found 415.1607.

tert-butyl (4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)carbamate (16b)



Following GP1: Compound **16b** was isolated as a yellow solid (167 mg, 0.38 mmol, 57%); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.83 (br s, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.22 (t, *J* = 5.7 Hz, 1H), 4.90 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.74 (t, *J* = 6.1 Hz, 1H), 3.25 (q, *J* = 6.6 Hz, 2H), 3.14 (q, *J* = 6.7 Hz, 2H), 2.86 – 2.66 (m, 3H), 2.11 – 2.03 (m, 1H), 1.65 (p, *J* = 7.1 Hz, 2H), 1.56 (p, *J* = 7.1 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 169.6, 168.8, 167.7, 156.1, 146.9, 136.2, 132.5, 116.7, 111.5, 110.0, 79.3, 48.9, 42.3, 40.1, 31.5, 28.5, 27.6, 26.5, 22.8; HRMS (ESI) *m/z* calculated for $[C_{22}H_{28}N_4O_6+H]^+$ = 445.2082, found 445.2087.

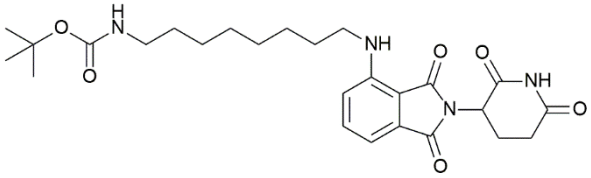
tert-butyl (6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)carbamate (16c)



Following **GP1**: Compound **2c** was isolated as a yellow solid (289 mg, 0.65 mmol, 46%); ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (br s, 1H), 7.57 (dd, *J* = 8.6, 7.1 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 7.0 Hz, 1H), 6.76 (t, *J* = 5.6 Hz, 1H), 6.53 (t, *J* = 6.0 Hz, 1H), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.28 (q, *J* = 6.8 Hz, 2H), 2.93 – 2.83 (m, 3H), 2.63 – 2.51 (m, 2H), 2.02 (s, 1H), 1.56 (p, *J* = 7.1

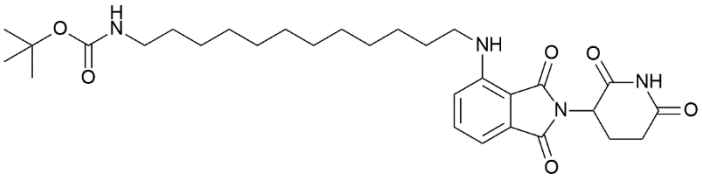
Hz, 2H), 1.36 (s, 15H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.8, 170.1, 168.9, 167.3, 155.6, 146.4, 136.2, 132.2, 117.1, 110.3, 109.0, 77.3, 48.5, 41.8, 31.0, 29.4, 28.6, 28.3, 26.0, 26.0, 22.1; HRMS (ESI) *m/z* calculated for $[C_{24}H_{31}N_4O_6 - H]^-$ = 471.2249, found 471.2232.

tert-butyl (8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)carbamate (16d)



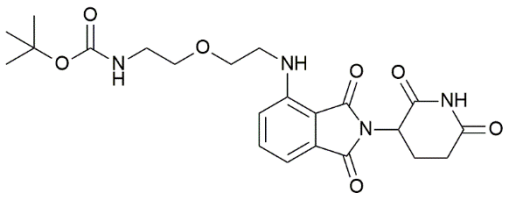
Following **GP1**: Compound **16d** was isolated as a yellow solid (233 mg, 0.46 mmol, 43%): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (br s, 1H), 7.48 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.08 (d, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.23 (t, *J* = 5.6 Hz, 1H), 4.91 (dd, *J* = 12.0, 5.3 Hz, 1H), 4.53 (br s, 1H), 3.25 (td, *J* = 6.8, 5.3 Hz, 2H), 3.10 (q, *J* = 6.8 Hz, 2H), 2.91 – 2.65 (m, 3H), 2.18 – 2.07 (m, 1H), 1.72 – 1.58 (m, 3H), 1.50 – 1.22 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.1, 169.7, 168.5, 167.8, 156.1, 147.2, 136.2, 132.7, 116.8, 111.5, 110.0, 79.2, 49.0, 42.8, 40.8, 31.6, 30.2, 29.3, 29.3, 28.6, 27.0, 26.8, 23.0; HRMS (ESI) *m/z* calculated for $[C_{26}H_{35}N_4O_6 - H]^-$ = 499.2562, found 499.2544.

tert-butyl (12-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)dodecyl)carbamate (16e)



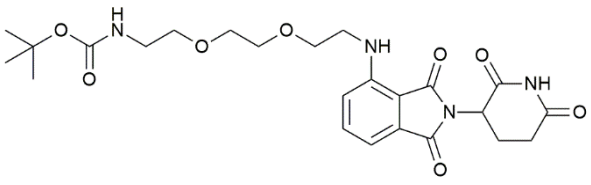
Following **GP1**: Compound **16e** was isolated as a yellow solid (273 mg, 0.49 mmol, 49%): ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (br s, 1H), 7.57 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.74 (t, *J* = 5.9 Hz, 1H), 6.52 (t, *J* = 6.0 Hz, 1H), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.31 – 3.25 (m, 2H), 2.94 – 2.80 (m, 3H), 2.63 – 2.51 (m, 2H), 2.06 – 1.92 (m, 1H), 1.61 – 1.49 (m, 2H), 1.36 (s, 9H), 1.34 – 1.17 (m, 18H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.8, 170.0, 168.9, 167.3, 155.5, 146.4, 136.2, 132.2, 117.2, 110.3, 109.0, 77.2, 48.5, 41.8, 31.0, 29.4, 29.0, 28.9, 28.9, 28.7, 28.7, 28.6, 28.3, 26.3, 26.2, 22.1; HRMS (ESI) *m/z* calculated for $[C_{30}H_{44}N_4O_6 + H]^+$ = 557.3334, found 557.3317.

tert-butyl (2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)carbamate (16f)



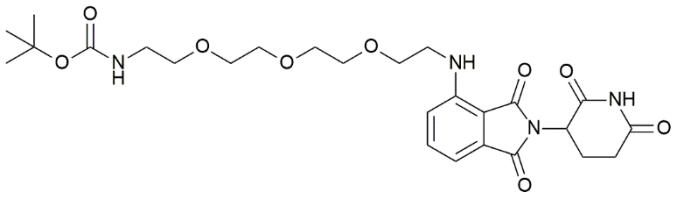
Following **GP1**: Compound **16f** was isolated as a yellow solid (255 mg, 0.55 mmol, 55%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.20 (br s, 1H), 7.50 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.51 (t, *J* = 5.8 Hz, 1H), 4.99 (br s, 1H), 4.92 (dd, *J* = 12.5, 5.4 Hz, 1H), 3.68 (t, *J* = 5.4 Hz, 2H), 3.55 (t, *J* = 5.3 Hz, 2H), 3.45 (q, *J* = 5.5 Hz, 2H), 3.33 (q, *J* = 5.5 Hz, 2H), 2.93 – 2.65 (m, 3H), 2.12 (dtd, *J* = 12.5, 4.9, 2.3 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.1, 169.5, 168.4, 167.7, 156.1, 147.0, 136.2, 132.6, 116.9, 111.9, 110.6, 79.4, 70.5, 69.4, 49.1, 42.4, 40.6, 31.6, 28.5, 22.9; HRMS (ESI) *m/z* calculated for $[C_{22}H_{28}N_4O_7 + H]^+$ = 461.2031, found 461.2014.

tert-butyl (2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)carbamate (16g)



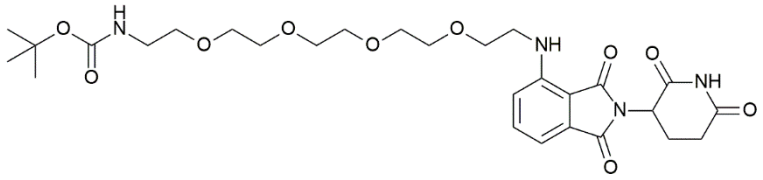
Following GP1: compound **16g** was isolated as a yellow solid (0.203 g, 0.402 mmol, 92%); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.78 (br s, 1H), 7.46 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.07 (d, *J* = 7.1 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.49 (t, *J* = 5.3 Hz, 1H), 5.12 – 5.02 (m, 1H), 4.90 (dd, *J* = 12.2, 5.4 Hz, 1H), 3.70 (t, *J* = 5.4 Hz, 2H), 3.66 – 3.59 (m, 4H), 3.54 (t, *J* = 5.3 Hz, 2H), 3.45 (q, *J* = 5.5 Hz, 2H), 3.29 (q, *J* = 5.5 Hz, 2H), 2.89 – 2.64 (m, 3H), 2.12 – 2.05 (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, 70.3, 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.

tert-butyl (2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)carbamate (16h)



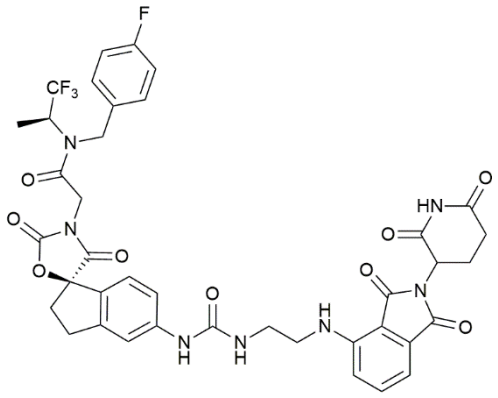
Following **GP1**: Compound **16h** was isolated as a yellow film (236 mg, 0.48 mmol, 48%): ^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.09 (br s, 1H), 7.58 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.73 (t, *J* = 5.9 Hz, 1H), 6.60 (t, *J* = 5.9 Hz, 1H), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.62 (t, *J* = 5.5 Hz, 2H), 3.59 – 3.44 (m, 10H), 3.35 (t, *J* = 6.1 Hz, 2H), 3.04 (q, *J* = 6.0 Hz, 2H), 2.88 (ddd, *J* = 17.1, 13.9, 5.4 Hz, 1H), 2.62 – 2.52 (m, 2H), 2.06 – 1.99 (m, 1H), 1.36 (s, 9H); ^{13}C NMR (151 MHz, DMSO-d_6) δ = 172.8, 170.0, 168.9, 167.3, 155.5, 146.4, 136.2, 132.1, 117.4, 110.7, 109.2, 77.6, 69.8, 69.5, 69.1, 68.9, 48.5, 41.7, 31.0, 28.2, 22.1; HRMS (ESI) *m/z* calculated for $[C_{26}H_{36}N_4O_9 - H]^-$ = 547.2410, found 547.2395.

tert-butyl (14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxatetradecyl)carbamate (16i)



Following **GP1**: Compound **16i** was isolated as a yellow-green film (296 mg, 0.59 mmol, 59%): ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.65 (br s, 1H), 7.46 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.07 (d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.47 (t, *J* = 5.7 Hz, 1H), 5.17 – 4.99 (m, 1H), 4.90 (dd, *J* = 12.3, 5.3 Hz, 1H), 3.70 (t, *J* = 5.4 Hz, 2H), 3.67 – 3.56 (m, 12H), 3.51 (d, *J* = 5.3 Hz, 2H), 3.45 (q, *J* = 5.5 Hz, 2H), 3.28 (q, *J* = 5.3 Hz, 2H), 2.90 – 2.62 (m, 3H), 2.09 (ddd, *J* = 12.2, 6.1, 3.2 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 171.4, 169.3, 168.6, 167.7, 156.1, 146.9, 136.1, 132.6, 116.9, 111.7, 110.4, 79.2, 70.8, 70.7, 70.7, 70.5, 70.3, 69.6, 49.0, 42.5, 40.4, 31.5, 28.5, 22.9; HRMS (ESI) *m/z* calculated for $[C_{28}H_{40}N_4O_{10} + H]^+$ = 593.2817, found 593.2807.

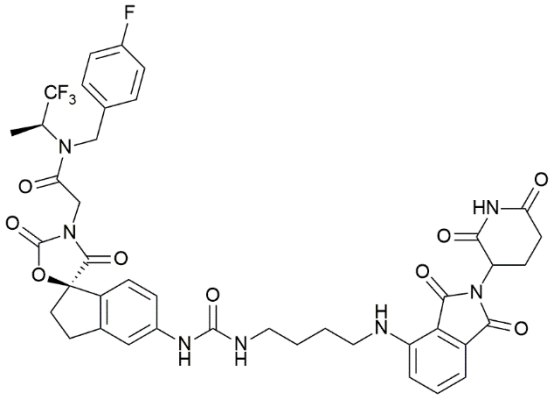
2-((1R)-5-(3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18a)



Following GP2: compound **18a** was isolated as a yellow solid (0.048 g, 0.058 mmol, 48%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 10.60 (br s, 1H), 8.42 (s, 1H), 7.58 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.36 (t, *J* = 7.0 Hz, 2H), 7.29 – 7.22 (m, 2H), 7.16 (dd, *J* = 11.9,

8.4 Hz, 3H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.57 (t, *J* = 6.0 Hz, 1H), 6.26 (t, *J* = 5.7 Hz, 1H), 5.22 (s, 1H), 5.00 (dd, *J* = 12.4, 5.6 Hz, 1H), 4.86 (d, *J* = 17.6 Hz, 1H), 4.77 – 4.49 (m, 2H), 4.40 (d, *J* = 16.8 Hz, 1H), 3.48 (q, *J* = 6.2 Hz, 2H), 3.40 (q, *J* = 6.0 Hz, 2H), 3.19 – 3.08 (m, 1H), 3.02 (ddd, *J* = 16.2, 8.8, 4.1 Hz, 1H), 2.88 – 2.80 (m, 1H), 2.71 – 2.53 (m, 3H), 2.49 – 2.46 (m, 1H), 2.10 – 2.02 (m, 1H), 1.39 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.0, 171.5, 168.9, 168.3, 166.6, 166.6, 160.9 (d, *J* = 243.7 Hz), 154.9, 153.3, 146.2, 145.5, 142.4, 135.4, 132.7, 131.8, 129.5, 127.6 (d, *J* = 8.3 Hz), 124.9 (q, *J* = 285.2 Hz), 123.5, 117.1, 116.7, 114.61 (d, *J* = 21.6 Hz), 113.5, 110.1, 109.4, 93.5, 51.2, 48.4, 45.2, 42.0, 41.1, 38.5, 34.5, 30.4, 29.2, 21.7, 10.9; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8; HRMS (ESI) *m/z* calculated for $[C_{39}H_{35}F_4N_7O_9+Na]^+$ = 844.2325, found 844.2336.

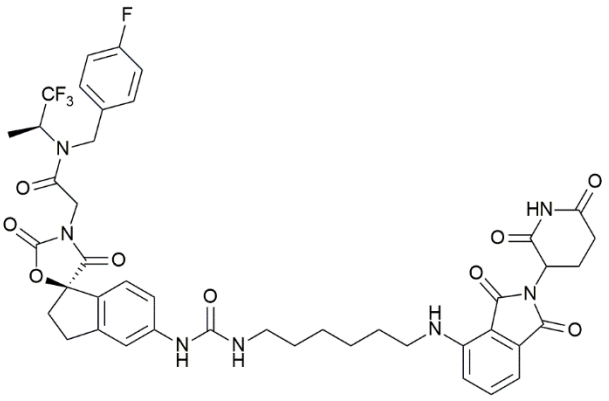
2-((1R)-5-(3-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18b)



Following GP2: compound **18b** was isolated as a yellow solid (57 mng, 0.067 mmol, 64%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 10.60 (br s, 1H), 8.30 (s, 1H), 7.56 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.51 (s, 1H), 7.40 – 7.30 (m, 2H), 7.28 – 7.21 (m, 2H), 7.15 (t, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 7.1 Hz, 1H), 6.40 (t, *J* = 6.0 Hz, 1H), 6.06 (t, *J* = 5.7 Hz, 1H), 5.21 (s, 1H), 4.99 (dd, *J* = 12.3, 5.6 Hz, 1H), 4.86 (d, *J* = 17.6 Hz, 1H), 4.64 (d, *J* = 17.9 Hz,

2H), 4.39 (d, *J* = 16.7 Hz, 1H), 3.36 (q, *J* = 6.7 Hz, 2H), 3.19 (q, *J* = 6.5 Hz, 2H), 3.17 – 3.10 (m, 1H), 3.01 (ddd, *J* = 16.3, 8.8, 4.1 Hz, 1H), 2.85 (ddd, *J* = 17.1, 13.4, 5.5 Hz, 1H), 2.73 – 2.53 (m, 4H), 2.51 – 2.45 (m, 1H), 2.07 (dtd, *J* = 13.4, 5.4, 2.8 Hz, 1H), 1.73 – 1.64 (m, 2H), 1.63 – 1.55 (m, 2H), 1.39 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.1, 171.6, 168.9, 168.5, 166.7, 166.7, 161.0 (d, *J* = 243.9 Hz), 154.7, 153.4, 146.3, 145.6, 142.7, 135.5, 132.8, 131.9, 129.3, 127.7 (d, *J* = 8.1 Hz), 125.0 (q, *J* = 284.2 Hz), 123.5, 116.9, 116.7, 114.7 (d, *J* = 21.7 Hz), 113.4, 109.9, 109.2, 93.6, 51.1, 48.4, 45.3, 41.5, 41.2, 38.5, 34.6, 30.5, 29.3, 26.6, 26.0, 21.8, 11.0; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.7. HRMS (ESI) *m/z* calculated for $[C_{41}H_{39}F_4N_7O_9+Na]^+$ = 872.2638, found 872.2610.

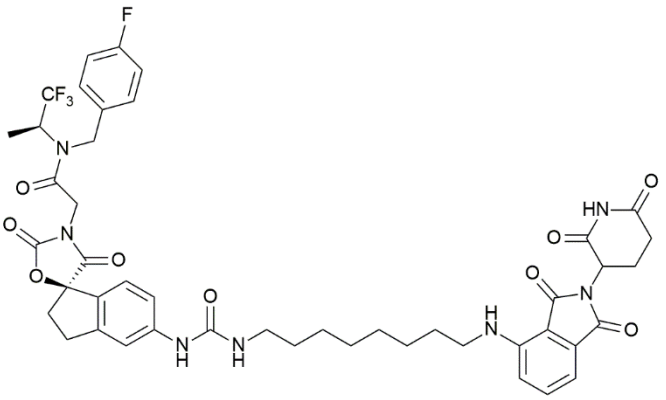
2-((1R)-5-(3-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18c)



Following GP2: compound **18c** was isolated as a yellow solid (55 mg, 0.063 mmol, 61%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 10.61 (br s, 1H), 8.28 (s, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.51 (s, 1H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.28 – 7.21 (m, 2H), 7.16 (t, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 7.1 Hz, 1H), 6.38 (t, *J* = 5.7 Hz, 1H), 5.99 (t, *J* = 5.7 Hz, 1H), 5.22 (s, 1H), 4.99 (dt, *J* = 10.7, 5.5 Hz, 1H), 4.86 (d, *J* = 17.6 Hz, 1H), 4.64 (d, *J* = 19.8 Hz, 2H), 4.39 (d, *J* = 16.5 Hz, 1H), 3.33 (q, *J* = 6.7 Hz, 2H), 3.18 – 3.07 (m, 2H), 3.01 (ddd, *J* =

16.4, 9.0, 4.2 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.72 – 2.53 (m, 3H), 2.49 – 2.45 (m, 1H), 2.12 – 1.99 (m, 1H), 1.72 – 1.58 (m, 2H), 1.55 – 1.47 (m, 2H), 1.47 – 1.34 (m, 8H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.0, 171.5, 168.9, 168.5, 166.6, 166.6, 160.9 (d, *J* = 243.6 Hz), 154.5, 153.3, 146.2, 145.5, 142.7, 135.5, 132.7, 131.8, 129.2, 127.6 (d, *J* = 8.3 Hz), 124.9 (q, *J* = 282.2 Hz), 123.4, 116.8, 116.5, 114.6 (d, *J* = 21.4 Hz), 113.2, 109.8, 109.1, 93.5, 48.4, 45.2, 41.6, 41.1, 38.7, 34.5, 30.4, 29.2, 29.0, 28.2, 25.5, 25.4, 21.7, 10.9; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8; HRMS (ESI) *m/z* calculated for $[C_{43}H_{43}F_4N_7O_9+Na]^+$ = 900.2951, found 900.293.

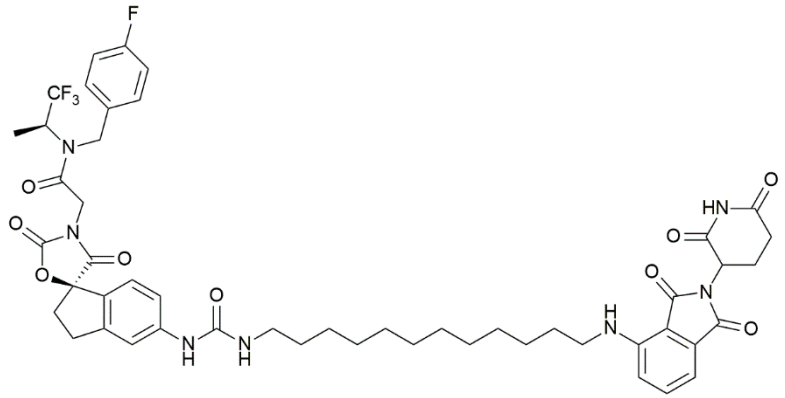
2-((1R)-5-(3-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18d)



Following GP2: compound **18d** was isolated as a yellow solid (80 mg, 0.088 mmol, 72%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 10.59 (br s, 1H), 8.28 (s, 1H), 7.57 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.35 (t, *J* = 6.9 Hz, 2H), 7.27 – 7.21 (m, 2H), 7.15 (t, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.36 (t, *J* = 5.9 Hz, 1H), 5.97 (t, *J* = 5.6 Hz, 1H), 5.21 (s, 1H), 4.99 (dd, *J* = 12.3, 5.6 Hz, 1H), 4.86 (d, *J* = 17.7 Hz, 1H), 4.64 (d, *J* = 19.9 Hz, 2H), 4.40 (d, *J* = 16.8 Hz, 1H), 3.31 (q, *J* = 6.7 Hz, 2H), 3.15 – 3.09 (m, 2H), 3.02 (td, *J* = 8.1, 7.6, 4.1 Hz, 1H), 2.86 (ddd, *J* = 17.0, 13.3, 5.5 Hz, 1H), 2.72 – 2.52 (m, 3H), 2.49 –

2.45 (m, 1H), 2.13 – 2.01 (m, 1H), 1.64 (p, *J* = 7.1 Hz, 2H), 1.48 (p, *J* = 6.8 Hz, 2H), 1.44 – 1.22 (m, 12H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.1, 171.6, 168.9, 168.5, 166.7, 166.7, 161.0 (d, *J* = 243.7 Hz), 154.6, 153.4, 146.3, 145.6, 142.7, 135.5, 132.7, 131.8, 129.3, 127.7 (d, *J* = 8.3 Hz) 125.0 (q, *J* = 283.9 Hz) 123.5, 116.9, 116.6, 114.7 (d, *J* = 21.6 Hz), 113.3, 109.9, 109.1, 93.6, 51.1, 48.4, 45.3, 41.7, 41.1, 39.1, 38.8, 34.6, 30.5, 29.3, 29.1, 28.3, 28.0, 28.0, 25.7, 25.7, 21.8, 10.9; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.7; HRMS (ESI) *m/z* calculated for $[C_{45}H_{47}F_4N_7O_9+Na]^+$ = 928.3264, found 928.3246.

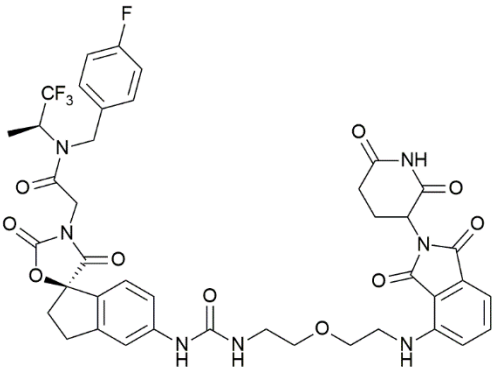
2-((1R)-5-(3-(12-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)dodecyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18e)



Following GP2: compound **18e** was isolated as a yellow solid (0.045 g, 0.047 mmol, 50%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 10.58 (br s, 1H), 8.30 (s, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.52 (s, 1H), 7.36 (s, 2H), 7.29 – 7.21 (m, 2H), 7.16 (t, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.37 (t, *J* = 6.0 Hz, 1H), 5.98 (t, *J* = 5.8 Hz, 1H), 5.22 (s, 1H), 5.00 (dd, *J* = 12.4, 5.5 Hz, 1H), 4.86 (dd, *J* = 17.8, 5.8 Hz, 1H), 4.77 – 4.50 (m, 2H), 4.39 (s, 1H), 3.31 (q, *J* = 7.1 Hz, 3H), 3.12 (h, *J* = 7.9, 6.6 Hz, 3H), 3.06 – 2.96 (m, 1H), 2.87 (ddd, *J* = 17.9, 13.3, 5.3 Hz, 1H), 2.73 – 2.54 (m, 3H), 2.13 – 2.03 (m, 1H), 1.63 (t, *J* = 7.7 Hz, 2H), 1.54 – 1.44 (m, 2H), 1.44 – 1.37 (m, 5H), 1.37 – 1.25 (m, 15H); ^{13}C NMR (151 MHz, 110 °C,

DMSO-d_6) δ = 173.0, 171.6, 168.9, 168.5, 166.7, 160.9 (d, *J* = 243.4 Hz), 154.5, 153.3, 146.3, 145.6, 142.7, 135.5, 132.8, 131.8, 129.2, 127.7 (d, *J* = 8.0 Hz), 124.41 (q, *J* = 285.8), 123.5, 123.5, 116.8, 116.6, 114.7 (d, *J* = 22.0 Hz), 113.2, 109.8, 109.1, 93.6, 51.0, 48.4, 45.2, 41.7, 41.1, 40.0, 39.9, 39.1, 38.8, 34.6, 34.5, 30.5, 29.3, 29.1, 28.3, 28.3, 28.1, 28.0, 25.8, 25.7, 21.7, 20.7, 10.9; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8; HRMS (ESI) *m/z* calculated for $[C_{49}H_{55}F_4N_7O_9+H]^+$ = 962.4070, found 962.4038.

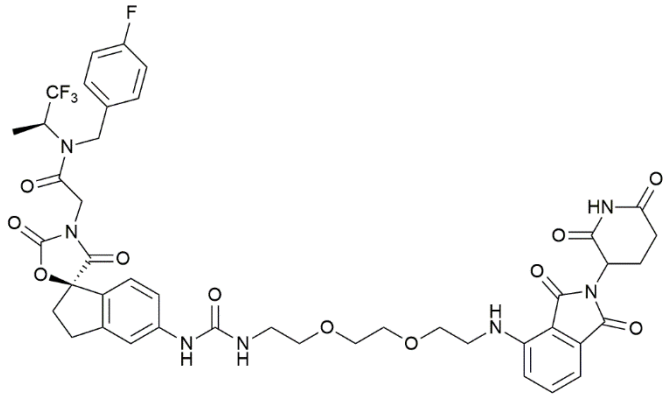
2-((1R)-5-(3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18f)



Following GP2: compound **18f** was isolated as a yellow solid (100 mg, 0.116 mmol, 74%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 10.61 (br s, 1H), 8.42 (d, *J* = 3.9 Hz, 1H), 7.56 (q, *J* = 7.1 Hz, 1H), 7.50 (d, *J* = 5.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.26 (q, *J* = 7.0, 5.2 Hz, 2H), 7.20 – 7.09 (m, 3H), 7.03 (t, *J* = 6.5 Hz, 1H), 6.53 (t, *J* = 6.1 Hz, 1H), 6.10 (t, *J* = 5.6 Hz, 1H), 5.22 (s, 1H), 5.06 – 4.93 (m, 1H), 4.86 (dd, *J* = 17.6, 5.7 Hz, 1H), 4.65 (d, *J* = 18.4 Hz, 2H), 4.47 – 4.29 (m, 1H), 3.70 (q, *J* = 5.7 Hz, 2H), 3.58 (t, *J* = 6.0 Hz, 2H), 3.51 (p, *J* = 5.8 Hz, 2H), 3.32 (p, *J* = 6.0 Hz, 2H), 3.18 – 3.09 (m, 1H), 3.06 – 2.97 (m, 1H), 2.89 – 2.78 (m, 1H), 2.73 – 2.53 (m, 3H), 2.49 – 2.44 (m, 1H), 2.13 – 1.95 (m, 1H), 1.45 – 1.33 (m, 3H). ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.0, 171.5, 168.9, 168.4, 166.7, 166.6, 160.9 (d, *J* = 242.6 Hz), 154.6,

153.3, 146.2, 145.6, 142.6, 135.5, 132.7, 131.8, 129.4, 127.7 (d, *J* = 8.2 Hz), 124.9 (q, *J* = 281.0 Hz), 123.5, 116.9, 116.8, 114.6 (d, *J* = 21.5 Hz), 113.3, 110.2, 109.4, 93.6, 69.3, 68.4, 51.0, 48.4, 45.2, 41.7, 41.1, 38.8, 34.5, 30.5, 29.3, 21.7, 10.9; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8; HRMS (ESI) *m/z* calculated for $[C_{41}H_{39}F_4N_7O_{10}+Na]^+$ = 888.25867, found 888.25753.

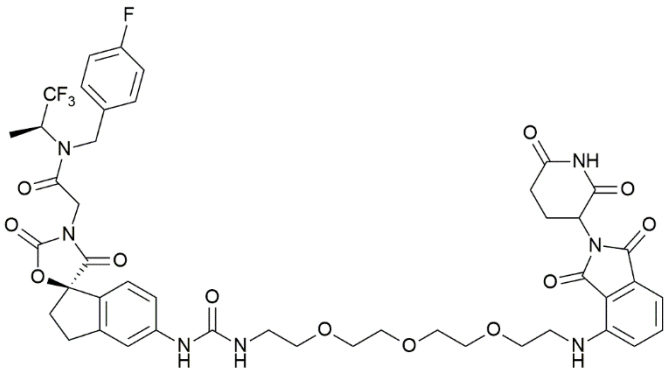
2-((1R)-5-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18g)



Following GP2: compound **18g** was isolated as a yellow solid (0.042 g, 0.046 mmol, 33%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ 10.60 (br s, 1H), 8.44 (s, 1H), 7.56 (dd, *J* = 8.6, 7.0 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.36 (d, *J* = 9.1 Hz, 2H), 7.28 – 7.21 (m, 2H), 7.16 (t, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.51 (d, *J* = 5.6 Hz, 1H), 6.04 (d, *J* = 5.3 Hz, 1H), 5.22 (s, 1H), 4.99 (dd, *J* = 12.4, 5.6 Hz, 1H), 4.85 (d, *J* = 17.6 Hz, 1H), 4.64 (s, 2H), 4.39 (d, *J* = 16.9 Hz, 1H), 3.68 (t, *J* = 5.5 Hz, 2H), 3.66 – 3.56 (m, 7H), 3.56 – 3.41 (m, 5H), 3.28 (q, *J* = 5.7 Hz, 2H), 3.18 – 3.08 (m, 1H), 3.01 (ddd, *J* = 16.2, 8.8, 4.0 Hz, 2H), 2.89 – 2.80 (m, 3H), 2.72 – 2.53 (m, 4H), 2.49 – 2.44 (m, 1H), 2.13 – 2.03 (m, 2H), 1.39 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.0, 171.5, 168.9, 168.4, 166.6, 166.6, 160.9 (d, *J* = 243.4 Hz), 154.5, 153.3, 146.2, 145.5, 142.6, 135.4, 132.7, 131.8, 129.3, 127.6

(d, *J* = 8.3 Hz), 124.9 (q, *J* = 283.1 Hz), 123.5, 122.1, 116.8, 116.8, 114.6 (d, *J* = 21.1 Hz), 113.2, 110.1, 109.4, 93.5, 69.4, 69.3, 69.2, 68.6, 51.0, 48.4, 45.2, 41.7, 41.1, 38.8, 34.5, 30.4, 29.2, 21.7, 10.9; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8; HRMS (ESI) *m/z* calculated for $[C_{43}H_{43}F_4N_7O_{11}+H]^+$ = 910.3029, found 910.3038.

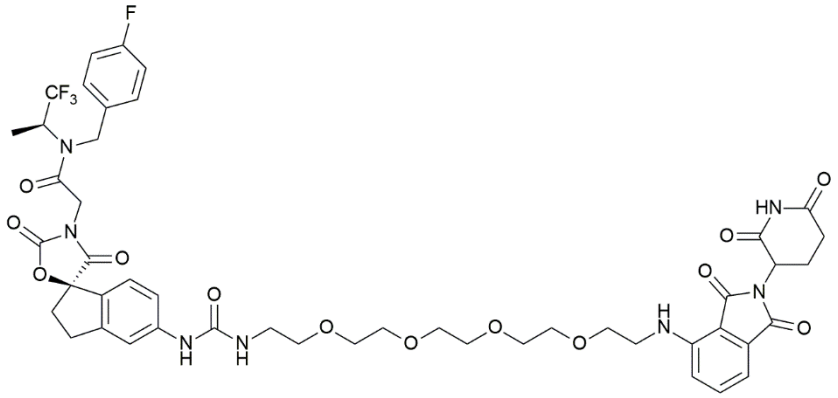
2-((1R)-5-(3-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)ethyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18h)



Following GP2: compound **18h** was isolated as a yellow solid (81 mg, 0.085 mmol, 57%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 10.61 (br s, 1H), 8.45 (s, 1H), 7.57 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.29 – 7.21 (m, 2H), 7.16 (t, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.51 (t, *J* = 6.0 Hz, 1H), 6.05 (t, *J* = 5.6 Hz, 1H), 5.22 (s, 1H), 5.00 (dd, *J* = 12.3, 5.5 Hz, 1H), 4.86 (d, *J* = 17.6 Hz, 1H), 4.65 (d, *J* = 19.7 Hz, 2H), 4.40 (d, *J* = 16.7 Hz, 1H), 3.68 (t, *J* = 5.5 Hz, 2H), 3.64 – 3.55 (m, 8H), 3.54 – 3.44 (m, 4H), 3.29 (q, *J* = 5.7 Hz, 2H), 3.18 – 3.10 (m, 1H), 3.02 (ddd, *J* = 16.2, 8.7, 4.1 Hz, 1H), 2.89 – 2.80 (m, 1H), 2.74 – 2.54 (m, 3H), 2.49 – 2.45 (m, 1H), 2.13 – 2.03 (m, 1H), 1.40 (d, *J* = 7.1 Hz, 3H);^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.0, 171.5, 168.8, 168.4, 166.6, 166.6, 160.9 (d, *J* = 243.7 Hz), 154.5, 153.3, 146.2, 145.5, 142.6, 135.4, 132.7, 131.8, 129.3, 127.6 (d, *J* = 8.3 Hz), 124.9 (q, *J* = 283.0 Hz), 123.5, 116.8, 116.8, 114.6 (d, *J* = 21.5

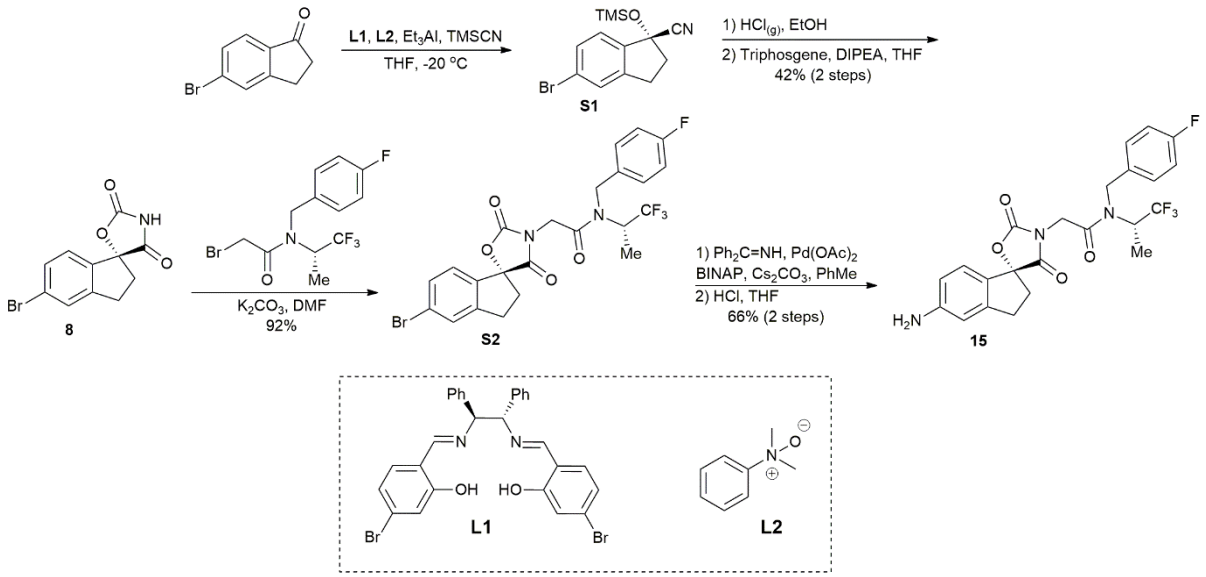
Hz), 113.3, 110.1, 109.3, 93.5, 69.4, 69.4, 69.2, 69.2, 68.6, 51.0, 48.4, 45.2, 41.7, 41.1, 38.9, 34.5, 30.4, 29.2, 21.7, 10.9z; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8. HRMS (ESI) *m/z* calculated for $[C_{45}H_{47}F_4N_7O_{12}+Na]^+$ = 976.3111, found 976.3112.

2-((1R)-5-(3-(14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxatetradecyl)ureido)-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (18i)



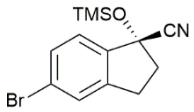
Following GPX: compound **18i** was isolated as a yellow solid (15 mg, 0.015 mmol, 16%); ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 10.59 (br s, 1H), 8.44 (s, 1H), 7.57 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.43 – 7.30 (m, 2H), 7.28 – 7.22 (m, 2H), 7.16 (t, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.52 (t, *J* = 5.8 Hz, 1H), 6.05 (t, *J* = 5.7 Hz, 1H), 5.22 (s, 1H), 5.00 (dd, *J* = 12.3, 5.6 Hz, 1H), 4.86 (d, *J* = 17.6 Hz, 1H), 4.65 (d, *J* = 19.1 Hz, 2H), 4.39 (d, *J* = 17.2 Hz, 1H), 3.67 (t, *J* = 5.5 Hz, 2H), 3.62 – 3.54 (m, 12H), 3.52 – 3.46 (m, 4H), 3.28 (q, *J* = 5.7 Hz, 2H), 3.20 – 3.08 (m, 1H), 3.02 (ddd, *J* = 16.2, 8.8, 4.1 Hz, 1H), 2.89 – 2.82 (m, 1H), 2.73 – 2.54 (m, 3H), 2.49 – 2.45 (m, 1H), 2.13 – 2.01 (m, 1H), 1.39 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 173.0, 171.5, 168.9, 168.4, 166.7, 166.6, 160.9 (d, *J* = 243.6 Hz), 154.6, 153.3, 146.2, 145.6, 142.6, 135.4, 132.8, 131.8, 129.3, 127.7 (d, *J* = 8.2 Hz), 125.0 (q, *J* = 283.7 Hz) 123.5, 116.8, 114.6 (d, *J* = 21.9 Hz), 113.3, 110.1, 109.3, 93.5, 69.4, 69.4, 69.3, 69.2, 68.6, 51.1, 48.4, 45.2, 41.7, 41.1, 38.9, 34.5, 30.5,

29.3, 21.7, 10.9. ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8; HRMS (ESI) *m/z* calculated for $[C_{47}H_{51}F_4N_7O_{13}+H]^+$ = 998.3523, found 998.3554.



Scheme S1. Chiral A-485 precursor synthesis.

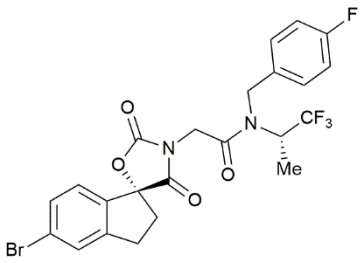
(R)-5-bromo-1-((trimethylsilyl)oxy)-2,3-dihydro-1H-indene-1-carbonitrile (S1)[4, 5]



To a solution of salen ligand 6,6'-((1E,1'E)-(((1S,2S)-1,2-diphenylethane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(3-bromophenol) (0.46 g, 0.80 mmol, 3 mol%) in anhydrous THF (20 mL) was added a solution of triethylaluminium (1 M, 0.80 mL, 0.80 mmol 3 mol%). The mixture was stirred at room temperature for one hour, after which 5-bromo-1-indanone (5.728 g, 26.7 mmol, 1.0 eq.) was quickly added to the mixture and stirred at room temperature for 15 minutes and then cooled to -20 °C. In a separate flask in a glovebox

under an N_2 atmosphere, *N*,*N*-dimethylaniline *N*-oxide (0.060 g, 0.44 mmol, 2 mol%) was added and the flask was capped and removed from the glovebox and anhydrous THF (20 mL) was added. Trimethylsilyl cyanide (6.7 mL, 53.6 mmol, 2.0 eq.) was added dropwise over 20 minutes and the mixture was stirred at room temperature for 1 hour. This solution was then added slowly to the mixture containing 5-bromo-1-indanone using a syringe pump over 80 minutes at an approximate rate of 0.3 mL/min. Once the addition was complete the reaction mixture was allowed to stir at -20 °C for 40 hours and was then slowly quenched with sat. aq. sodium carbonate solution (40 mL) and water (50 mL). The aqueous solution was then extracted with EtOAc (3 x 100 mL), and the combined organic layers were dried over anhydrous sodium sulphate, filtered, and reduced *in vacuo*. The crude residue was adsorbed to silica gel and purified by silica gel flash column chromatography (1 – 10% EtOAc in hexanes) to afford **S1** (6.032 g, 19.4 mmol, 73%) as a yellow liquid; $[\alpha]_D^{20}$ = +19.3 (c 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.46 – 7.41 (m, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 3.14 – 3.04 (m, 1H), 2.98 (ddd, *J* = 16.1, 7.9, 5.7 Hz, 1H), 2.71 (ddd, *J* = 13.5, 7.9, 5.8 Hz, 1H), 2.43 (ddd, *J* = 13.3, 7.8, 5.7 Hz, 1H), 0.22 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ =144.9, 141.6, 130.8, 128.6, 125.7, 124.3, 120.7, 76.1, 43.0, 29.4, 1.3.

2-((R)-5-bromo-2',4'-dioxo-2,3-dihydrospiro[indene-1,5'-oxazolidin]-3'-yl)-N-(4-fluorobenzyl)-N-((S)-1,1,1-trifluoropropan-2-yl)acetamide (S2)[4]



To a solution of spirocyclic imide **8** (0.375 g, 1.32 mmol, 1.0 eq.) and (S)-2-bromo-N-(4-fluorobenzyl)-N-(1,1,1-trifluoropropan-2-yl)acetamide[2] (0.5077 g, 1.5 mmol, 1.1 eq.) in DMF

(5 mL) was added potassium carbonate (0.582 g, 4.2 mmol, 3.2 eq.) and the reaction was stirred at 0 °C for 2 hours. The reaction was then quenched with water (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered, and the volatiles were removed *in vacuo*. The crude residue was purified by silica gel flash column chromatography (0 - 25% EtOAc in DCM) to afford **S2** (0.6992 g, 1.28 mmol, 97%) as a white solid; ^{1}H NMR (600 MHz, 110 °C, DMSO-d_6) δ = 7.63 (d, *J* = 1.8 Hz, 1H), 7.52 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.42 – 7.32 (m, 3H), 7.16 (t, *J* = 8.5 Hz, 2H), 5.32 – 5.15 (m, 1H), 4.91 – 4.83 (m, 1H), 4.65 (d, *J* = 17.8 Hz, 2H), 4.41 (d, *J* = 16.8 Hz, 1H), 3.26 – 3.18 (m, 1H), 3.11 (ddd, *J* = 16.7, 8.8, 4.6 Hz, 1H), 2.73 (ddd, *J* = 14.7, 8.7, 6.2 Hz, 1H), 2.55 (ddd, *J* = 14.5, 8.5, 4.6 Hz, 1H), 1.40 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, 110 °C, DMSO-d_6) δ = 172.4, 166.6, 160.9 (d, *J* = 243.8 Hz), 153.1, 147.3, 136.3, 132.7, 130.0, 127.7, 127.6 (d, *J* = 8.2 Hz), 125.1, 124.9 (q, *J* = 283.4 Hz), 123.7, 114.6 (d, *J* = 21.8 Hz), 92.5, 51.0, 45.2, 41.2, 34.2, 29.0, 10.9; ^{19}F NMR (376 MHz, 110 °C, DMSO-d_6) δ = -72.2, -115.8; HRMS (ESI) *m/z* calculated for $[C_{23}H_{19}BrF_4N_2O_4+Na]^+$ = 565.0357, found 565.0342.

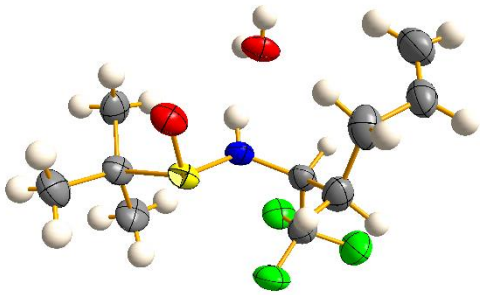


Figure S1. Crystal structure of 4

Table S1. Crystal data and structure refinement for 4.

Identification code	**4**
Empirical formula	$C_{10}H_{20}F_3NO_2S•H_2O$

Formula weight	275.33
Temperature/K	173
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	6.0280(5)
b/Å	12.5634(8)
c/Å	18.7272(16)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1418.25(19)
Z	4
ρ_{calc}g/cm^3	1.289
μ/mm^{-1}	2.301
F(000)	584.0
Crystal size/mm^3	0.386 × 0.173 × 0.05
Radiation	CuKα (λ = 1.54178)
2θ range for data collection/°	8.474 to 130.376
Index ranges	$-7 \leq h \leq 7$, $-14 \leq k \leq 14$, $-22 \leq l \leq 20$
Reflections collected	6416
Independent reflections	2391 [R_{int} = 0.0431, R_{sigma} = 0.0520]
Data/restraints/parameters	2391/0/166
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0427, wR_2 = 0.1056
Final R indexes [all data]	R_1 = 0.0514, wR_2 = 0.1104
Largest diff. peak/hole / e Å^{-3}	0.26/-0.26
Flack parameter	-0.01(2)

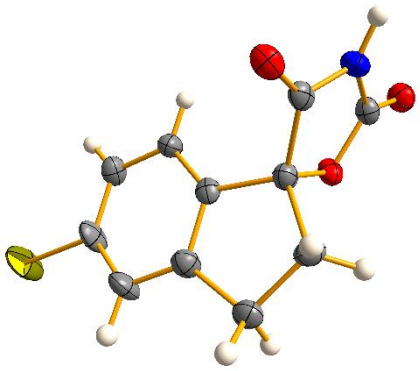


Figure S2. Crystal structure of 8

Table S2. Crystal data and structure refinement for 8

Identification code	**8**	**8** – 2nd crystal
Empirical formula	$C_{11}H_8BrNO_3$	$C_{11}H_8BrNO_3$
Formula weight	282.09	282.09
Temperature/K	173	173
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a/Å	8.1072(2)	8.1112(2)
b/Å	8.1810(2)	8.1755(3)
c/Å	32.6881(7)	32.6852(9)
α/°	90	90
β/°	90	90
γ/°	90	90
Volume/Å^3	2168.04(9)	2167.46(11)
Z	8	8
ρ_{calc}g/cm^3	1.728	1.729
μ/mm^{-1}	5.121	5.123
F(000)	1120.0	1120.0
Crystal size/mm^3	0.364 × 0.117 × 0.052	0.332 × 0.226 × 0.038
Radiation	CuKα (λ = 1.54178)	CuKα (λ = 1.54178)

2θ range for data collection/°	5.406 to 136.466	5.408 to 136.482
Index ranges	$-9 \leq h \leq 9$, $-9 \leq k \leq 9$, $-39 \leq l \leq 39$	$-9 \leq h \leq 9$, $-9 \leq k \leq 8$, $-39 \leq l \leq 37$
Reflections collected	15161	14513
Independent reflections	3947 [R_{int} = 0.0406, R_{sigma} = 0.0413]	3939 [R_{int} = 0.0556, R_{sigma} = 0.0549]
Data/restraints/parameters	3947/150/327	3939/210/327
Goodness-of-fit on F^2	1.097	1.170
Final R indexes [I>=2σ (I)]	R_1 = 0.0345, wR_2 = 0.0831	R_1 = 0.0533, wR_2 = 0.1256
Final R indexes [all data]	R_1 = 0.0358, wR_2 = 0.0838	R_1 = 0.0555, wR_2 = 0.1267
Largest diff. peak/hole / e $Å^{-3}$	0.81/-0.35	0.57/-0.55
Flack parameter	-0.007(11)	0.069(16)

Single Crystal Data Collection, Solution, and Refinement

Single crystals of **4** and **8** were grown by slow cooling in their respective solvents. Suitable crystals were 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 crystals were kept at 173 K during data collection. Diffractions spots were integrated and scaled with SAINT[5] and the space group was determined with XPREP.[6] Using Olex2,[7] the structure was solved with the ShelXT[8] structure solution program using Intrinsic Phasing and refined with the ShelXL[9] refinement package using Least Squares minimisation.

Biological Assays

***In vitro* biotinylation binding assay**

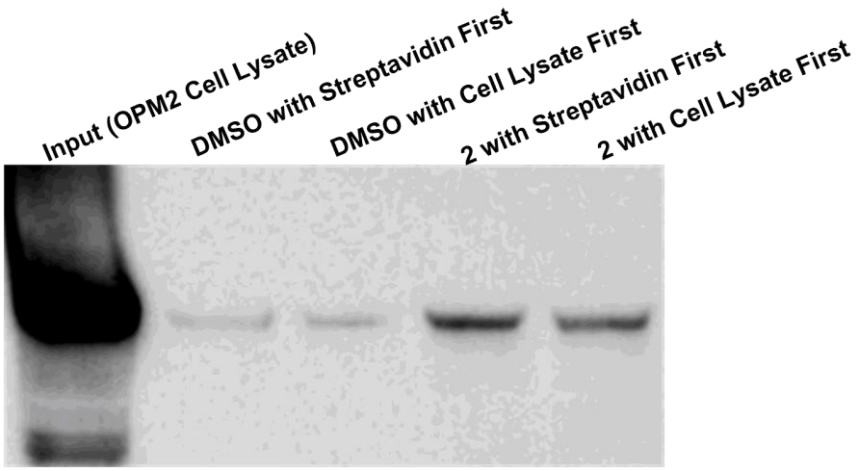


Figure S3. *In vitro* biotinylation binding study

Biotinylated ligands were coupled with Pierce Streptavidin Magnetic Beads (Thermo Scientific) by incubating them for 3 hours at room temperature in streptavidin binding buffer (50 mM TrispH 7.5, 300 mM NaCl, 0.05% NP40). Coupled streptavidin beads were incubated with OPM2 cell lysate overnight at 4°C. Beads were washed with binding buffer and quenched with 4x SDSPAGE gel loading buffer. Samples were separated on SDS-PAGE, followed by immunoblot analysis anti-p300 mAb (Santa Cruz Sc-584 X).

Cell viability assay (MTS)

Compound	EC_{50} (nM)
18a	>500
18b	>500
18c	345±35

18d	>500
18e	>500
18f	>500
18g	294±32
18h	>500
18i	422±60
A-485	139±6

Table S3. Calculated EC_{50} values for cell viability against MM1.S cells.

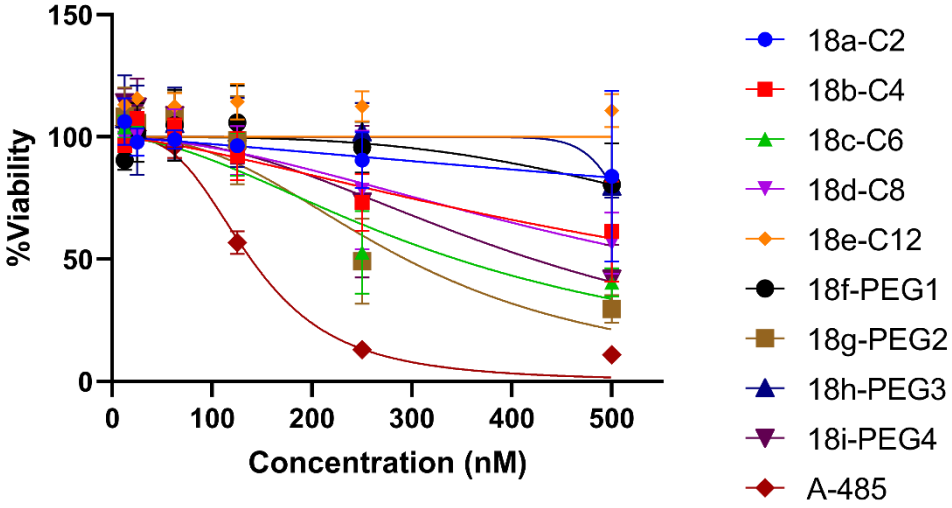


Figure S4. Cell viability of compounds **18a-i** and **A-485** against MM1.S cells from 12.5 – 500 nM.

MM1.S cells were plated in 96-well plates at a concentration of 2×10^5 cells/well and treated with compounds **18a-i** for 72 hours at the indicated concentrations in triplicate. The cellular proliferation was then analysed through (3-(4,5-dimethylthiazol-2-yl)-5-(3-

carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS) dye absorbance using CellTiter96^{TM} AQueous Dye (Promega). The MTS assay data was analysed using a SpectraMax iD3 Microplate Reader instrument (ThermoFisher Scientific). EC_{50} values were calculated using the [Inhibitor] vs. normalized response function from GraphPad Prism 9.3.1 using standard error for reported uncertainties.

Immunoblotting

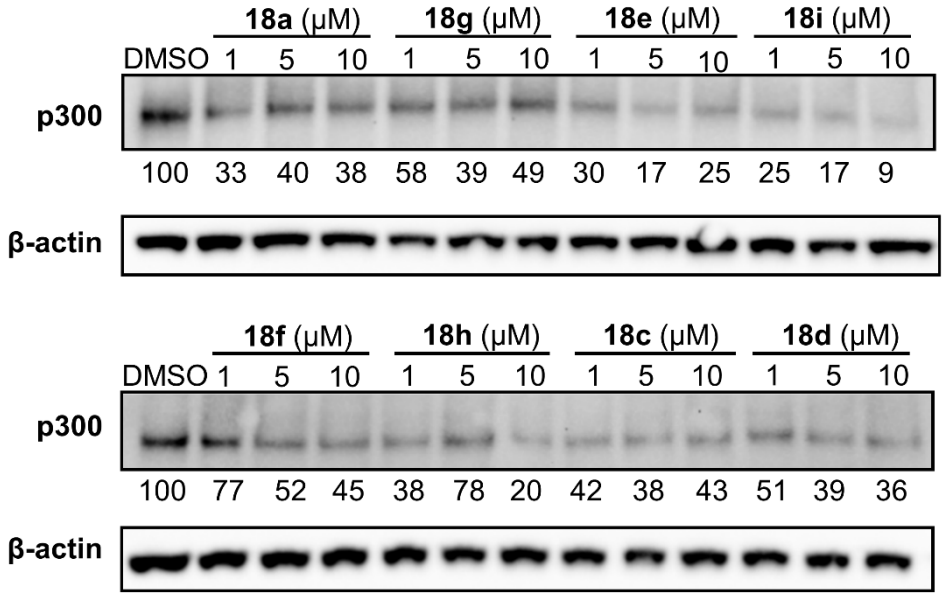
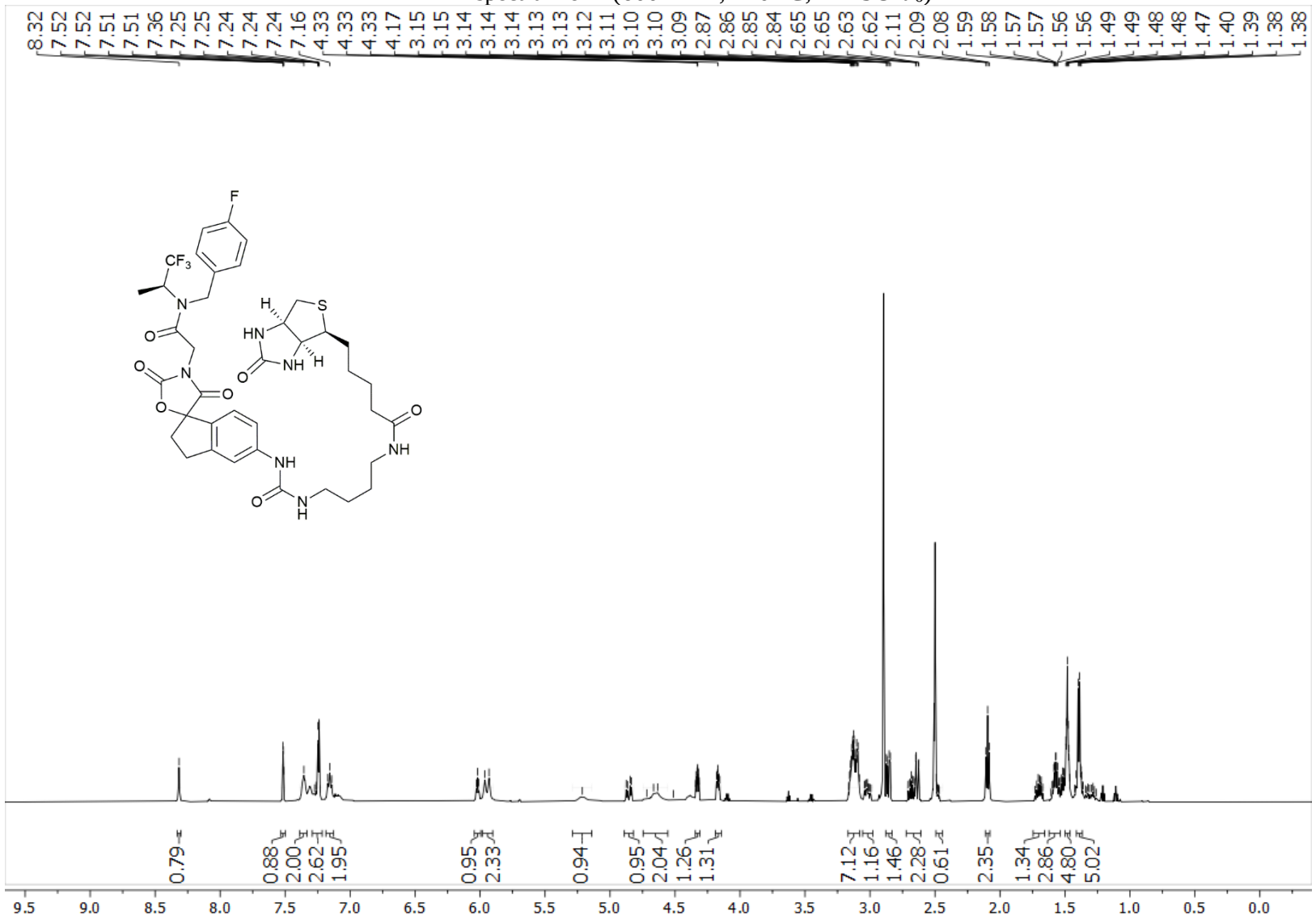


Figure S5. Immunoblot for p300 after 24 h of treatment with DMSO or A-485-pomalidomide conjugates in MM1.S cells.

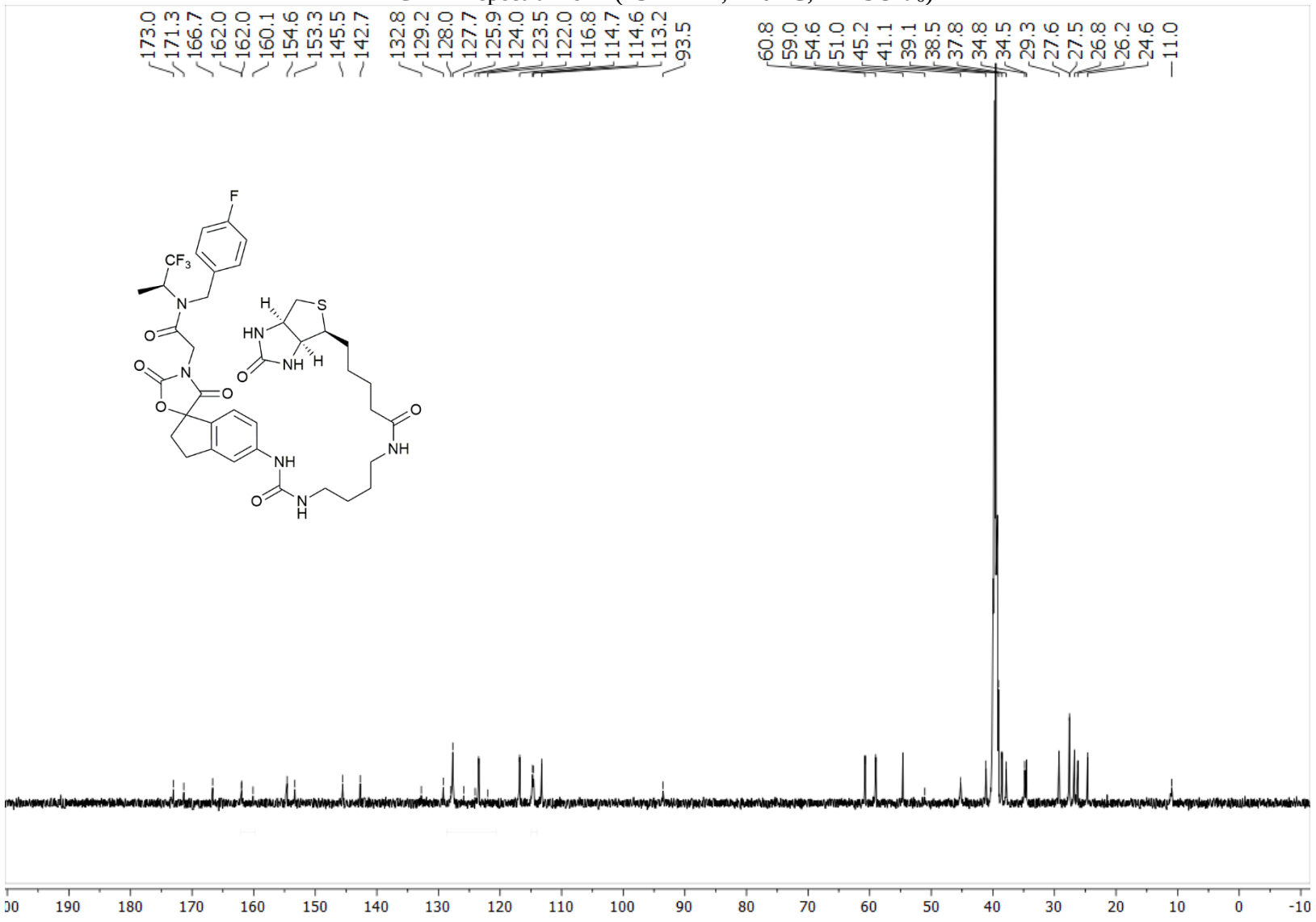
MM1.S cells were plated in 6-well plates at a concentration of 2×10^6 cells/well and incubated for 24 hours at 37 °C in a 5% CO_2 atmosphere in RPMI 1640 media. PROTACs were then added to MM1.S cells and incubated for an additional 24 h. Cells were then lysed with RIPA lysis buffer on ice for 30 minutes, followed by centrifugation at 14,000 rpm for 15 minutes at 4 °C. Supernatant was collected and protein concentration was measured using absorbance. Lysates were then combined 1:1 with Laemmli 2x sample buffer and denatured at 90 °C. Proteins were then resolved through sodium dodecyl sulphate (SDS) gels (BuPage 3 – 8%, tris-

acetate gel, Invitrogen), followed by transfer to polyvinylidene fluoride (PVDF) membranes using semi-dry transfer apparatus. Membranes were blocked using phosphate-buffered saline solution containing 0.1 tween 20 (PBST) containing 5% w/v skim milk for 30 minutes at room temperature. Incubation was done with 1:1000 p300 rabbit antibody (Cell Signaling Technology, 54062S) and 1:5000 β-actin mouse antibody (Cell Signaling Technology, 3700S) followed by washing with PBST and incubation with 1:5000 anti-rabbit horseradish peroxidase IgG (Cell Signaling Technology, 7074S) and 1:5000 anti-mouse horseradish peroxidase IgG (Cell Signaling Technology, 7076S). The membranes were washed with PBST and then immunoreactive proteins were imaged using a BioRad ChemiDoc imaging system. Band intensities were analysed using ImageLab software and quantified using ImageJ software, bands were reported as a relative amount as the ratio of each protein band relative to the lane's DMSO vehicle control and β-actin loading control.

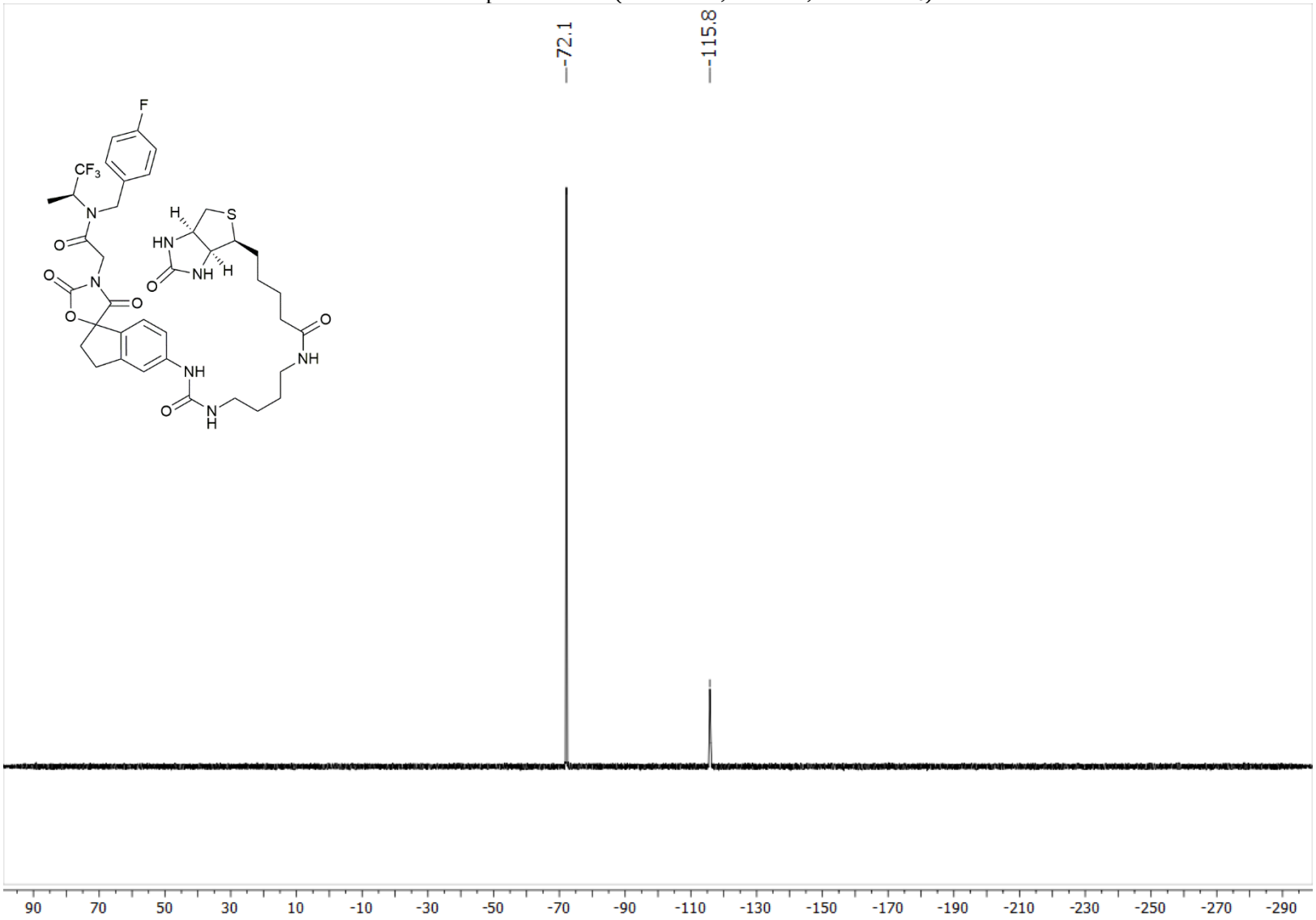
^{1}H NMR spectrum of **2** (600 MHz, 110 °C, DMSO-d_6)



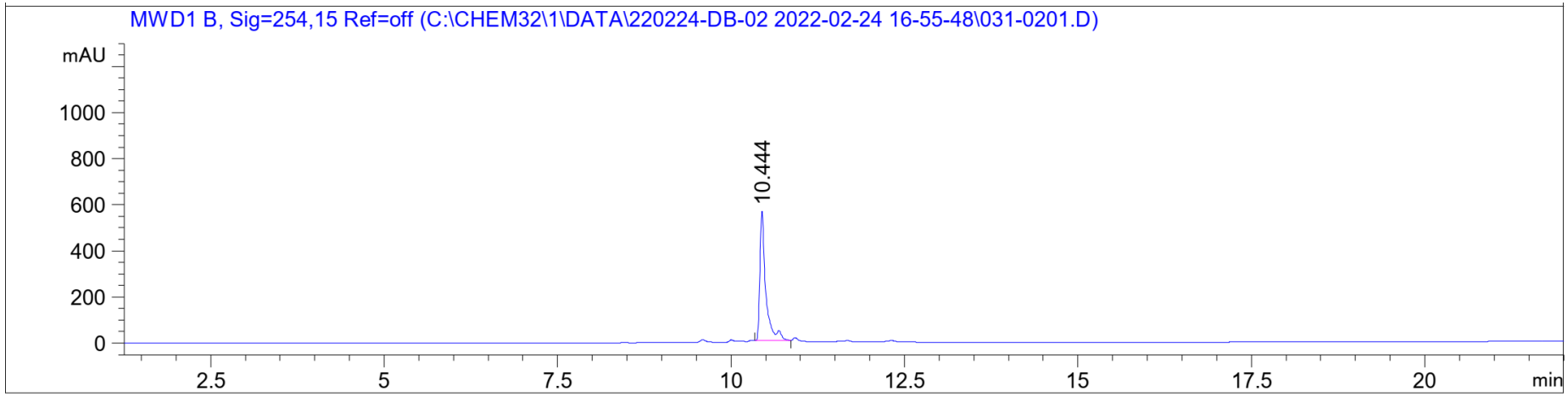
^{13}C NMR spectrum of **2** (151 MHz, 110 °C, DMSO-d_6)



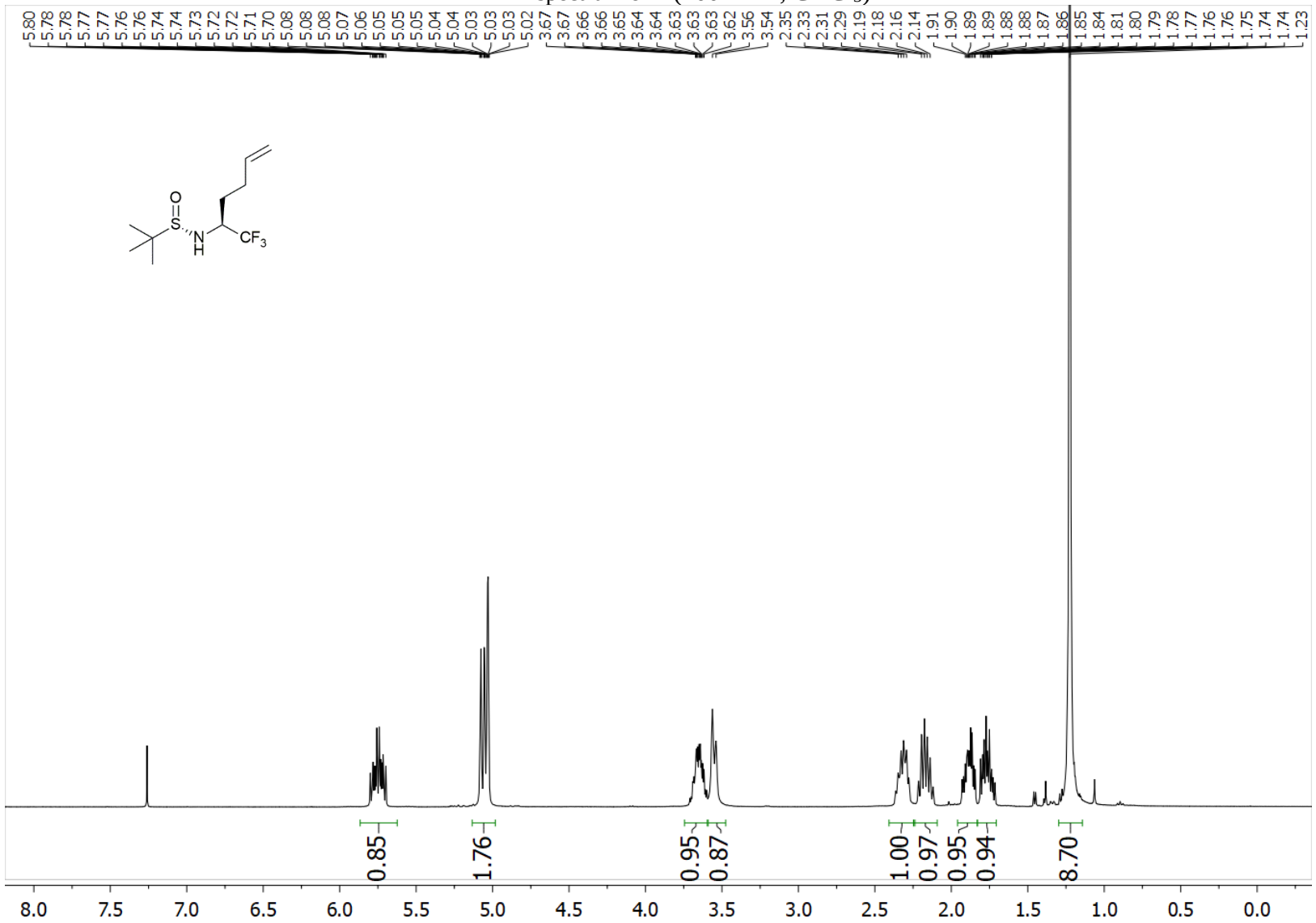
^{19}F NMR spectrum of **2** (376 MHz, 110 °C, DMSO-d_6)



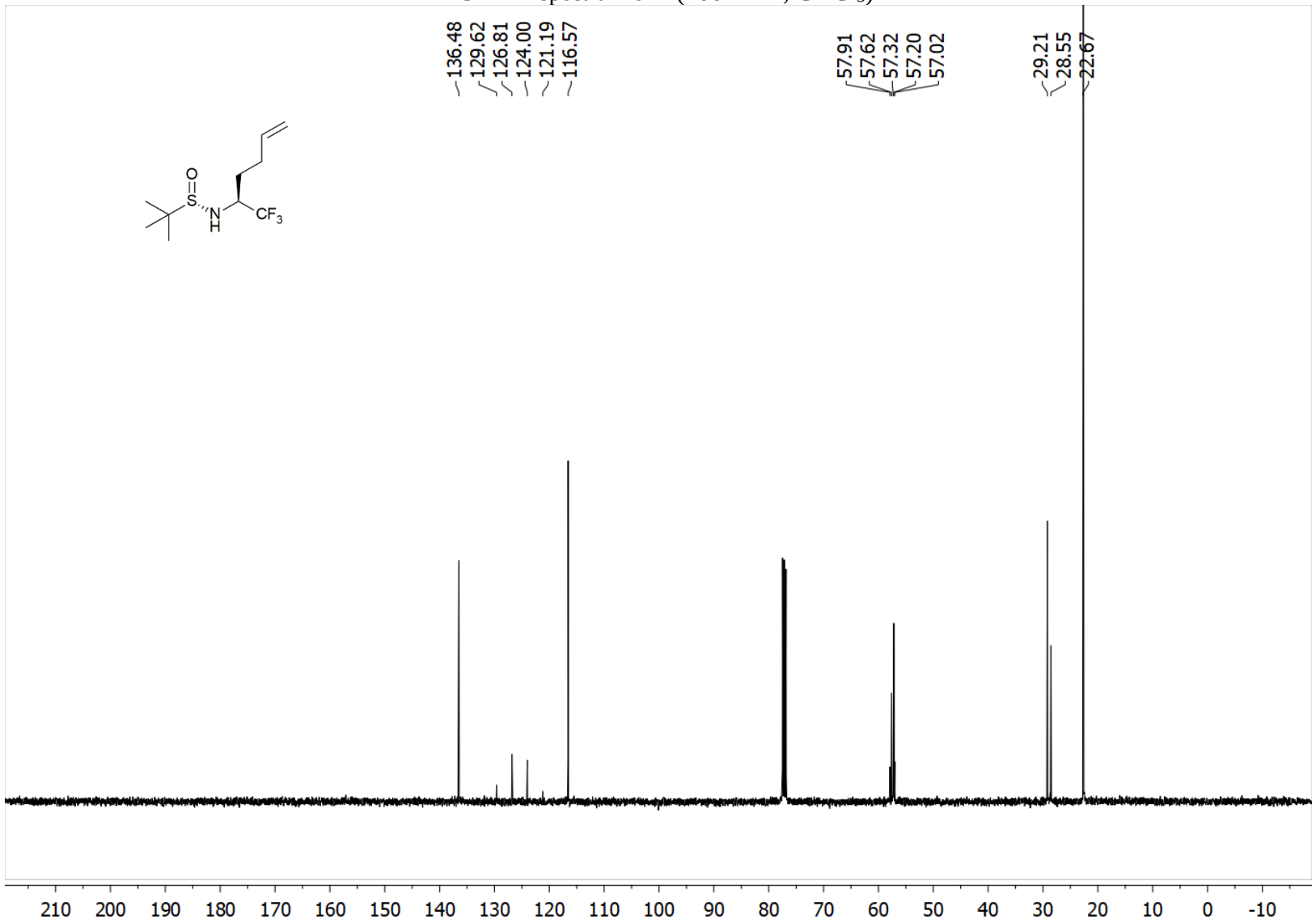
HPLC trace of **2** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



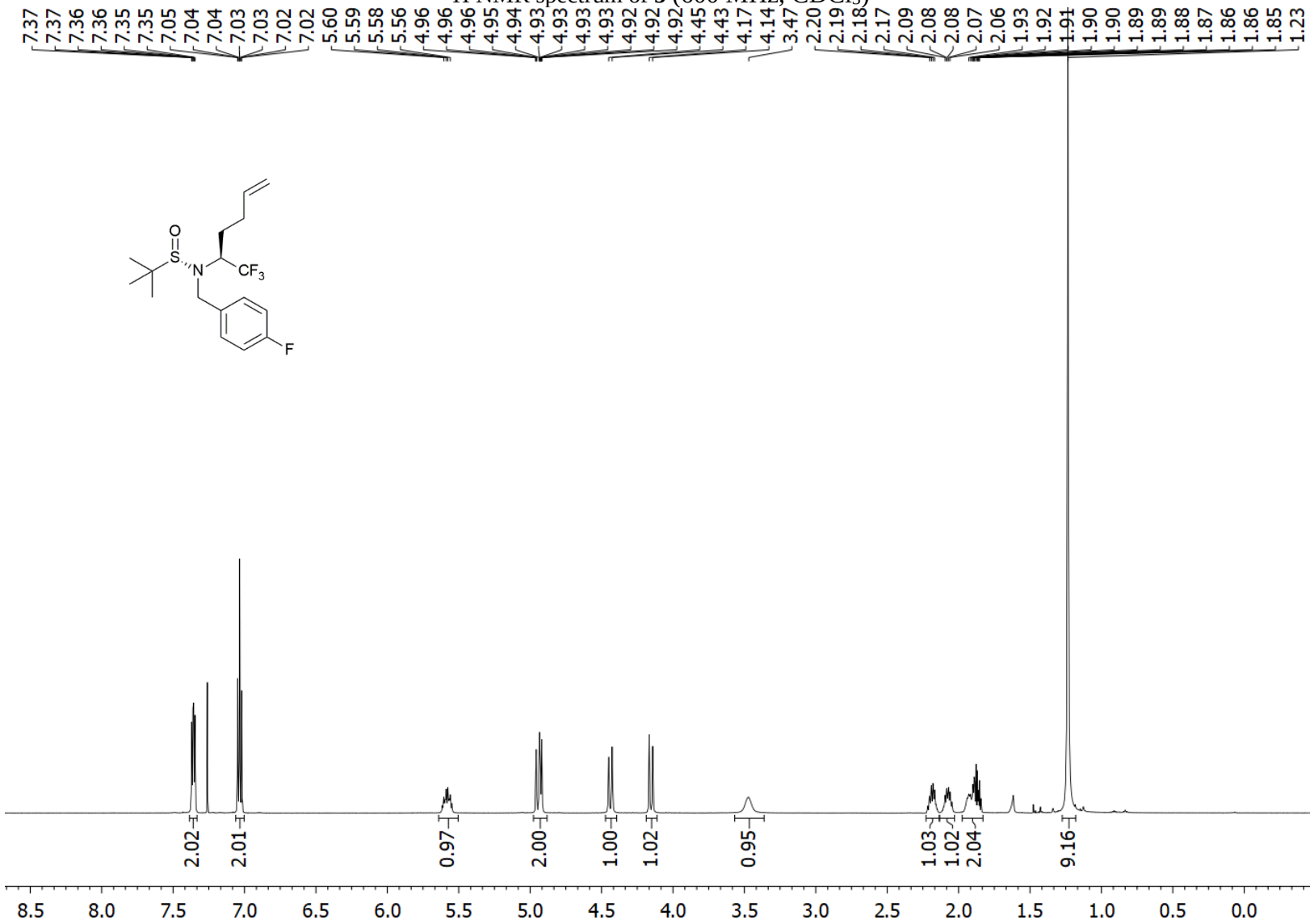
^{1}H NMR spectrum of **4** (400 MHz, $CDCl_3$)



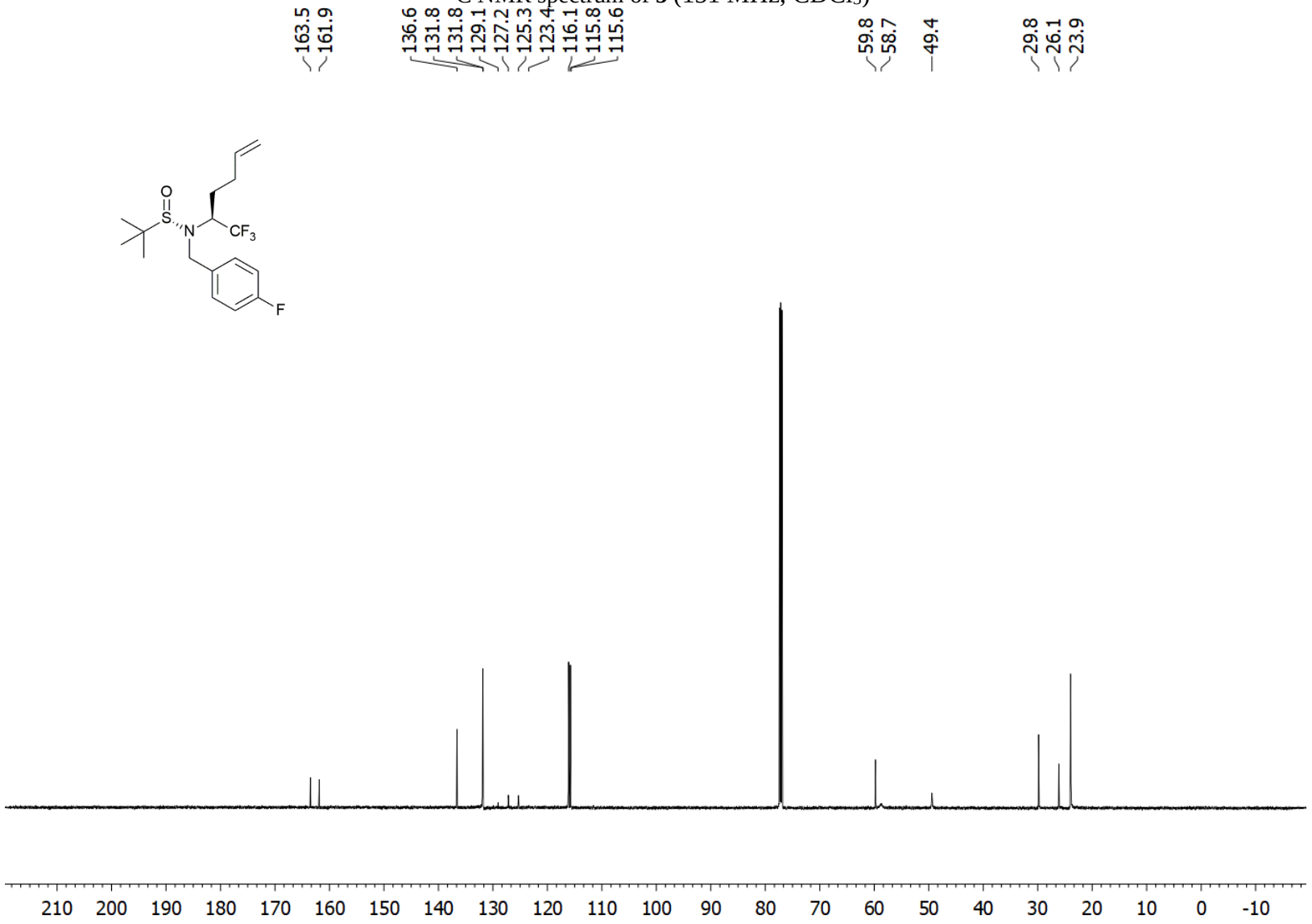
^{13}C NMR spectrum of **2** (100 MHz, $CDCl_3$)



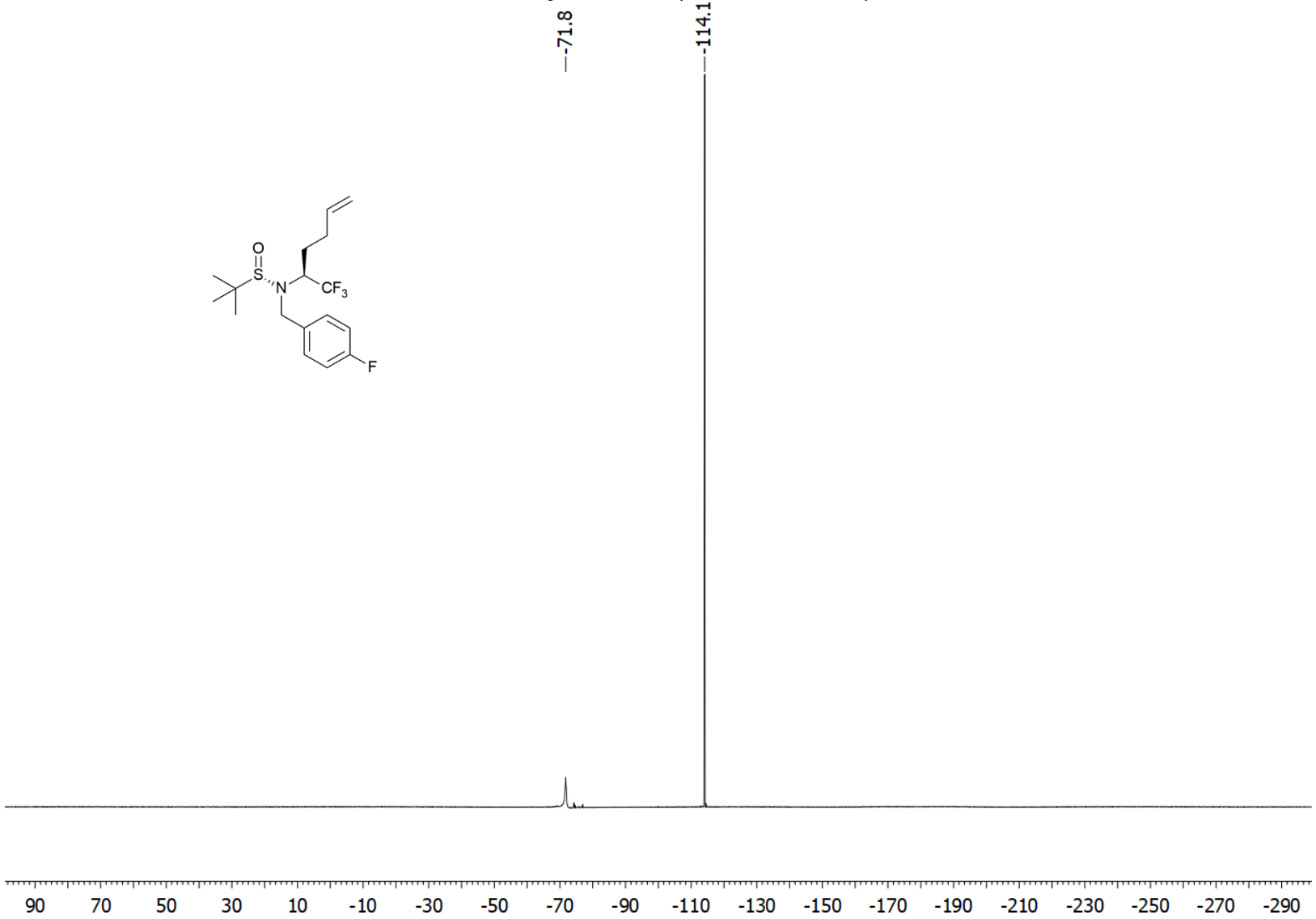
^{1}H NMR spectrum of **5** (600 MHz, $CDCl_3$)



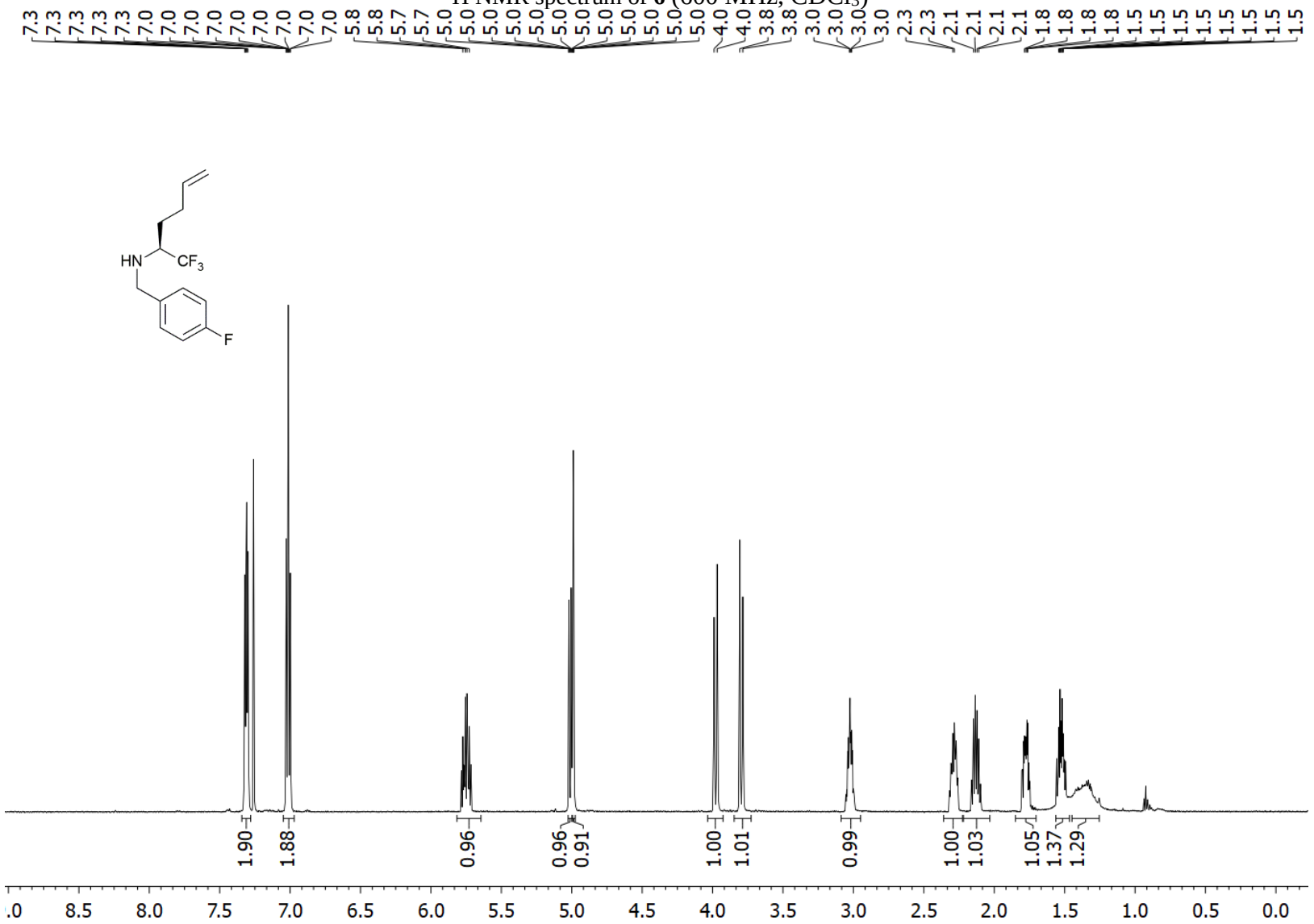
^{13}C NMR spectrum of **5** (151 MHz, $CDCl_3$)



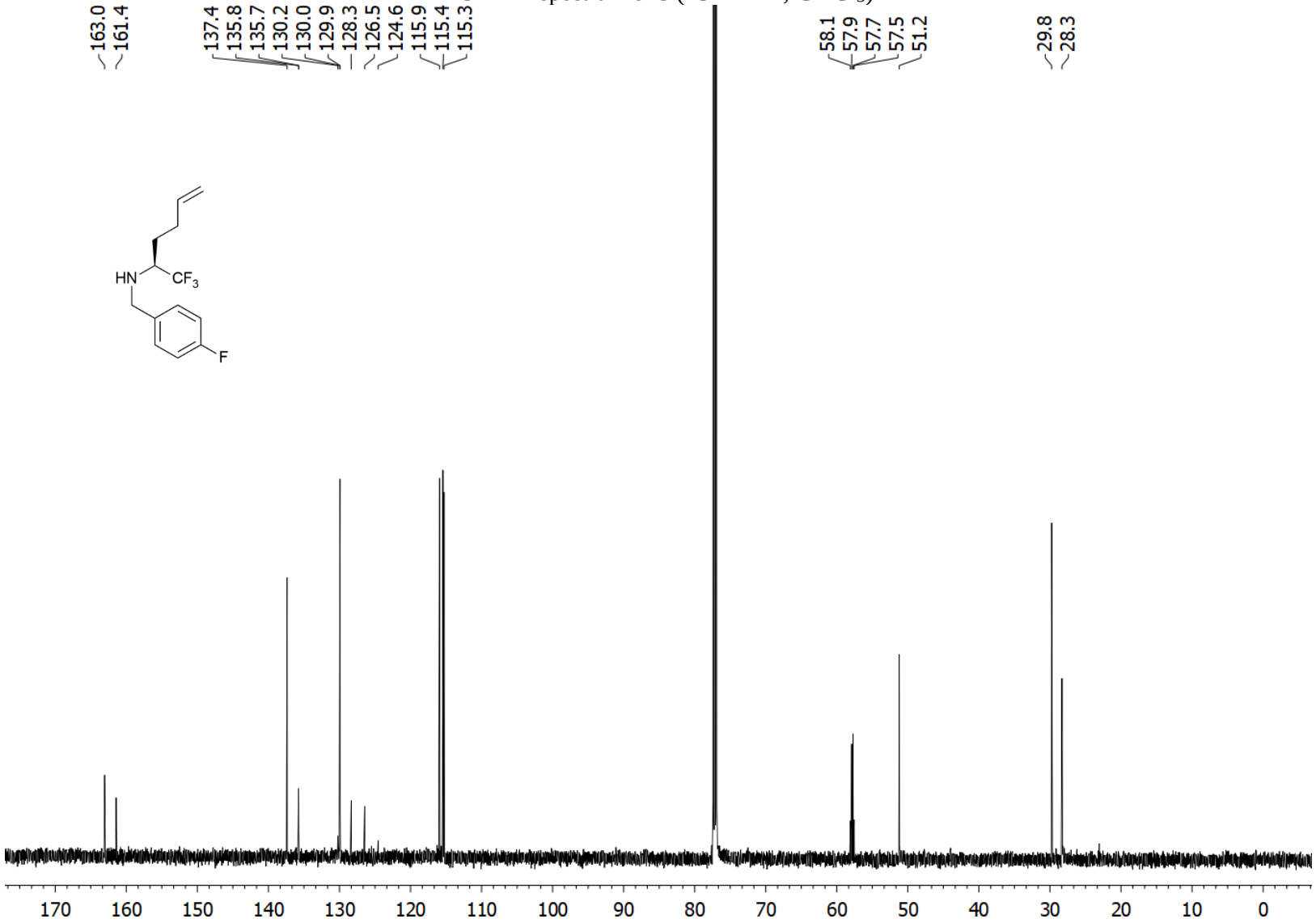
^{19}F NMR spectrum of **5** (376 MHz, $CDCl_3$)



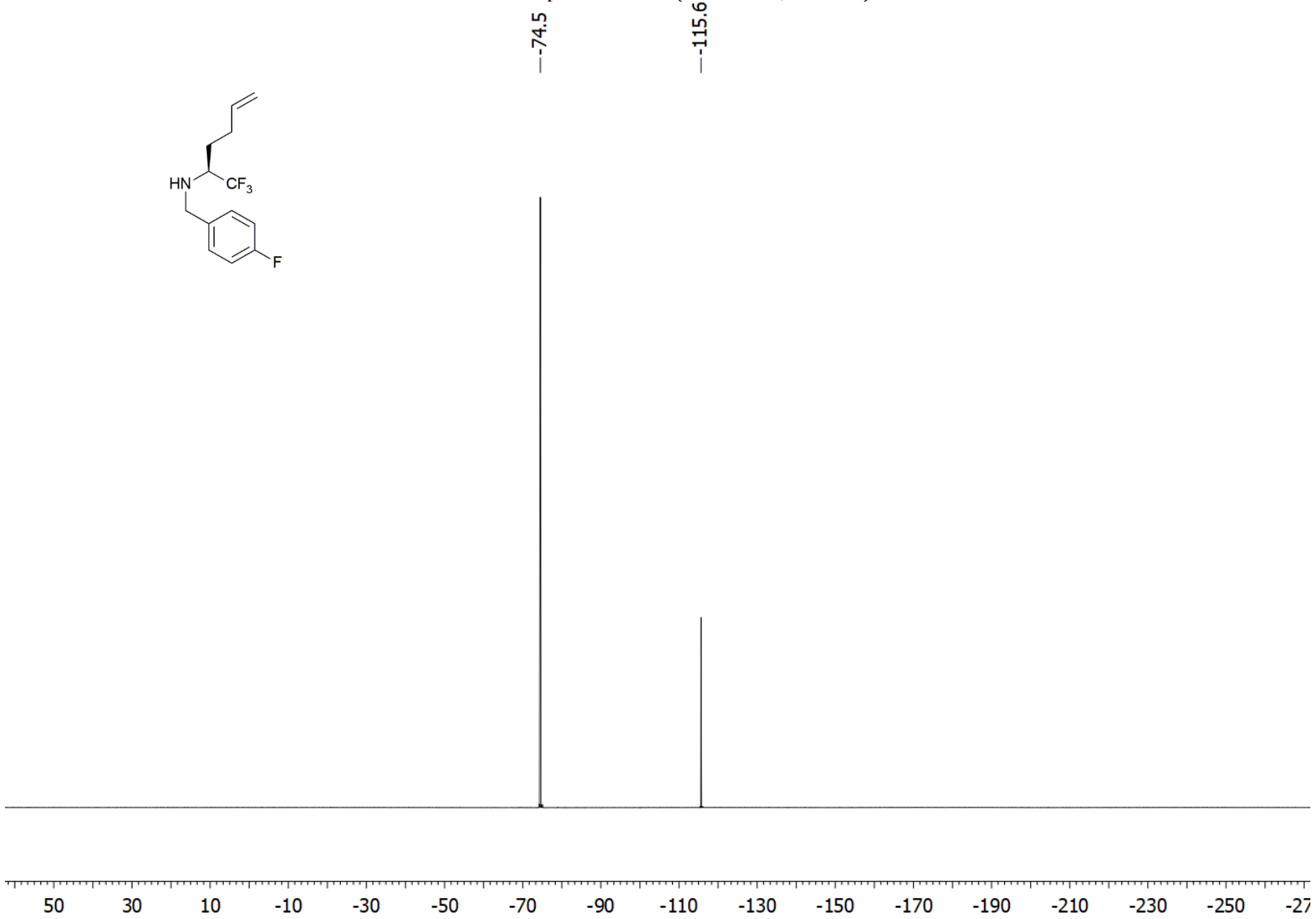
^{1}H NMR spectrum of **6** (600 MHz, $CDCl_3$)



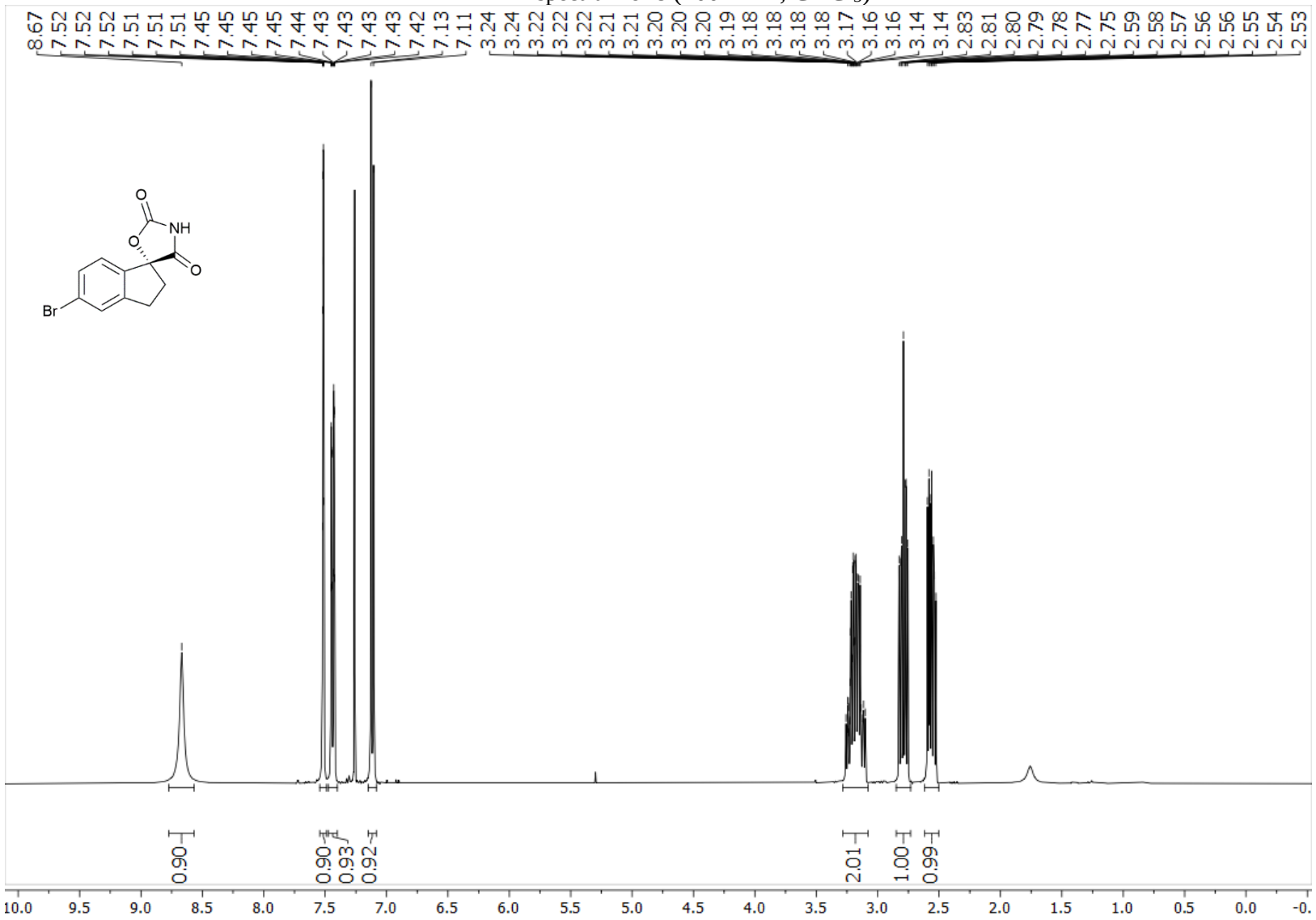
^{13}C NMR spectrum of **5** (151 MHz, $CDCl_3$)



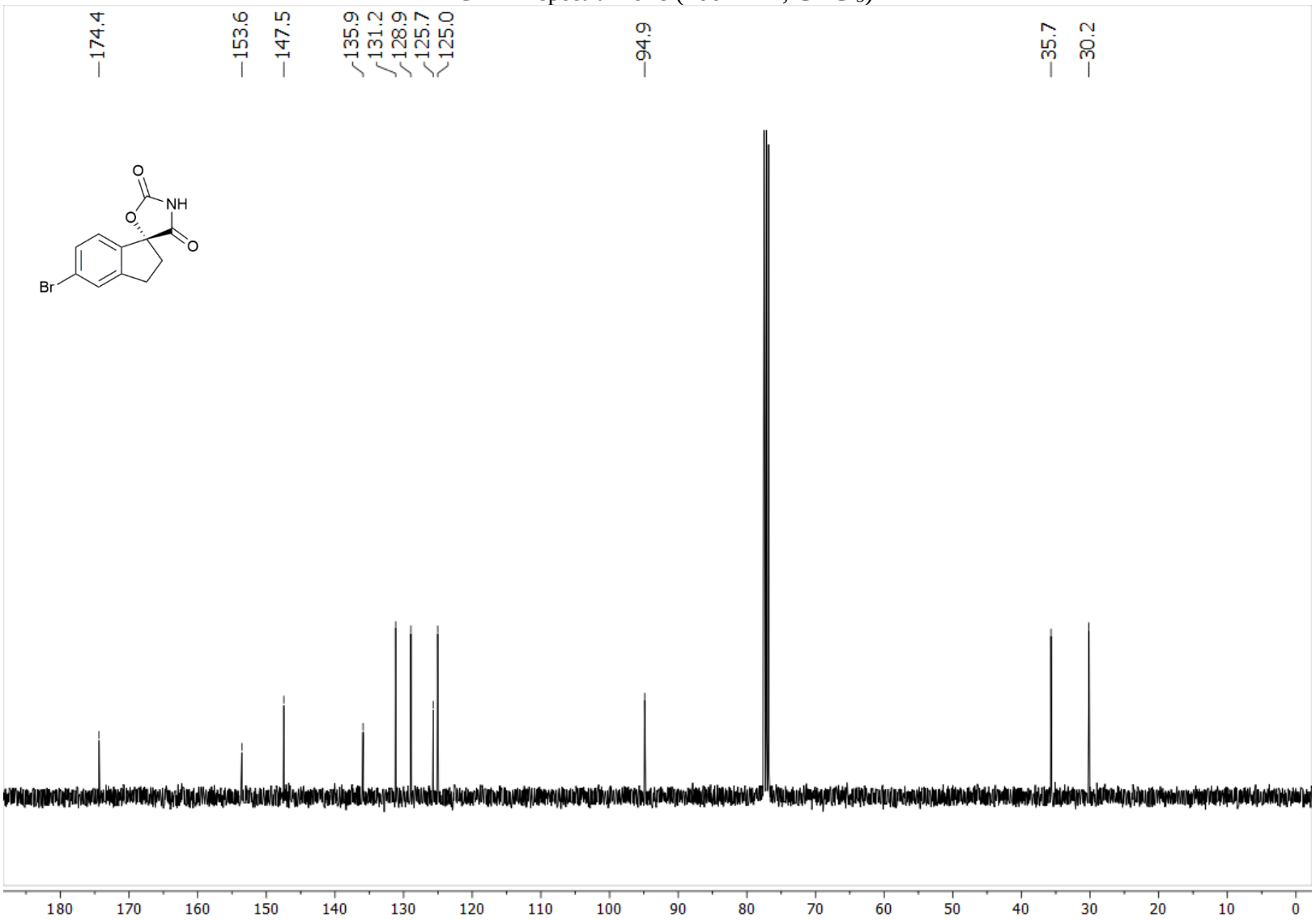
^{19}F NMR spectrum of **5** (376 MHz, $CDCl_3$)



^{1}H NMR spectrum of **8** (400 MHz, $CDCl_3$)



^{13}C NMR spectrum of **8** (100 MHz, $CDCl_3$)



Chiral gas chromatograph of **8**

Chromatogram : 190709 DB-3-208 enantio 1 40 min1_channel1

System : GC
Method : db-2-170
User : Tom Back

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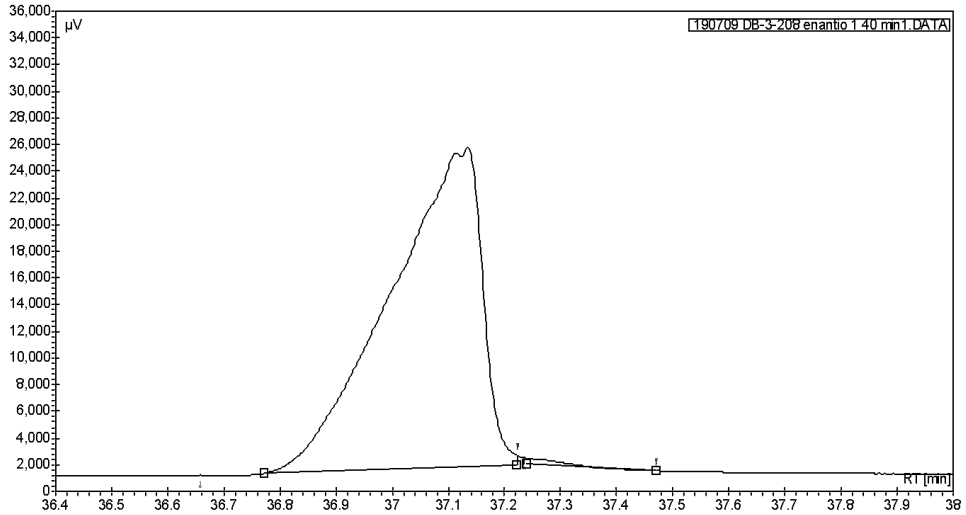
Processed : 7/9/2019 6:25:17 PM
Printed : 7/9/2019 6:26:18 PM



Peak results :

190709 DB-3-208 enantio 1 40 min1.DATA [Front (FID)]

Index	Name	Time [Min]	Quantity [ppm]	Area [µV.Min]
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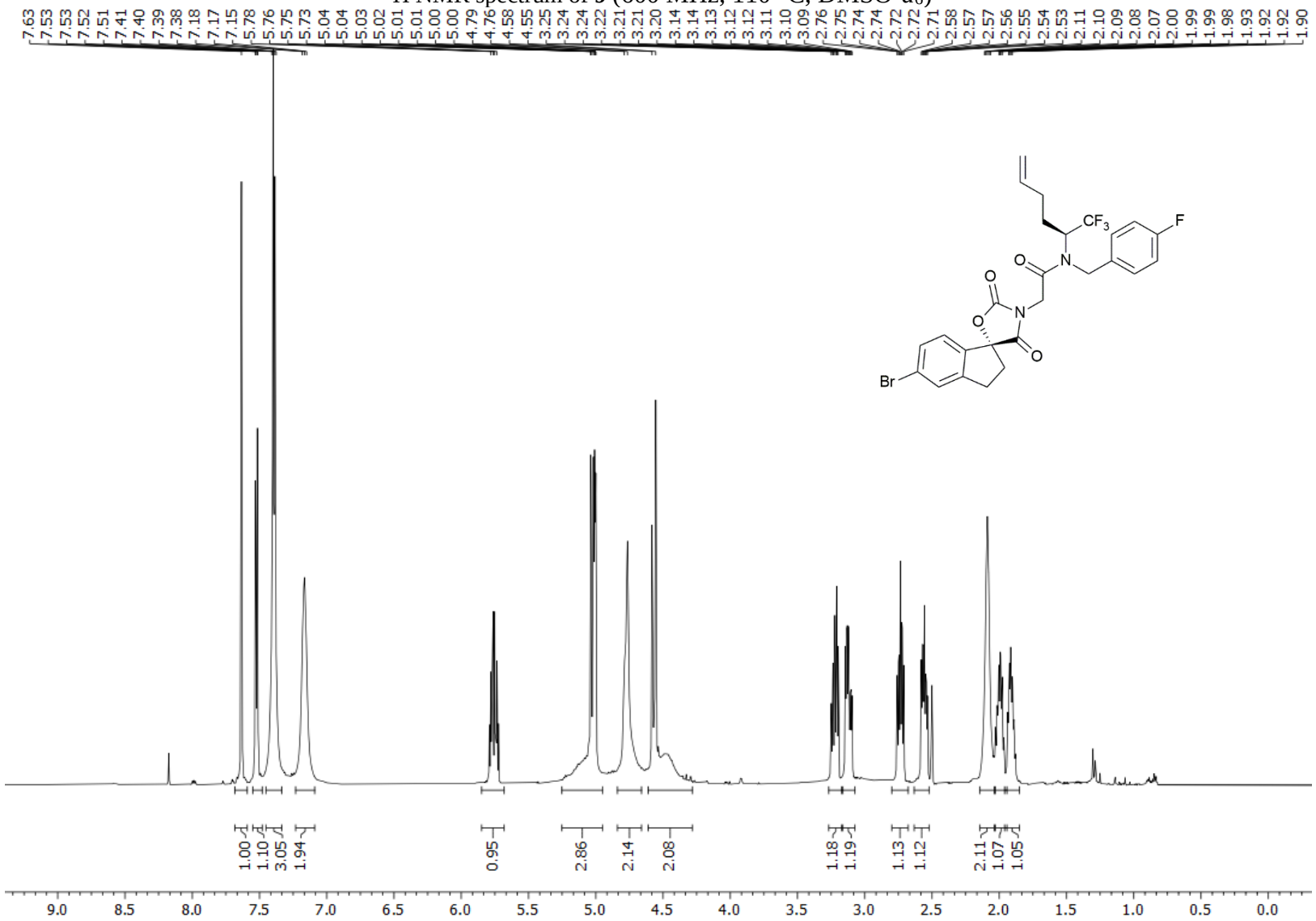
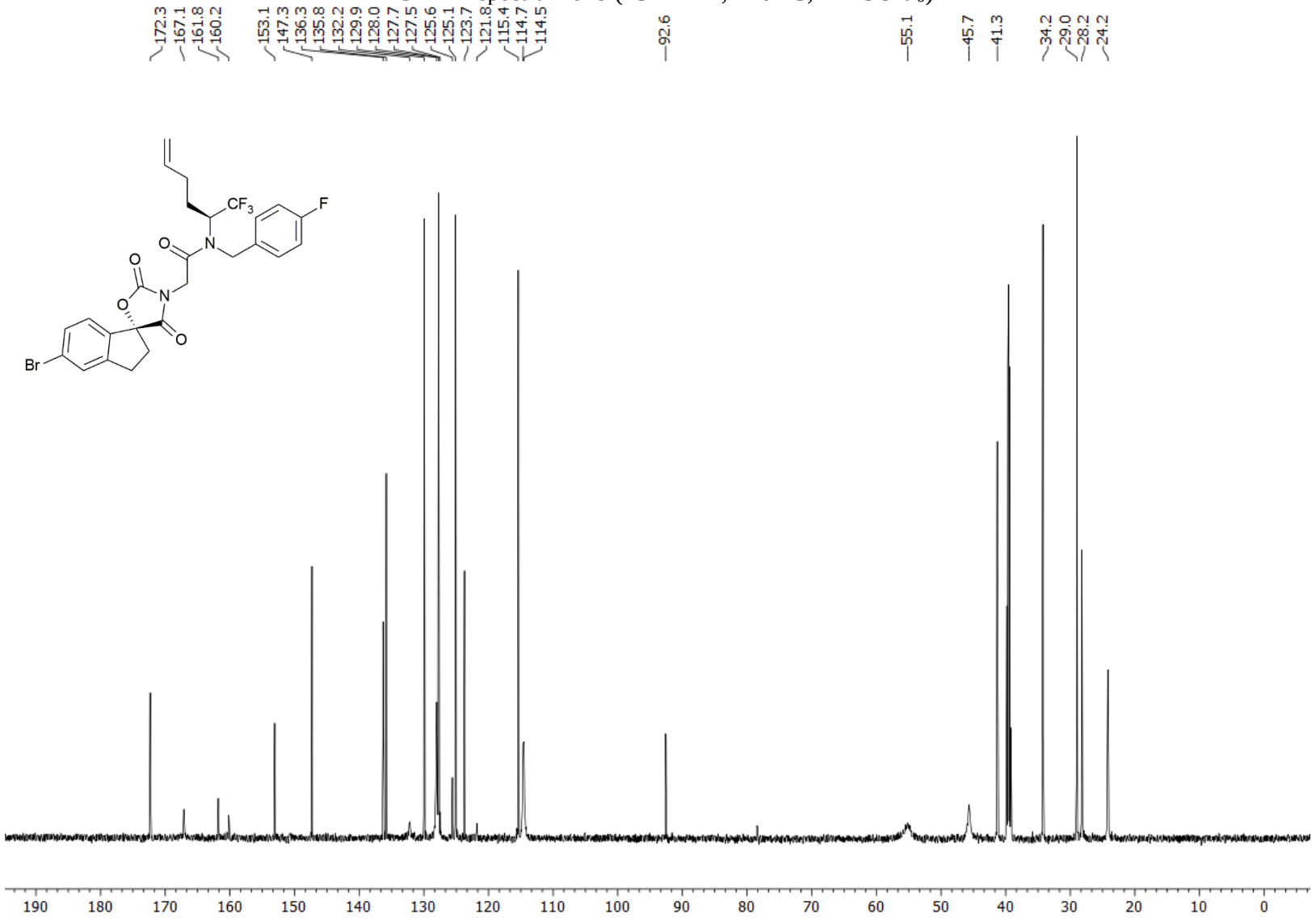
1	UNKNOWN	37.24	0.00	25.6
Total			0.00	4537.9

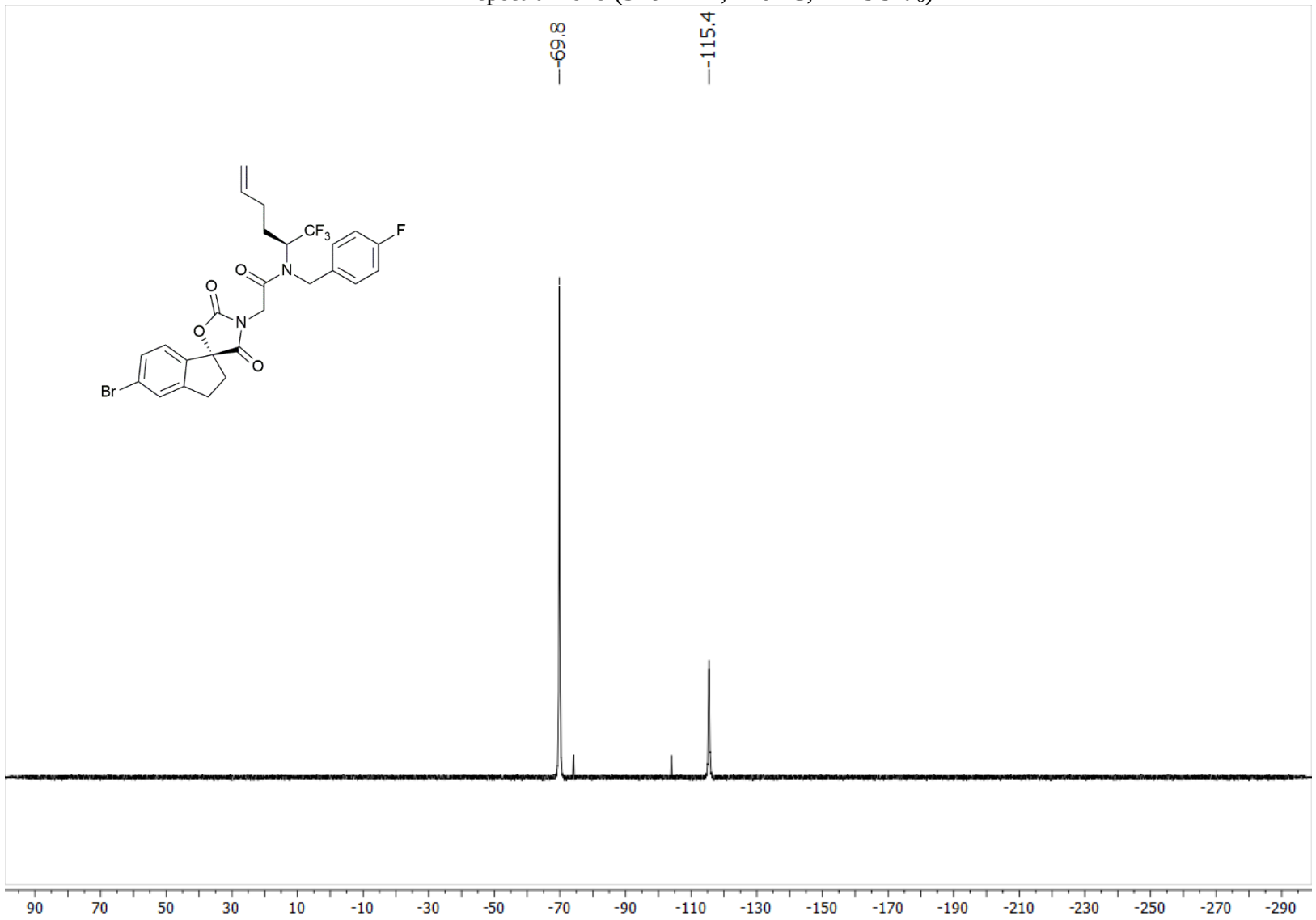
^{1}H NMR spectrum of **9** (600 MHz, 110 °C, DMSO-d_6)



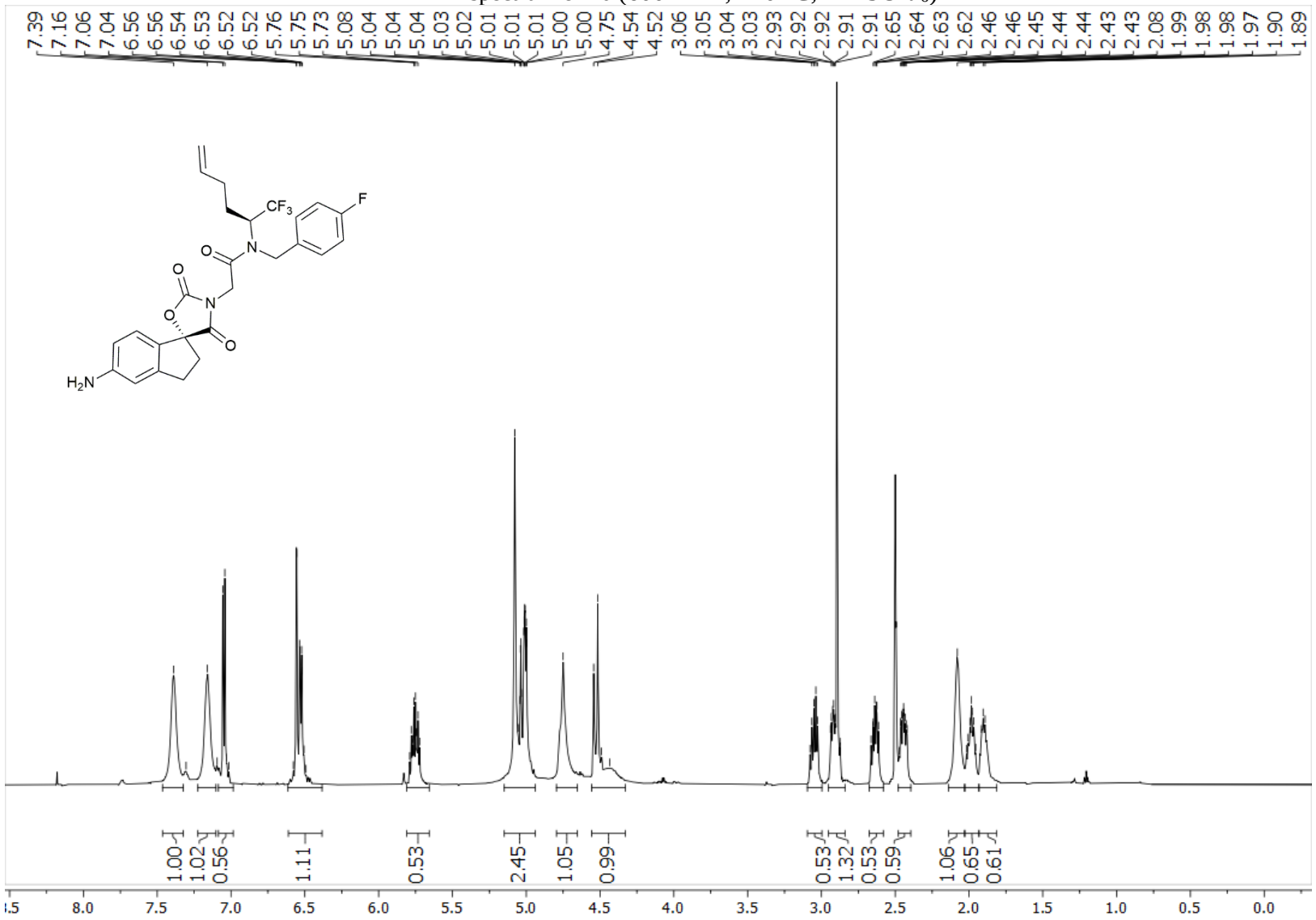
^{13}C NMR spectrum of **9** (151 MHz, 110 °C, DMSO-d_6)



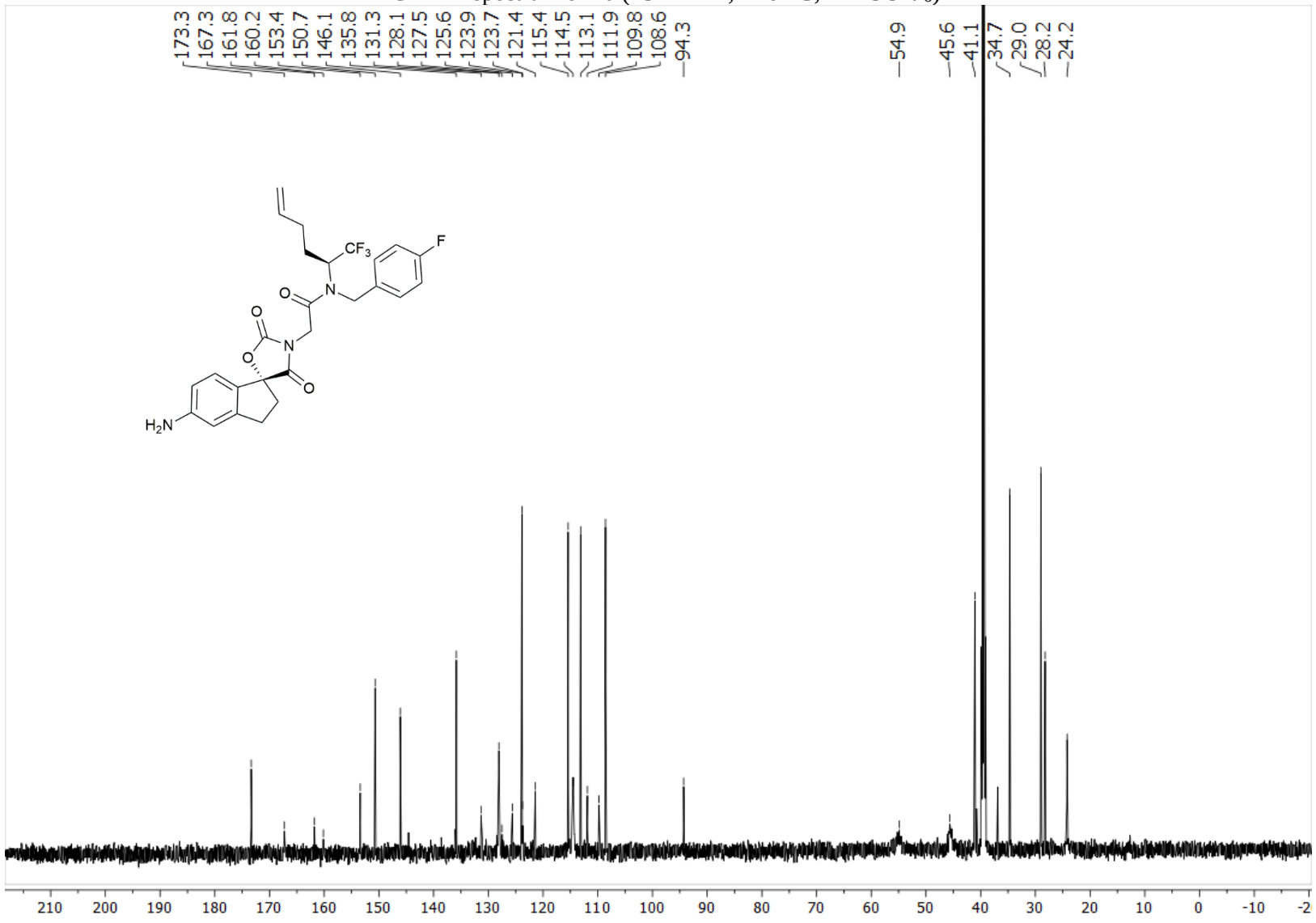
^{19}F NMR spectrum of **9** (376 MHz, 110 °C, DMSO-d_6)



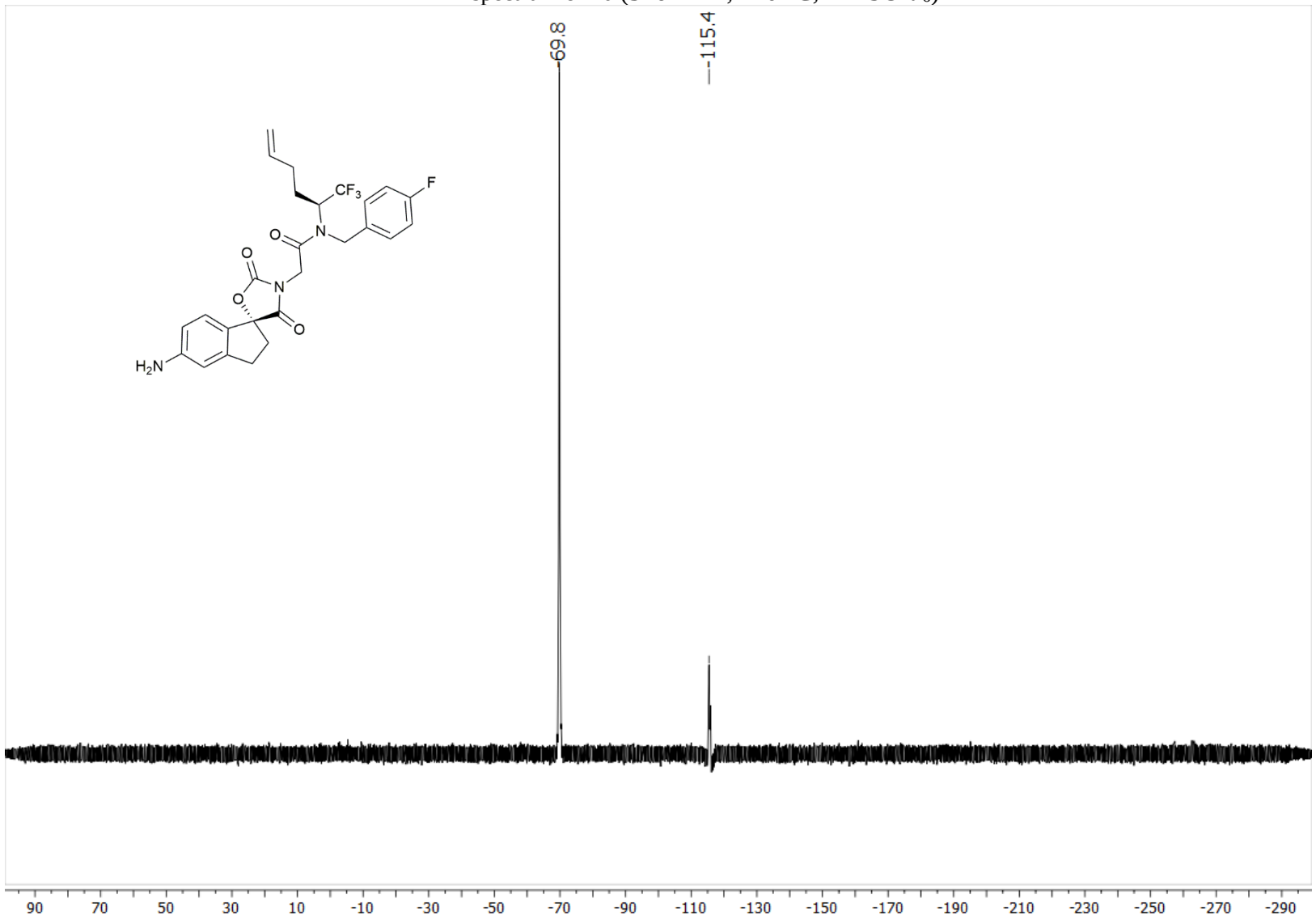
^{1}H NMR spectrum of **10** (600 MHz, 110 °C, DMSO-d_6)



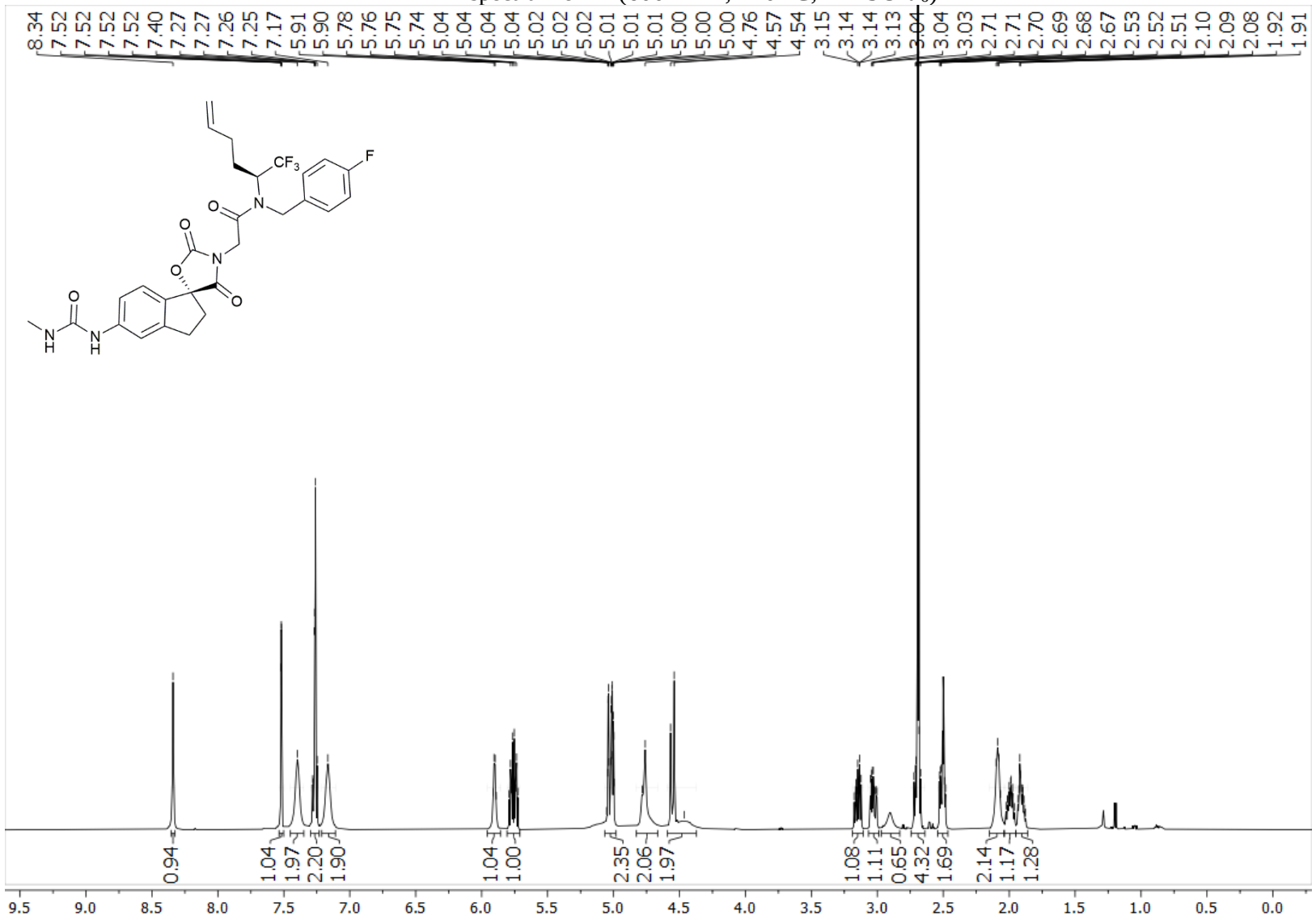
^{13}C NMR spectrum of **10** (151 MHz, 110 °C, DMSO-d_6)



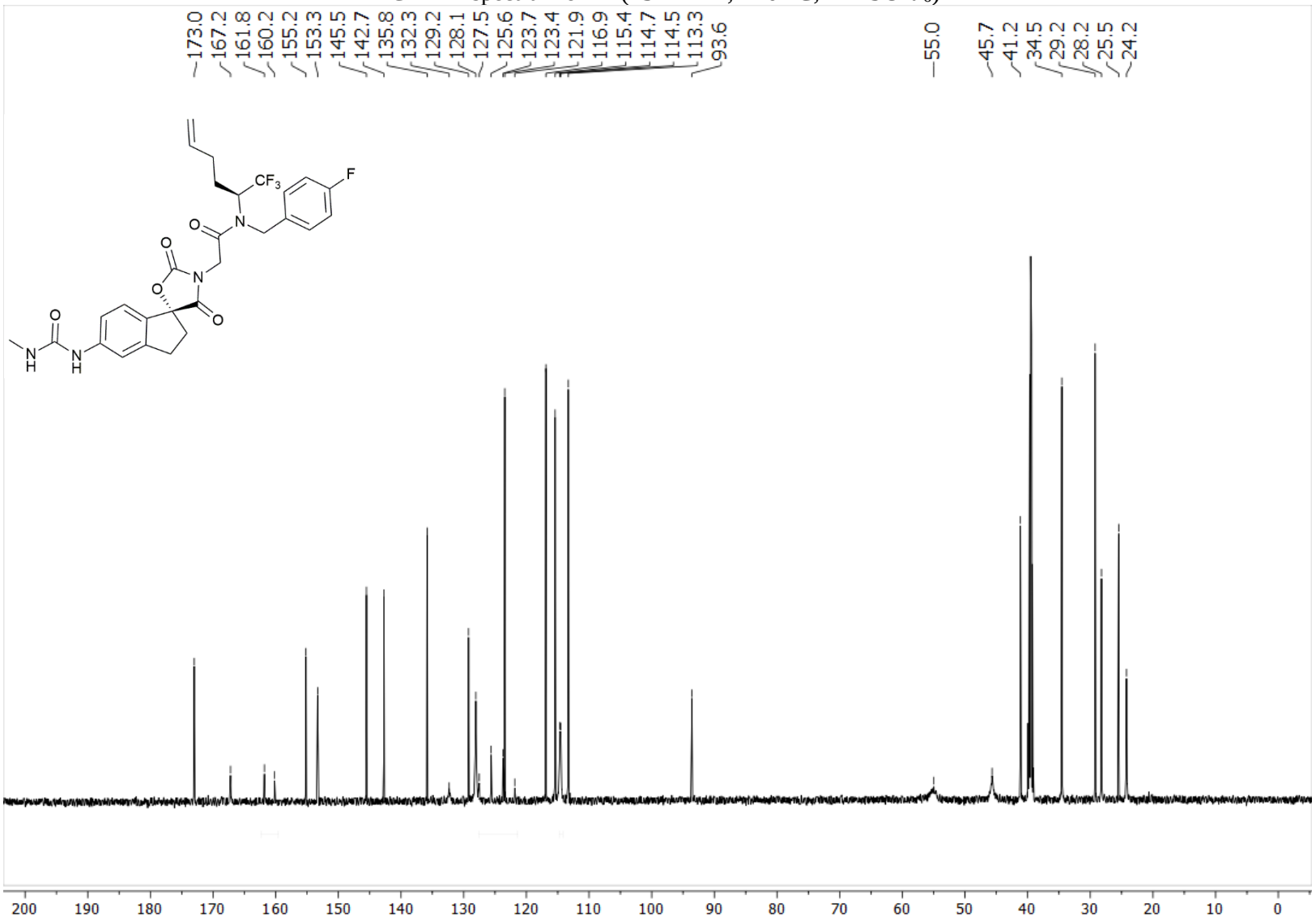
^{19}F NMR spectrum of **10** (376 MHz, 110 °C, DMSO-d_6)



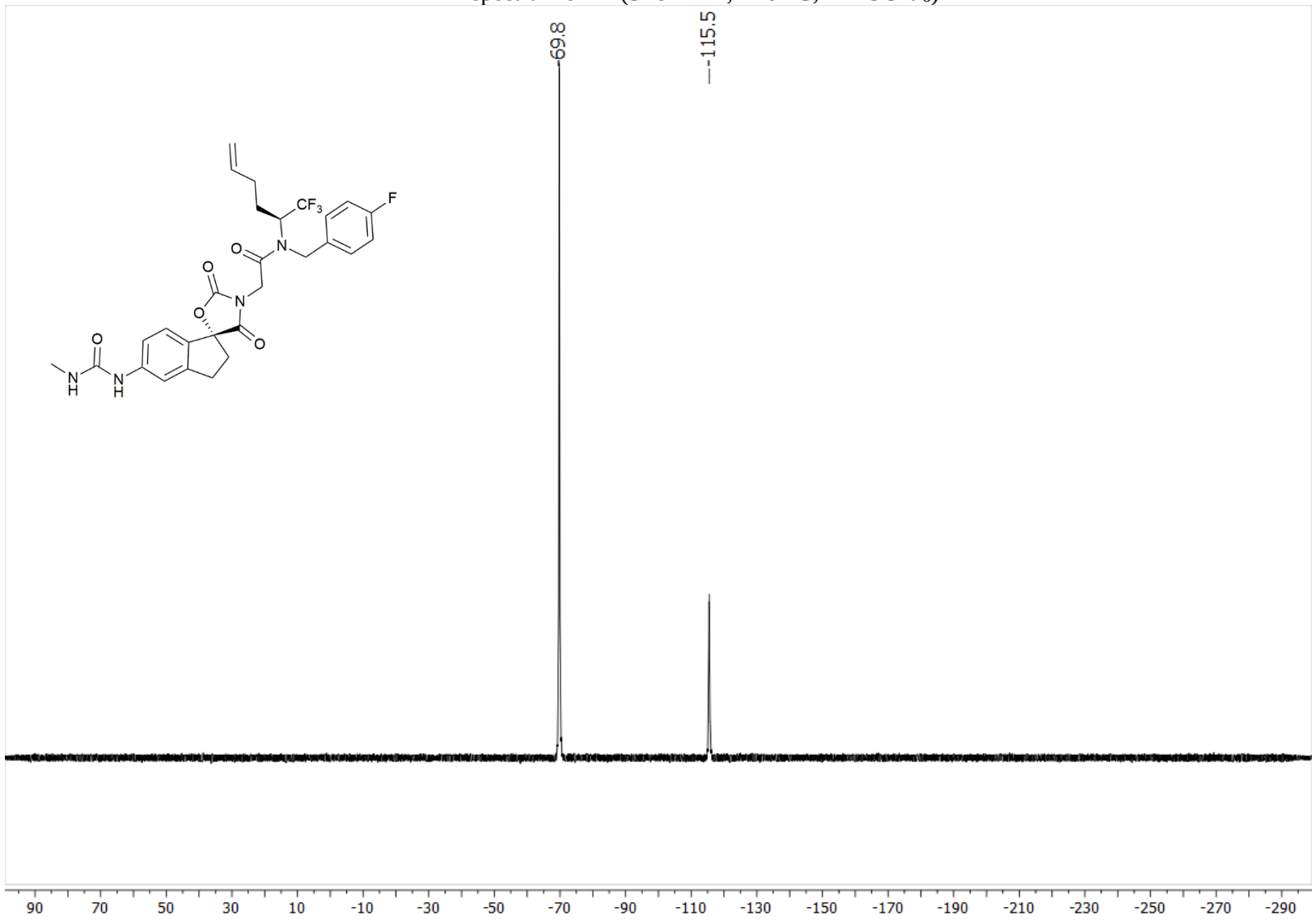
[1]H NMR spectrum of **11** (600 MHz, 110 °C, DMSO-d_6)



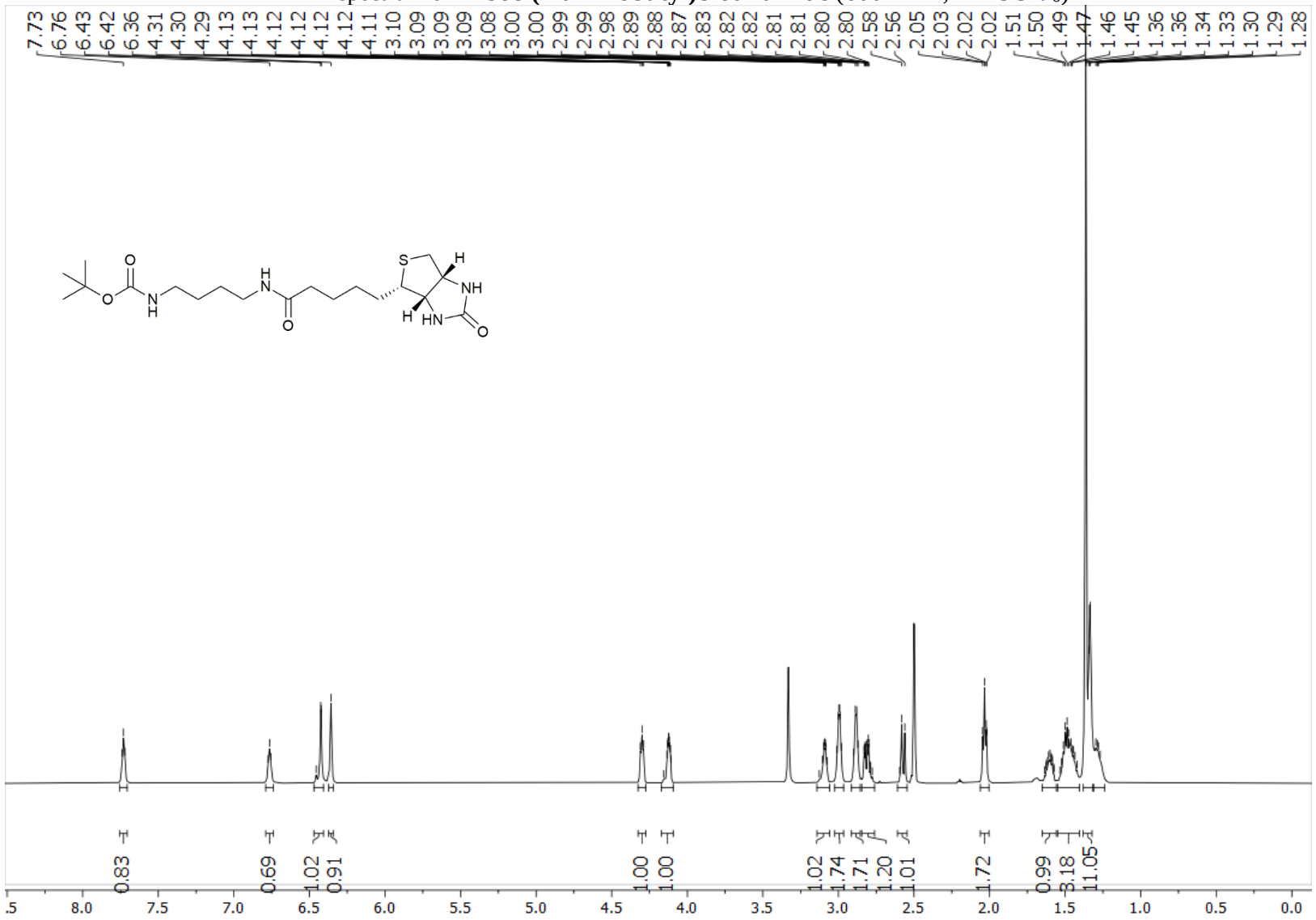
^{13}C NMR spectrum of **11** (151 MHz, 110 °C, DMSO-d_6)



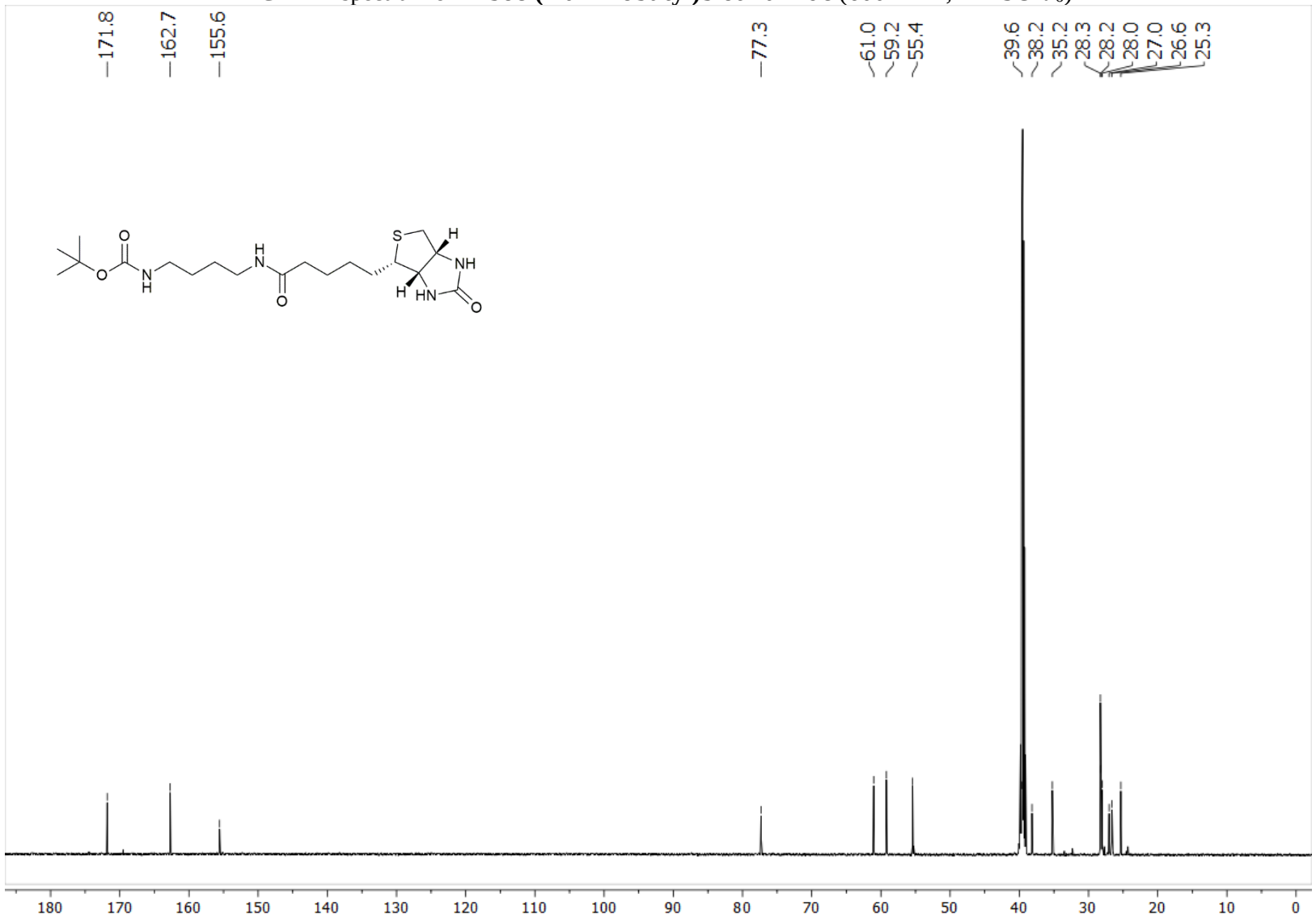
^{19}F NMR spectrum of **11** (376 MHz, 110 °C, DMSO-d_6)



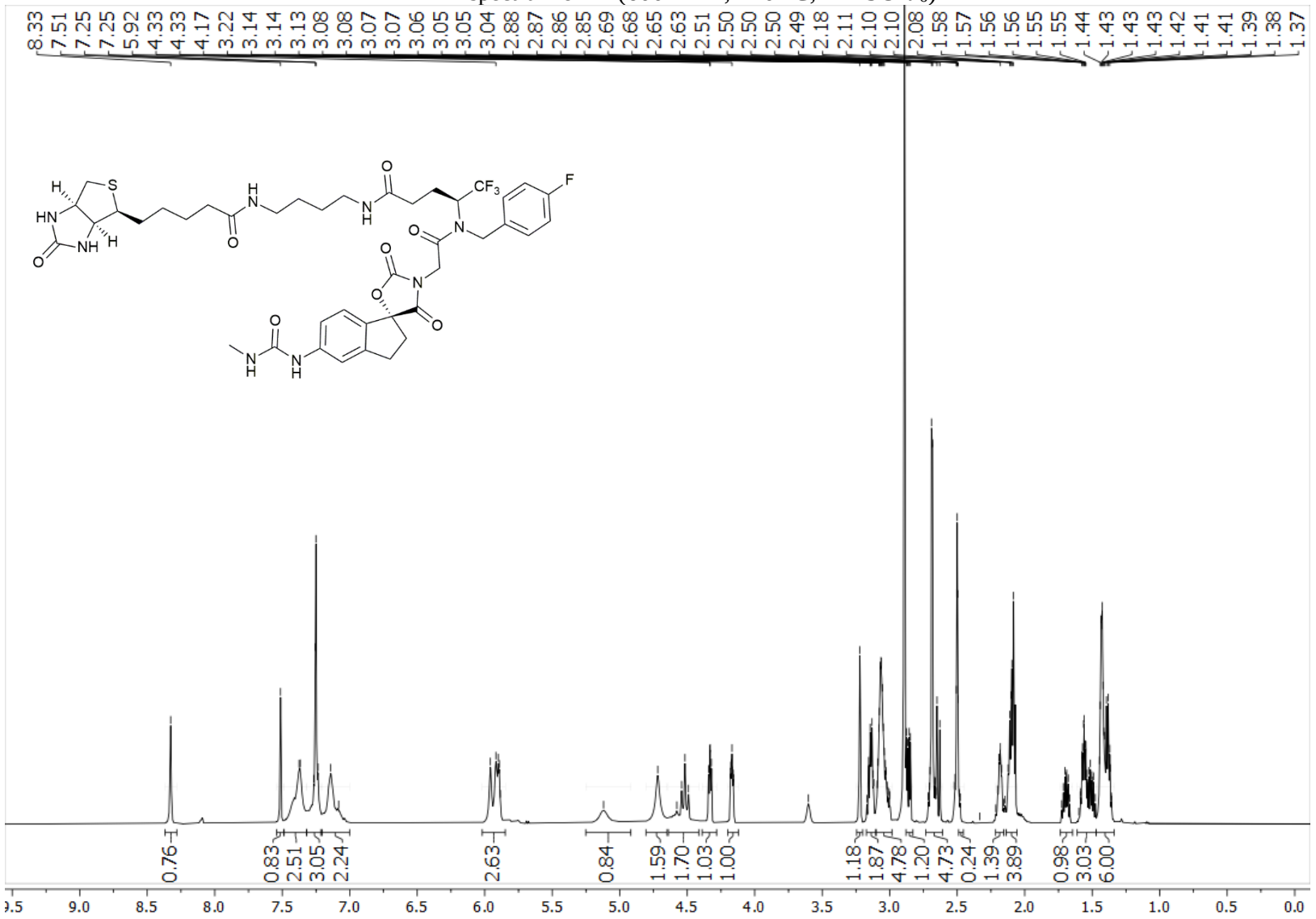
^{1}H NMR spectrum of ***N*-boc-(4-aminobutyl)biotinamide** (600 MHz, DMSO-d_6)



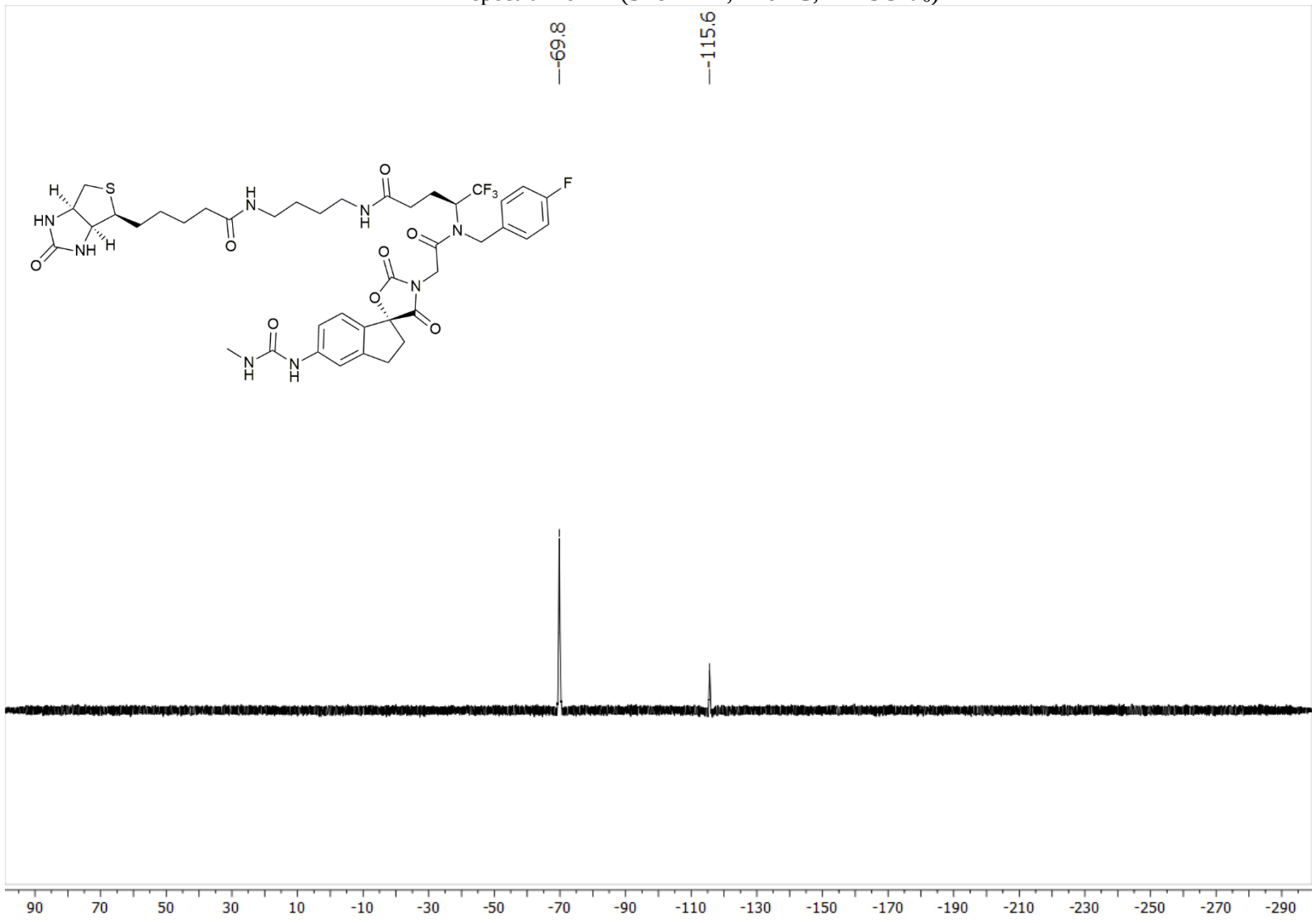
^{13}C NMR spectrum of ***N*-boc-(4-aminobutyl)biotinamide** (600 MHz, DMSO-d_6)



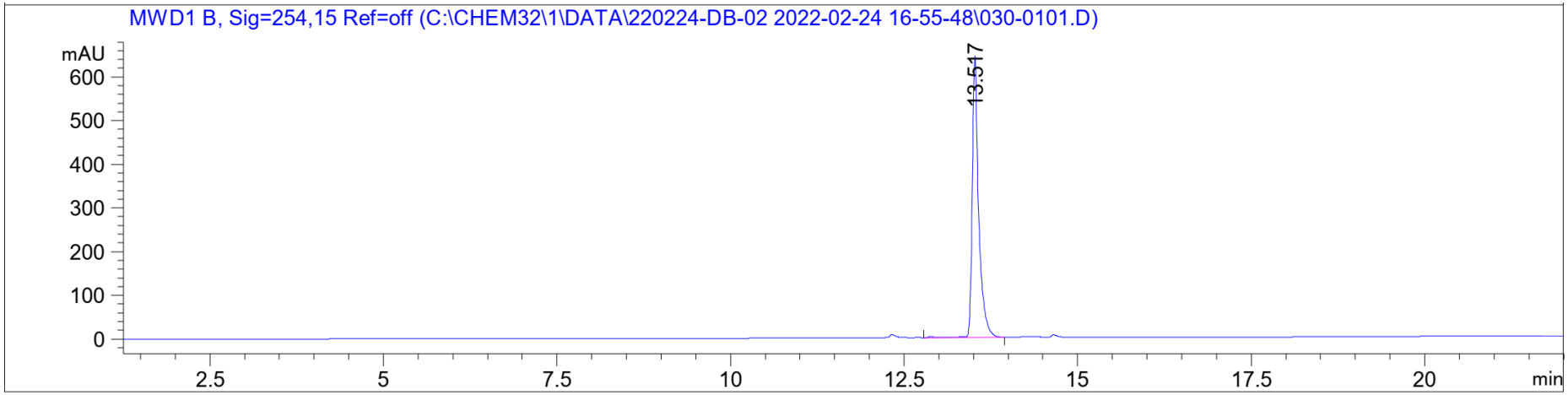
^{1}H NMR spectrum of **14** (600 MHz, 110 °C, DMSO-d_6)



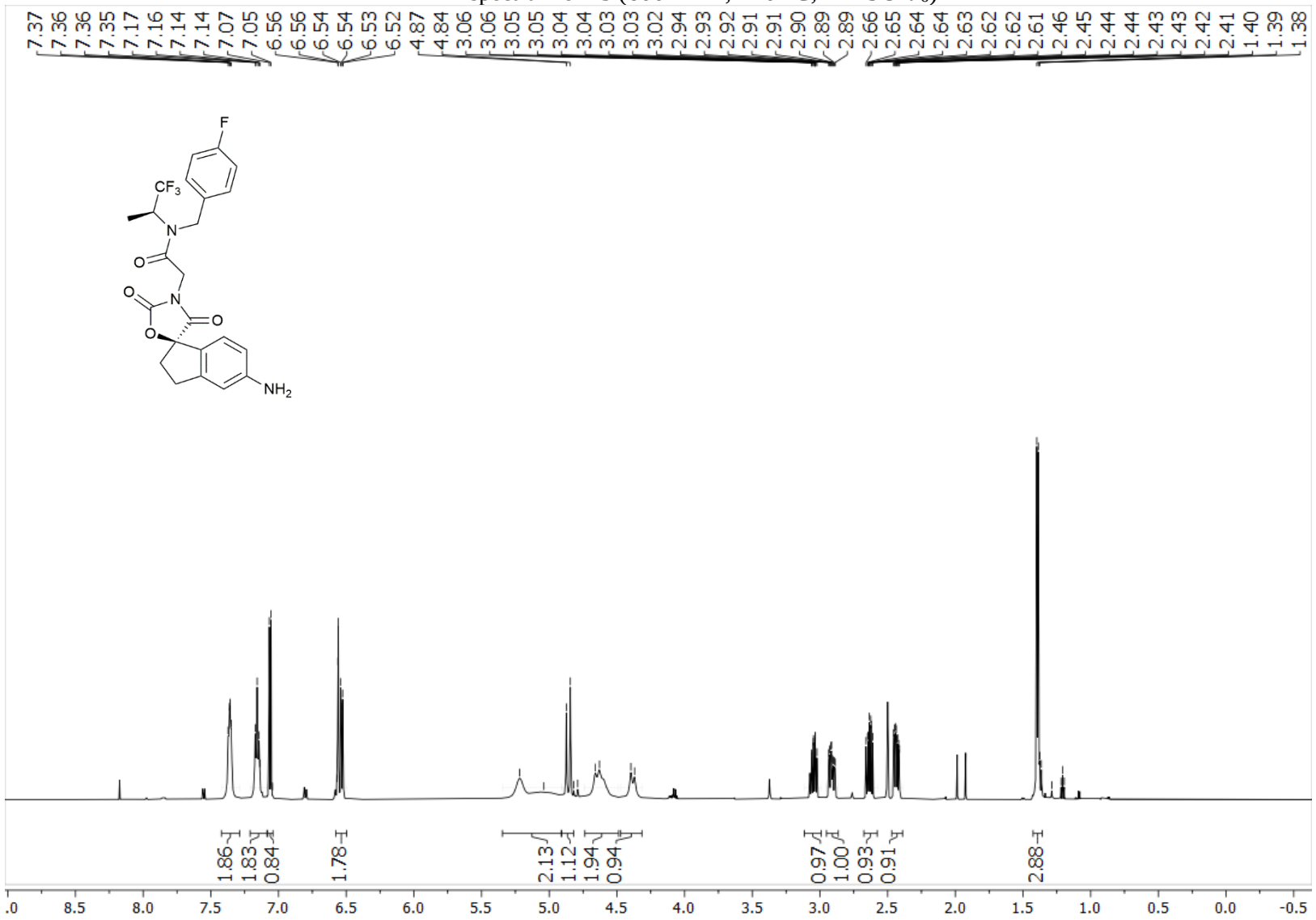
^{19}F NMR spectrum of **14** (376 MHz, 110 °C, DMSO-d_6)



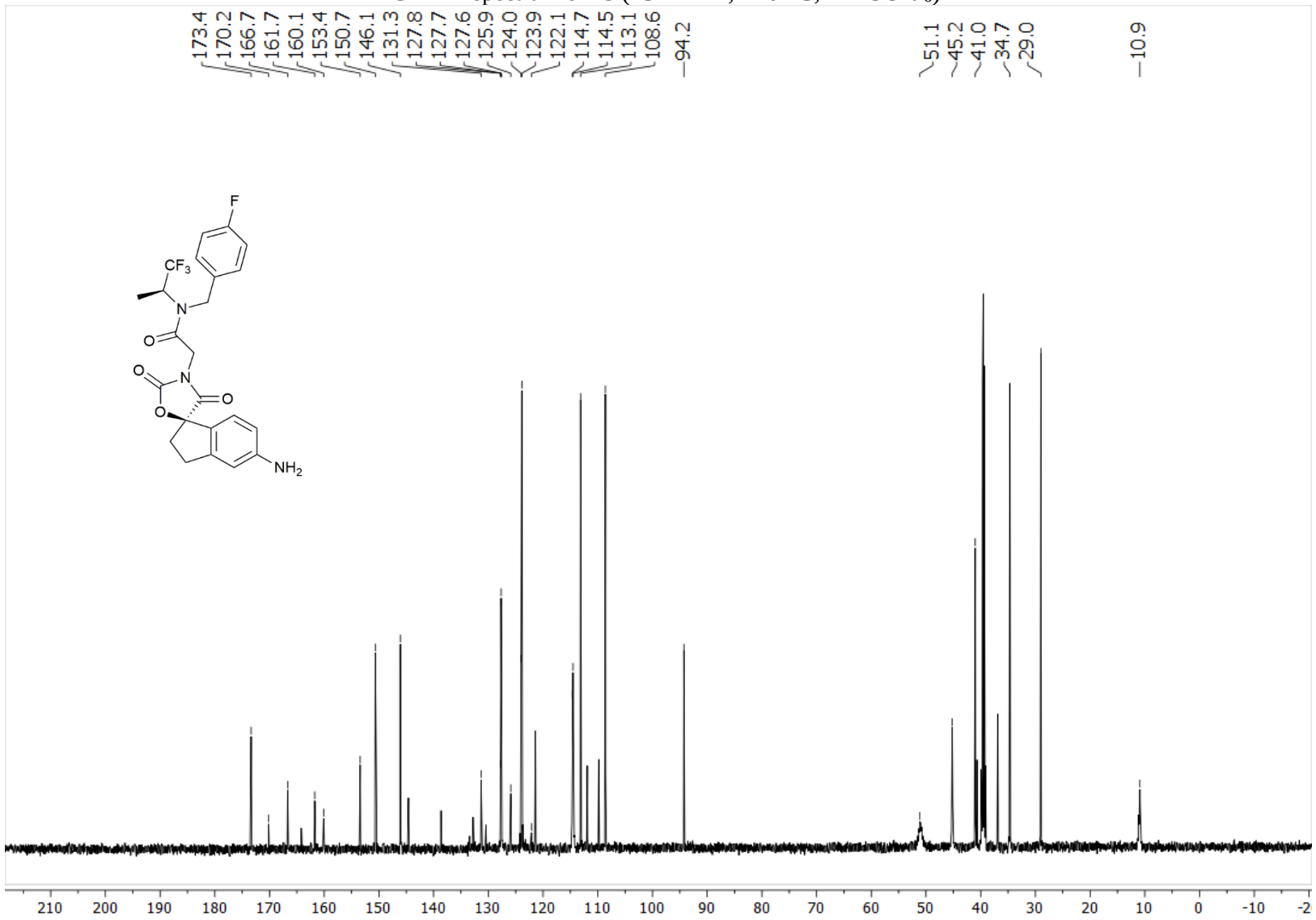
HPLC trace of **14** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



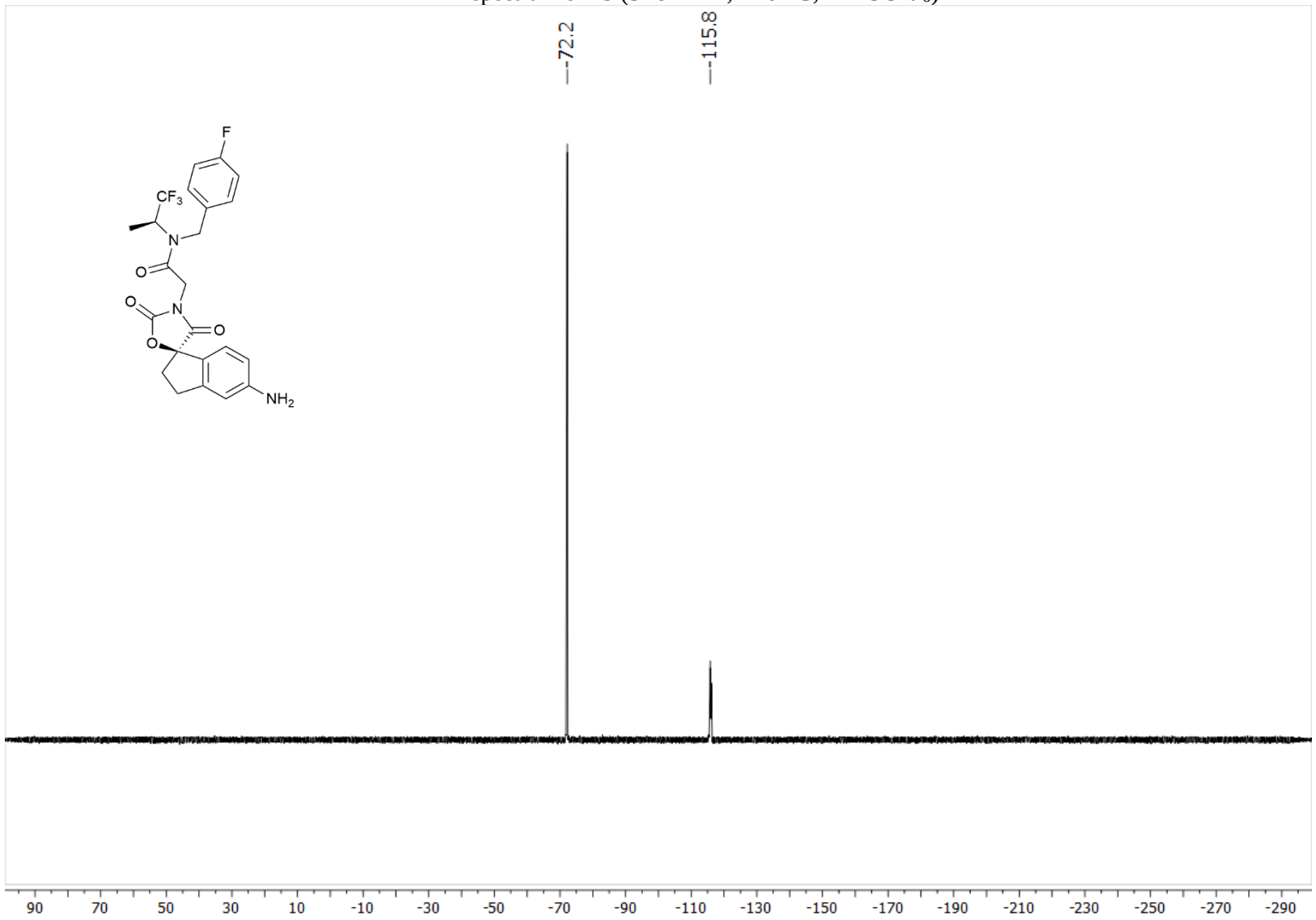
[1]H NMR spectrum of **15** (600 MHz, 110 °C, DMSO-d_6)



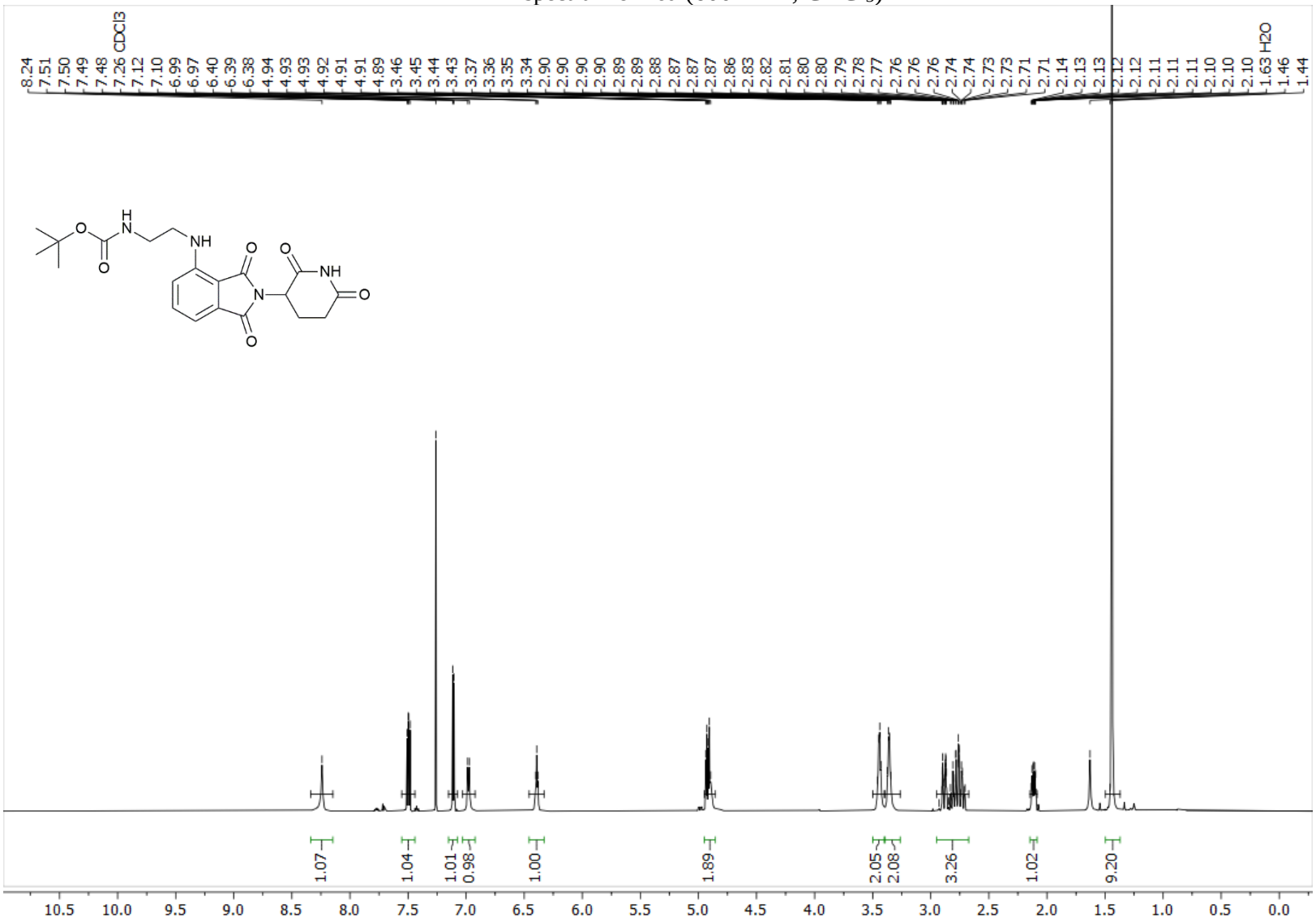
^{13}C NMR spectrum of **15** (151 MHz, 110 °C, DMSO-d_6)



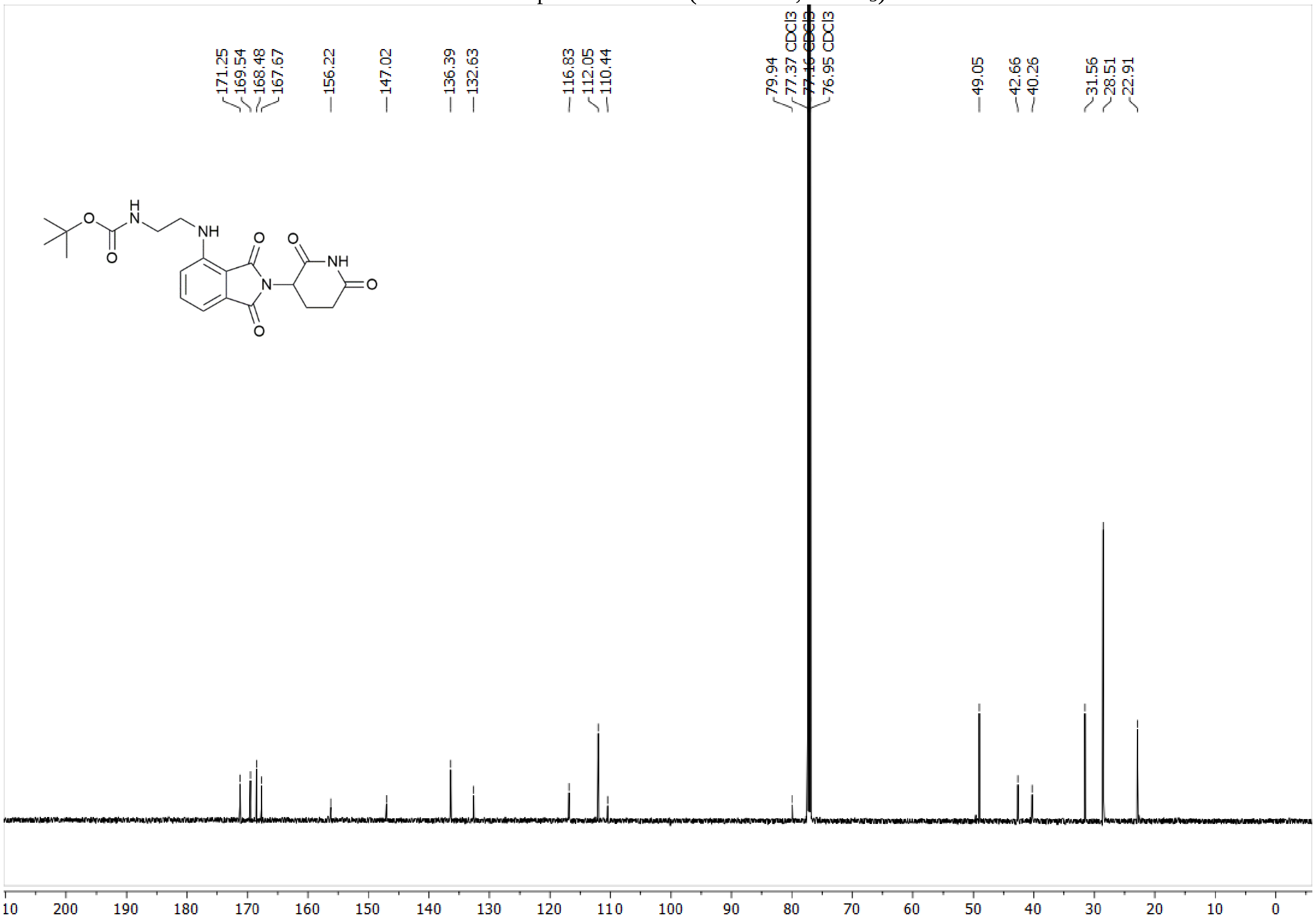
^{19}F NMR spectrum of **15** (376 MHz, 110 °C, DMSO-d_6)



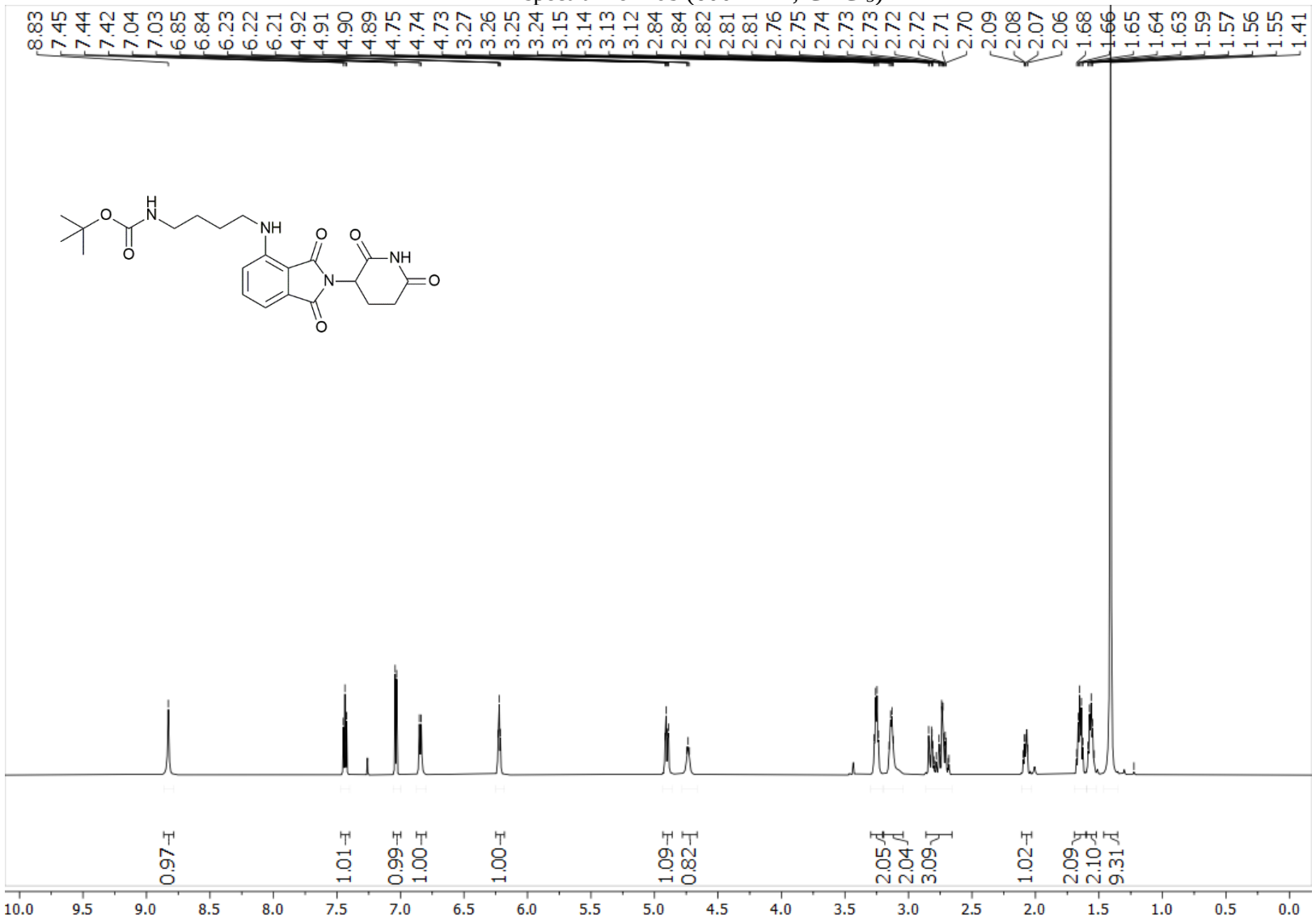
^{1}H NMR spectrum of **16a** (600 MHz, $CDCl_3$)



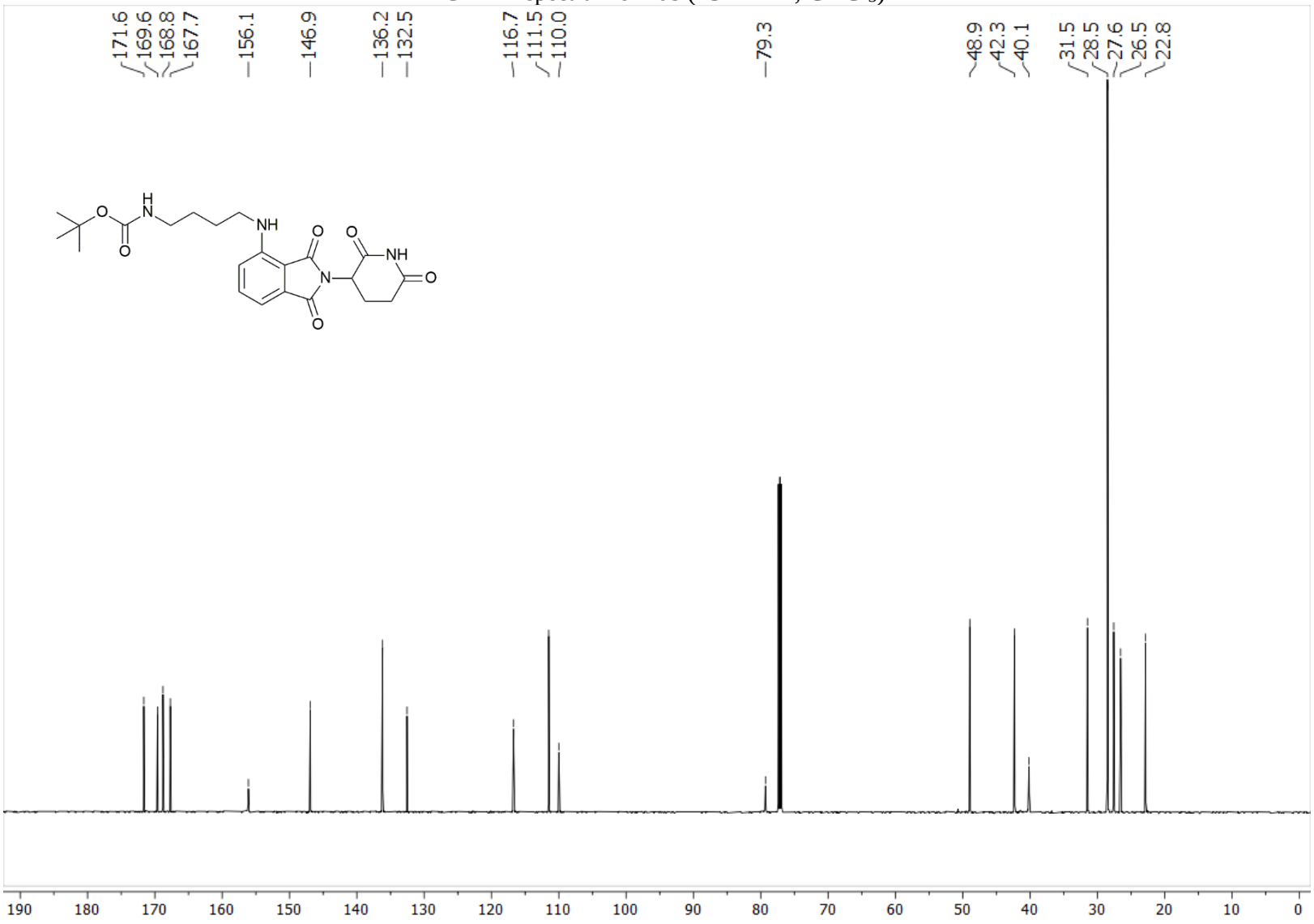
^{13}C NMR spectrum of **16a** (151 MHz, $CDCl_3$)



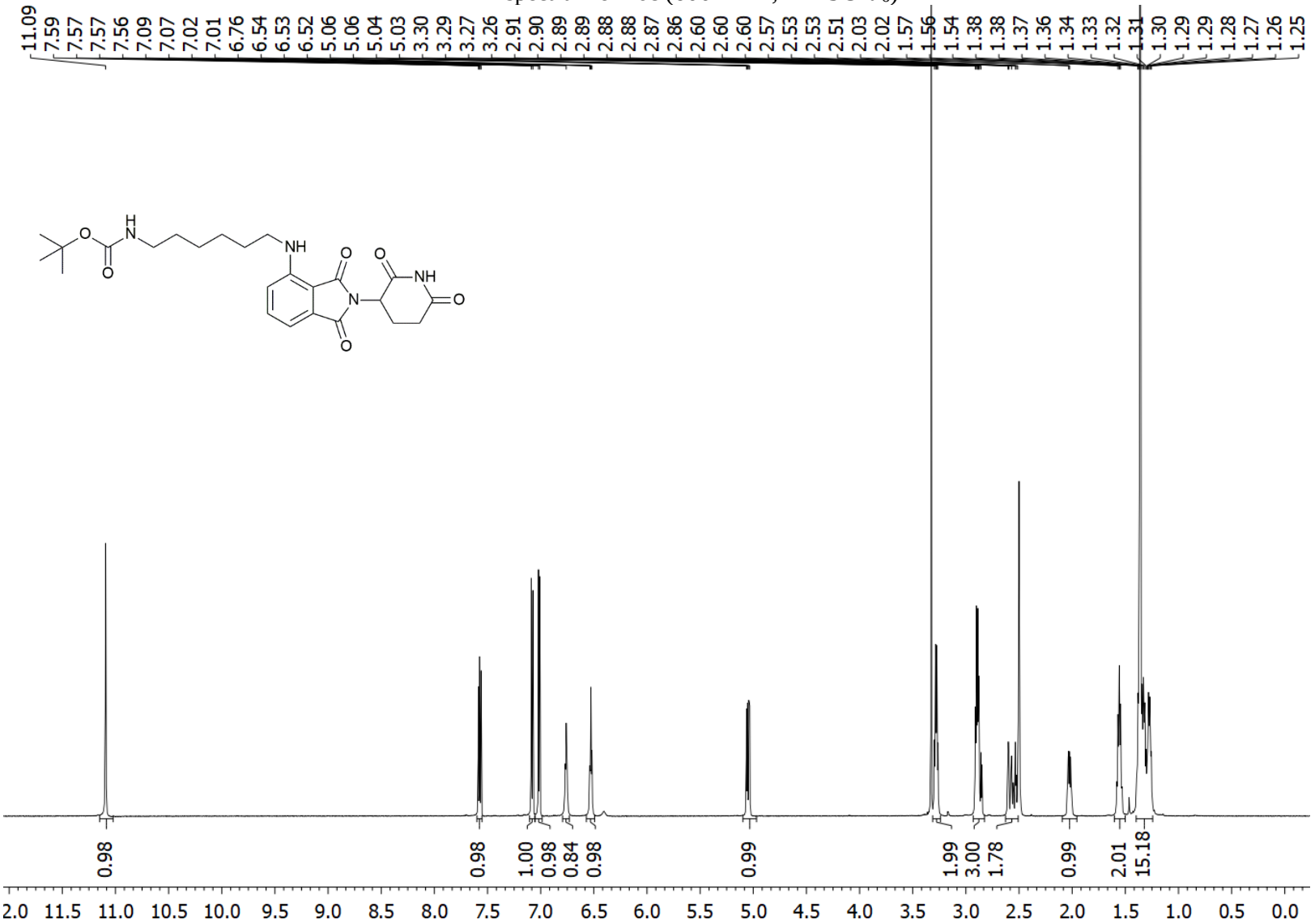
^{1}H NMR spectrum of **16b** (600 MHz, $CDCl_3$)



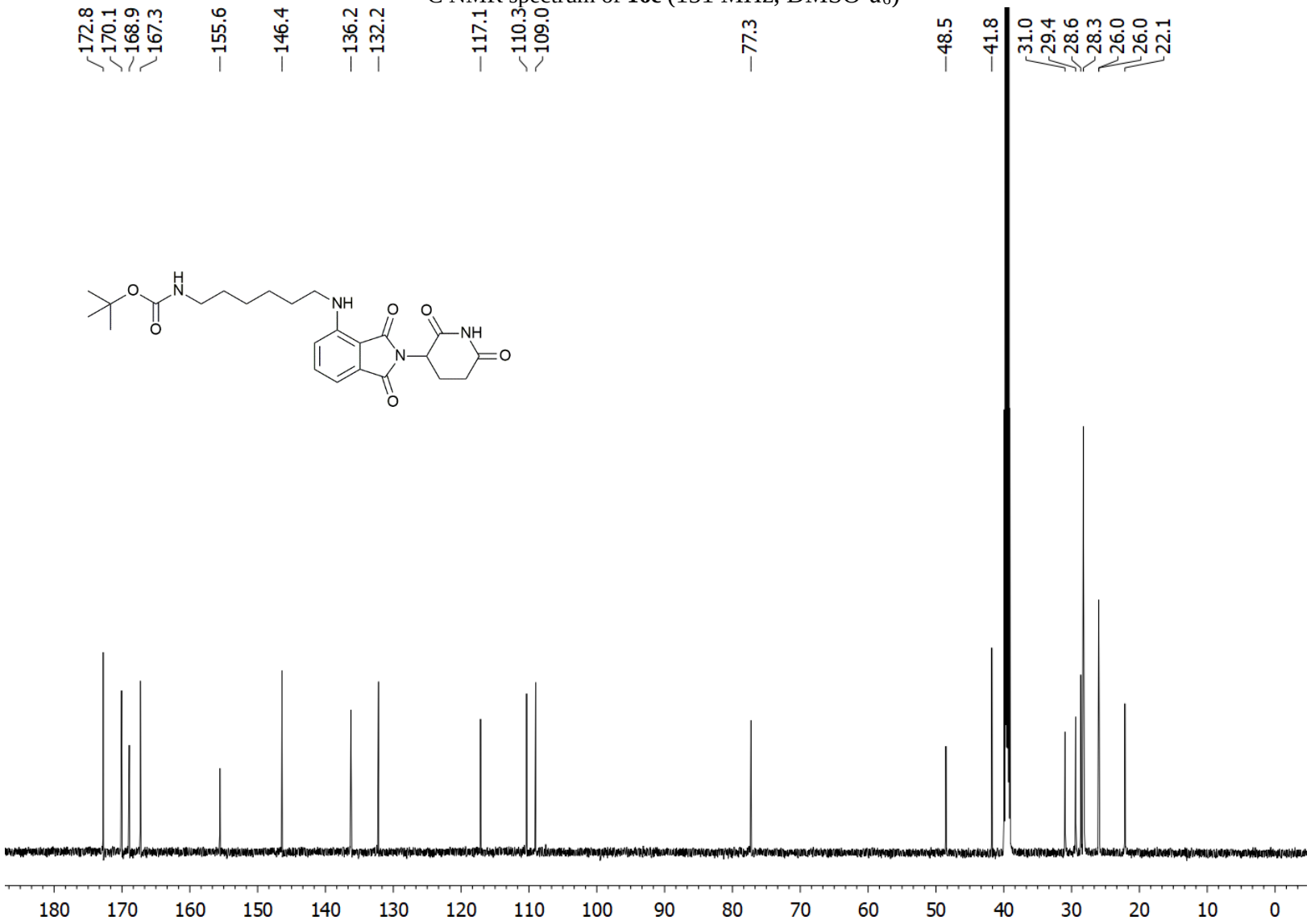
^{13}C NMR spectrum of **16b** (151 MHz, $CDCl_3$)



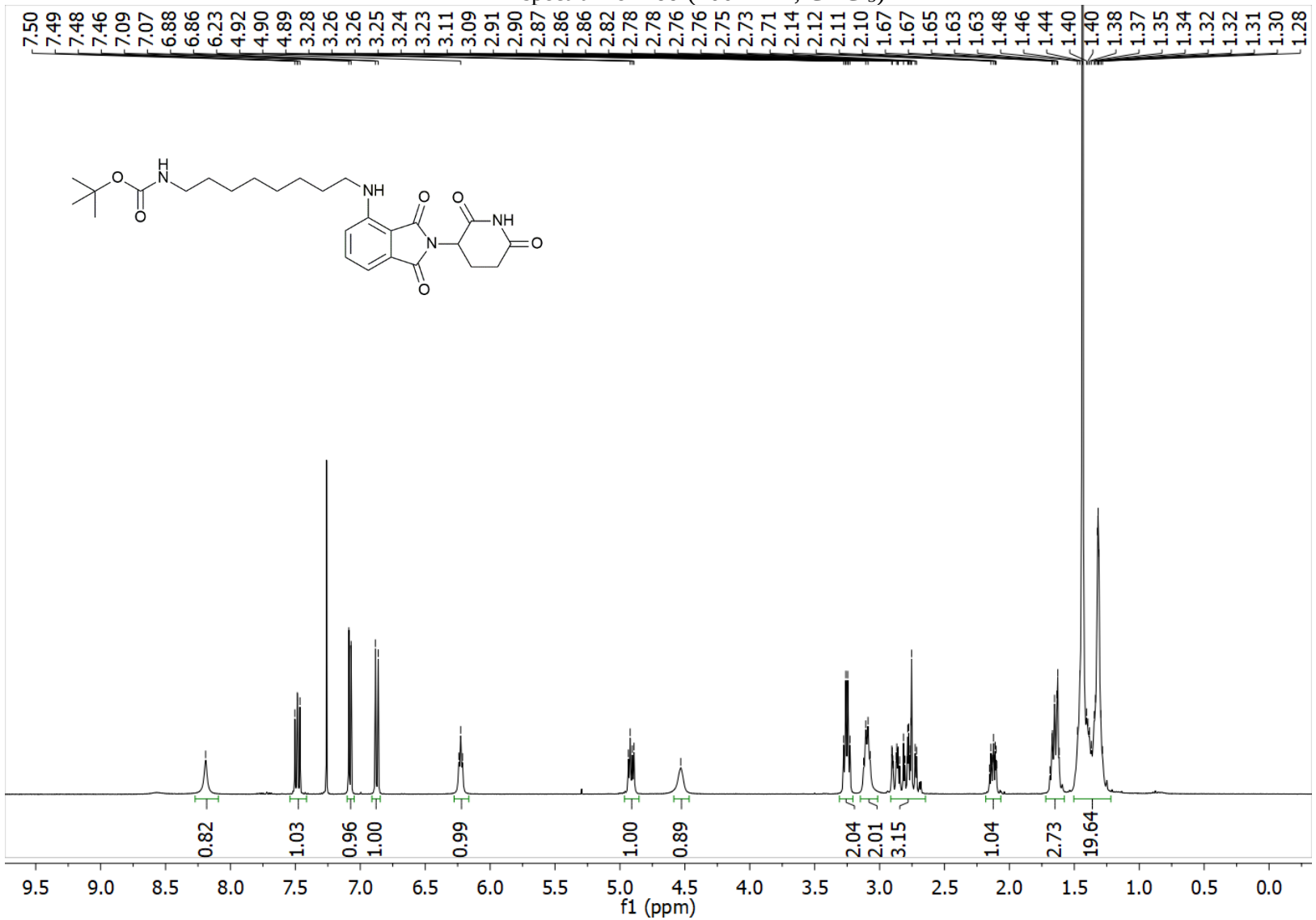
^{1}H NMR spectrum of **16c** (600 MHz, DMSO-d_6)



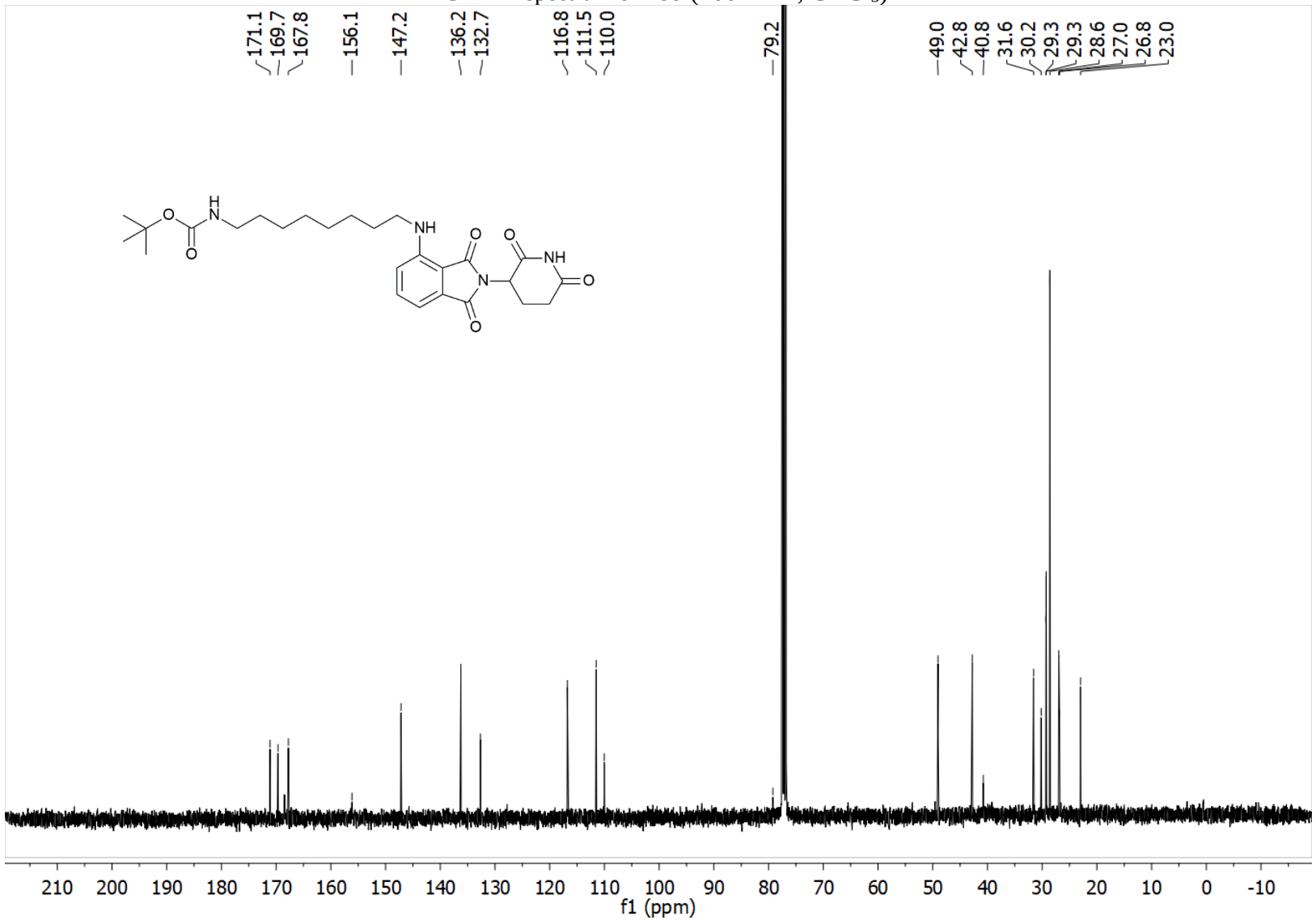
^{13}C NMR spectrum of **16c** (151 MHz, DMSO-d_6)



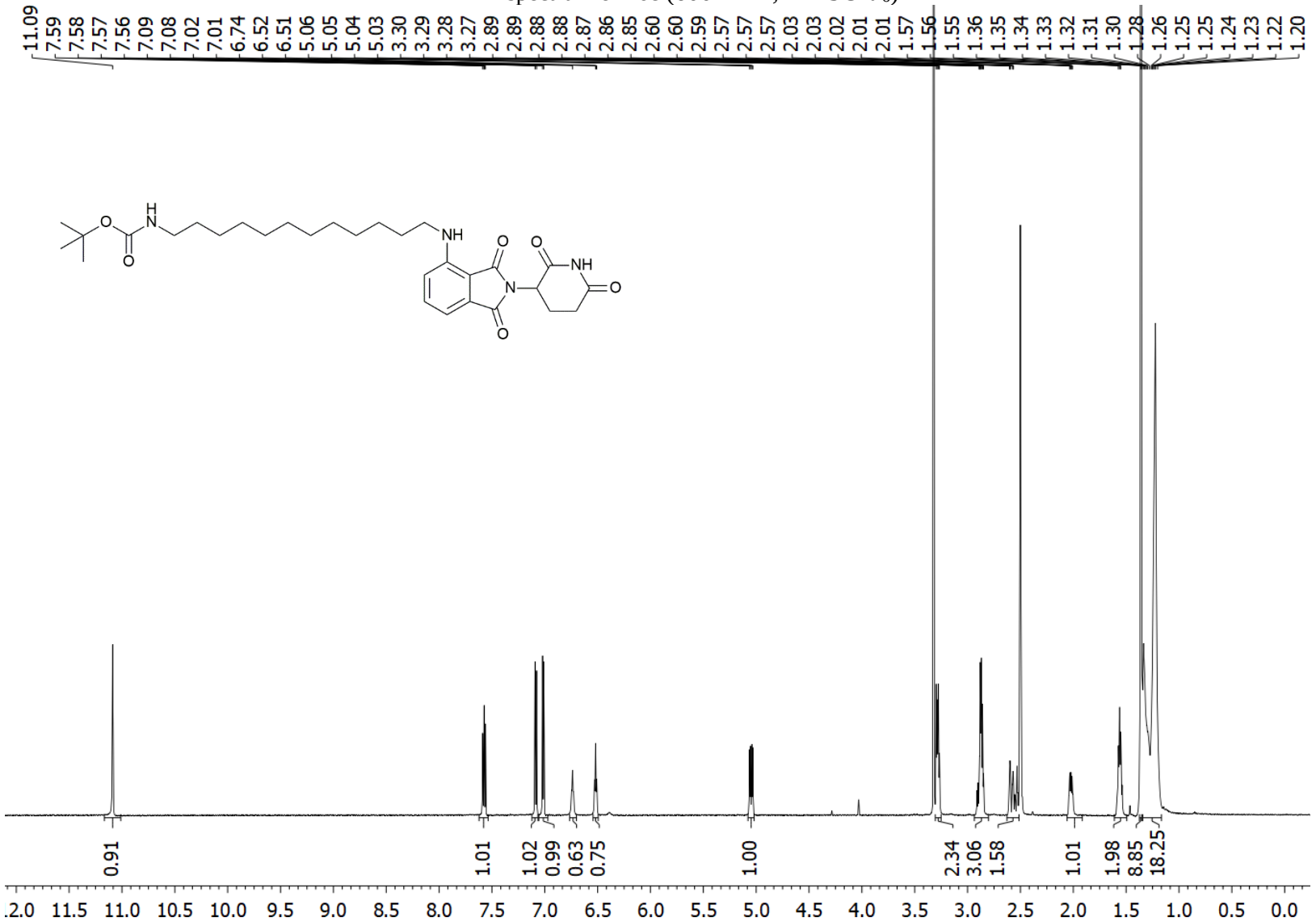
^{1}H NMR spectrum of **16d** (400 MHz, $CDCl_3$)



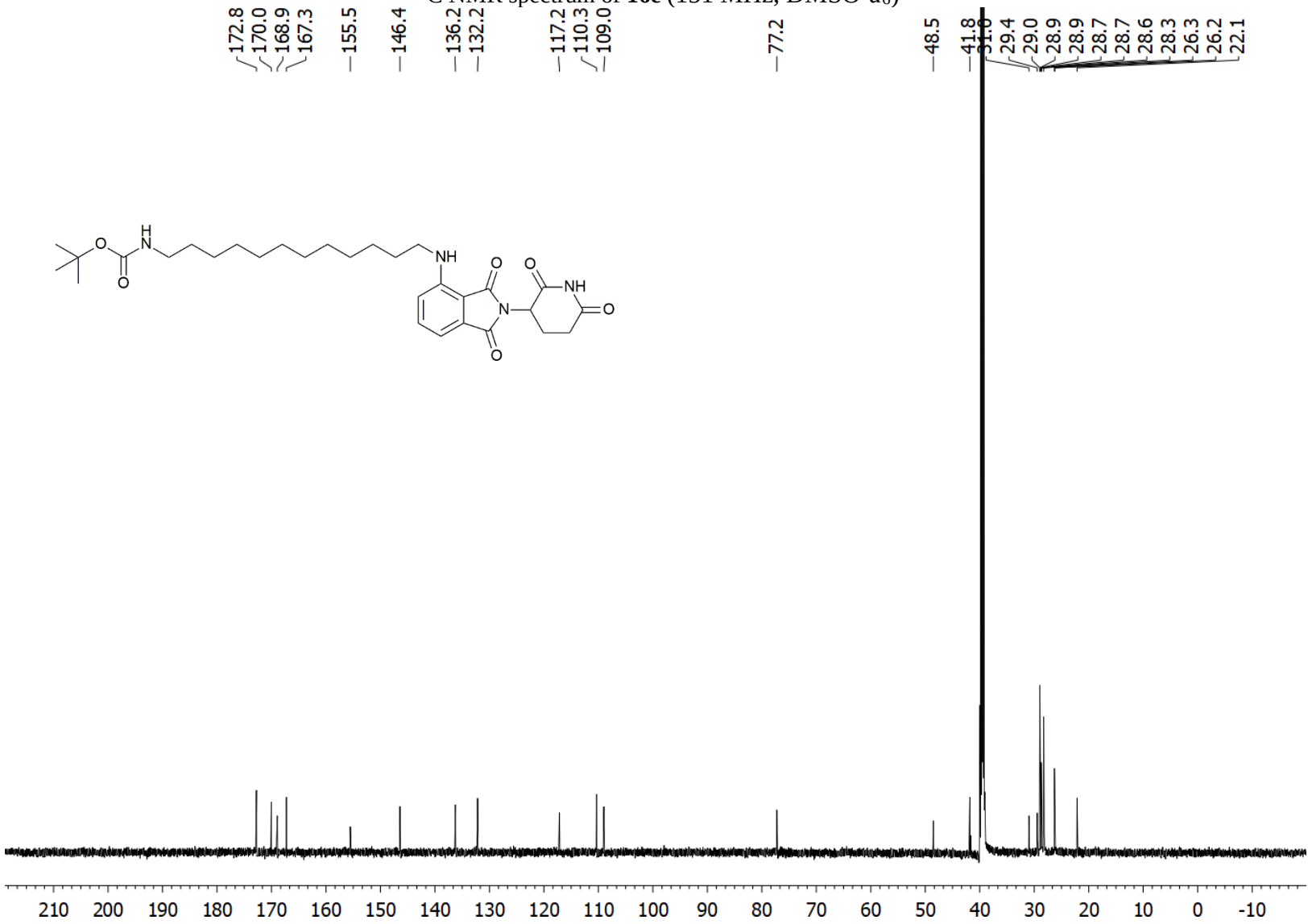
^{13}C NMR spectrum of **16d** (100 MHz, $CDCl_3$)



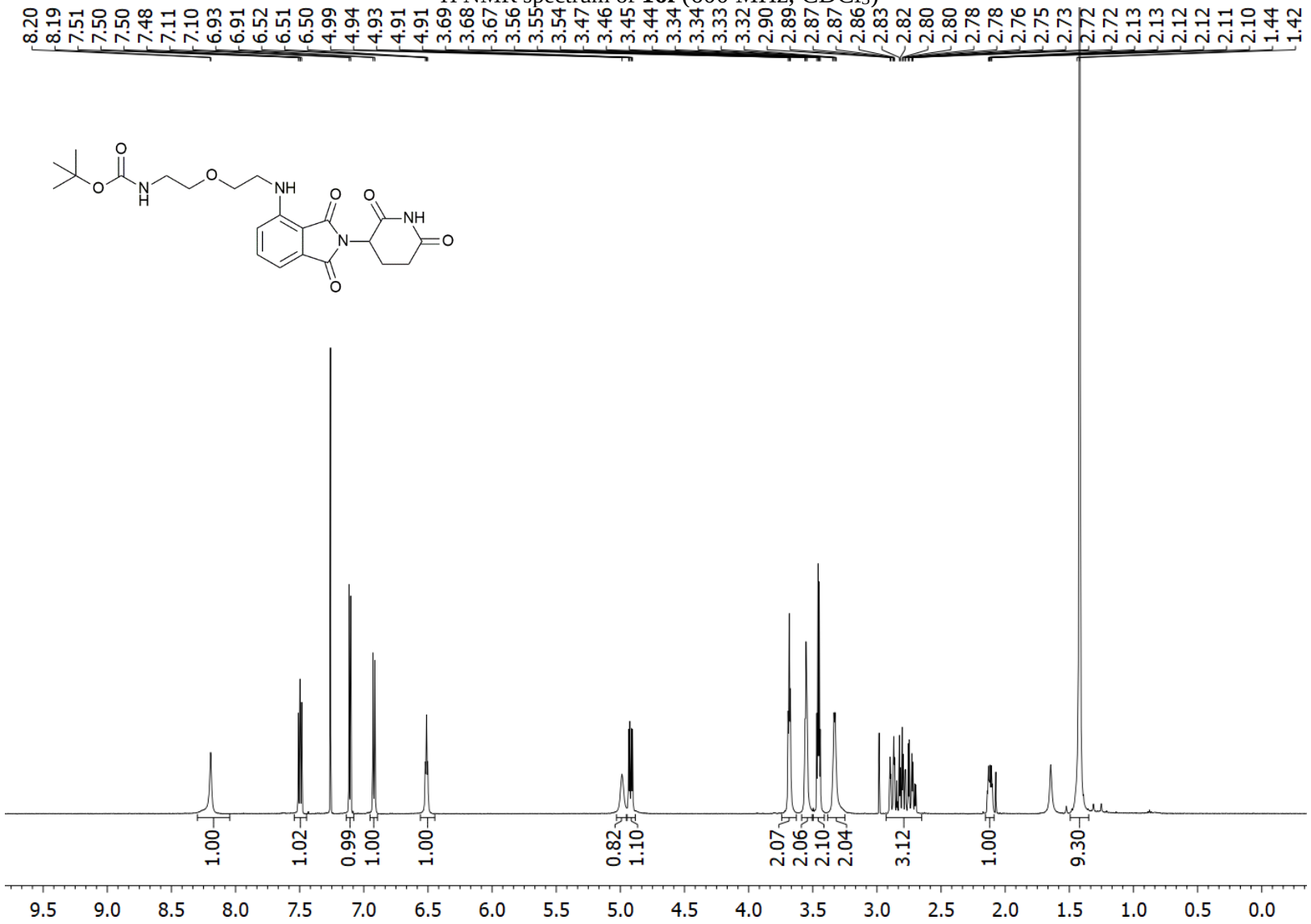
^{1}H NMR spectrum of **16e** (600 MHz, DMSO-d_6)



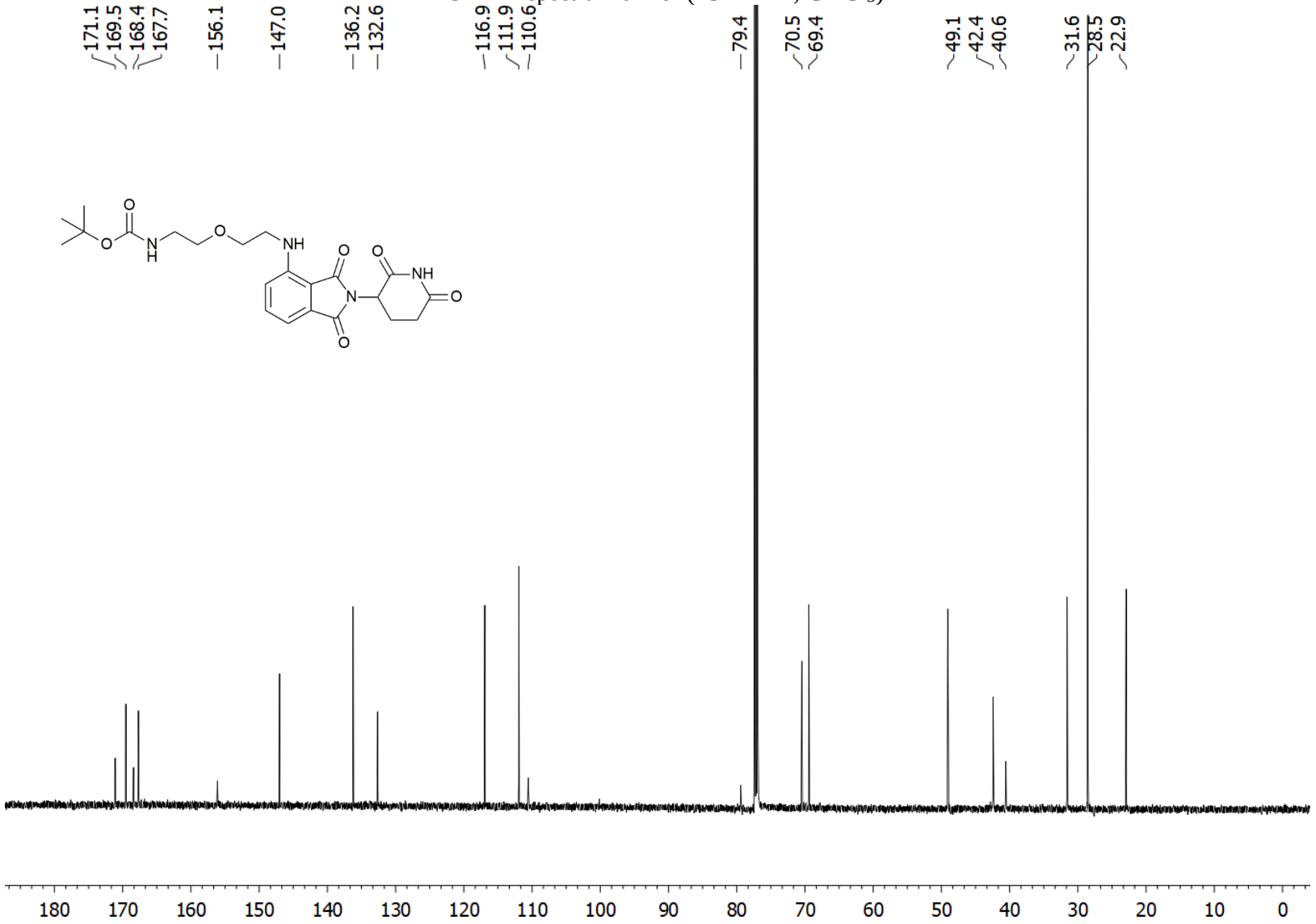
^{13}C NMR spectrum of **16e** (151 MHz, DMSO-d_6)



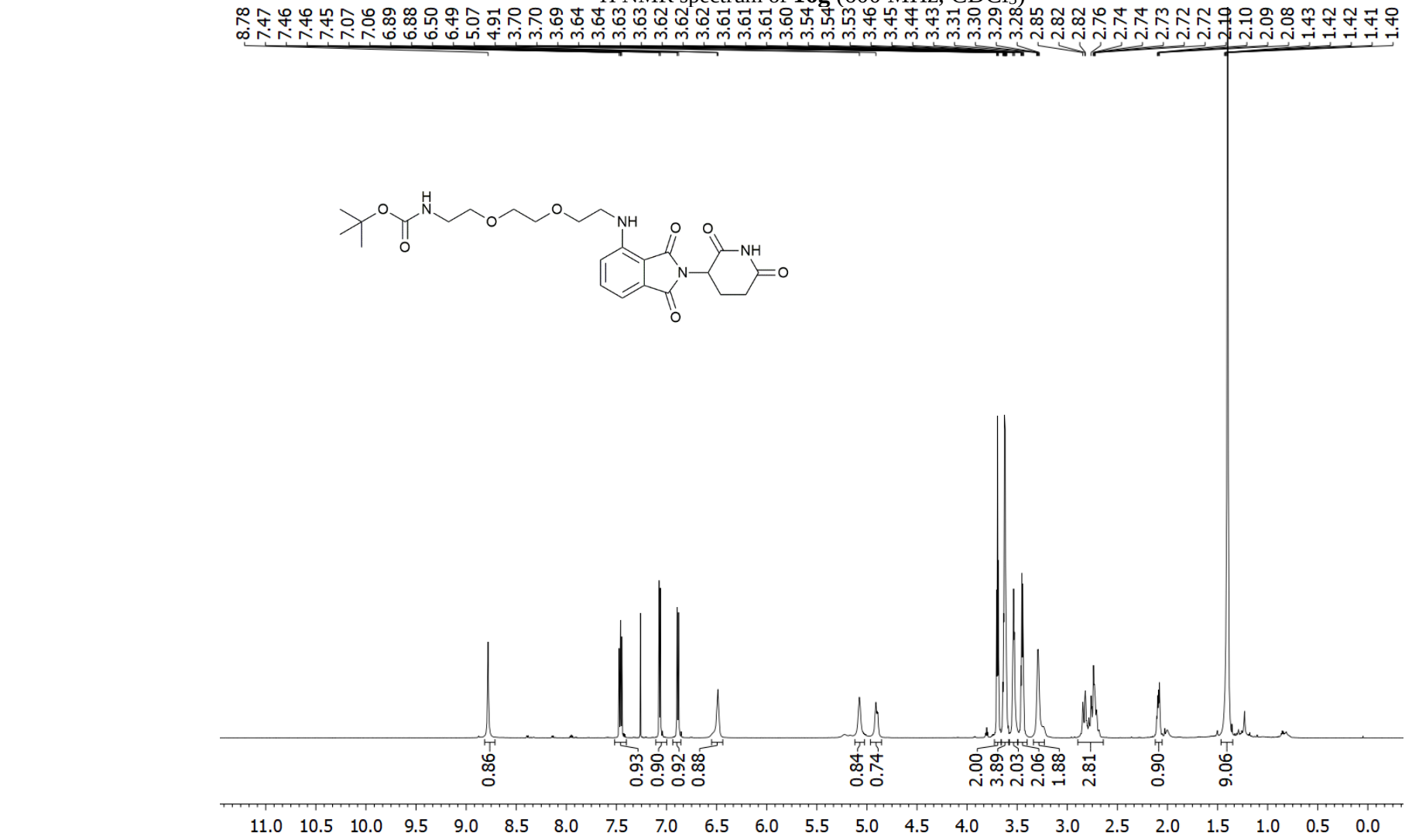
^{1}H NMR spectrum of **16f** (600 MHz, $CDCl_3$)



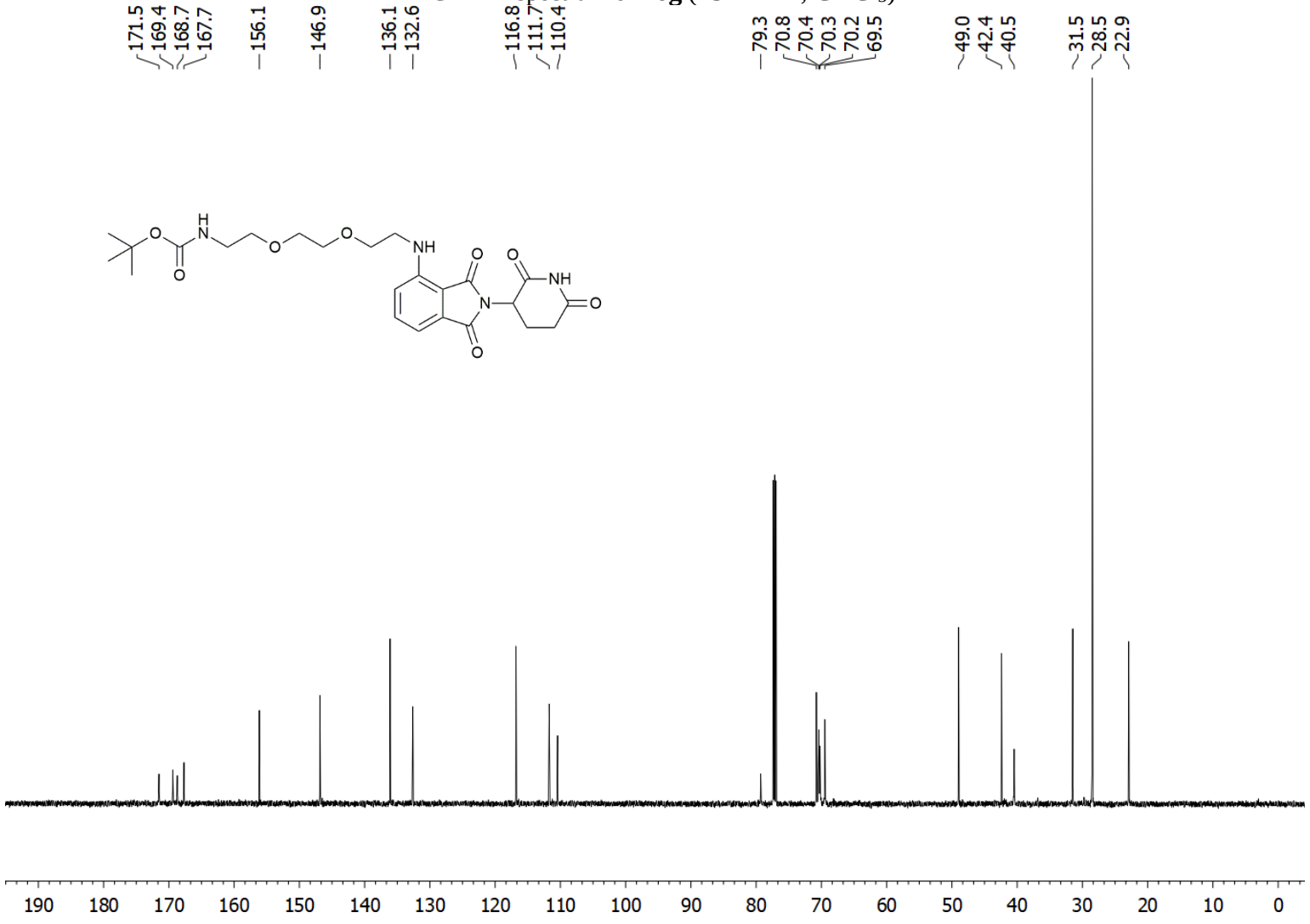
^{13}C NMR spectrum of **16f** (151 MHz, $CDCl_3$)



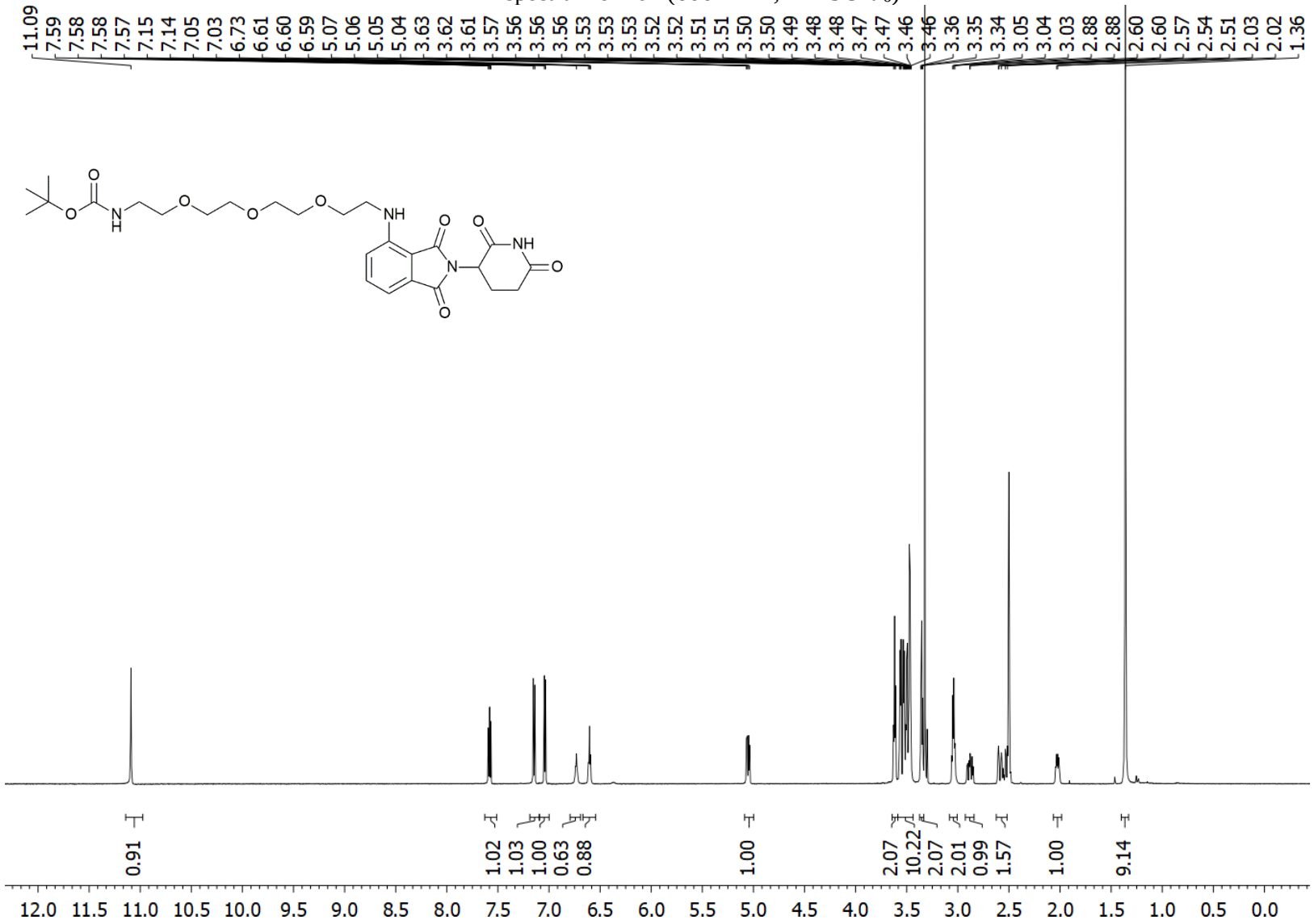
^{1}H NMR spectrum of **16g** (600 MHz, $CDCl_3$)



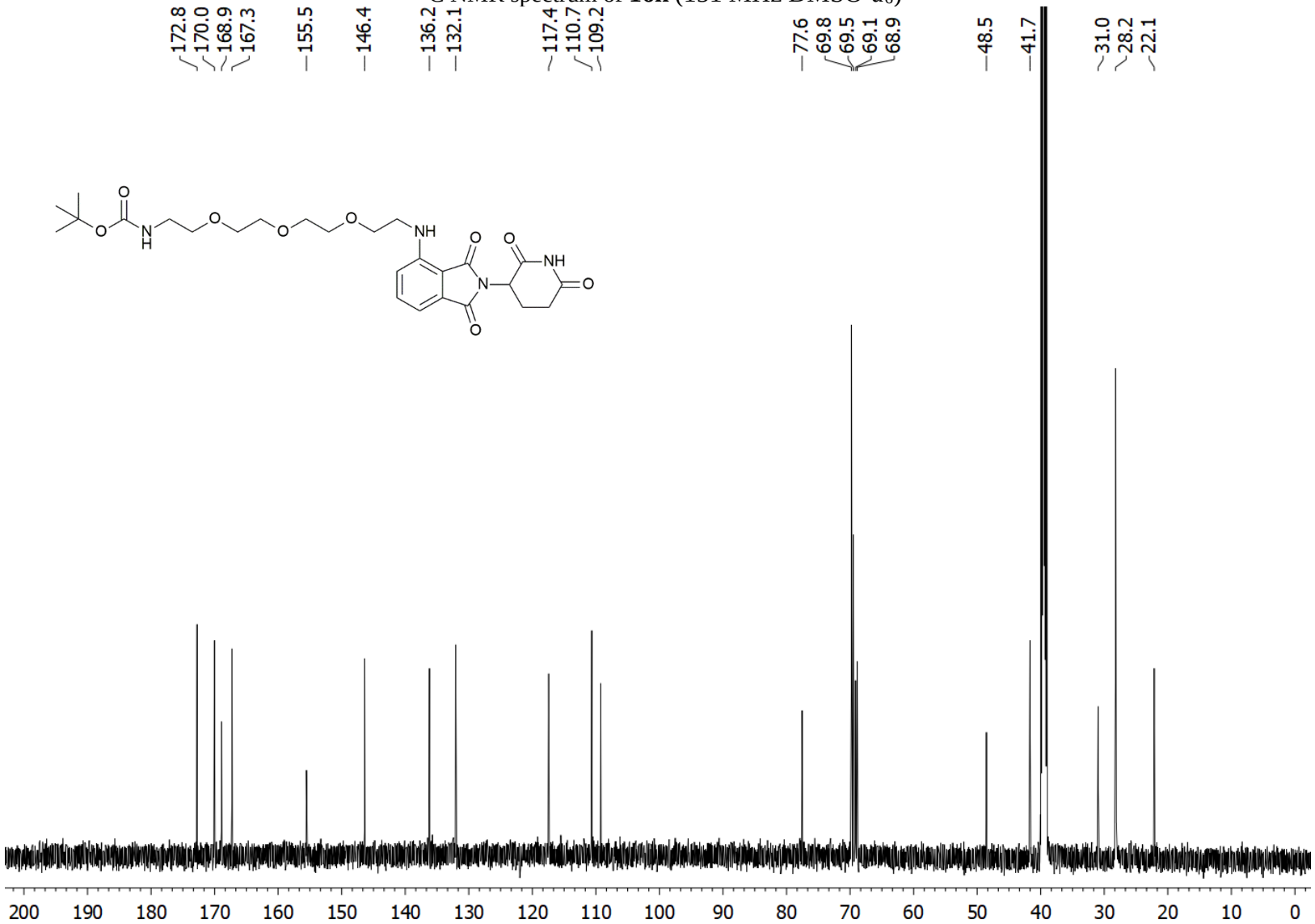
^{13}C NMR spectrum of **16g** (151 MHz, $CDCl_3$)



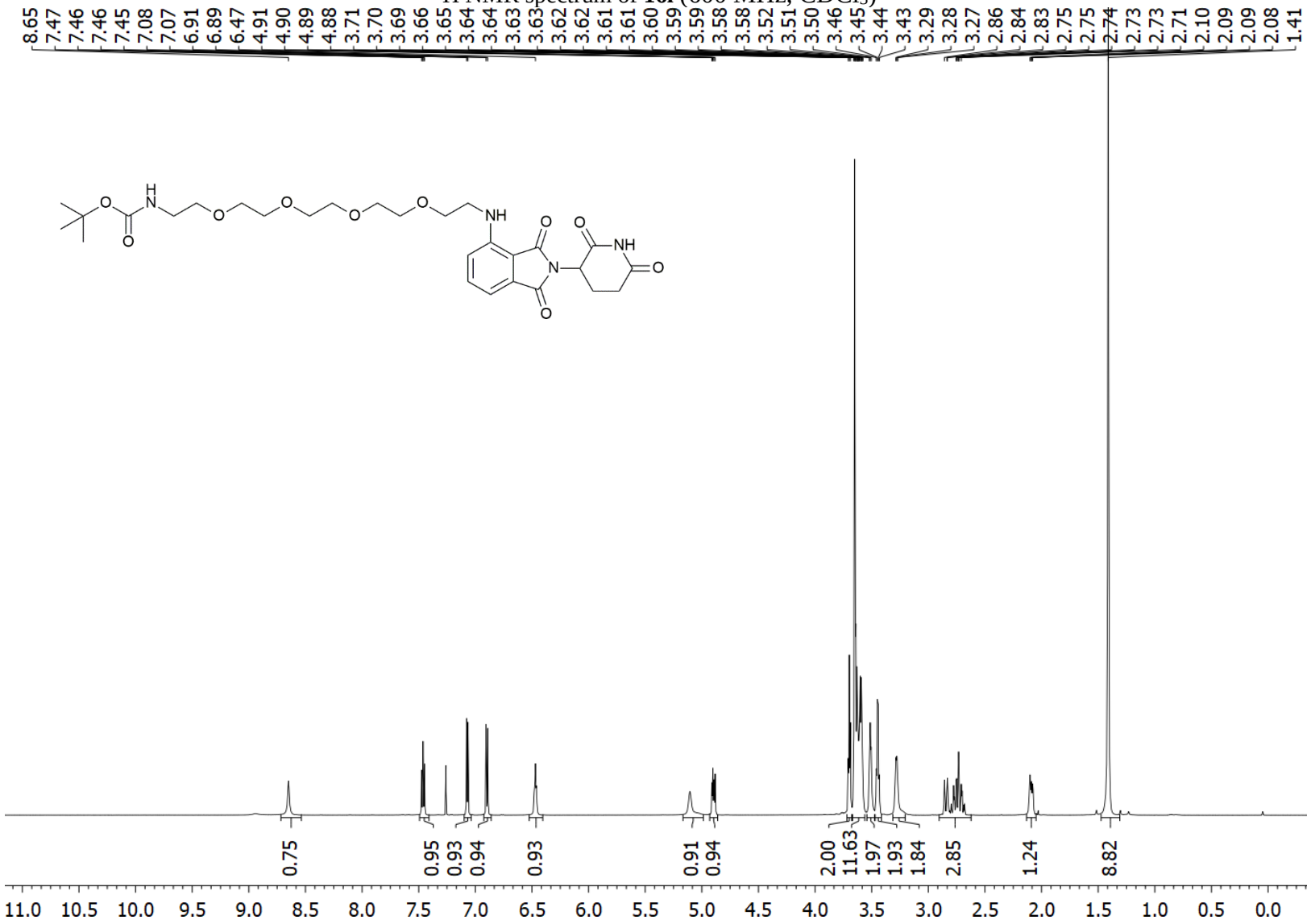
^{1}H NMR spectrum of **16h** (600 MHz, DMSO-d_6)



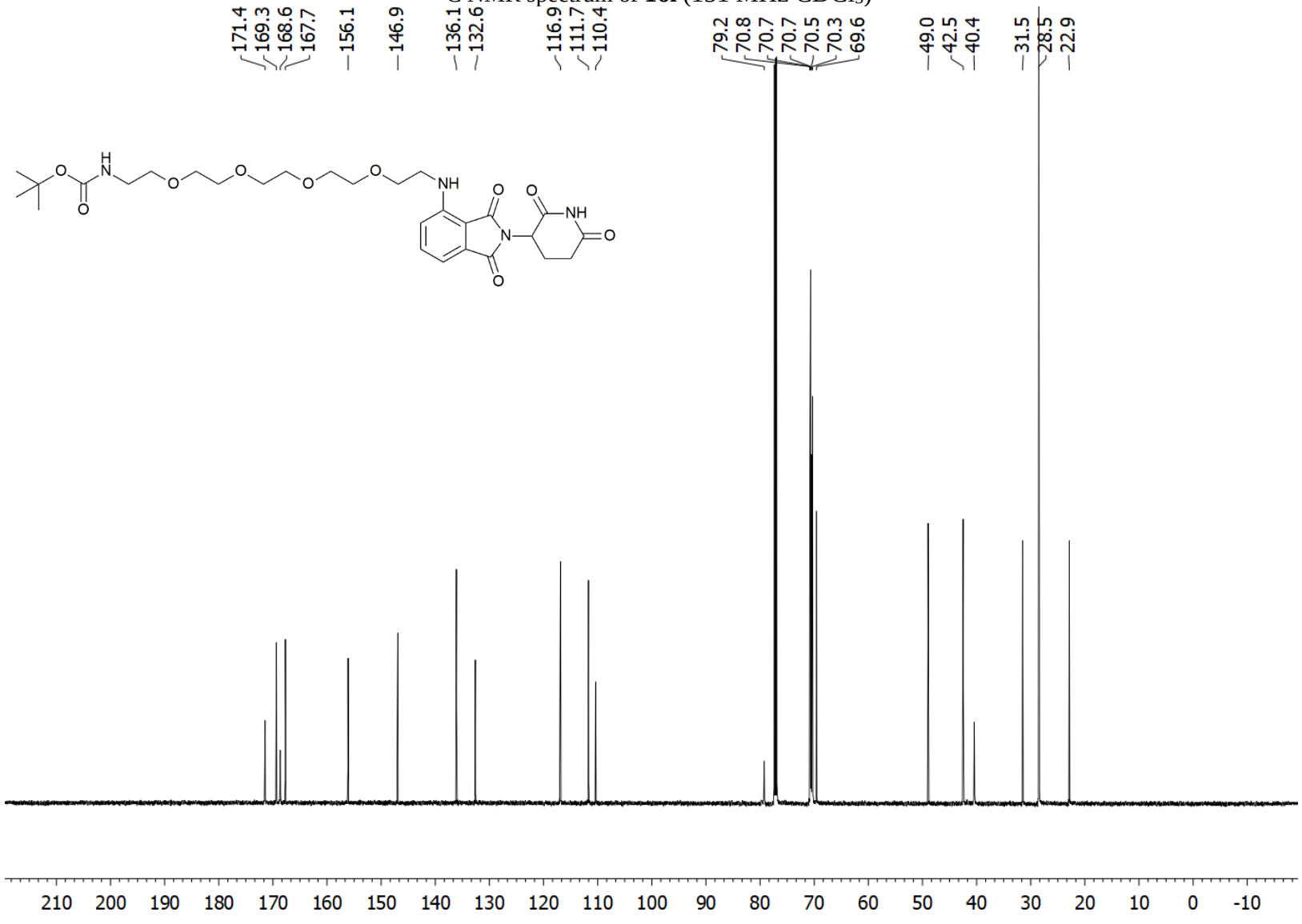
^{13}C NMR spectrum of **16h** (151 MHz DMSO-d_6)



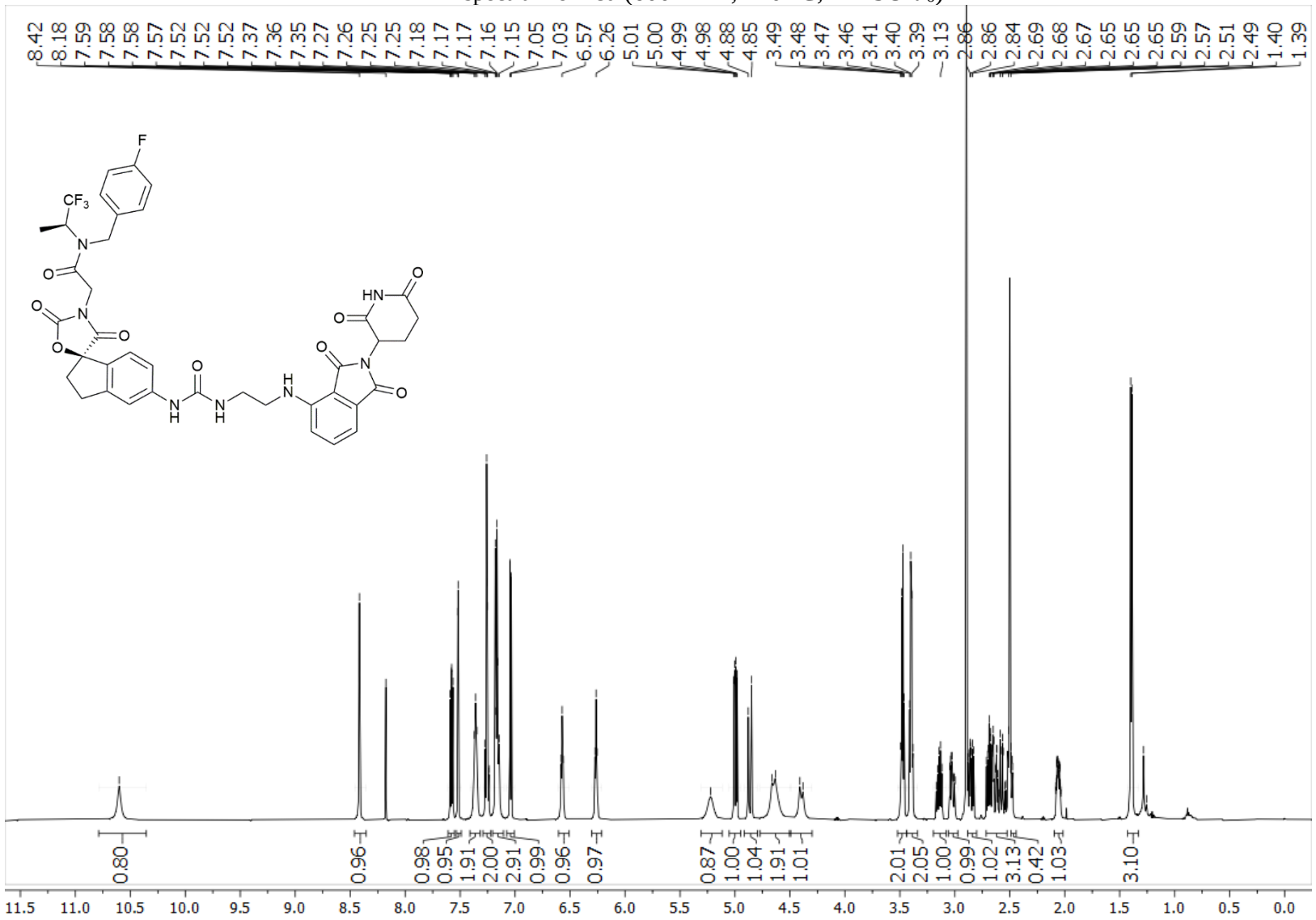
^{1}H NMR spectrum of **16i** (600 MHz, $CDCl_3$)



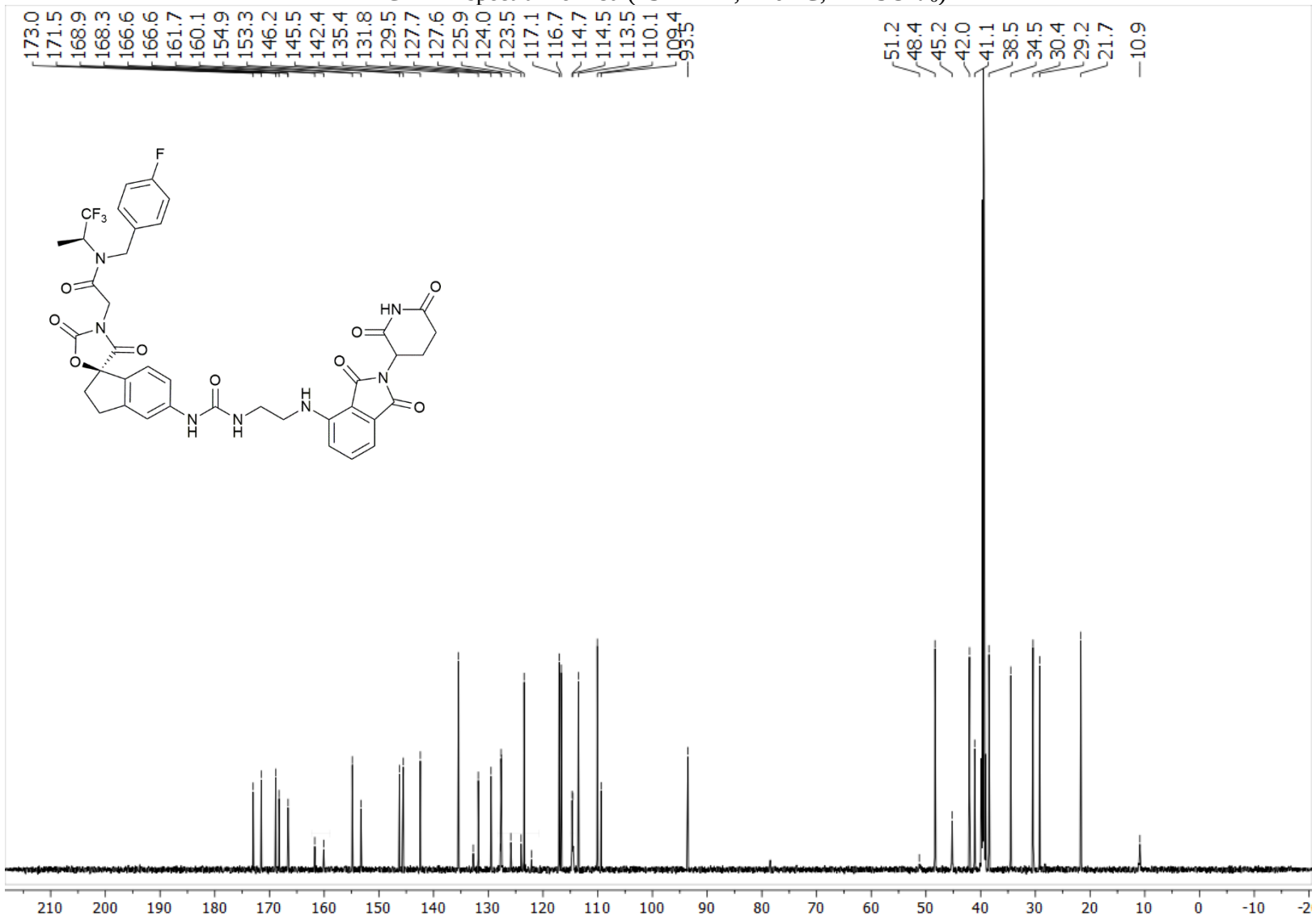
^{13}C NMR spectrum of **16i** (151 MHz $CDCl_3$)



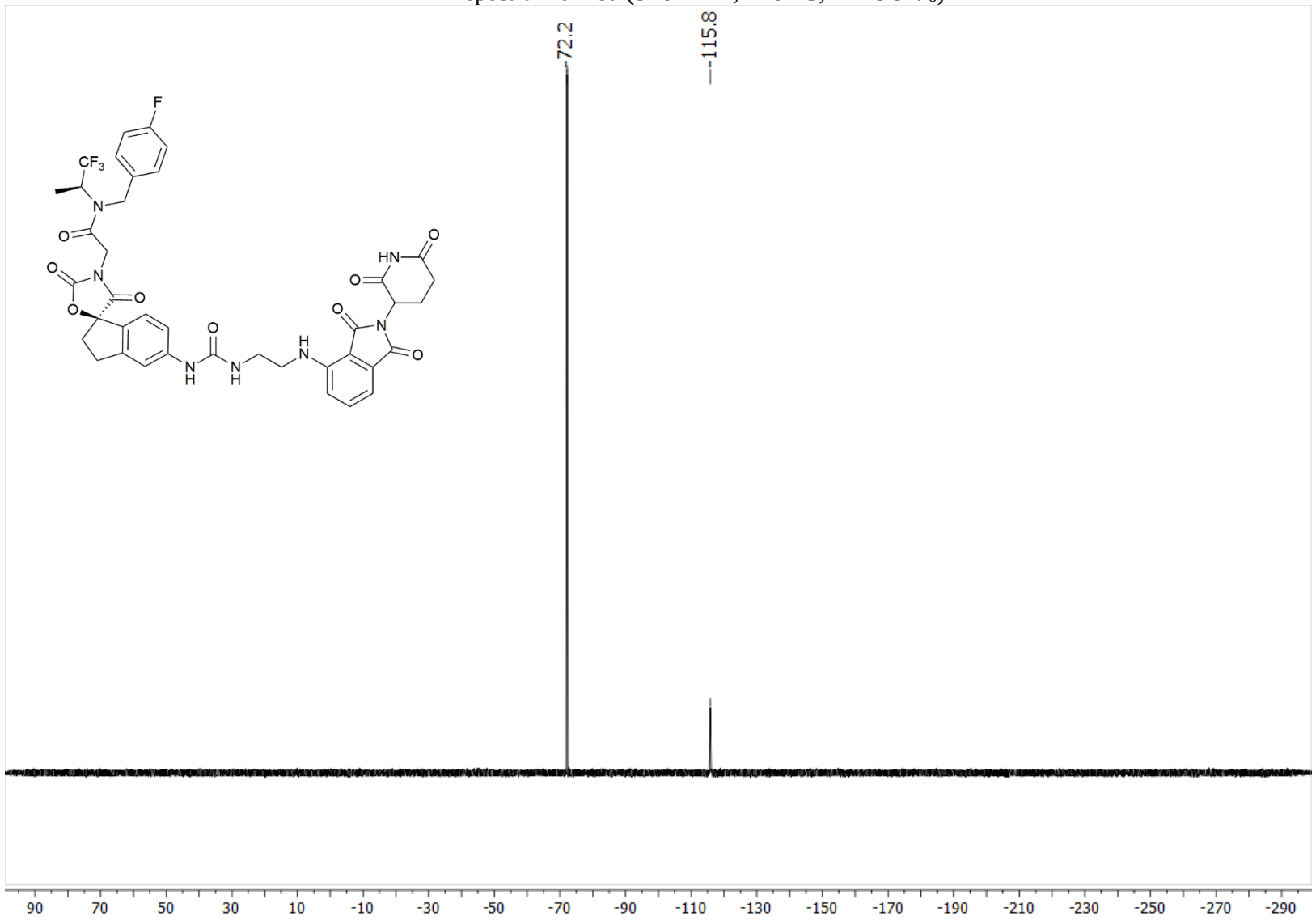
^{1}H NMR spectrum of **18a** (600 MHz, 110 °C, DMSO-d_6)



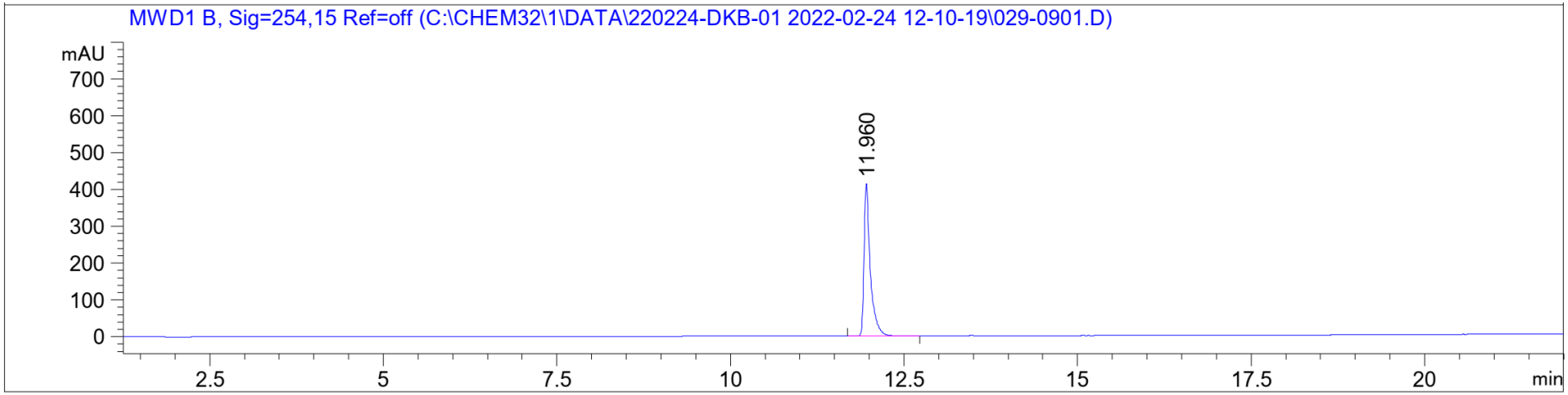
^{13}C NMR spectrum of **18a** (151 MHz, 110 °C, DMSO-d_6)



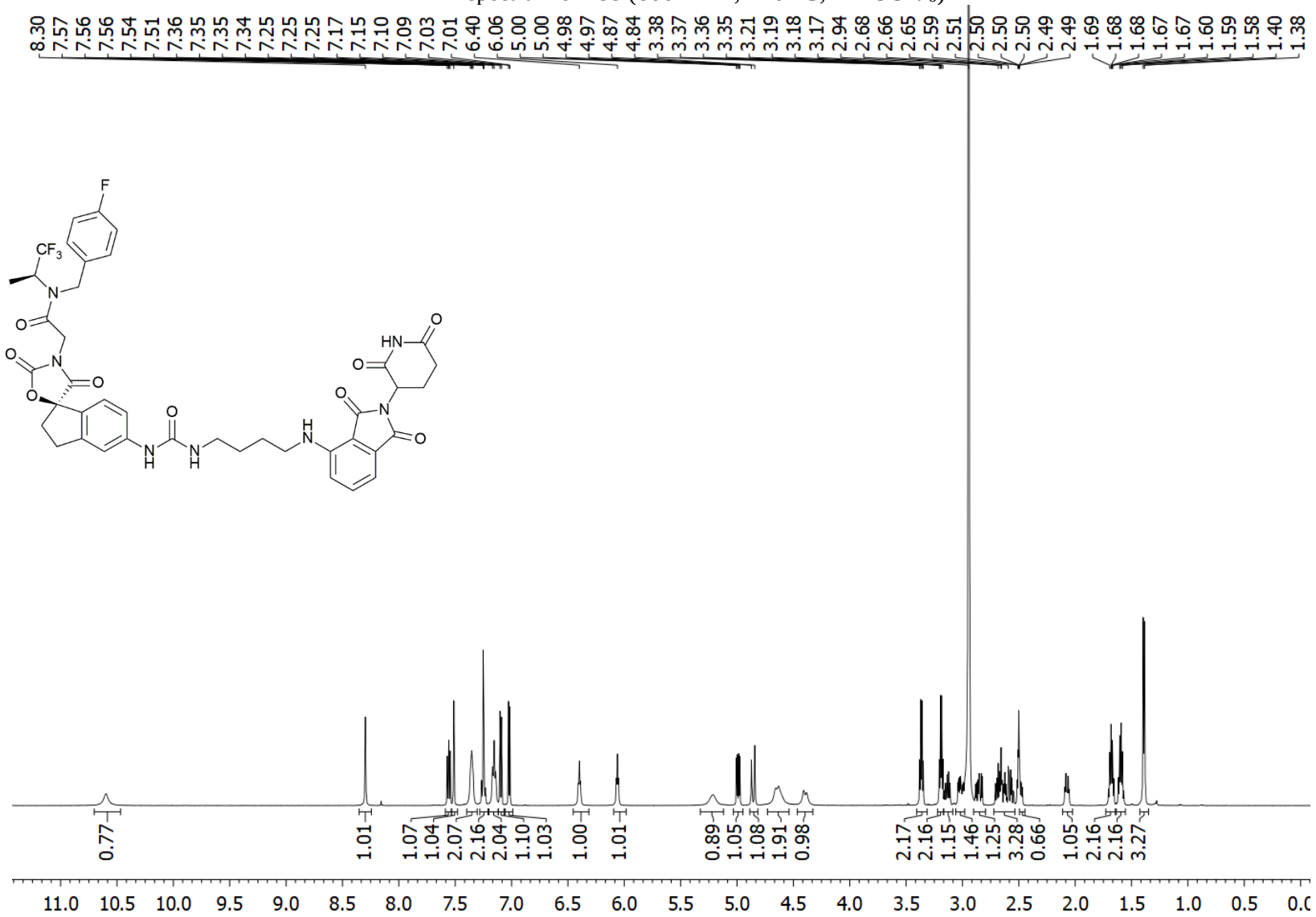
^{19}F NMR spectrum of **18a** (376 MHz, 110 °C, DMSO-d_6)



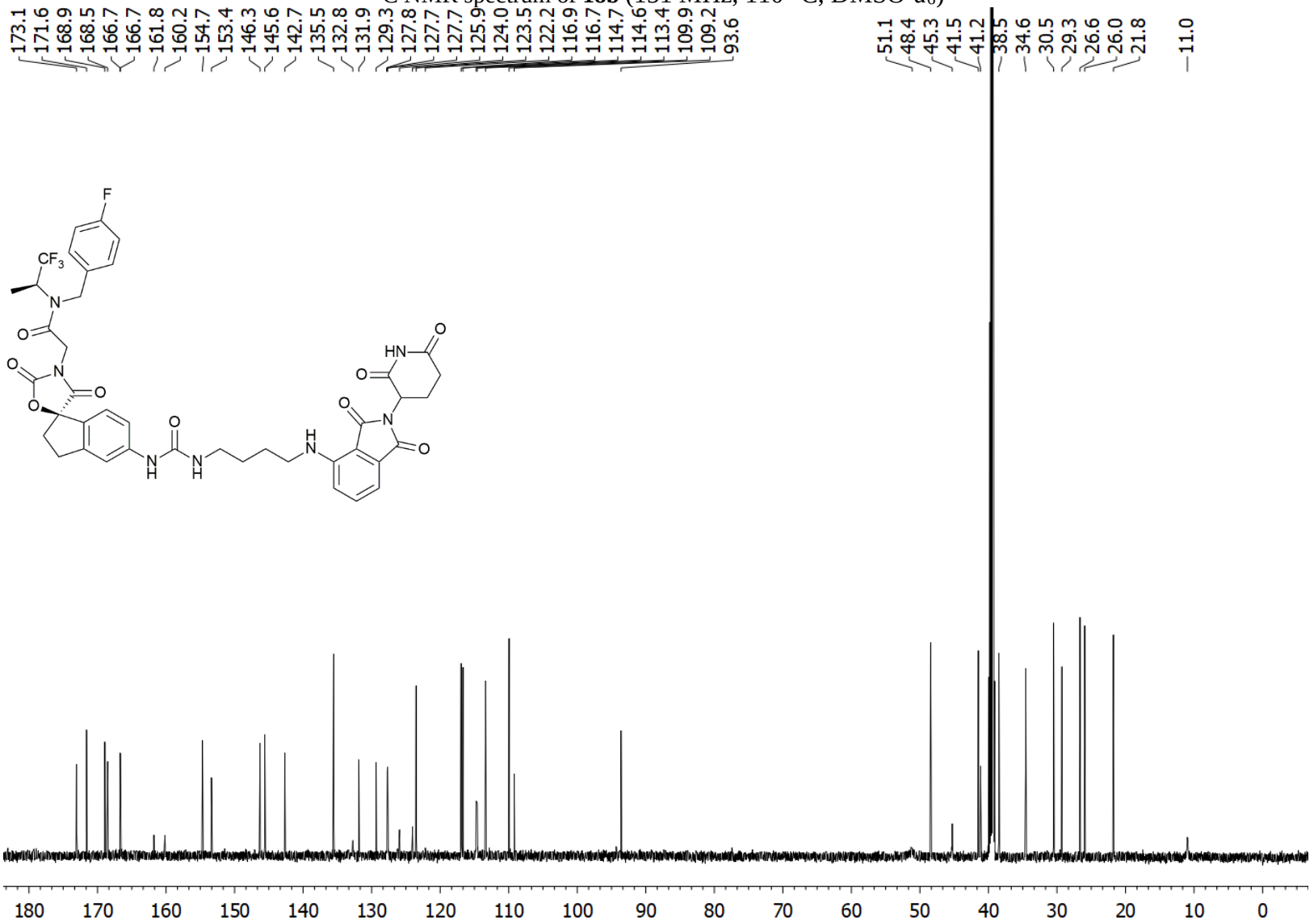
HPLC trace of **18a** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



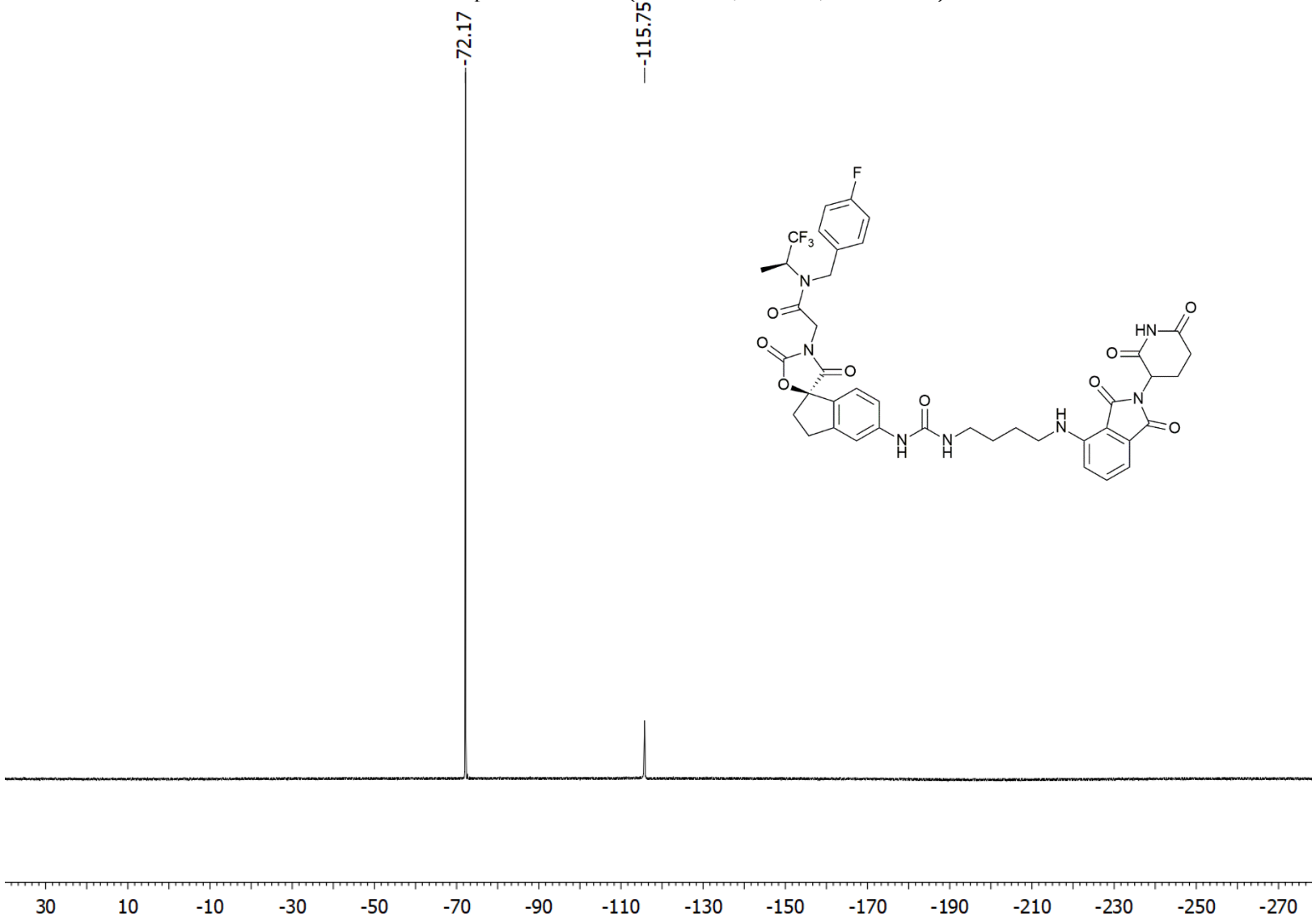
^{1}H NMR spectrum of **18b** (600 MHz, 110 °C, DMSO-d_6)



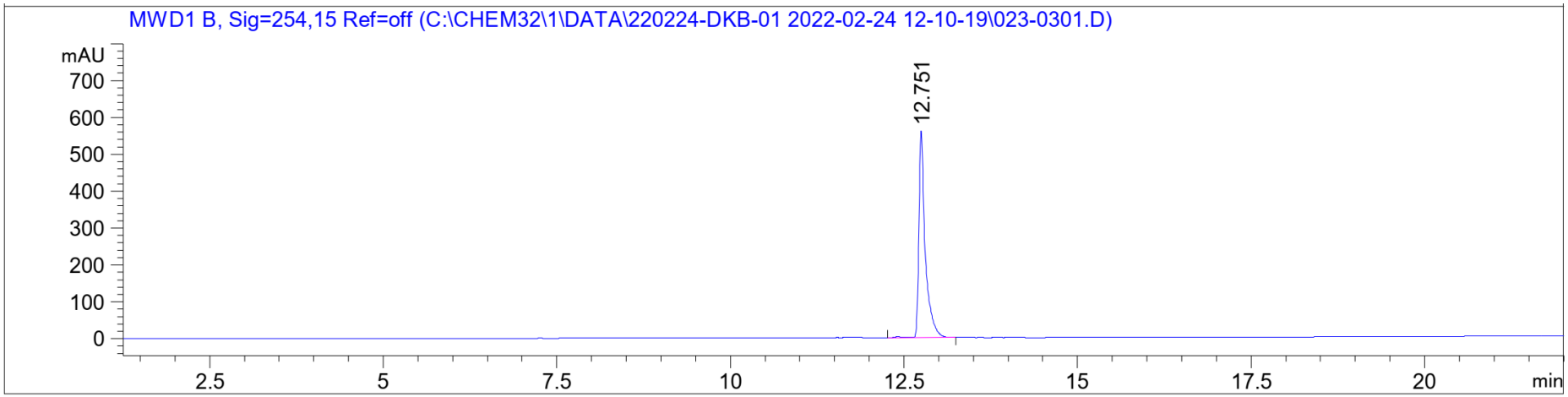
^{13}C NMR spectrum of **18b** (151 MHz, 110 °C, DMSO-d_6)



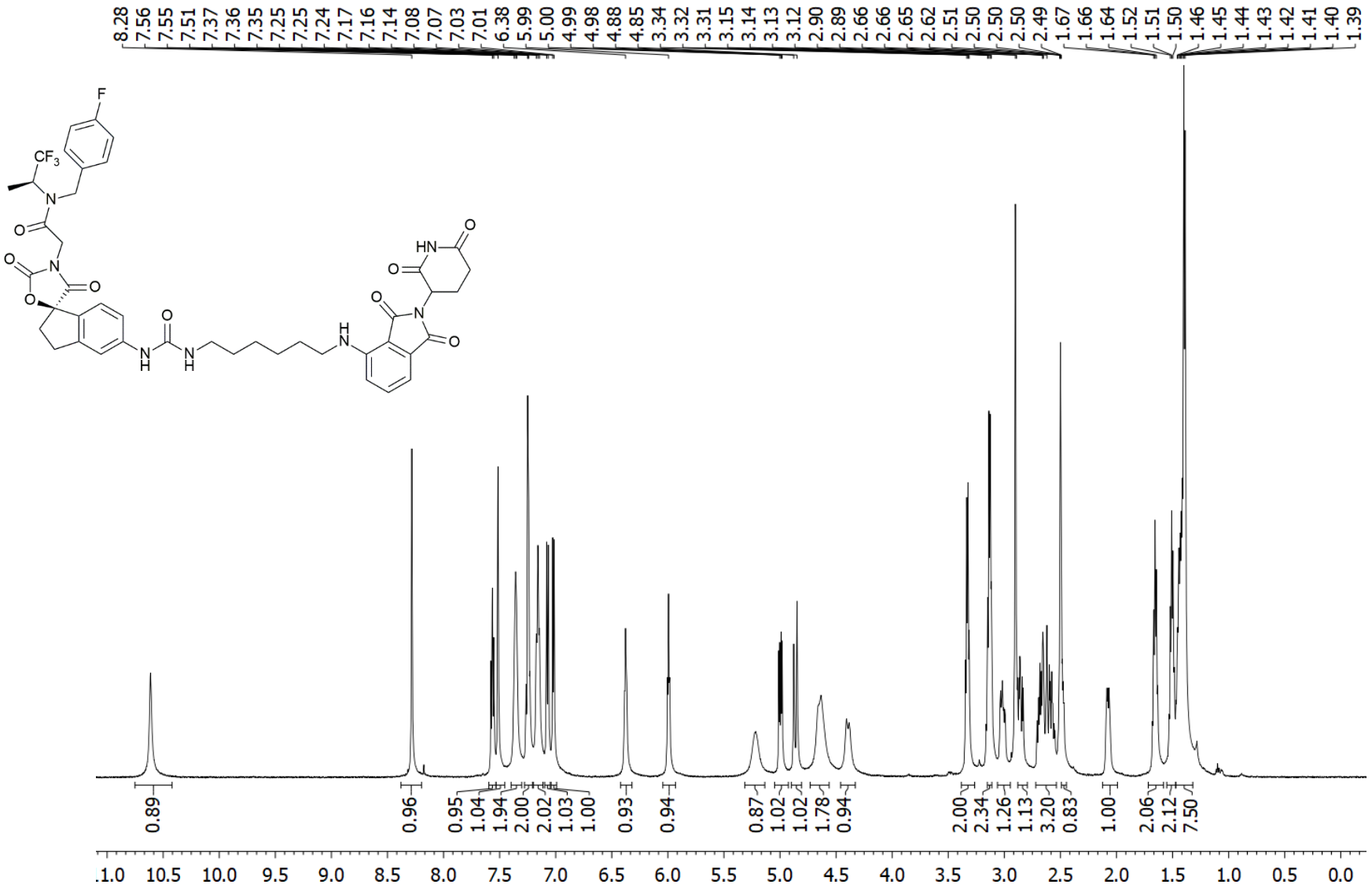
^{19}F NMR spectrum of **18b** (376 MHz, 110 °C, DMSO-d_6)



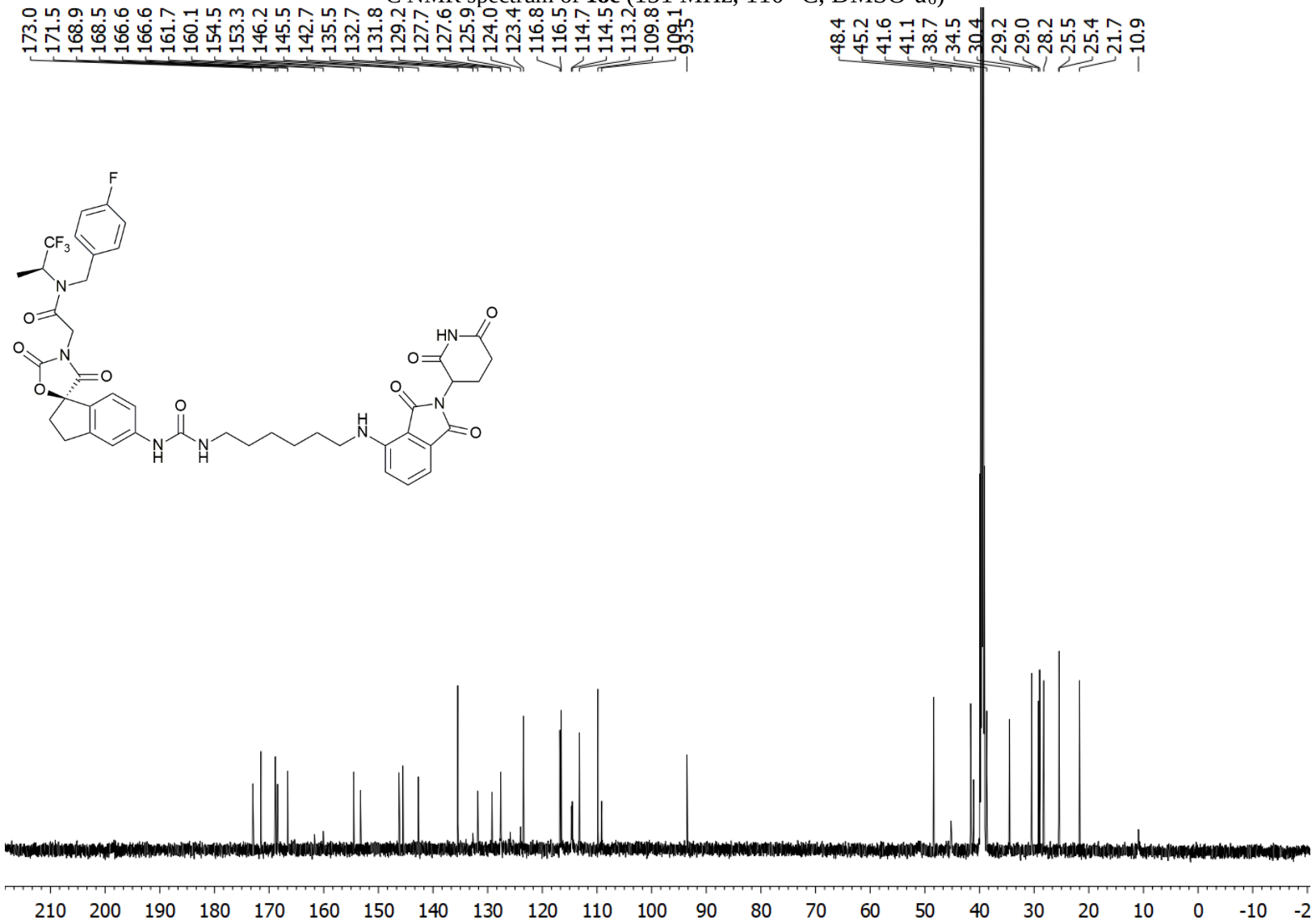
HPLC trace of **18b** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



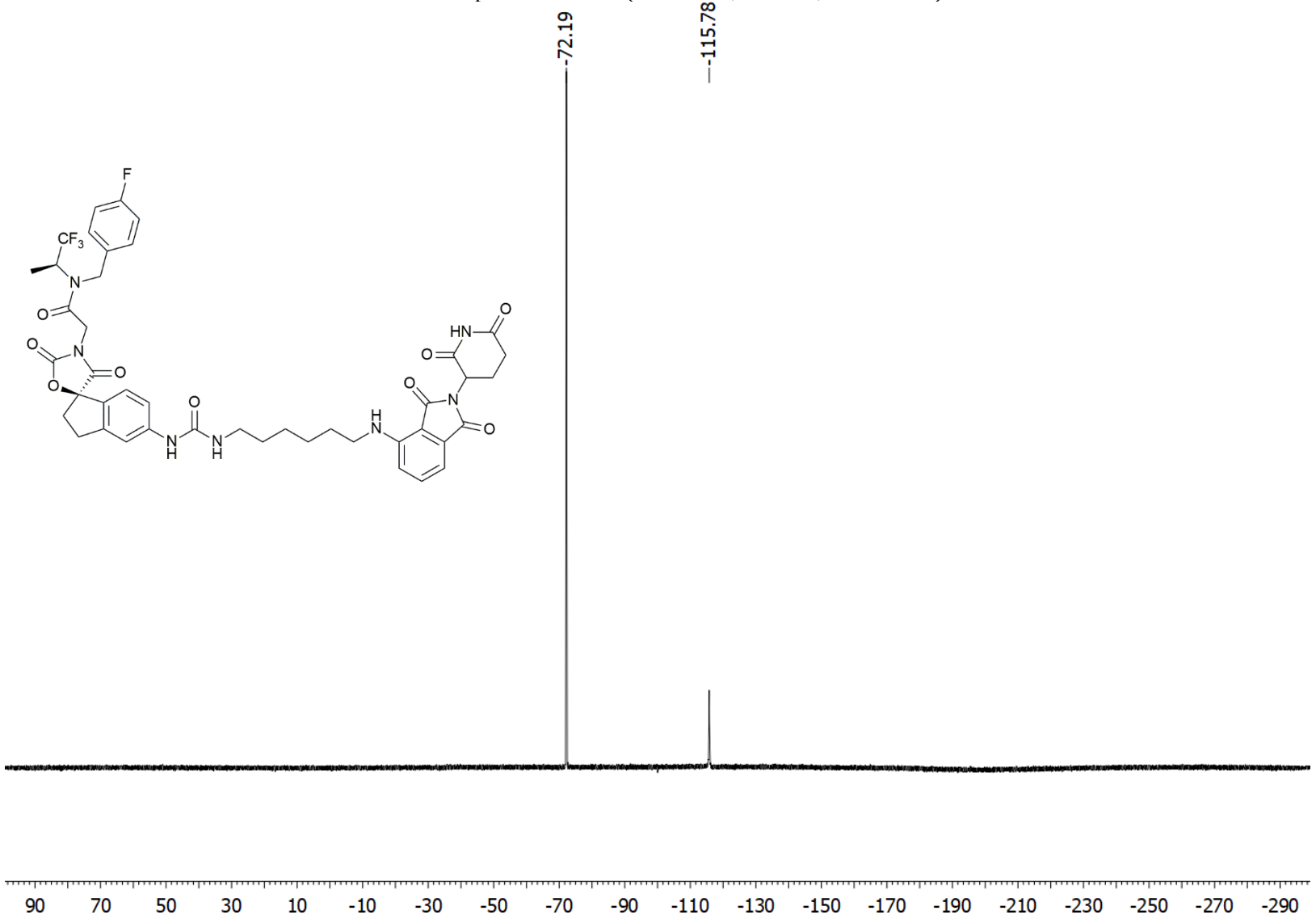
^{1}H NMR spectrum of **18c** (600 MHz, 110 °C, DMSO-d_6)



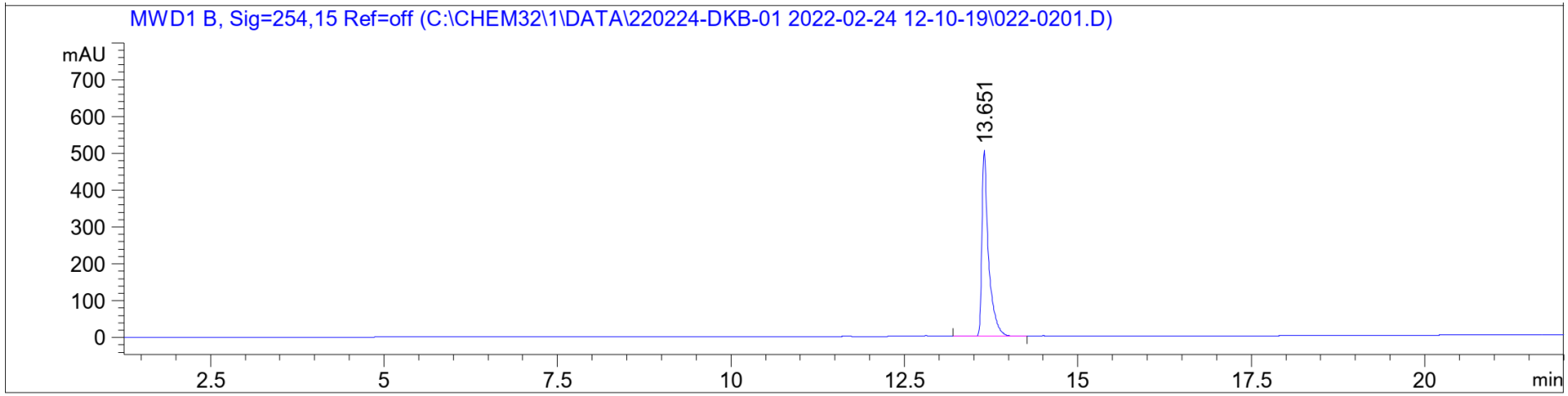
^{13}C NMR spectrum of **18c** (151 MHz, 110 °C, DMSO-d_6)



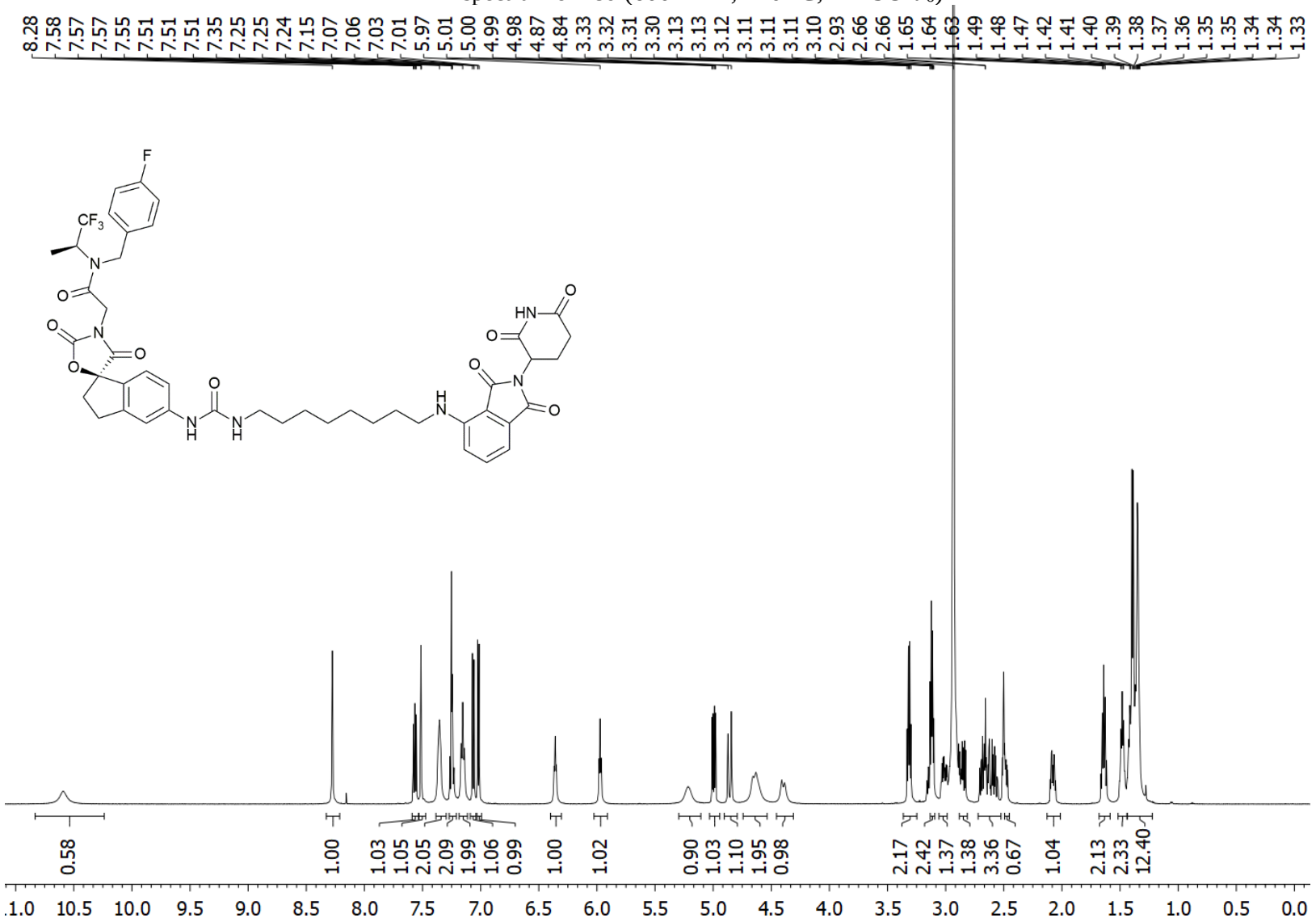
^{19}F NMR spectrum of **18c** (376 MHz, 110 °C, DMSO-d_6)



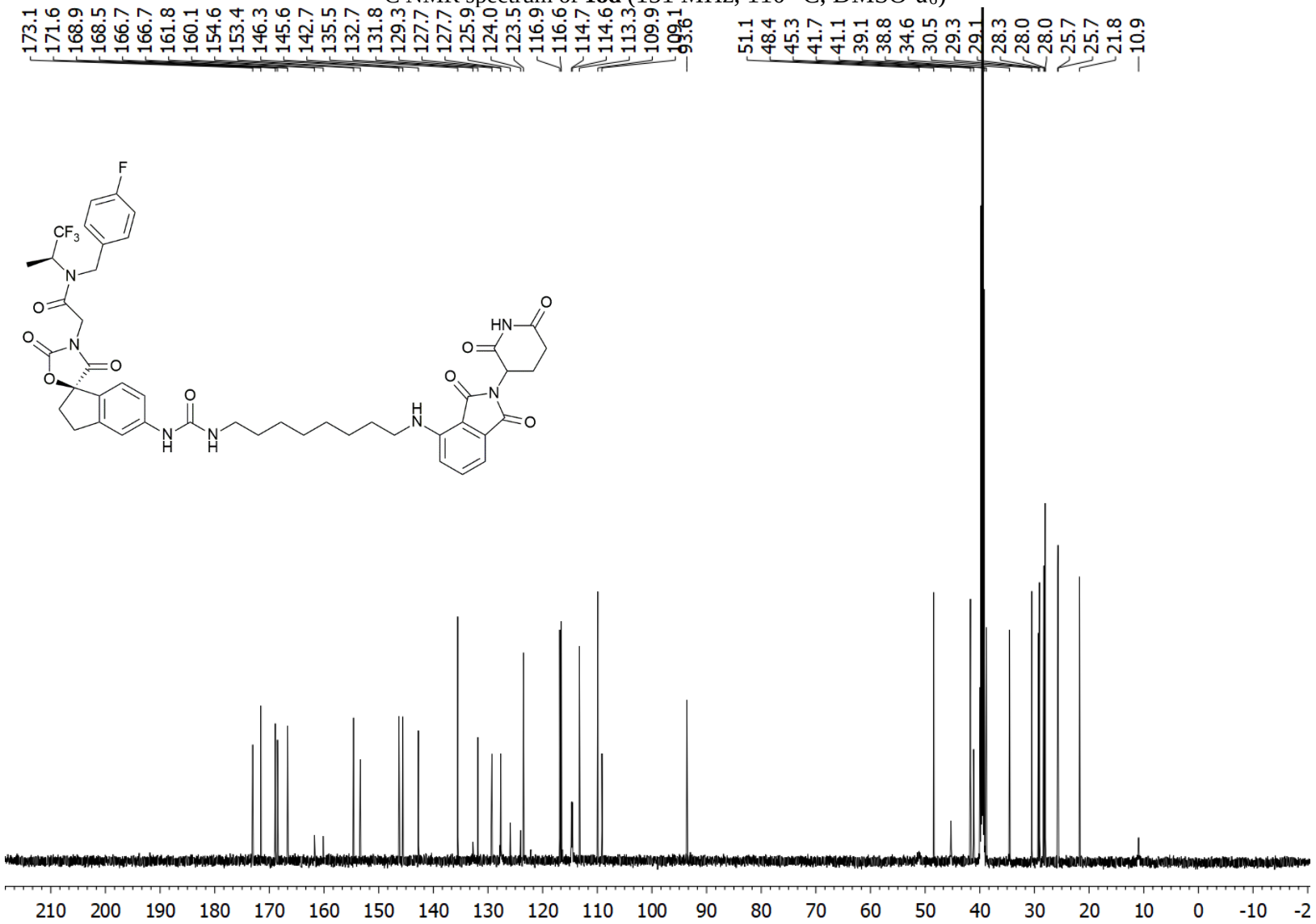
HPLC trace of **18c** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



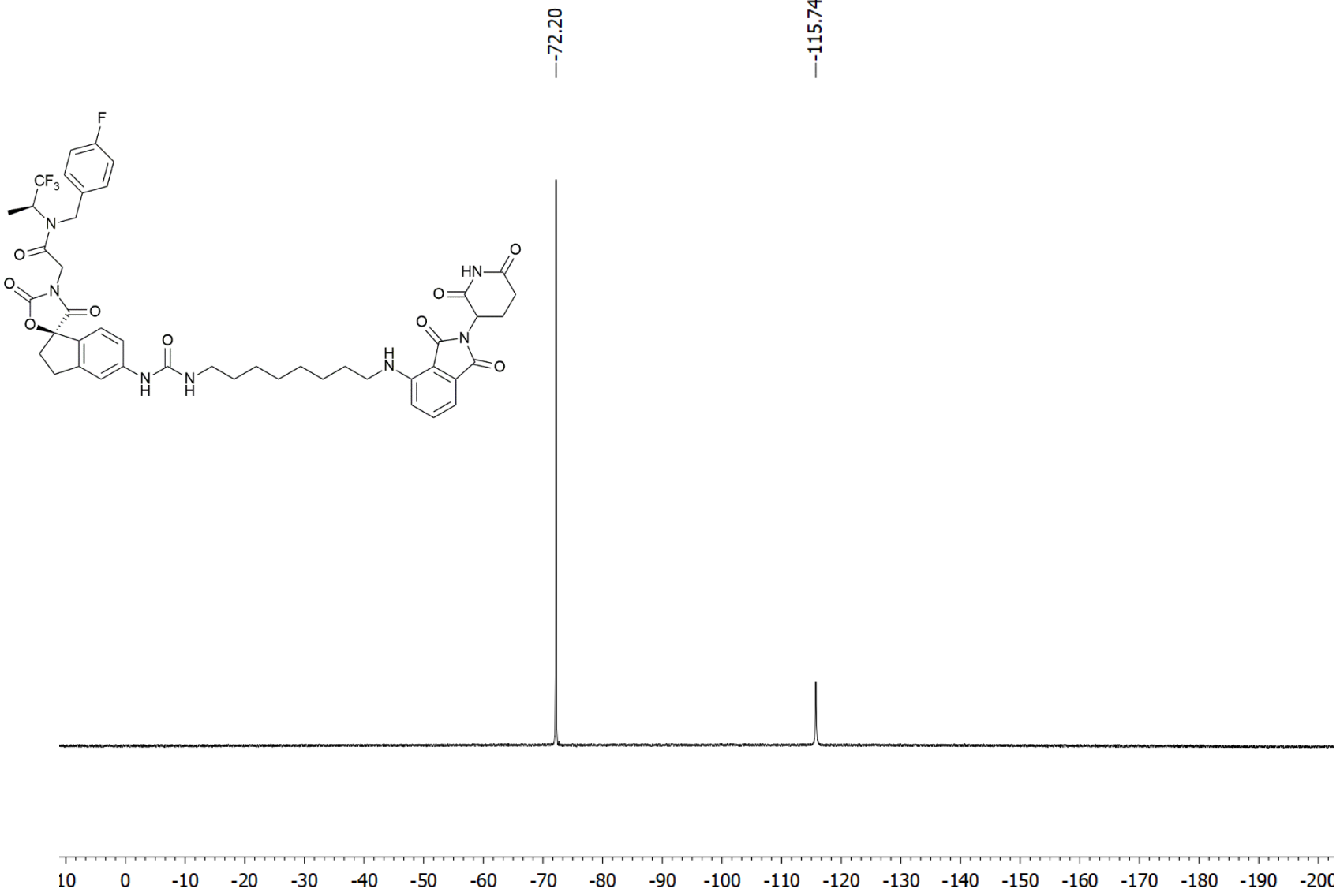
^{1}H NMR spectrum of **18d** (600 MHz, 110 °C, DMSO-d_6)



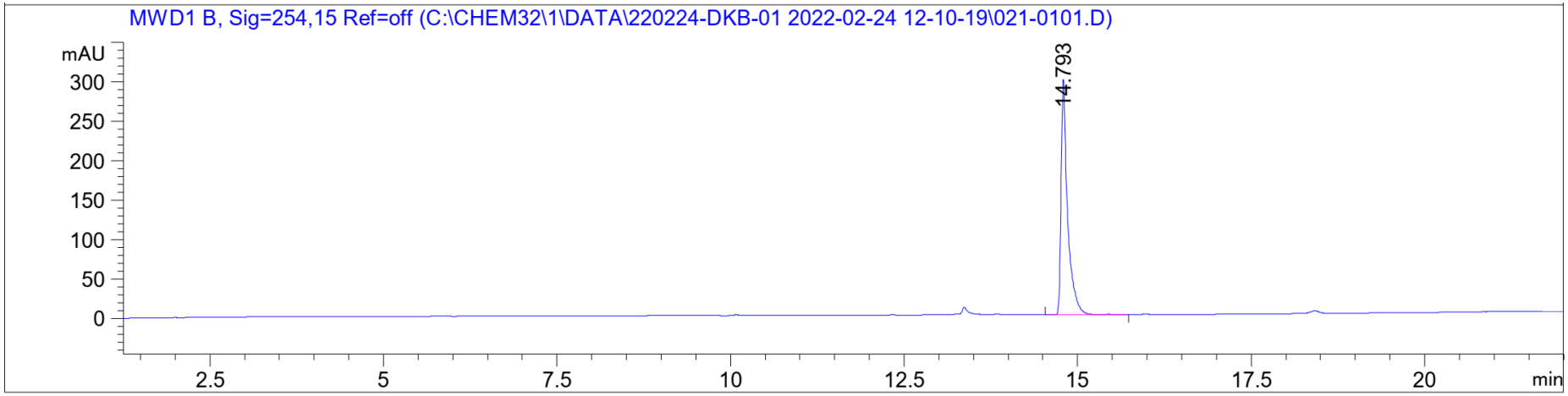
^{13}C NMR spectrum of **18d** (151 MHz, 110 °C, DMSO-d_6)



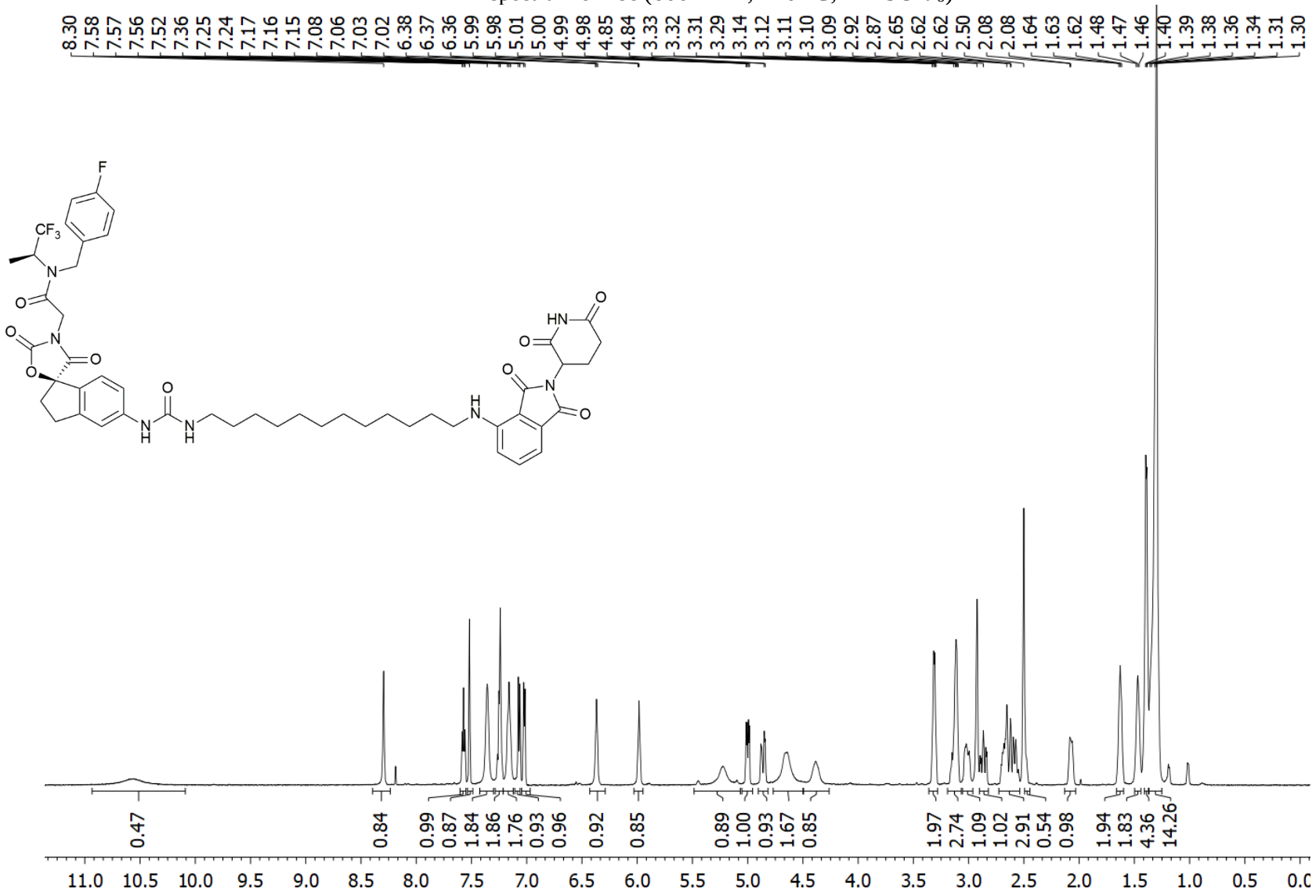
^{19}F NMR spectrum of **18d** (376 MHz, 110 °C, DMSO-d_6)



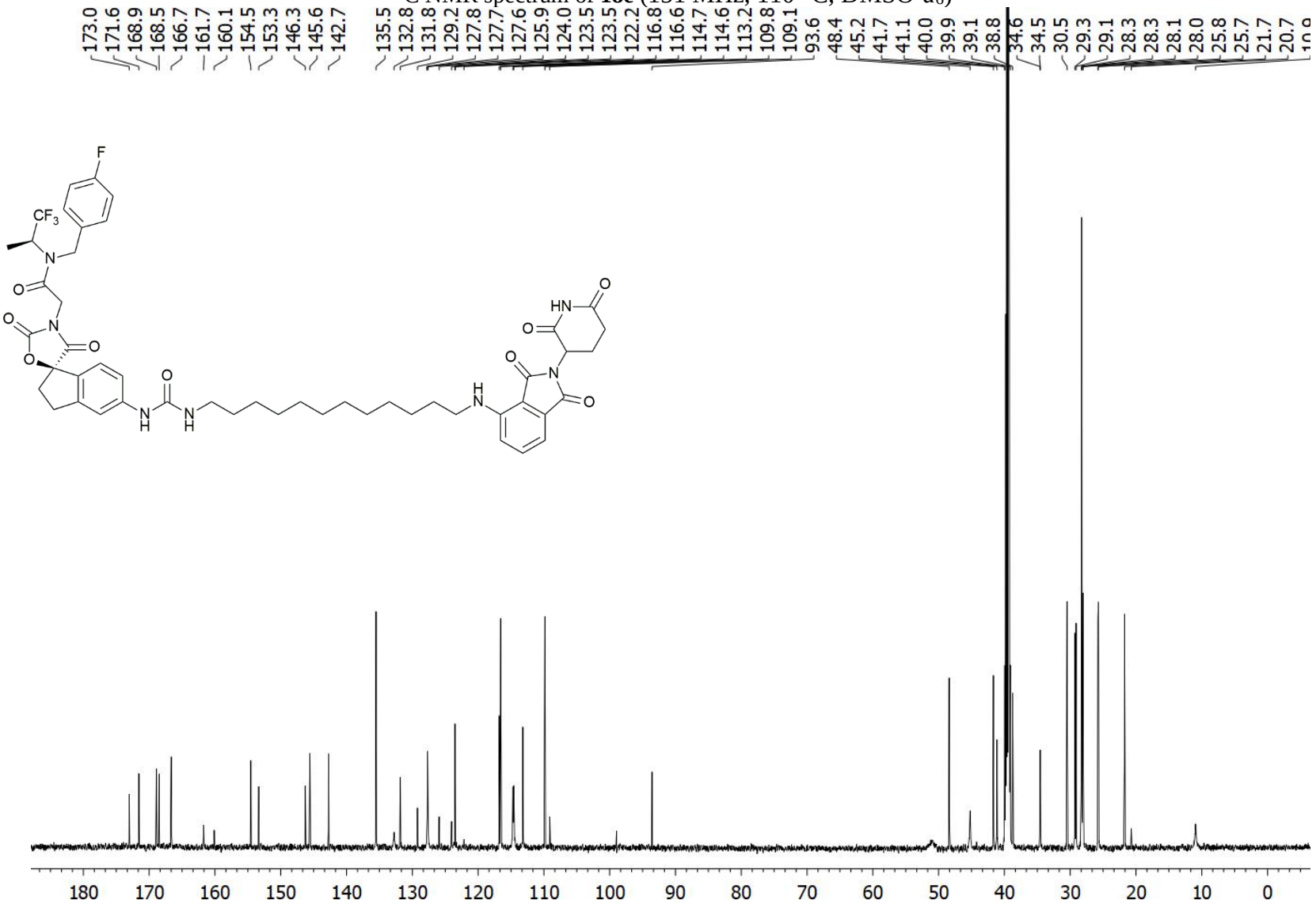
HPLC trace of **18d** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



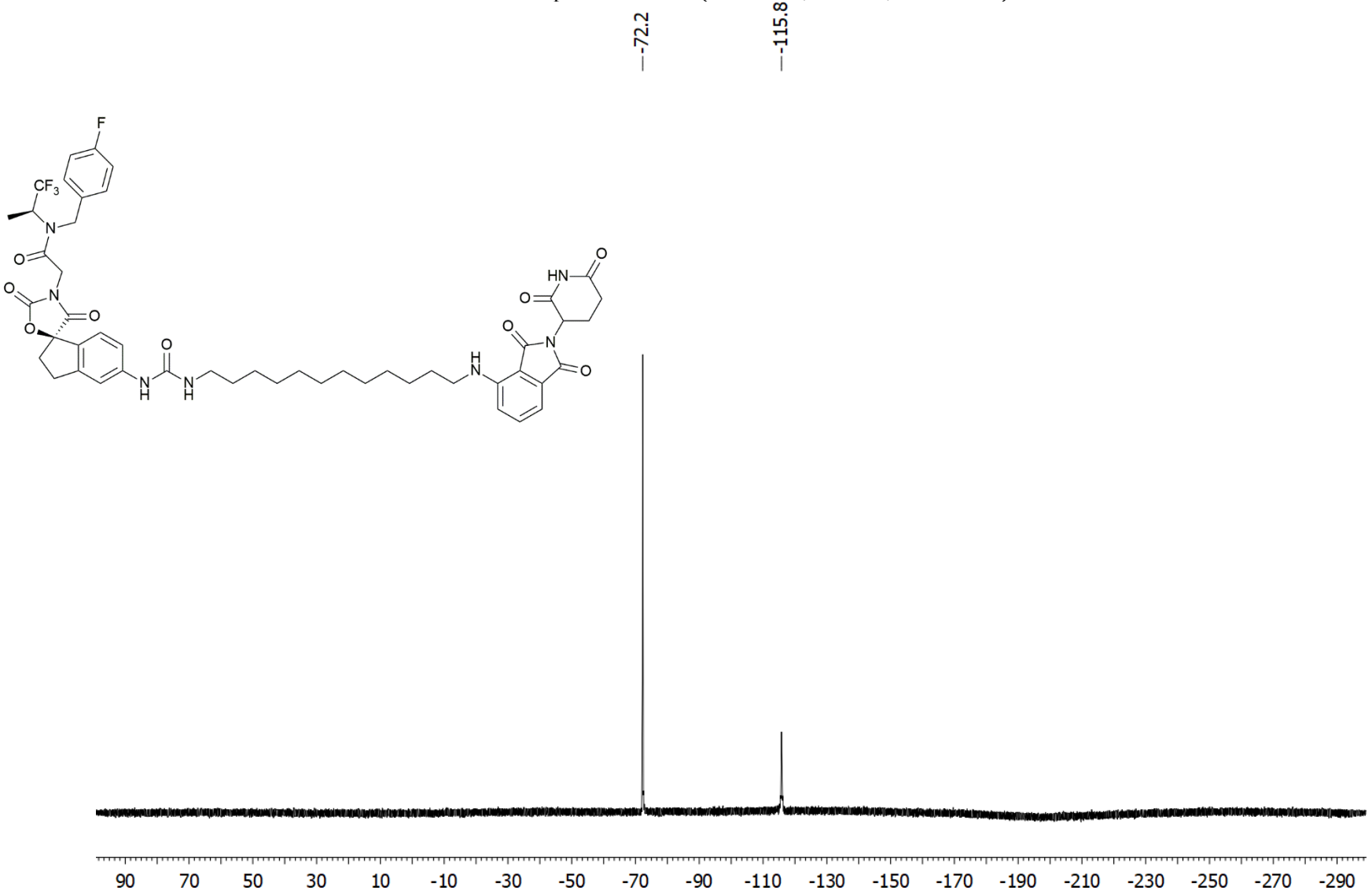
^{1}H NMR spectrum of **18e** (600 MHz, 110 °C, DMSO-d_6)



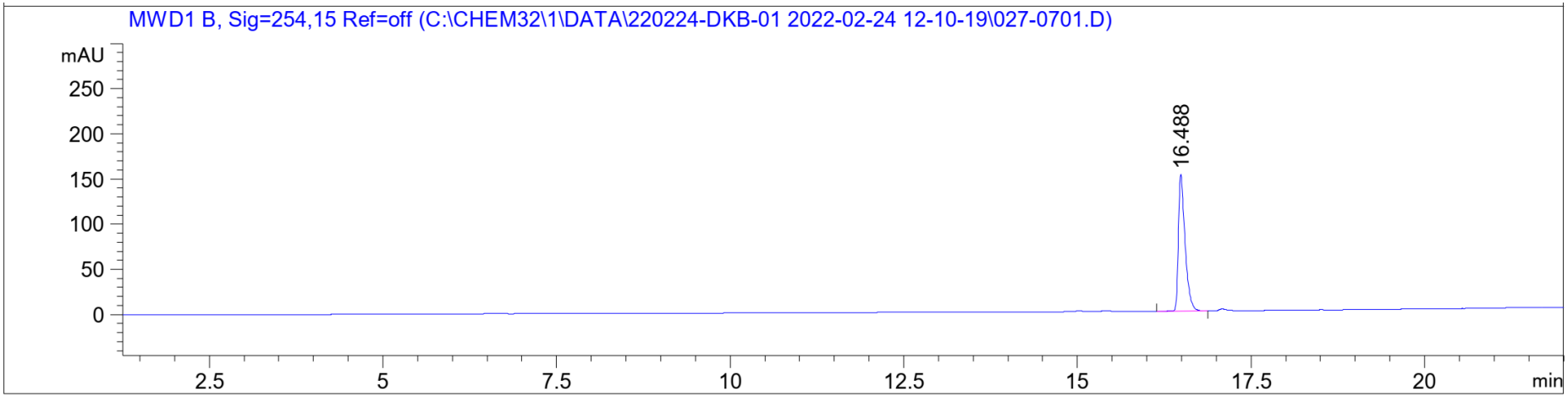
^{13}C NMR spectrum of **18e** (151 MHz, 110 °C, DMSO-d_6)



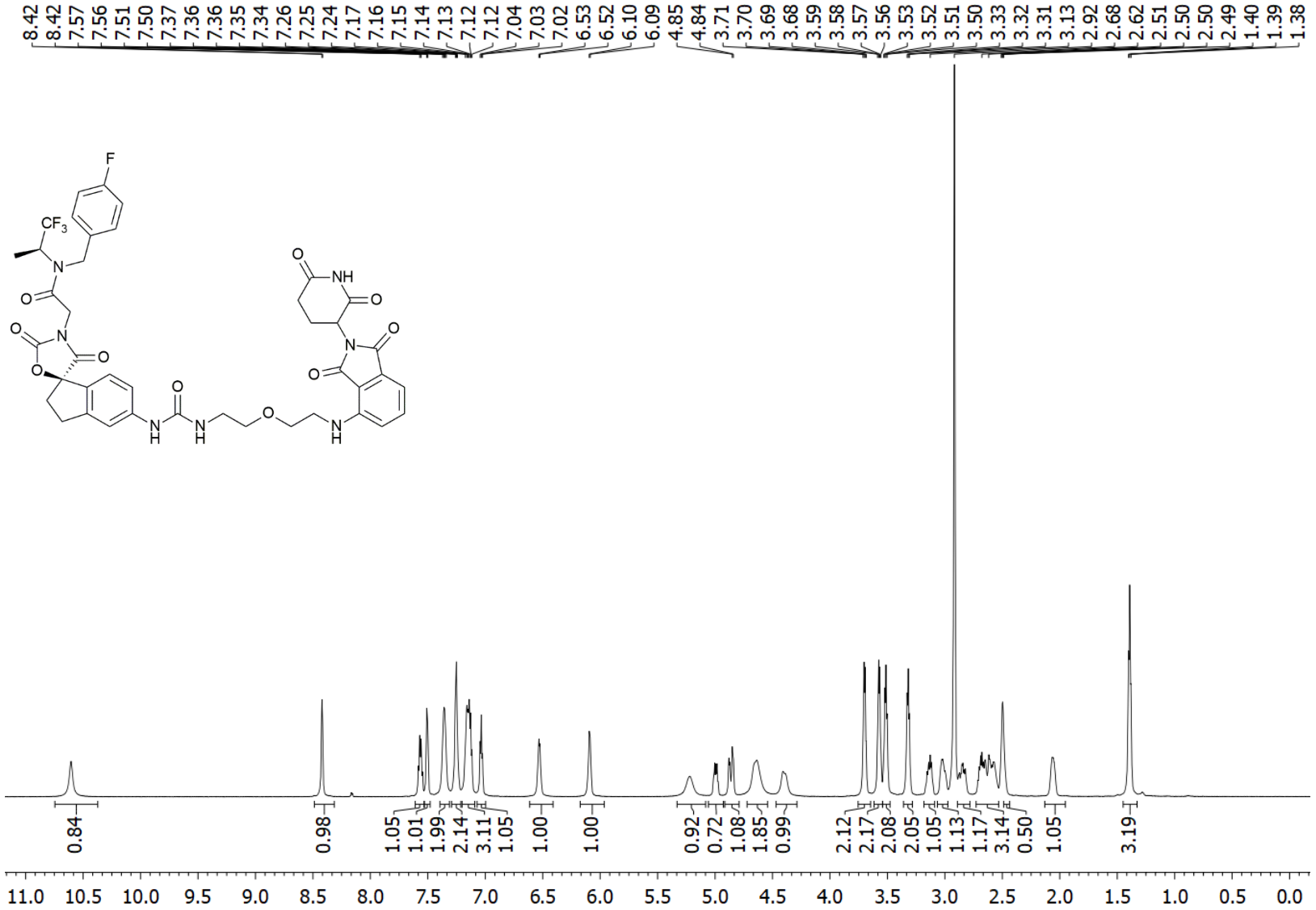
^{19}F NMR spectrum of **18e** (376 MHz, 110 °C, DMSO-d_6)



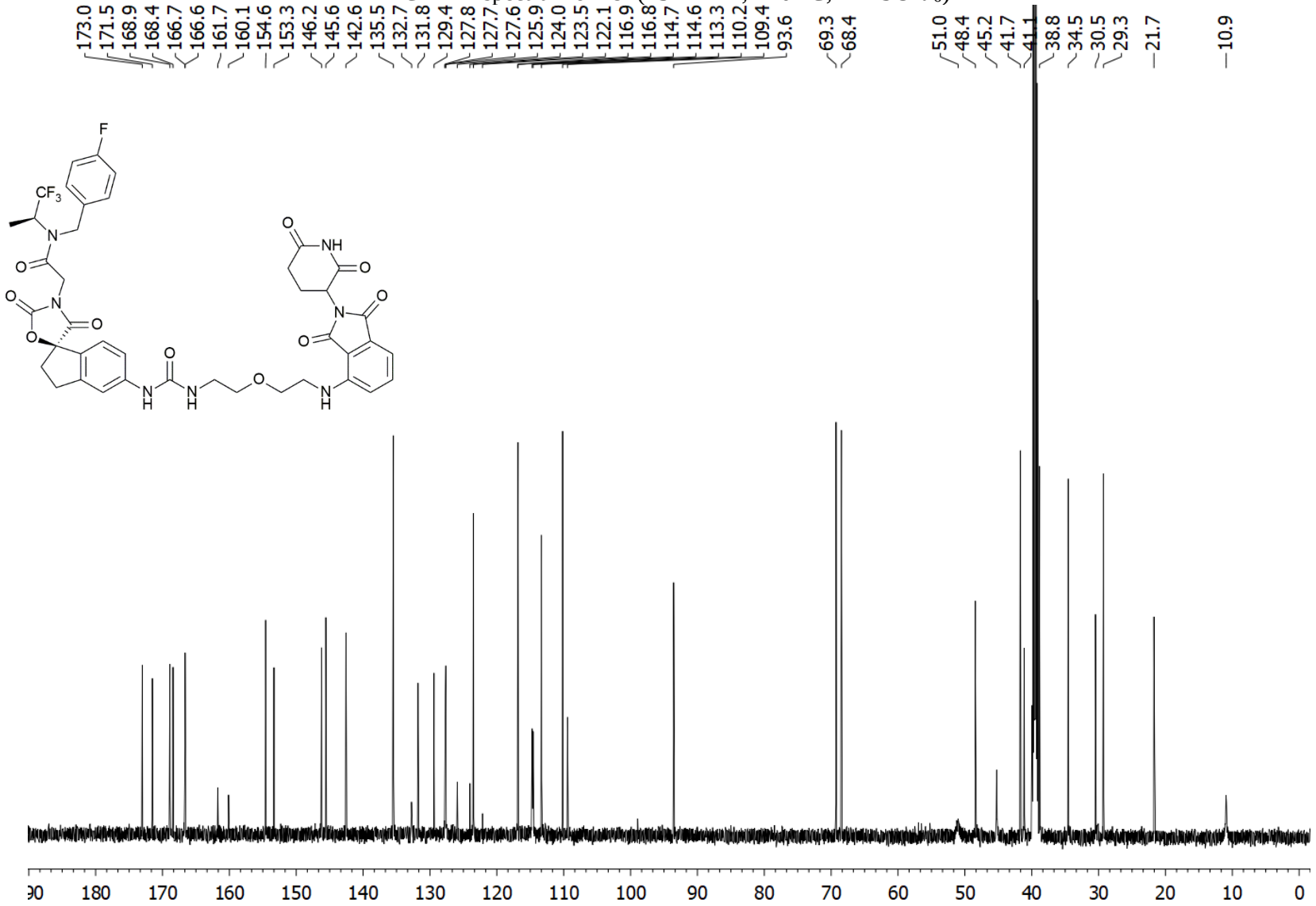
HPLC trace of **18e** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



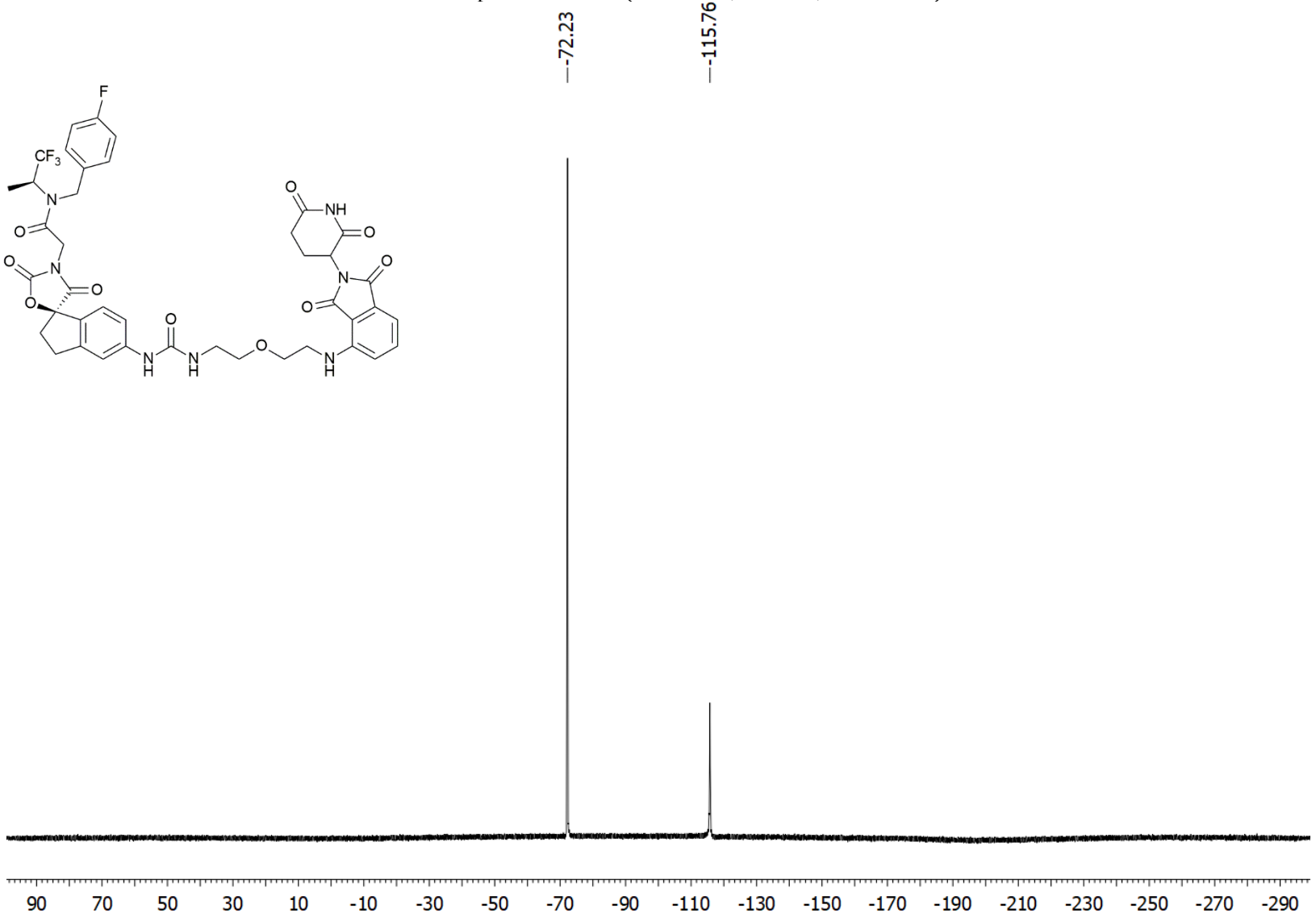
^{1}H NMR spectrum of **18f** (600 MHz, 110 °C, DMSO-d_6)



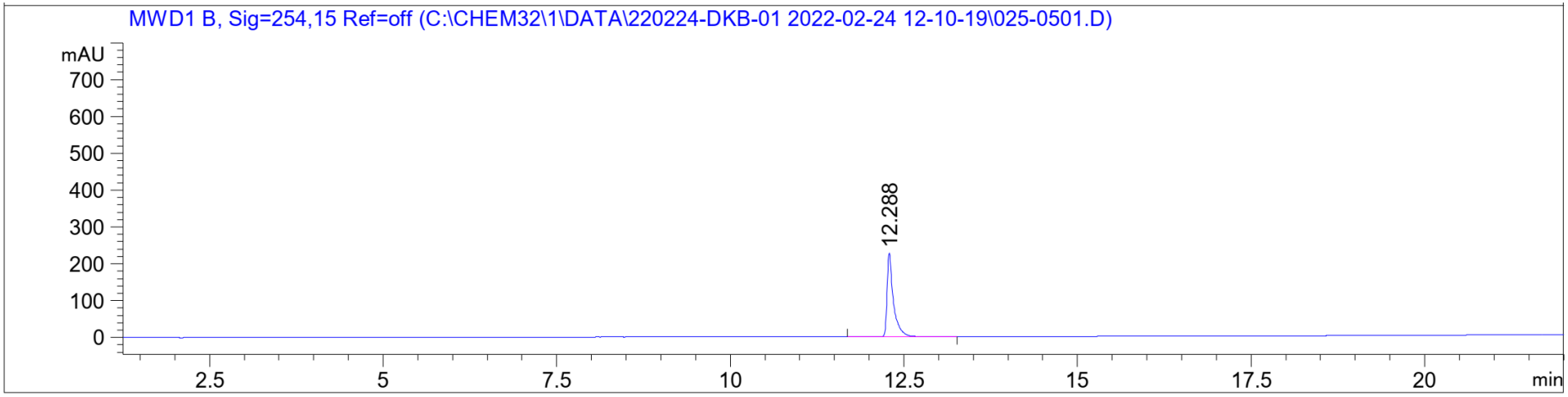
^{13}C NMR spectrum of **18f** (151 MHz, 110 °C, DMSO-d_6)



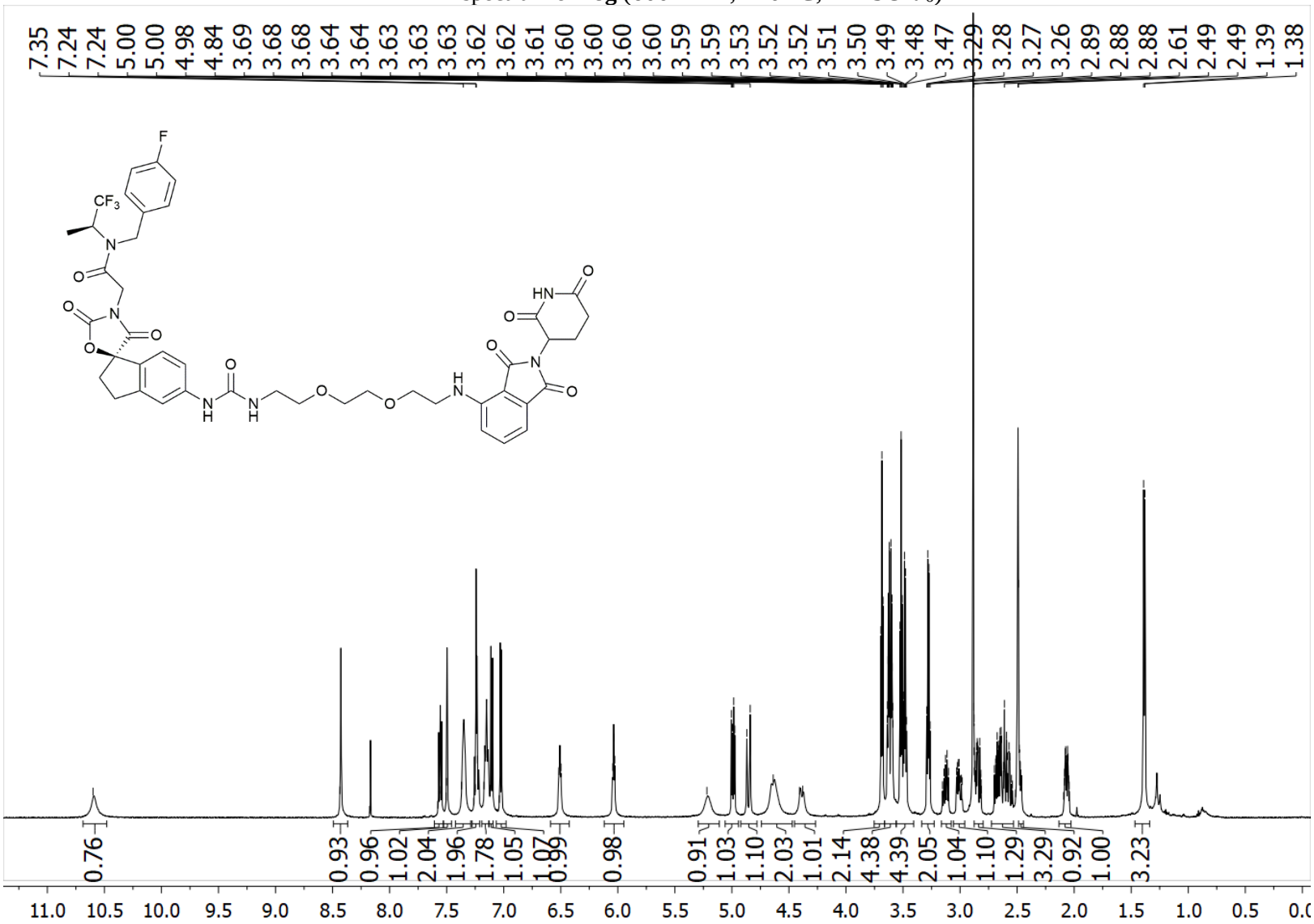
^{19}F NMR spectrum of **18f** (376 MHz, 110 °C, DMSO-d_6)



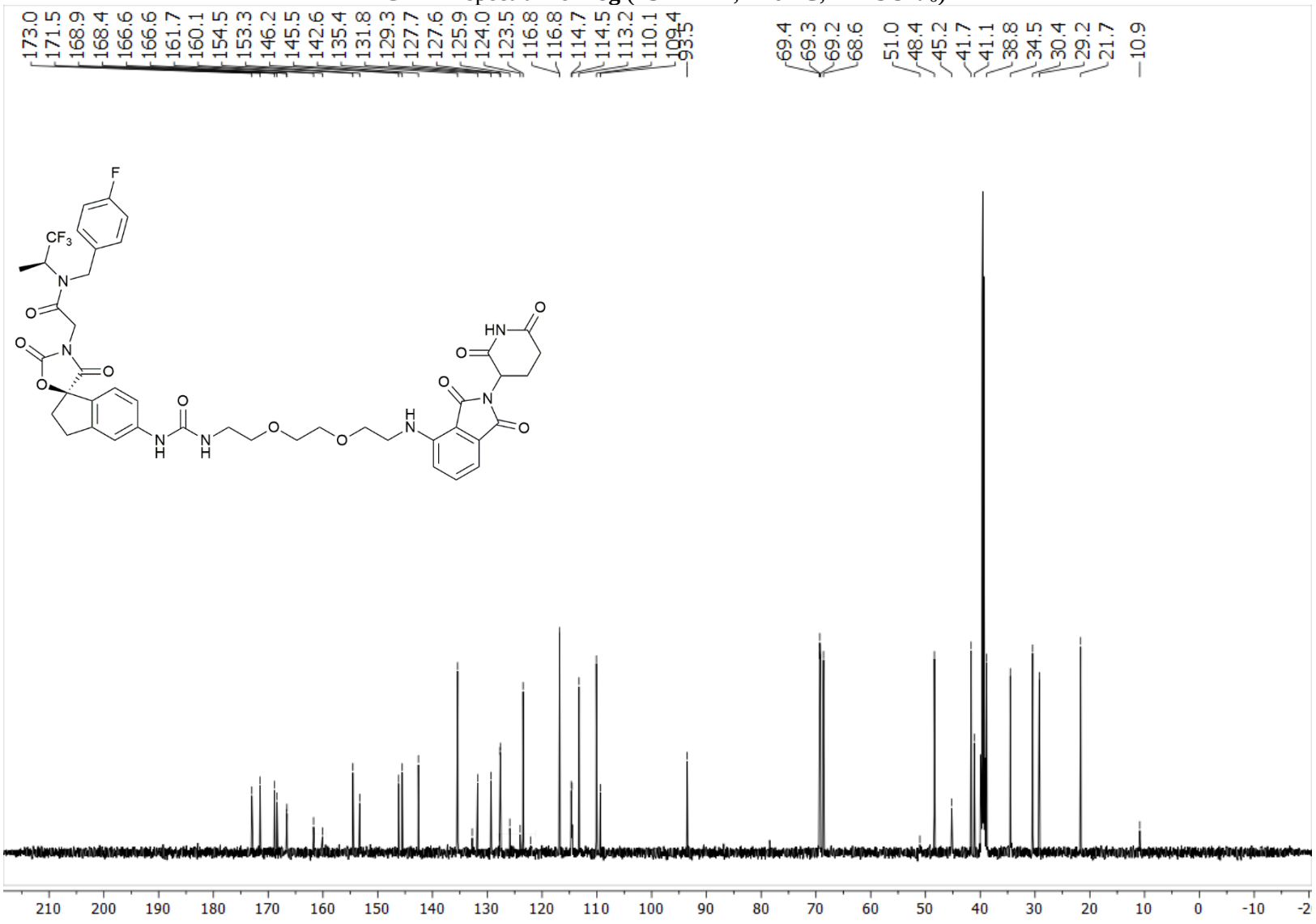
HPLC trace of **18f** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



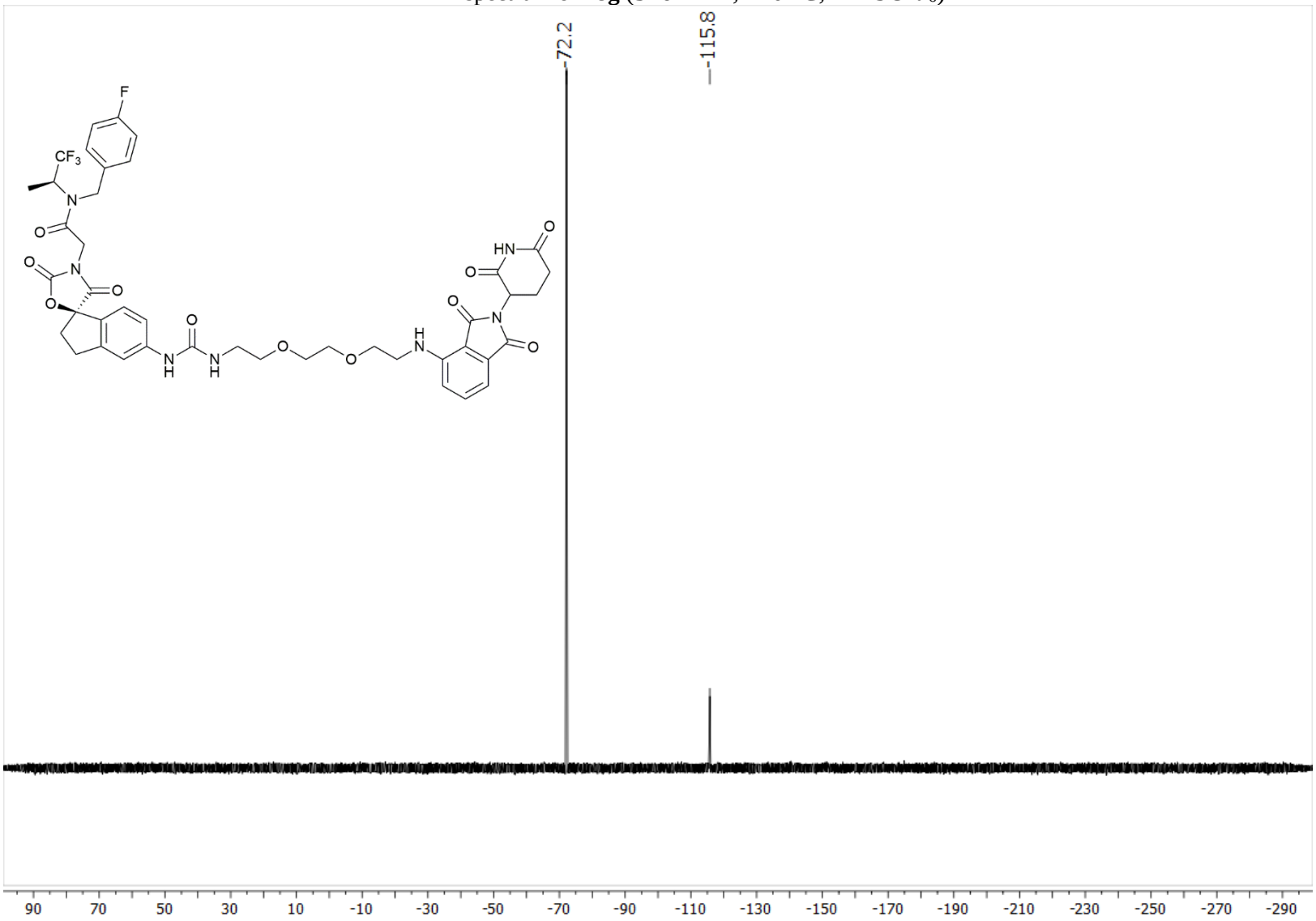
^{1}H NMR spectrum of **18g** (600 MHz, 110 °C, DMSO-d_6)



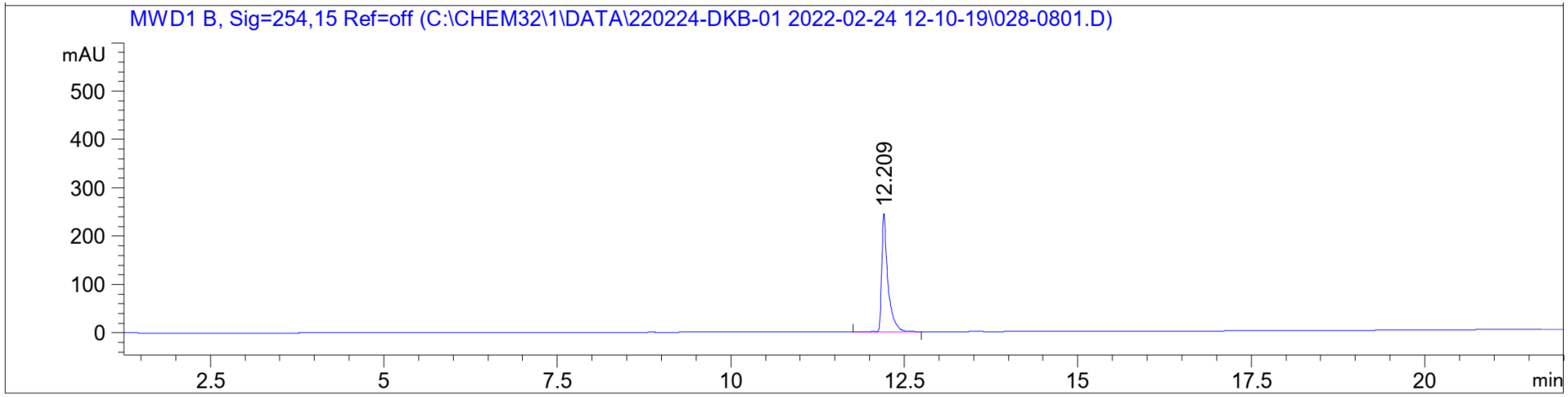
^{13}C NMR spectrum of **18g** (151 MHz, 110 °C, DMSO-d_6)



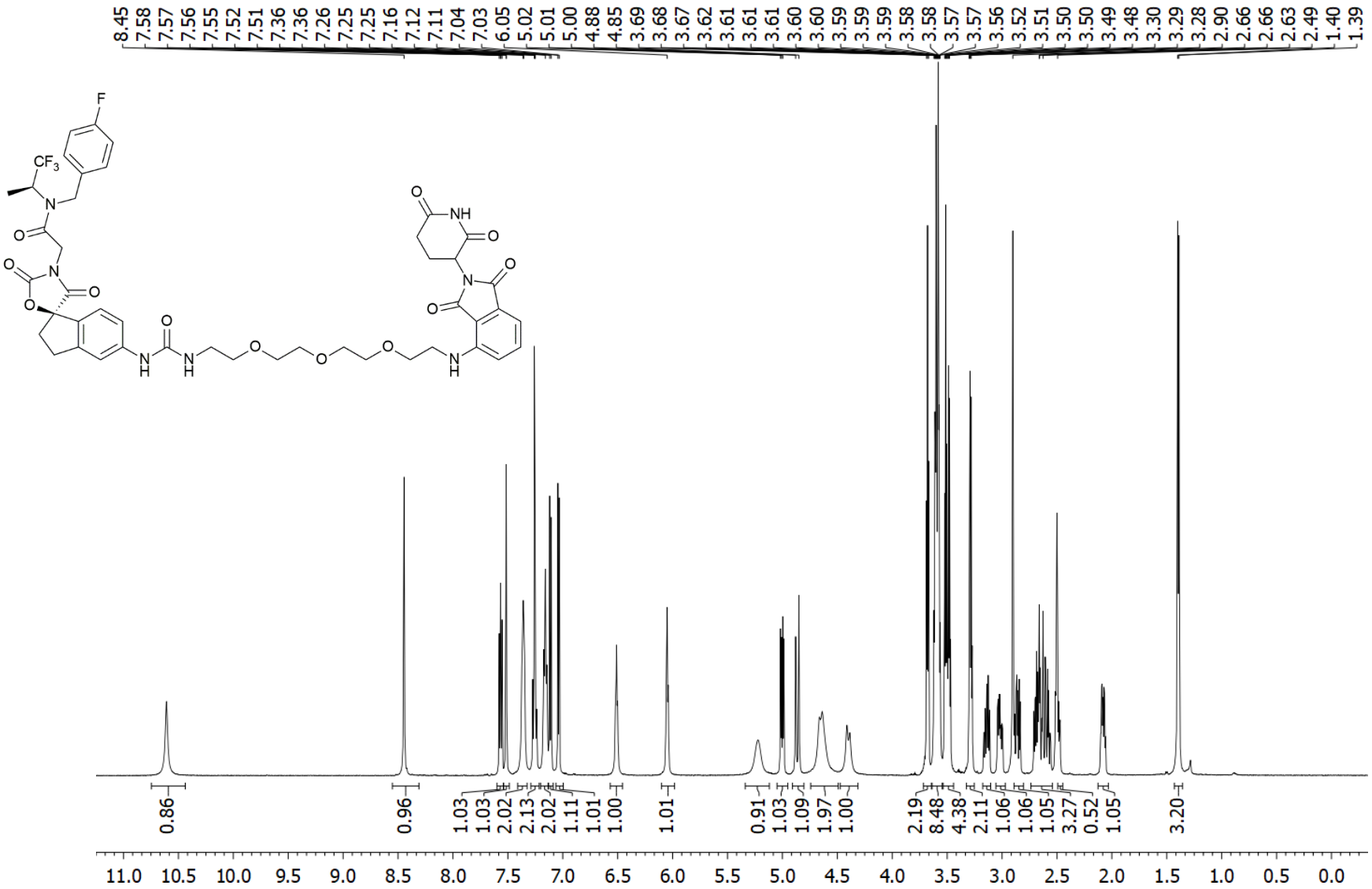
^{19}F NMR spectrum of **18g** (376 MHz, 110 °C, DMSO-d_6)



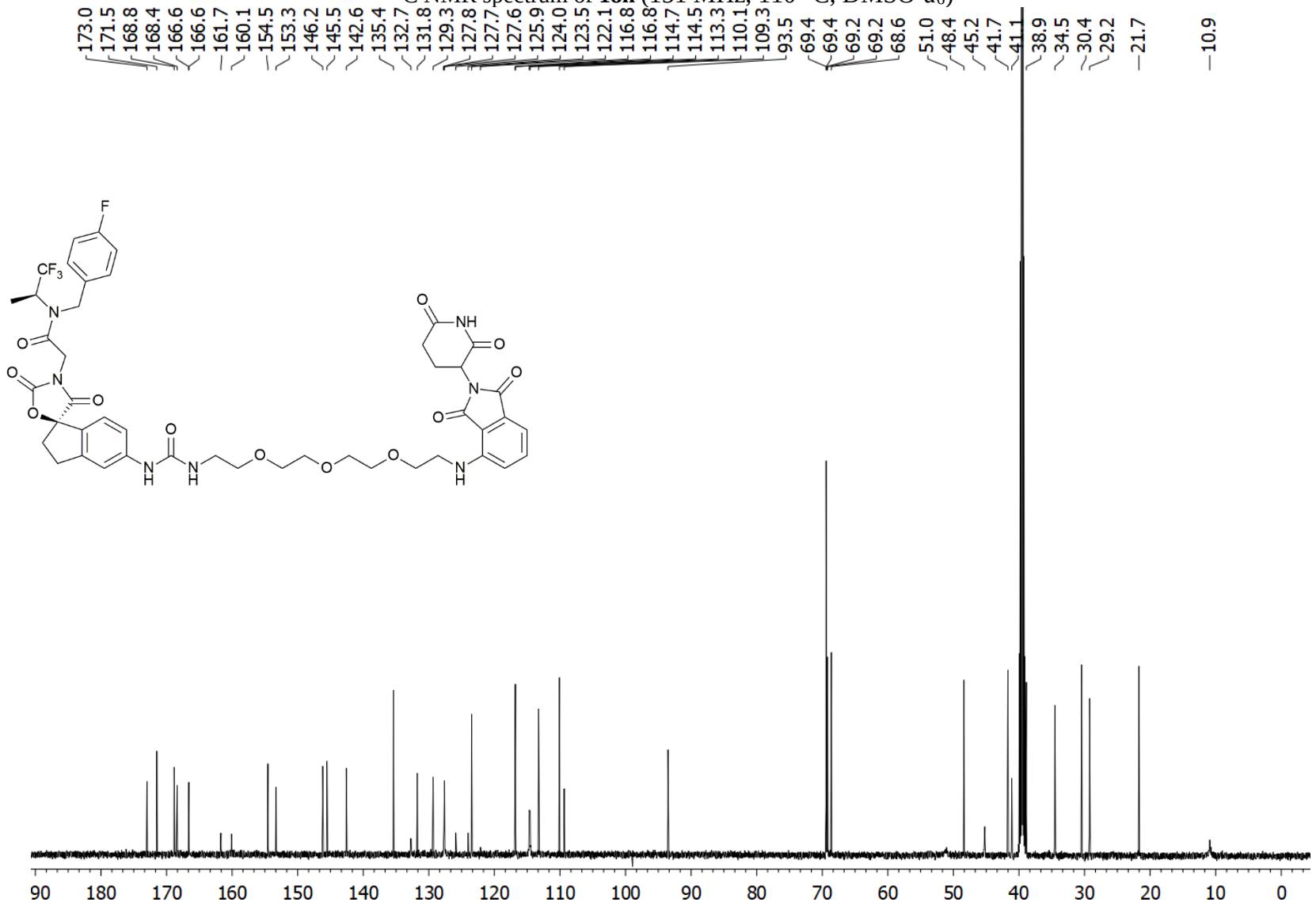
HPLC trace of **18g** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



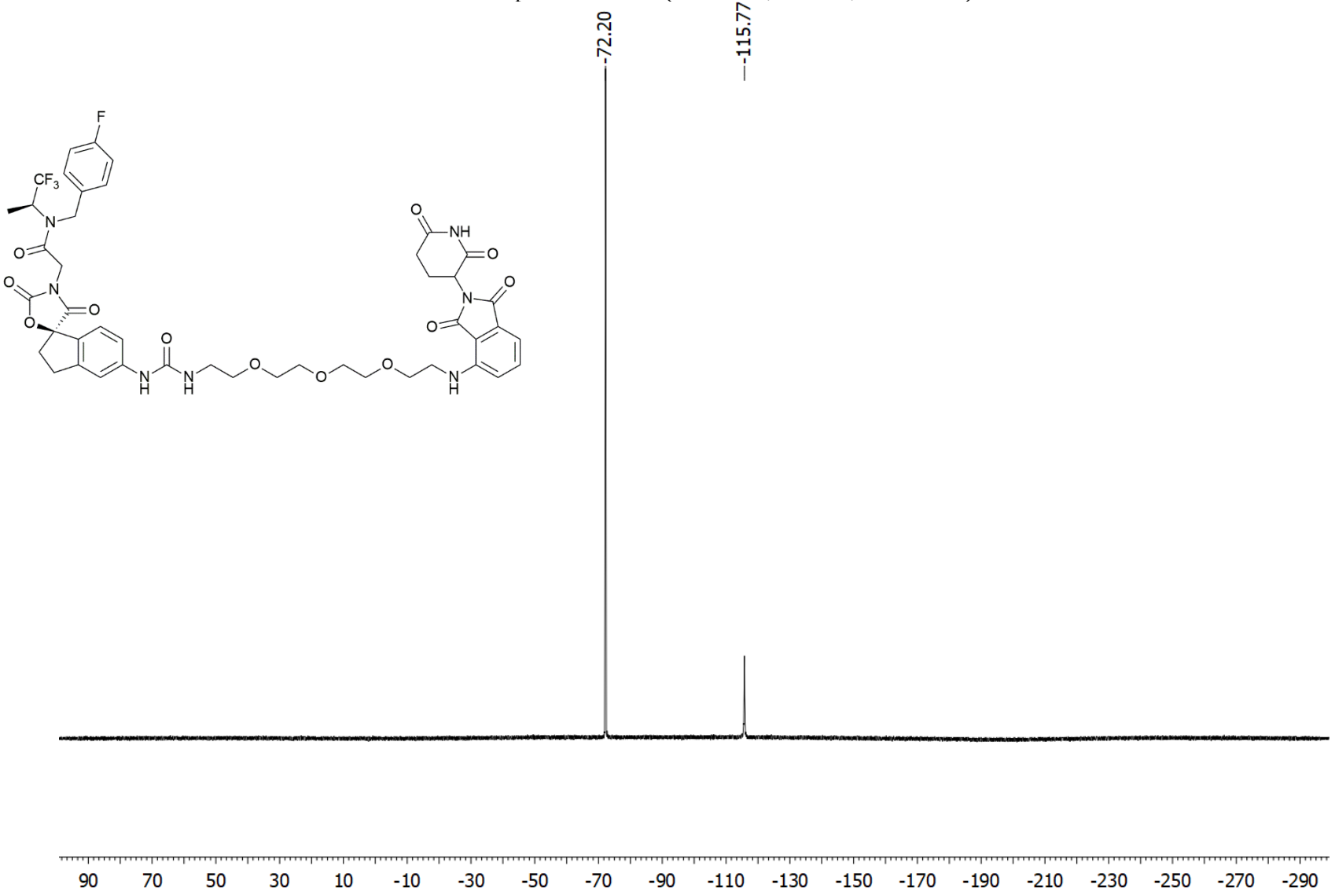
^{1}H NMR spectrum of **18h** (600 MHz, 110 °C, DMSO-d_6)



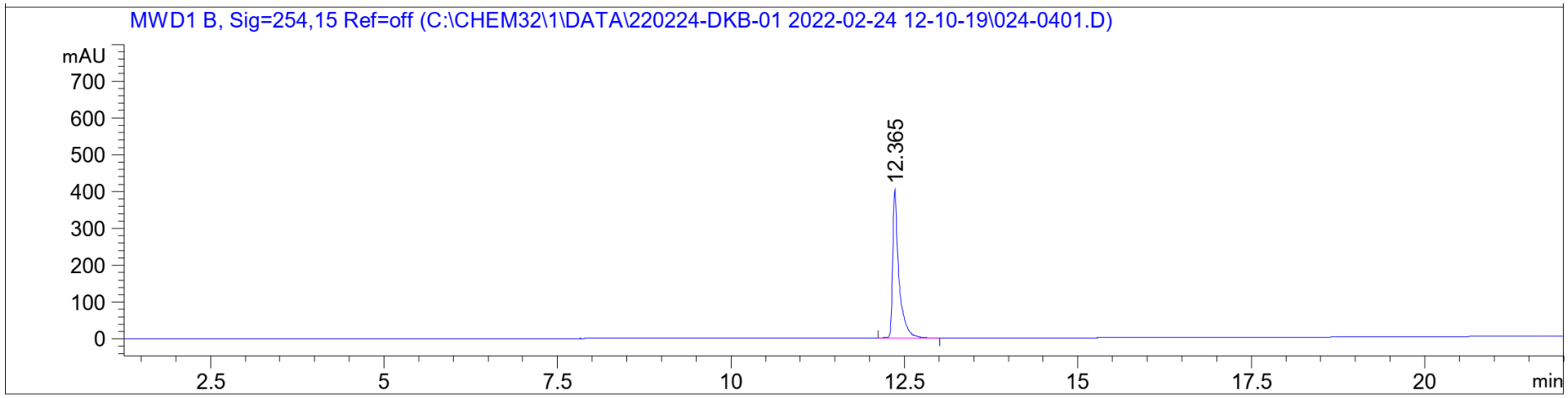
^{13}C NMR spectrum of **18h** (151 MHz, 110 °C, DMSO-d_6)



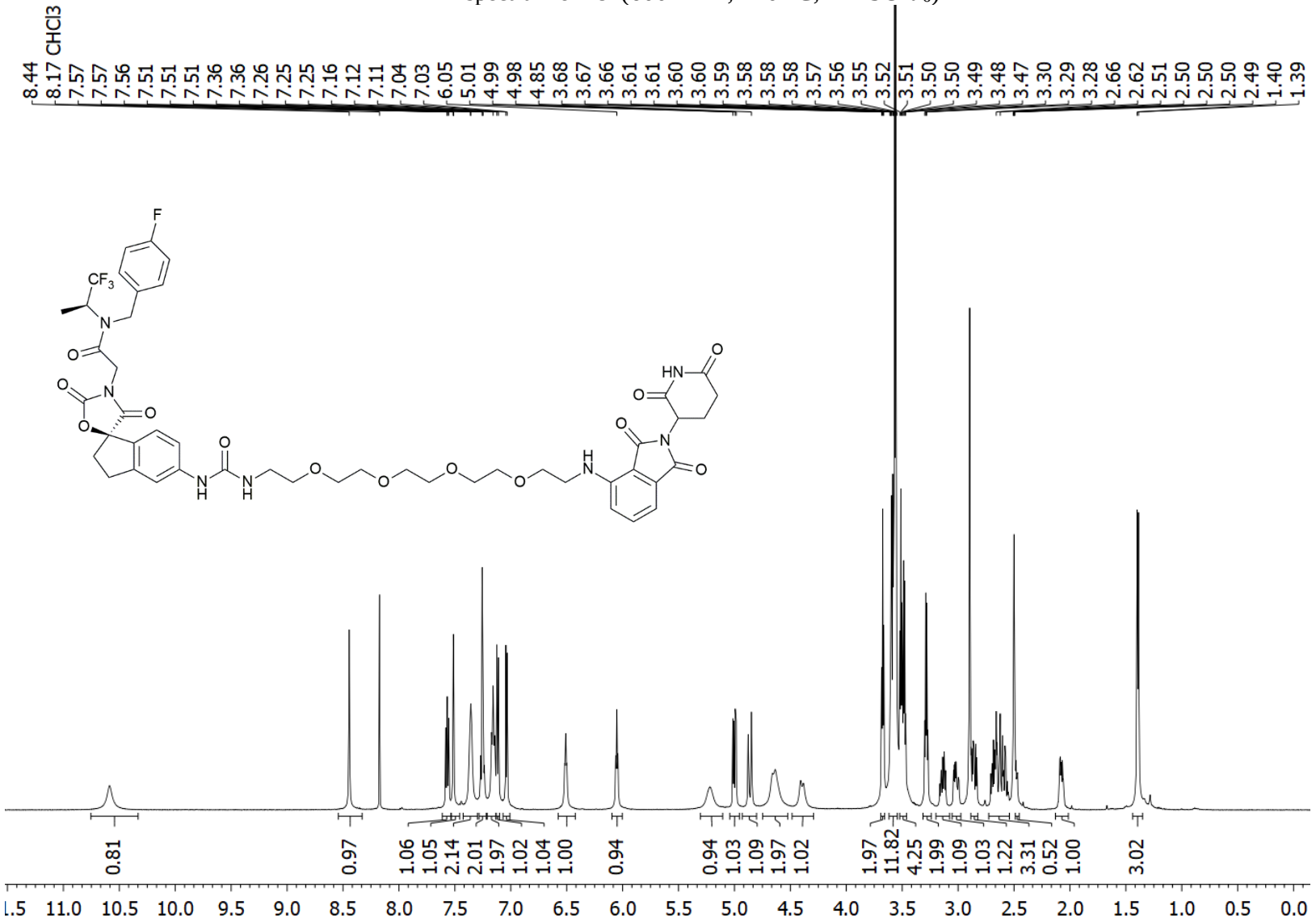
^{19}F NMR spectrum of **18h** (376 MHz, 110 °C, DMSO-d_6)



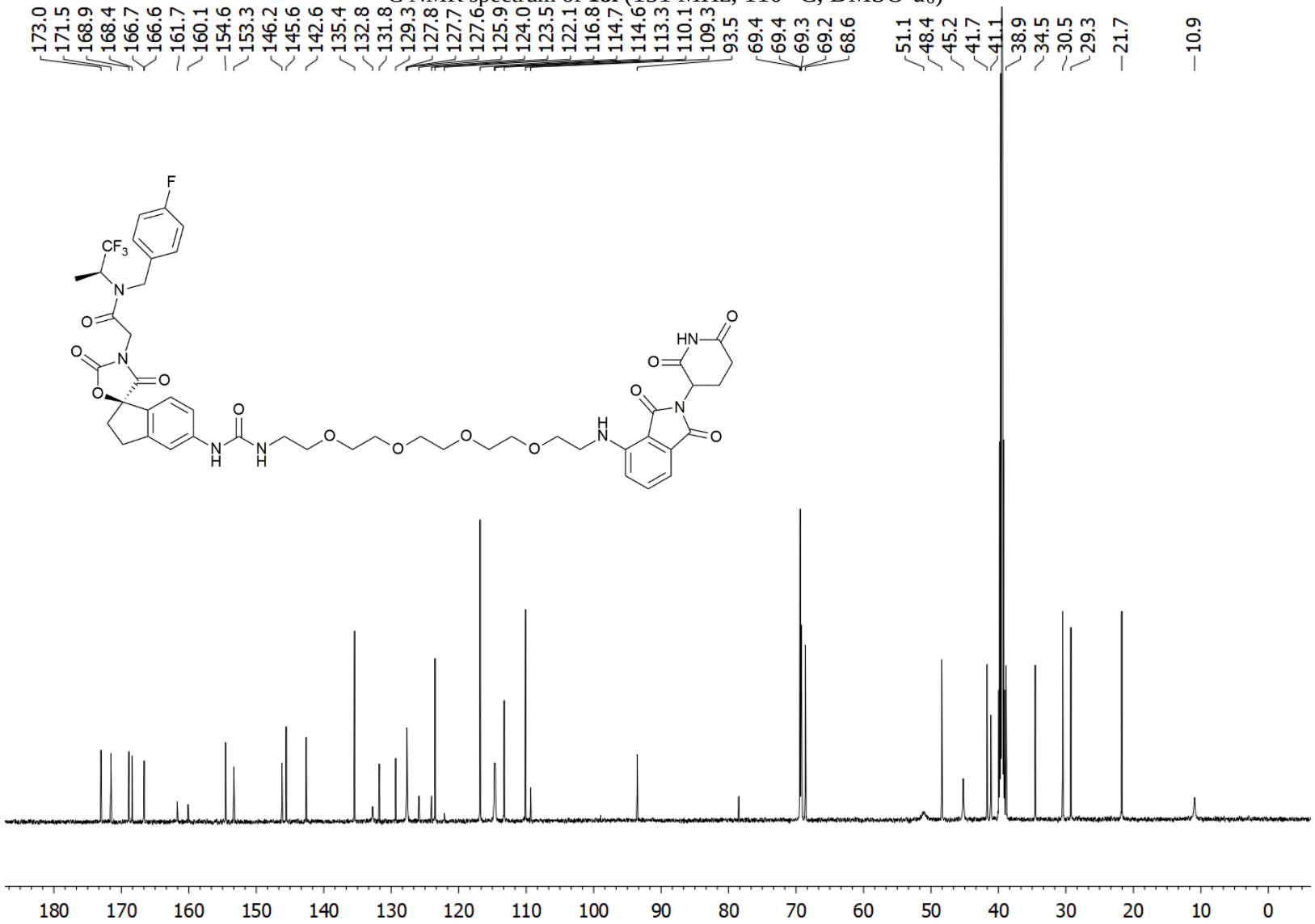
HPLC trace of **18h** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



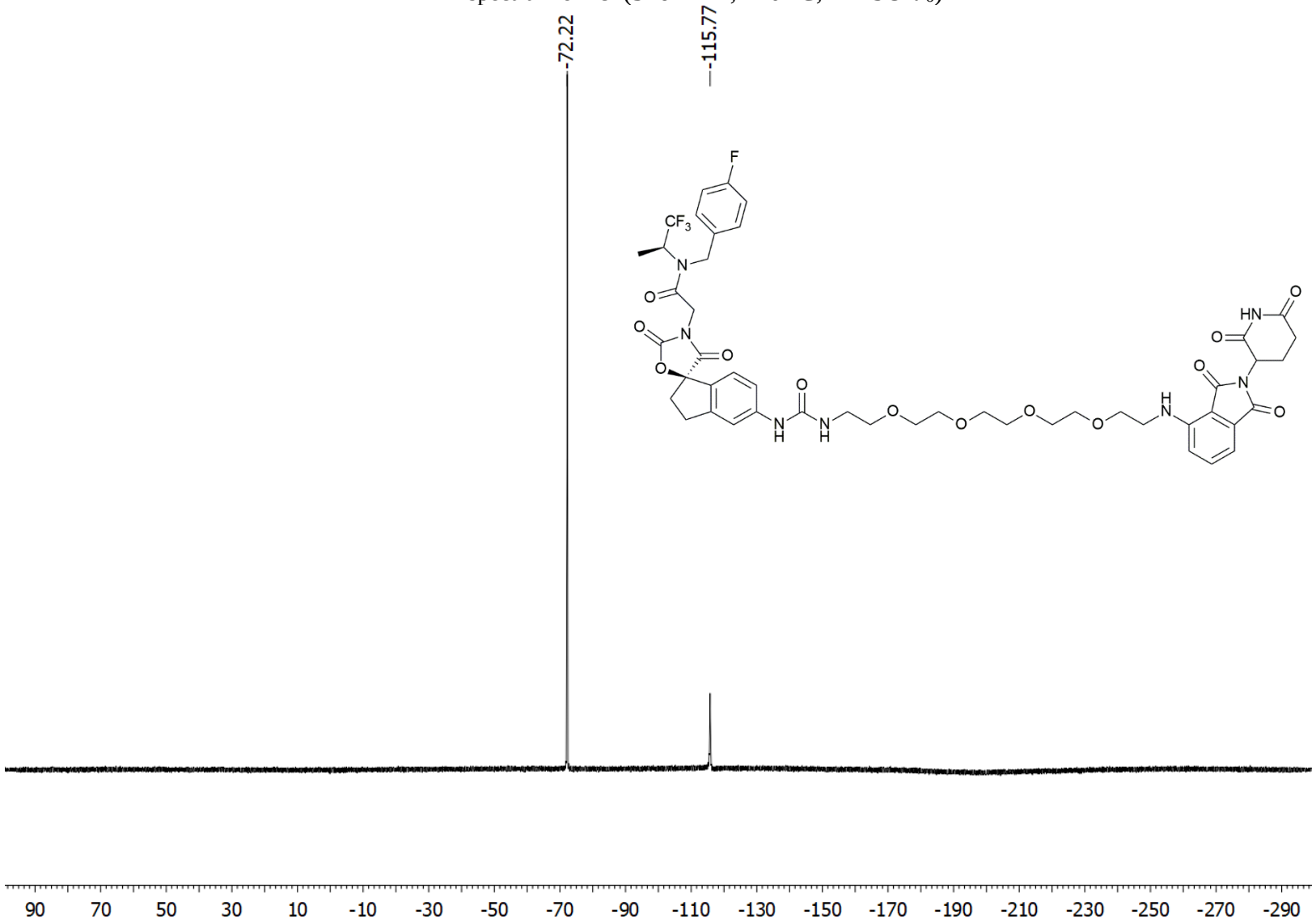
^{1}H NMR spectrum of **18i** (600 MHz, 110 °C, DMSO-d_6)



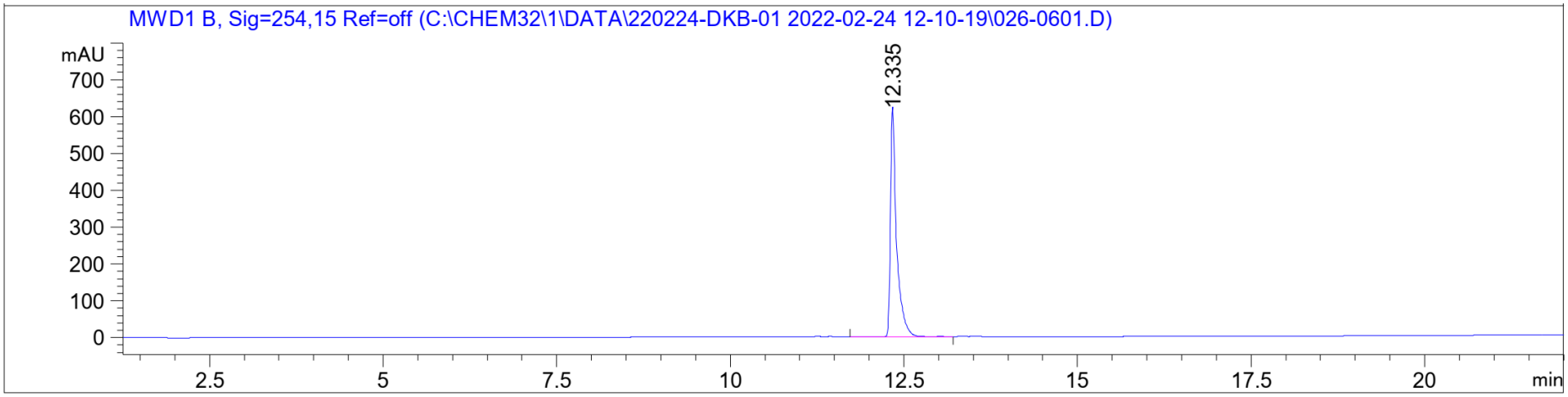
^{13}C NMR spectrum of **18i** (151 MHz, 110 °C, DMSO-d_6)



^{19}F NMR spectrum of **18i** (376 MHz, 110 °C, DMSO-d_6)



HPLC trace of **18i** (5:95 – 95:5 MeCN:H_2O over 20 minutes)



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