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Supplementary Information

Use of ionic liquids in amidation reactions for Proteolysis Targeting Chimeras synthesis

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1. Experimental Procedures

1.1 General Information

ILs were synthesized and purified following a previously reported procedure.[1,2]

Unless otherwise noted, starting materials, reagents, and solvents were purchased from commercial suppliers and were used without further purification.

Reactions were routinely monitored by thin-layer chromatography (TLC) performed on silica gel 60 F254 (layer 0.2 mm) pre-coated aluminium foil (with fluorescent indicator UV254) (Sigma-Aldrich). Developed plates were air-dried and visualized by UV detector (λ: 254/365 nm) and/or by staining and warming with potassium permanganate or ninhydrin solutions. Automated flash chromatography was performed using Biotage® Selekt with Sfär Silica HC Duo 5g or 10g cartridges. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature at 400 and 101 MHz, respectively, on a Bruker Avance III HD 400 spectrometer in the indicated solvent by using residual solvent peak as internal standard. Chemical shifts are reported in ppm (δ) and the coupling constants (*J*) are given in Hertz (Hz). Peak multiplicities are abbreviated as follows: s (singlet), br (broad signal), d (doublet), dd (double doublet), t (triplet), dt (double triplet), q (quartet), and m (multiplet). High-Resolution Mass Spectroscopy (HRMS) analyses were carried out on Agilent Technologies 6540 UHD Accurate Mass Q-TOF LC-MS system. The analyses were carried out according to the method listed below. The mobile phase was a mixture of water (solvent A) and acetonitrile (solvent B), both containing formic acid at 0.1%. Method: Acquity UPLC BEH C18 1.7 µm (C18, 150 x 2.1 mm) column at 40° C using a flow rate of 0.65 mL/min in a 10 min gradient elution. Gradient elution was as follows: 99.5:0.5 (A/B) to 5:95 (A/B) over 8 min, 5:95 (A/B) for 2 min, and then reversion back to 99.5:0.5 (A/B) over 0.1 min. Mass spectra are recorded on a mass spectrometer using positive mode electro spray ionization. HPLC analyses were performed with an Agilent 1200 series system. Chromatography was performed on an Agilent Eclips XDB-C18 column reversed-phase (4.6x150 mm, 5 µm particle size) at 25°C, using a gradient elution at 1.0 mL min^{-1}. The mobile phase was a mixture of water containing formic acid at 0.1% (solvent A) and acetonitrile (solvent B). Gradient elution was as follows: 30% to 100% of B over 10 min, 100% of B for 2 min, 100% to 80% of B from 12 to 23 min, 80% to 30% of B for 1 min and 30% of B from 24 to 30 min; injection volume: 10 µL. The column was re-equilibrated for 15 min between individual runs. Melting points were determined in capillary tubes (Büchi Melting Point Apparatus model 535).

1.2 Synthetic procedures

1.2.1 General Procedure A: coupling amidation for the synthesis of PROTAC 3a (Entries 1-6, Table 2).

Under nitrogen atmosphere, to a stirred solution of indomethacin (**1**) (0.056 mmol, 1.0 equiv), amine derivative (**2a**) (0.056 mmol, 1.0 equiv.) and DIPEA or Et_3N (0.168 mmol, 3.0 equiv.) in dry DMF (1.0 mL) at 0°C, was added the opportune coupling agent (0.070 mmol, 1.25 equiv.) and then the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water and was extracted with EA (3x10 mL). The reunited organic phases were washed with water (3x20 mL), brine (1x15 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude was then purified by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 95:5 to 90:10) to afford the titled compound as a light-yellow solid. In particular, by using 1) HBTU/DIPEA, the yield was 25% (entry 1, Table 2), 2) DCC-DMAP/ DIPEA, the yield was 31% (entry 2, Table 2), 3) HOBt-EDC*HCl/DIPEA the yield was 23% (entry 3, Table 2), 4) PyBOP/DIPEA the yield was 26% (entry 4, Table 2), 5) COMU/DIPEA, the yield was 34% (entry 5, Table 2), 6) HATU/DIPEA, the yield was 28% (entry 6, Table 2).

The spectroscopic data for **PROTAC 3a** are in agreement with those reported in the literature.[3] ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.98 (s, 1H), 8.38 (d, *J* = 7.4 Hz, 1H), 7.98 – 7.89 (m, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.66 (dd, *J* = 16.6, 8.0 Hz, 4H), 7.40 (dd, *J* = 21.8, 7.8 Hz, 4H), 7.12 (s, 1H), 6.93 (d, *J* = 9.1 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 5.13 – 5.07 (m, 1H), 4.96 – 4.87 (m, 1H), 4.53 – 4.38 (m, 2H), 4.27 (br s, 1H), 3.75 (s, 3H), 3.66 – 3.43 (m, 5H), 3.22 – 3.14 (m, 2H), 2.49 – 2.16 (m, 18H), 2.06 – 1.96 (m, 1H), 1.84 – 1.73 (m, 1H), 1.37 (d, *J* = 6.7 Hz, 3H), 0.93 (s, 9H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 171.69, 171.07, 170.23, 169.92, 169.76, 168.30, 155.99, 151.94, 148.20, 145.14, 138.02, 135.64, 134.72, 131.59 (2C), 131.34, 130.75, 130.13, 129.50 (2C), 129.27 (2C), 126.83 (2C), 114.97, 114.80, 111.53, 102.56, 69.23, 59.01, 57.24, 56.95, 56.65, 55.92, 53.27, 52.88, 48.16, 45.11, 41.51, 38.18, 36.65, 35.79, 31.67, 30.62, 28.42 (3C), 26.90, 22.90, 16.45, 13.84. HRMS (ESI/Q-TOF) *m/z* [M+H]+ calcd for $C_{52}H_{63}ClN_8O_8S$ 995.42563, found 995.42844.

1.2.2 General Procedure B: coupling amidation for the synthesis of PROTAC 3a (entries 1-10, Table 3).

Under nitrogen atmosphere, to a stirred solution of indomethacin (**1**) (0.056 mmol, 1.0 equiv.), amine derivative (**2a**) (0.056 mmol, 1.0 equiv.) and DIPEA (0.168 mmol, 3.0 equiv.) in the opportune solvent (1.0 mL) at 0°C, was added HATU (0.070 mmol, 1.25 equiv.) and then the reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water

and was extracted with EA (3x10 mL). The reunited organic phases were washed with water (3x20 mL), brine (1x15 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude was then purified by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 95:5 to 90:10) to afford the titled compound as a light-yellow solid. In particular, by using 1) DCM, the yield was 28% (entry 1, Table 3), 2) CPME, the yield was 14% (entry 2, Table 3), 3) 2-Me-THF, the yield was 17% (entry 3, Table 3), 4) [OMIM][NTf_2], the yield was 55% (entry 4, Table 3), 5) [OMIM][PF_6], the yield was 68% (entry 5, Table 3), 6) [OMIM][ClO_4], the yield was 75% (entry 6, Table 3), 7) [BMIM][BF_6], the yield was 68% (entry 7, Table 3), 8) [BMIM][PF_6], the yield was 73% (entry 8, Table 3), 9) [BMIM][NTf_2], the yield was 30% (entry 9, Table 3), 10) [TBMA][MsO], the yield was 32% (entry 10, Table 3).
The spectroscopic data for **PROTAC 3a** are in agreement with those reported in the literature.[3]

1.2.3 Operational procedure for 0.279 mmol-scale preparation of PROTAC 3a.

General procedure B (reaction time 2.5 h) was followed by using indomethacin (**1**) (0.100 g, 0.279 mmol), amine derivative (**2a**) (0.193 g, 0279 mmol), DIPEA (0.029 mL, 0.168 mmol), HATU (0.133 g, 0.349 mmol) in [OMIM][ClO_4] as solvent (5.0 mL), to afford the titled compound as light-yellow solid (0.188 g, 68% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 95:5 to 90:10).
The spectroscopic data for **PROTAC 3a** are in agreement with those reported in the literature.[3]

(2*S*,4*R*)-1-((*S*)-2-(5-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl) acetamido)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (3b).

General procedure B (2 h) was followed, by using indomethacin (**1**) (0.020 g, 0.056 mmol) and VHL-linker intermediate (**2b**)[4] (0.032 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as light-yellow solid (0.029 g, 59% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 99:1 to 95:5, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.44–7.28 (m, 5H), 6.97 (d, *J* = 2.3 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 6.69 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.34 (d, *J* = 8.8 Hz, 1H), 5.92 (t, *J* = 5.9 Hz, 1H), 5.13–5.02 (m, 1H), 4.73 (t, *J* = 8.0 Hz, 1H), 4.51 (d, *J* = 8.9 Hz, 1H), 4.46 (s, 1H), 4.02 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 3H), 3.72–3.57 (m, 2H), 3.53 (dd, *J* = 11.3, 3.3 Hz, 1H), 3.32–3.19 (m, 1H), 3.14–3.00 (m, 1H), 2.62–2.46 (m, 4H), 2.36 (s, 3H), 2.20 (t, *J* = 6.7 Hz, 2H), 2.12–2.00 (m, 1H), 1.61–1.50 (m, 2H), 1.49–1.35 (m, 5H), 1.01 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.43, 172.18, 170.40, 169.69, 168.53, 156.27,

150.45, 147.77, 143.47, 139.59, 136.54, 133.61, 131.29, 131.18 (2C), 130.99, 130.48, 130.38, 129.54 (2C), 129.24 (2C), 126.51 (2C), 115.11, 112.86, 112.11, 101.26, 70.00, 58.35, 57.52, 56.89, 55.84, 48.86, 38.52, 35.39, 35.18, 35.11, 32.09, 28.47, 26.49 (3C), 22.25, 21.87, 15.79, 13.40. HRMS (ESI/Q-TOF) *m/z* [M+H]+ calcd for $C_{47}H_{55}ClN_6O_7S$ 883.36142, found 883.36275.

(2*S*,4*R*)-1-((*S*)-2-(7-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl) acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (3c).

General Procedure B (2 h) was followed by using indomethacin (**1**) (0.020 g, 0.056 mmol) and VHL-linker intermediate (**2c**)[4] (0.034 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as light-yellow solid (0.027 g, 53% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 99:1 to 95:5, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.44–7.34 (m, 4H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 9.1 Hz, 1H), 6.69 (dd, *J* = 9.2, 2.0 Hz, 1H), 6.27 (d, *J* = 8.3 Hz, 1H), 5.77–5.68 (m, 1H), 5.14–5.03 (m, 1H), 4.74 (t, *J* = 7.9 Hz, 1H), 4.57 (d, *J* = 8.6 Hz, 1H), 4.47 (s, 1H), 4.13 (d, *J* = 11.7 Hz, 1H), 3.82 (s, 3H), 3.62 (s, 2H), 3.57 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.16 (dd, *J* = 13.5, 7.1 Hz, 2H), 2.59–2.43 (m, 4H), 2.37 (s, 3H), 2.26–2.02 (m, 3H), 1.65–1.44 (m, 5H), 1.44–1.29 (m, 2H), 1.30–1.14 (m, 4H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.76, 172.16, 170.04, 169.77, 168.41, 156.20, 150.33, 148.46, 143.26, 139.63, 136.41, 133.56, 131.63, 131.22 (2C), 130.96, 130.84, 130.37, 129.57 (2C), 129.25 (2C), 126.45 (2C), 115.10, 112.89, 112.06, 101.15, 69.99, 58.32, 57.59, 56.77, 55.77, 48.86, 39.33, 35.96, 35.56, 34.89, 32.22, 29.05, 28.16, 26.53 (3C), 26.06, 25.14, 22.29, 16.08, 13.30. HRMS (ESI/Q-TOF) *m/z* [M+H]+ calcd for $C_{49}H_{59}ClN_6O_7S$ 911.39272, found 911.39345.

(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-14-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-4,13-dioxo-6,9-dioxa-3,12-diazatetradecanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (3d).

General Procedure A (1.5 h) was followed, by using indomethacin (**1**) (0.020 g, 0.056 mmol) and VHL-linker intermediate (**2d**)[4] (0.034 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as light-yellow solid (42 mg, 80% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH 99:1 to 95, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (br s, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 3H), 7.40 (d,

J = 7.9 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 1H), 6.96 (s, 1H), 6.81 (s, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 5.08–4.96 (m, 1H), 4.67 (d, *J* = 9.2 Hz, 1H), 4.47 (s, 1H), 4.31 (t, *J* = 7.9 Hz, 1H), 3.99–3.43 (m, 16H), 3.40–3.32 (m, 1H), 2.56 (s, 3H), 2.40–2.27 (m, 4H), 2.09–2.00 (m, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 9H). HRMS (ESI/Q-TOF) *m/z* [M+H]+ calcd for $C_{48}H_{57}ClN_6O_9S$ 929.36690, found 929.36968.

(2*S*,4*R*)-1-((*S*)-2-(2-(4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl) acetyl)piperazin-1-yl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(thiazol-5- yl)phenyl)ethyl)pyrrolidine-2-carboxamide (3e).

General Procedure B (1.5 h) was followed, by using indomethacin (**1**) (0.020 g, 0.056 mmol) and VHL-linker intermediate (**2e**)[5] (0.034 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as light-yellow solid (43 mg, 84% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH 99:1 to 95:5, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.31 (m, 5H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 6.68 – 6.62 (m, 1H), 5.12 – 5.04 (m, 1H), 4.73 (t, *J* = 7.8 Hz, 1H), 4.55 – 4.43 (m, 2H), 4.13 (d, *J* = 11.7 Hz, 1H), 3.90 – 3.76 (m, 4H), 3.71 (s, 2H), 3.65 – 3.50 (m, 4H), 3.01 (s, 2H), 2.61 – 2.43 (m, 7H), 2.43 – 2.32 (m, 4H), 2.11 – 2.00 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.76, 169.47, 168.77 (2C), 168.31, 156.02, 150.31, 148.52, 143.07, 139.40, 135.31, 133.79, 131.54, 131.24 (2C), 130.95, 130.84, 130.60, 129.58 (2C), 129.17 (2C), 126.44 (2C), 114.92, 113.00, 111.47, 101.61, 70.11, 58.13 (2C), 56.62, 55.77, 53.79, 53.15 (2C), 48.86, 35.32, 34.70, 31.93, 30.25, 29.71, 26.58 (3C), 22.22, 16.11, 13.44. HRMS (ESI/Q-TOF) *m/z* [M + H]+ calcd for $C_{48}H_{56}ClN_7O_7S$ 910.37232, found 910.37507.

***N*1-(3-(4-(3-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl) acetamido)propyl)piperazin-1-yl)propyl)-*N*4-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide (3f).**

General Procedure B (2 h) was followed, by using indomethacin (**1**) (0.020 g, 0.056 mmol) and VHL-linker intermediate (**2f**)[6] (0.043 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as light-yellow solid (24 mg, 40% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH 99:1 to 95: 5, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.00 (br s, 1H), 7.85 (br s, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.31 (m, 4H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.65

(dd, *J* = 9.1, 2.0 Hz, 1H), 6.36 (br s, 1H), 5.14 – 5.01 (m, 1H), 4.87 – 4.78 (m, 1H), 4.63 – 4.53 (m, 1H), 4.48 – 4.41 (m, 1H), 4.11 – 4.01 (m, 1H), 3.79 (s, 3H), 3.64 – 3.51 (m, 3H), 3.45 (s, 2H), 3.42 – 3.16 (m, 4H), 2.87 – 2.19 (m, 22H), 1.85 – 1.54 (m, 4H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H). HRMS (ESI/Q-TOF) *m/z* [M + Na]+ calcd for $C_{56}H_{72}ClN_9O_8S$ 1088.48053, found 1088.4833.

The spectroscopic data for **PROTACs 3b-3f** are in agreement with those reported in the literature.[3, 6]

2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-N-(2-(2-(2-((2-(2,6 dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)acetamide (4a).
General Procedure B (2 h) was followed, by using indomethacin (**1**) (0.020 g, 0.056 mmol) and CRBN-linker intermediate (4-((2-(2-(2-aminoethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione hydrochloride)[5] (0.025 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (18 mg, 43% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH 99:1 to 95:5, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (br s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.54 – 7.42 (m, 3H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.97 – 6.89 (m, 1H), 6.90 – 6.83 (m, 2H), 6.71 – 6.63 (m, 1H), 6.32 (br s, 1H), 4.91 – 4.79 (m, 1H), 3.79 (s, 3H), 3.67 (s, 2H), 3.64 – 3.58 (m, 2H), 3.55 – 3.36 (m, 10H), 2.86 – 2.64 (m, 3H), 2.34 (s, 3H), 2.12 – 2.05 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.06, 169.29, 168.46, 168.34, 167.52, 156.19, 146.63, 139.50, 136.41, 136.08, 133.62, 132.53, 131.21 (2C), 130.89, 130.40, 129.19 (2C), 116.78, 115.02, 112.79, 112.12, 111.81, 110.42 (2C), 101.02, 70.61, 70.09, 69.77, 69.08, 55.74, 48.85, 42.23, 39.54, 32.10, 31.32, 29.70, 22.86, 13.31. HRMS (ESI/Q-TOF) *m/z* [M + Na]+ calcd for $C_{38}H_{38}ClN_5O_9$766.22503, found 766.2273.

2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(10-((3-(2,6 dioxopiperidin-3-yl)-4-oxo-3,4-dihydrobenzo[*d*][1,2,3]triazin-6 yl)amino)decyl)acetamide (4b).
General Procedure B (1.5 h) was followed, by using indomethacin (**1**) (0.020 g, 0.056 mmol) and CRBN-linker intermediate (3-(6-((10-aminodecyl)amino)-4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl)piperidine-2,6-dione hydrochloride)[7] (0.026 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (23 mg, 55% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH/Acetone

88:2:10, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.20 (br s, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.91 – 6.83 (m, 2H), 6.73 – 6.65 (m, 1H), 5.80 – 5.70 (m, 1H), 5.60 (br s, 1H), 3.81 (s, 3H), 3.63 (s, 2H), 3.31 – 3.13 (m, 4H), 3.00 – 2.76 (m, 3H), 2.42 – 2.29 (m, 4H), 1.71 – 1.63 (m, 2H), 1.42 – 1.15 (m, 14H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.94, 169.75, 168.39, 168.04, 156.26, 156.00, 151.80, 139.62, 136.57, 136.30, 133.55, 131.20 (2C), 130.89, 130.37, 130.31, 129.24 (2C), 121.95, 121.46, 115.11, 112.96, 112.38, 101.74, 100.78, 58.14, 55.74, 43.49, 39.61, 32.27, 31.03, 29.47, 29.23, 29.11, 29.04, 28.85, 26.84, 26.73, 26.68, 23.23, 13.28. HRMS (ESI/Q-TOF) *m/z* [M + Na]+ calcd for $C_{41}H_{46}ClN_7O_6$ 790.30903, found 790.3115.

2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(7-(4-(2-(2,6 dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)-7 oxoheptyl)acetamide (4c).

General Procedure B (1 h) was followed, by using indomethacin (**1**) (0.020 g, 0.056 mmol) and CRBN-linker intermediate (5-(4-(7-aminoheptanoyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)-6-fluoroisoindoline-1,3-dione hydrochloride)[8] (0.029 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (24 mg, 53% yield) after purification by automated flash chromatography on SiO_2 cartridge (PET/EA 10:90 to 100 EA v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.55 – 7.46 (m, 3H), 7.38 (d, *J* = 7.0 Hz, 1H), 6.92 – 6.83 (m, 2H), 6.73 – 6.66 (m, 1H), 5.67 (br s, 1H), 4.94 (dd, *J* = 12.1, 5.1 Hz, 1H), 3.90 – 3.74 (m, 5H), 3.64 (s, 4H), 3.32 – 3.15 (m, 6H), 2.94 – 2.70 (m, 3H), 2.38 (s, 3H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.18 – 2.11 (m, 1H), 1.61 – 1.53 (m, 2H), 1.49 – 1.36 (m, 2H), 1.35 – 1.21 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.62, 170.64, 169.89, 168.36, 167.86, 166.71, 166.17 (d, *J*= 2.4 Hz), 158.28 (d, *J*= 256.2 Hz), 156.26, 145.37 (d, *J*= 9.1 Hz), 139.62, 136.34, 133.55, 131.22 (2C), 130.90, 130.31, 129.25 (2C), 128.97 (d, *J*= 2.8 Hz), 124.94 (d, *J*= 9.7 Hz), 115.11, 113.89 (d, *J*= 4.5 Hz), 112.88, 112.32 (d, *J*= 12.5 Hz), 112.31, 100.85, 55.78, 50.22, 49.90, 49.49, 45.30, 41.22, 39.48, 32.97, 32.25, 31.42, 29.29, 28.81, 26.44, 24.94, 22.66, 13.29. HRMS (ESI/Q-TOF) *m/z* [M + Na]+ calcd for $C_{43}H_{44}ClFN_6O_8$ 849.27854, found 849.28.

2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(4-((2-(2,6-dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisoindolin-5-yl)amino)butyl)acetamide (4d).

General Procedure B (3 h) was followed, by using indomethacin (**1**) (0.020 g, 0.056 mmol) and CRBN-linker intermediate (5-((4-aminobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)-6-

fluoroisoindoline-1,3-dione hydrochloride)[8] (0.022 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (30 mg, 78% yield) after purification by automated flash chromatography on SiO_2 cartridge (PET/EA 50:50 to 100 EA v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.70 – 7.64 (m, 2H), 7.51 – 7.46 (m, 2H), 7.37 (d, *J* = 9.8 Hz, 1H), 7.01 (d, *J* = 7.1 Hz, 1H), 6.90 – 6.82 (m, 2H), 6.69 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.67 (t, *J* = 6.1 Hz, 1H), 4.91 (dd, *J* = 12.3, 5.3 Hz, 1H), 4.80 (br s, 1H), 3.80 (s, 3H), 3.66 (s, 2H), 3.31 – 3.19 (m, 4H), 2.92 – 2.68 (m, 3H), 2.39 (s, 3H), 2.15 – 2.09 (m, 1H), 1.61 – 1.52 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.87, 170.11, 168.37, 168.23, 167.34, 166.81 (d, *J* = 2.9 Hz), 156.26, 153.62 (d, J = 248.4 Hz), 142.47 (d, *J* = 12.8 Hz), 139.73, 136.45, 133.43, 131.24 (2C), 130.94, 130.21, 130.08 (d, *J* = 2.3 Hz), 129.26 (2C), 118.37 (d, *J* = 8.7 Hz), 115.13, 112.71, 112.19, 110.05 (d, *J* = 22.4 Hz), 105.36 (d, *J* = 5.3 Hz), 101.00, 55.81, 49.27, 42.84, 39.00, 32.26, 31.45, 27.27, 25.97, 22.74, 13.24. HRMS (ESI/Q-TOF) *m/z* [M+Na]+ calcd for $C_{36}H_{33}ClFN_5O_7$ 724.19502, found 724.19524.

1-benzyl-5-butoxy-*N*-(2-(4-(4-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutanoyl)piperazin-1-yl)ethyl)-2-methyl-1*H*-indole-3-carboxamide (5a).

General Procedure B (3.5 h) was followed, by using 1-benzyl-5-butoxy-2-methyl-1*H*-indole-3-carboxylic acid (0.019 g, 0.056 mmol) and VHL-linker intermediate (**2a**)[3] (0.039 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (31 mg, 54% yield) after purification by automated flash chromatography on SiO2 cartridge (DCM/MeOH 99:1 to 90:10 v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.60 – 7.50 (m, 1H), 7.45 – 7.33 (m, 5H), 7.30 – 7.26 (m, 1H), 7.26 – 7.21 (m, 2H), 7.14 (d, *J* = 8.9 Hz, 1H), 6.96 (d, *J* = 6.6 Hz, 2H), 6.81 (dd, *J* = 8.9, 2.0 Hz, 2H), 6.59 (br s, 1H), 5.30 (s, 2H), 5.14 – 5.02 (m, 1H), 4.76 (t, *J* = 8.0 Hz, 1H), 4.55 – 4.40 (m, 2H), 4.08 – 3.97 (m, 3H), 3.76 – 3.50 (m, 8H), 2.79 – 2.44 (m, 17H), 2.15 – 2.05 (m, 1H), 1.79 – 1.72 (m, 2H), 1.53 – 1.42 (m, 5H), 1.05 (s, 9H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.95, 172.06, 170.25, 169.83, 154.85, 150.25, 148.47, 143.30, 142.37, 136.59, 131.61, 131.55, 130.80, 129.53 (2C), 128.90 (2C), 127.61, 126.44 (2C), 126.14, 125.93 (2C), 110.50 (2C), 107.70, 103.91, 70.03, 68.53 (2C), 58.30, 58.01, 56.90, 56.61, 52.74, 52.54, 48.83, 46.54, 45.26, 41.78, 35.80, 35.67, 35.04, 31.61, 30.94, 28.35, 26.52 (3C), 22.26, 19.31, 16.11, 13.92, 11.76. HRMS (ESI/Q-TOF) *m/z* [M+Na]+ calcd for $C_{54}H_{70}N_8O_7S$ 997.49804, found 997.5009.

***N*-(3-((2-(4-(4-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5 yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutanoyl)piperazin-1-yl)ethyl)carbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (5b).**

General Procedure B (4 h) was followed, by using 2-(5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid (0.027 g, 0.056 mmol) and VHL-linker intermediate (**2a**)[3] (0.039 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (34 mg, 54% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH 99:1 to 90:10 v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.22 (br s, 1H), 8.88 (s, 1H), 8.66 (s, 3H), 7.82 (s, 1H), 7.67 – 7.46 (m, 4H), 7.46 – 7.33 (m, 4H), 6.75 – 6.55 (m, 2H), 5.12 – 5.02 (m, 1H), 4.81 – 4.72 (m, 1H), 4.54 – 4.41 (m, 2H), 4.08 – 4.01 (m, 1H), 3.69 – 3.47 (m, 6H), 2.86 – 2.46 (m, 16H), 2.15 – 2.06 (m, 1H), 1.95 – 1.82 (m, 4H), 1.68 – 1.56 (m, 4H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H). HRMS (ESI/Q-TOF) *m/z* [M+Na]+ calcd for $C_{56}H_{64}F_3N_{11}O_7S_2$ 1146.42759, found 1146.4297.

(2*S*,4*R*)-1-((*S*)-2-(4-(4-(2-(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetamido)ethyl)piperazin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (5c).

General Procedure B (18 h) was followed, by using JQ1 carboxylic acid ((*S*)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetic acid) (0.022 g, 0.056 mmol) and VHL-linker intermediate (**2a**)[3] (0.039 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (36 mg, 62% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH 99:1 to 90:10 v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.61 (d, *J* = 7.0 Hz, 1H), 7.51 – 7.27 (m, 8H), 7.06 (br s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.77 (t, *J* = 7.8 Hz, 1H), 4.66 – 4.60 (m, 1H), 4.54 (d, *J* = 8.6 Hz, 1H), 4.45 (br s, 1H), 4.09 – 4.00 (m, 1H), 3.73 – 3.30 (m, 9H), 2.76 – 2.37 (m, 19H), 2.16 – 2.06 (m, 2H), 1.67 (s, 3H), 1.47 (d, *J* = 6.7 Hz, 3H), 1.04 (s, 9H). HRMS (ESI/Q-TOF) *m/z* [M+Na]+ calcd for $C_{52}H_{64}ClN_{11}O_6S_2$ 1060.40632, found 1060.4079.

(2*S*,4*R*)-1-((*S*)-2-(4-(4-(2-(3-(*N*-(1,3-dimethyl-2-oxo-6-(3-propoxyphenoxy)-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)sulfamoyl)benzamido)ethyl)piperazin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (5d).

General Procedure B (7 h) was followed, by using IACs-7e carboxylic acid (3-(*N*-(1,3-dimethyl-2-oxo-6-(3-propoxyphenoxy)-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)sulfamoyl)benzoic acid) (0.028 g, 0.056 mmol) and VHL-linker intermediate (**2a**)[3] (0.039 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (28 mg, 44% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH 95:5 to 90:10 v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.14 (br s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.52 (m, 1H), 7.43 – 7.34 (m,5H), 7.34 – 7.30 (m, 1H), 7.19 (br s, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 6.95 – 6.70 (m, 2H), 6.59 – 6.53 (m, 1H), 6.37 (s, 1H), 6.08 – 6.00 (m, 2H), 5.13 – 5.03 (m, 1H), 4.75 (t, *J* = 8.1 Hz, 1H), 4.57 – 4.49 (m, 1H), 4.45 (br s, 1H), 4.09 – 4.00 (m, 1H), 3.81 (t, *J* = 6.5 Hz, 2H), 3.68 – 3.47 (m, 8H), 3.43 (s, 3H), 3.24 (s, 3H), 2.73 – 2.42 (m, 14H), 2.13 – 2.06 (m, 1H), 1.81 – 1.73 (m, 2H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.10 – 0.96 (m, 12H). HRMS (ESI/Q-TOF) *m/z* [M+H]+ calcd for $C_{58}H_{72}N_{10}O_{11}S_2$ 1149.48962, found 1149.4908.

(2*S*,4*R*)-1-((*S*)-2-(4-(4-(2-(2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1 yl)methyl)benzamido)ethyl)piperazin-1-yl)-4-oxobutanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (5e).

General Procedure B (7 h) was followed, by using 2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoic acid (0.017 g, 0.056 mmol) and VHL-linker intermediate (**2a**)[3] (0.039 g, 0.056 mmol) in [OMIM][ClO_4] as solvent (0.056 M), to afford the titled compound as yellow solid (21 mg, 40% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH 95:5 to 90:10 v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.78 (d, *J* = 112.0 Hz, 1H), 8.67 (s, 1H), 8.41 (d, *J* = 7.1 Hz, 1H), 7.92 (d, *J* = 5.7 Hz, 1H), 7.79 – 7.54 (m, 5H), 7.39 – 7.32 (m, 4H), 7.19 (d, *J* = 11.4 Hz, 1H), 7.11 – 6.96 (m, 2H), 5.14 – 5.05 (m, 1H), 4.75 (t, *J* = 8.0 Hz, 1H), 4.55 (d, *J* = 8.6 Hz, 1H), 4.45 (br s, 1H), 4.38 – 4.22 (m, 3H), 4.05 (d, *J* = 11.3 Hz, 1H), 3.76 – 3.58 (m, 5H), 2.84 – 2.40 (m, 15H), 2.17 – 2.09 (m, 1H), 1.94 – 1.85 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H). HRMS (ESI/Q-TOF) *m/z* [M+Na]+ calcd for $C_{49}H_{58}FN_9O_7S$ 958.40562, found 958.4065.

Procedure for the synthesis of [OMIM][ClO_4].

The ionic liquid [OMIM][ClO_4] was prepared by anion exchange reaction starting from [OMIM][Br]. The latter was solubilized in the minimum quantity of deionized water, the solution was cooled at 0°C, 70% $HClO_4$ was added (mole ratio 1:2) and the reaction was left under magnetic stirring for 1h. The two-phase liquid system obtained was then transferred into a separating funnel and extracted twice with a mixture of dichloromethane/ethyl ether 1/1 (v/v). The combined organic phases were washed with deionized water until neutral. The organic phase was evaporated to dryness to give a viscous liquid which was subsequently dried under vacuum over P_2O_5. To verify complete exchange, the Fuchsin test for bromide was performed which was negative.^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H, N-CH-N), 7.42 – 7.35 (m, 1H, CH), 7.35 – 7.28 (m, 1H, CH), 4.18 (t, J = 7.5 Hz, 2H, N-CH_2), 3.97 (s, 3H, N-CH_3), 1.93 – 1.82 (m, 2H, CH_2), 1.39 – 1.18 (m, 10H, 5CH_2), 0.85 (t, J = 6.6 Hz, 3H, CH_3).

2. Determination of Viscosity, Melting Point and Density for [OMIM][ClO_4]

Density measure

The density value of [OMIM][ClO_4] was measured by weighting the samples in a 1.0 ± 0.01 mL volumetric flask. The flask was held in a thermostated bath for 1 h and then brought to volume by eliminating the suitable amount of liquid with a pipette. The flask was then thermostated at room temperature for 1 h and then weighed on analytical balance to obtain the density value at that temperature (20°C). The experiment was performed in duplicate.

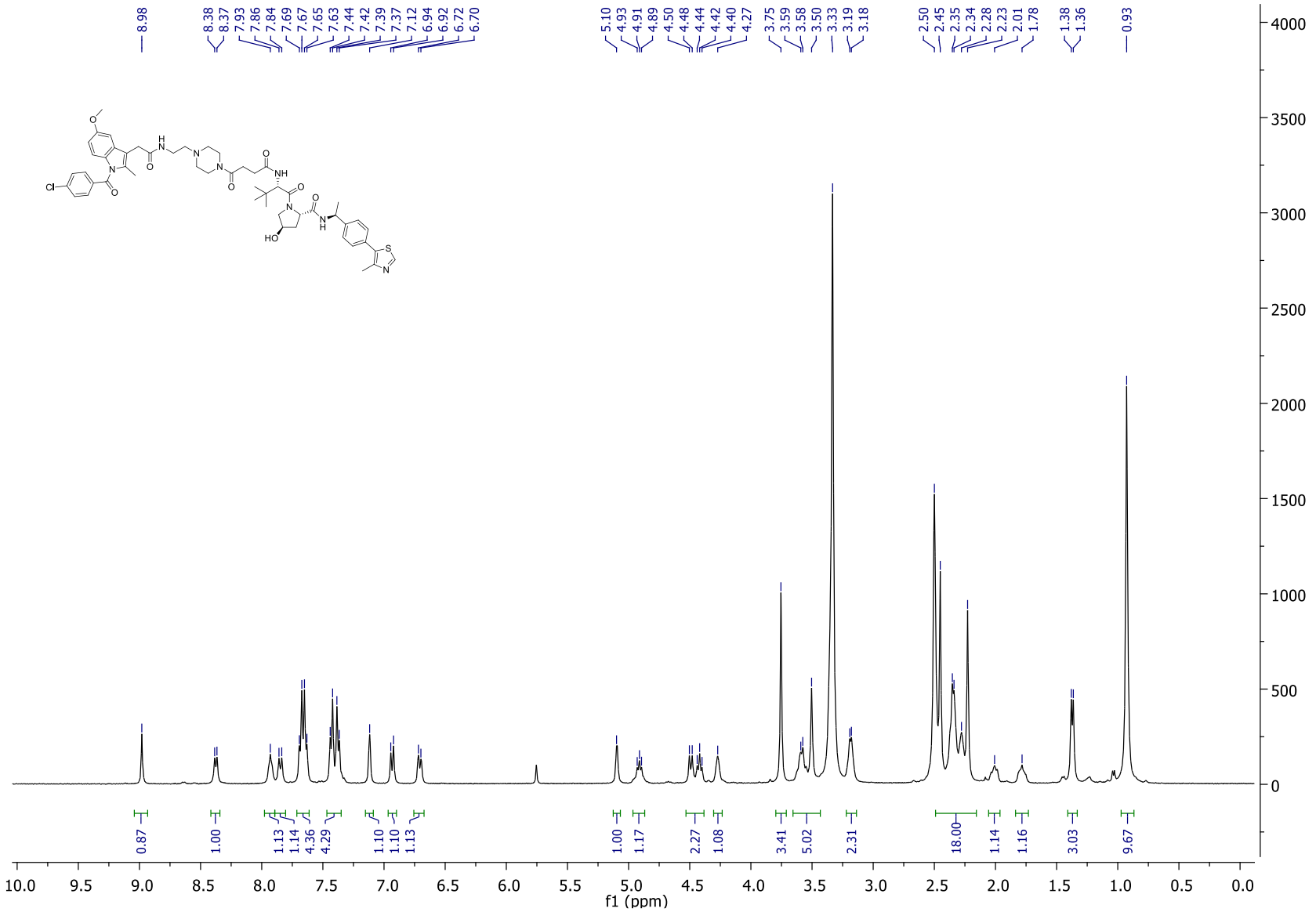
Viscosity measure

The viscosity of [OMIM][ClO_4] was measured in duplicated using a "Fungilab Viscolead mod. ADV L" rotational viscometer, fitted with a thermostatic jacket and a temperature probe. The viscometer jacket was connected to an external thermostated bath (20°C). The viscosity measurements were obtained using a spindle attachment.

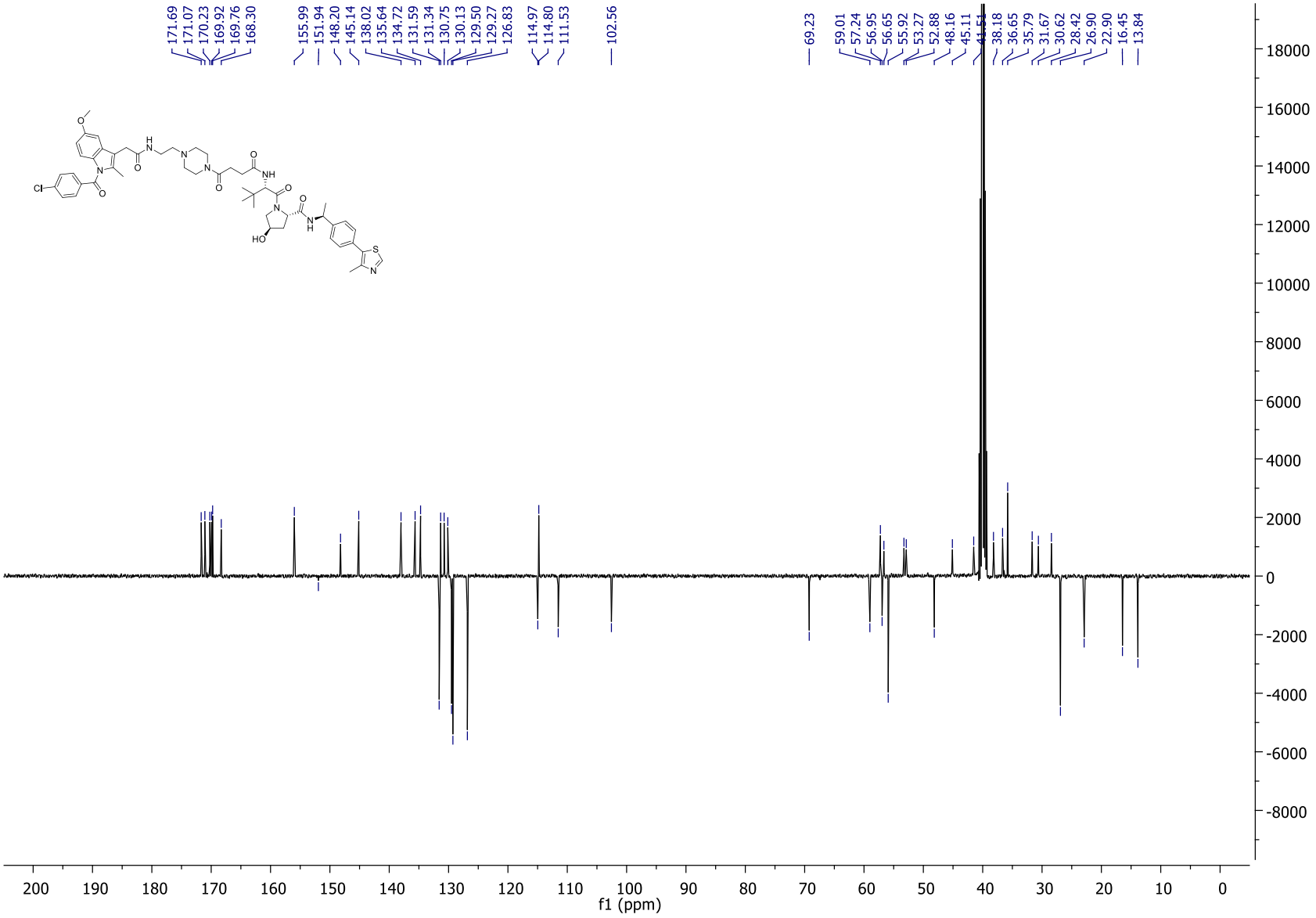
Melting point determination

In a 10 mL round-bottomed flask, equipped with a thermometer, was introduced [OMIM][ClO_4]. Then was immersed in an acetone/liquid nitrogen mixture and cooled to -78°C. After total freezing it was removed from the bath and the melting point temperature was recorded. The experiment was performed in duplicate.

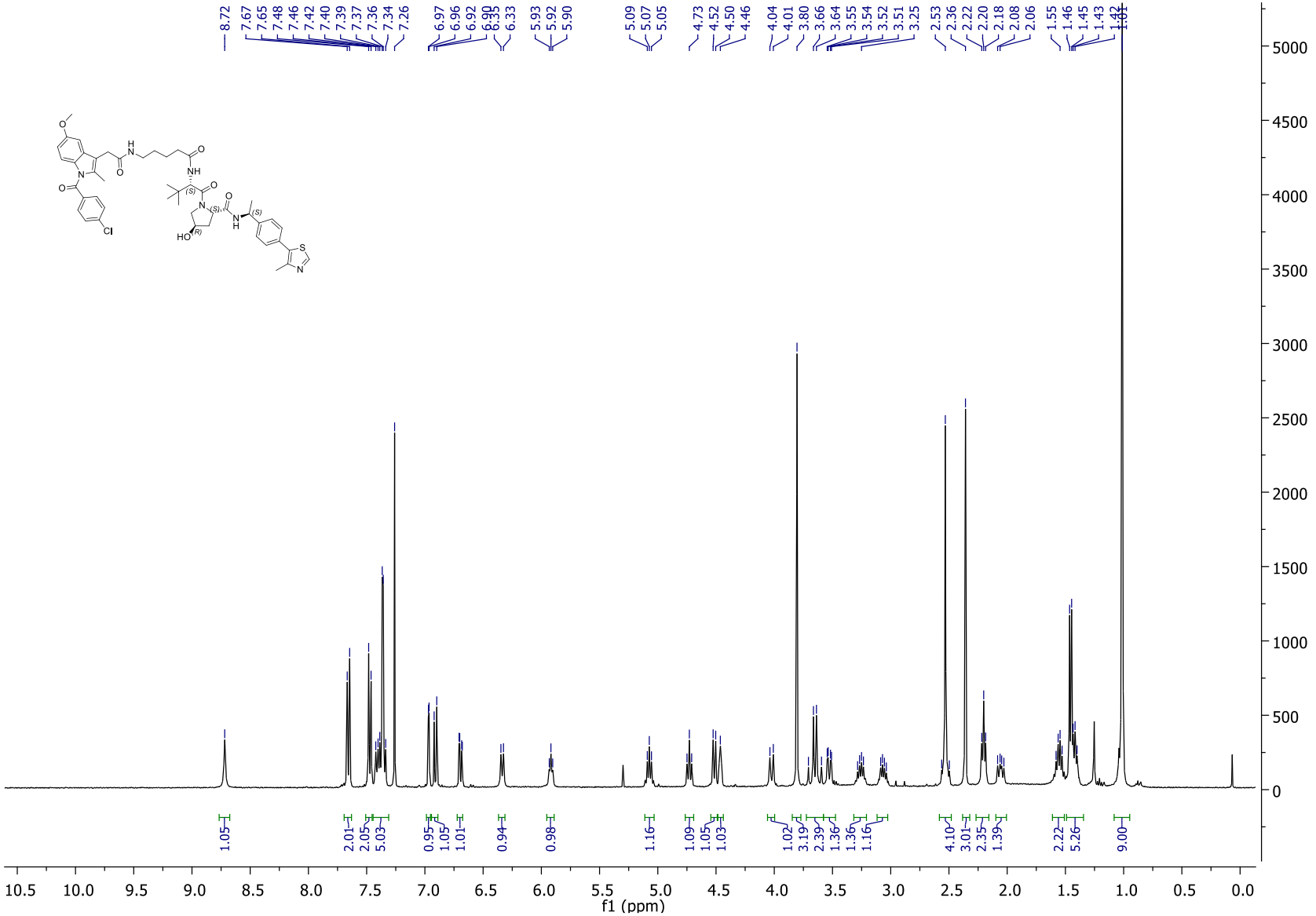
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **3a.**



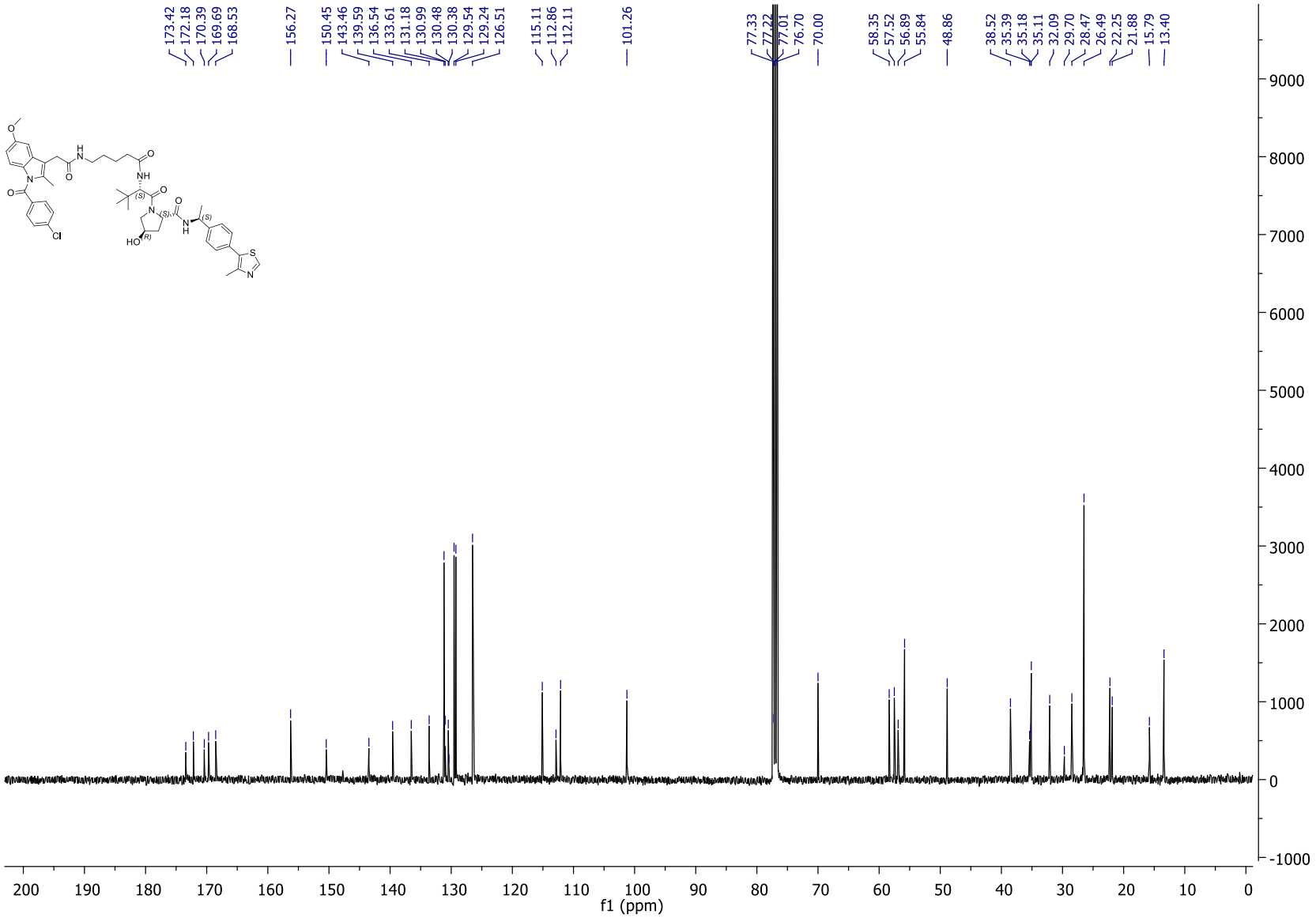
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of compound **3a.**



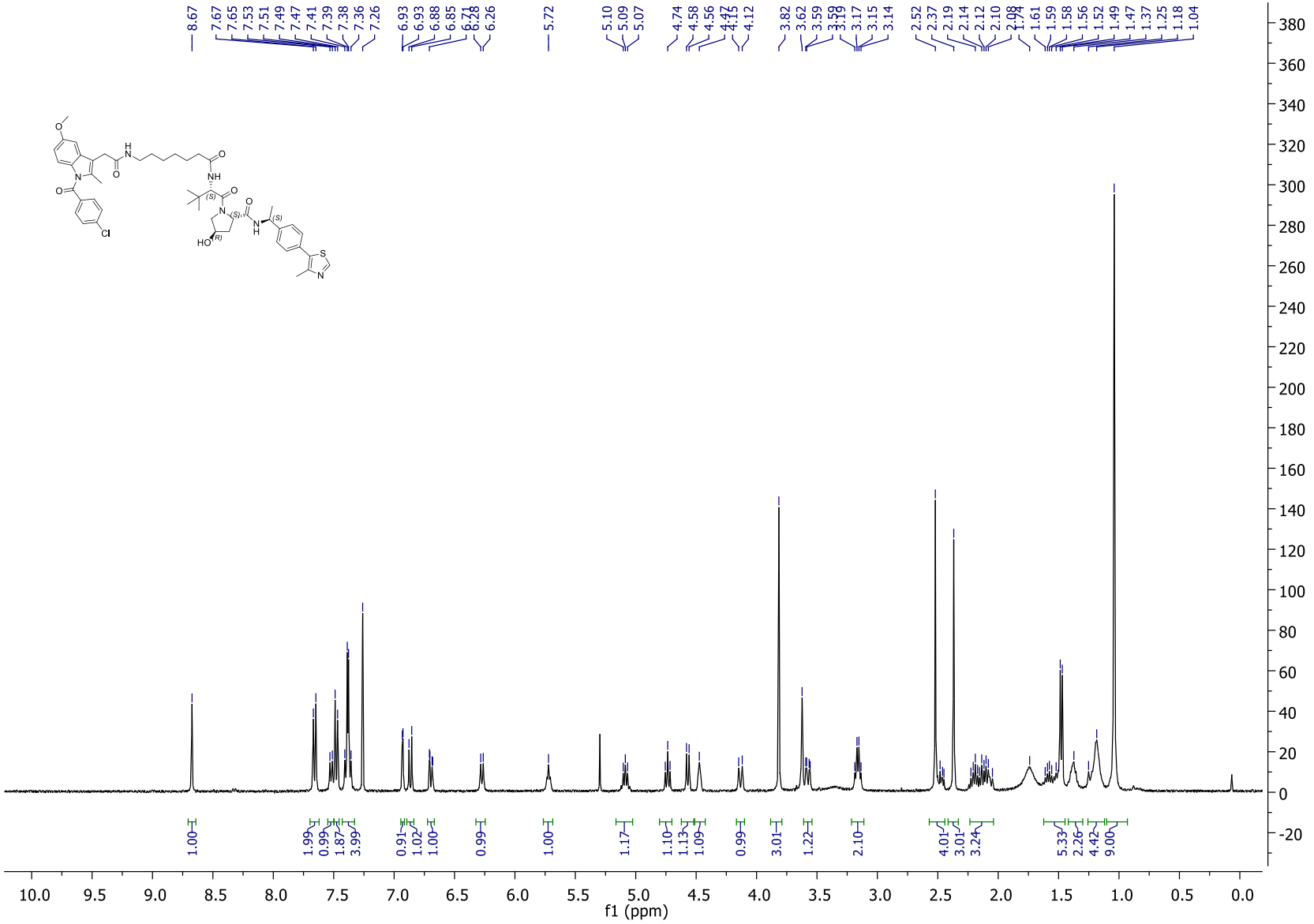
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3b.**



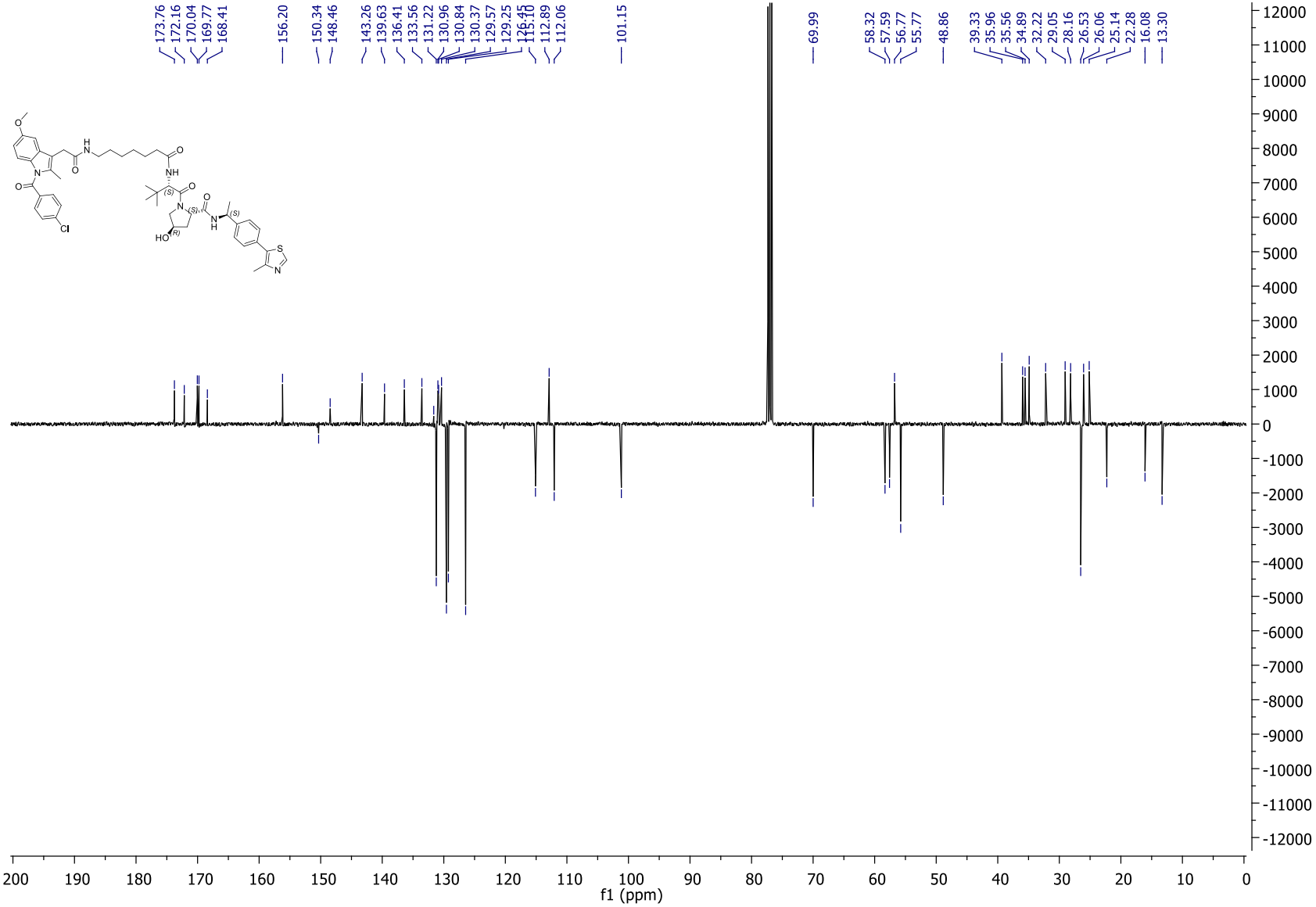
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **3b.**



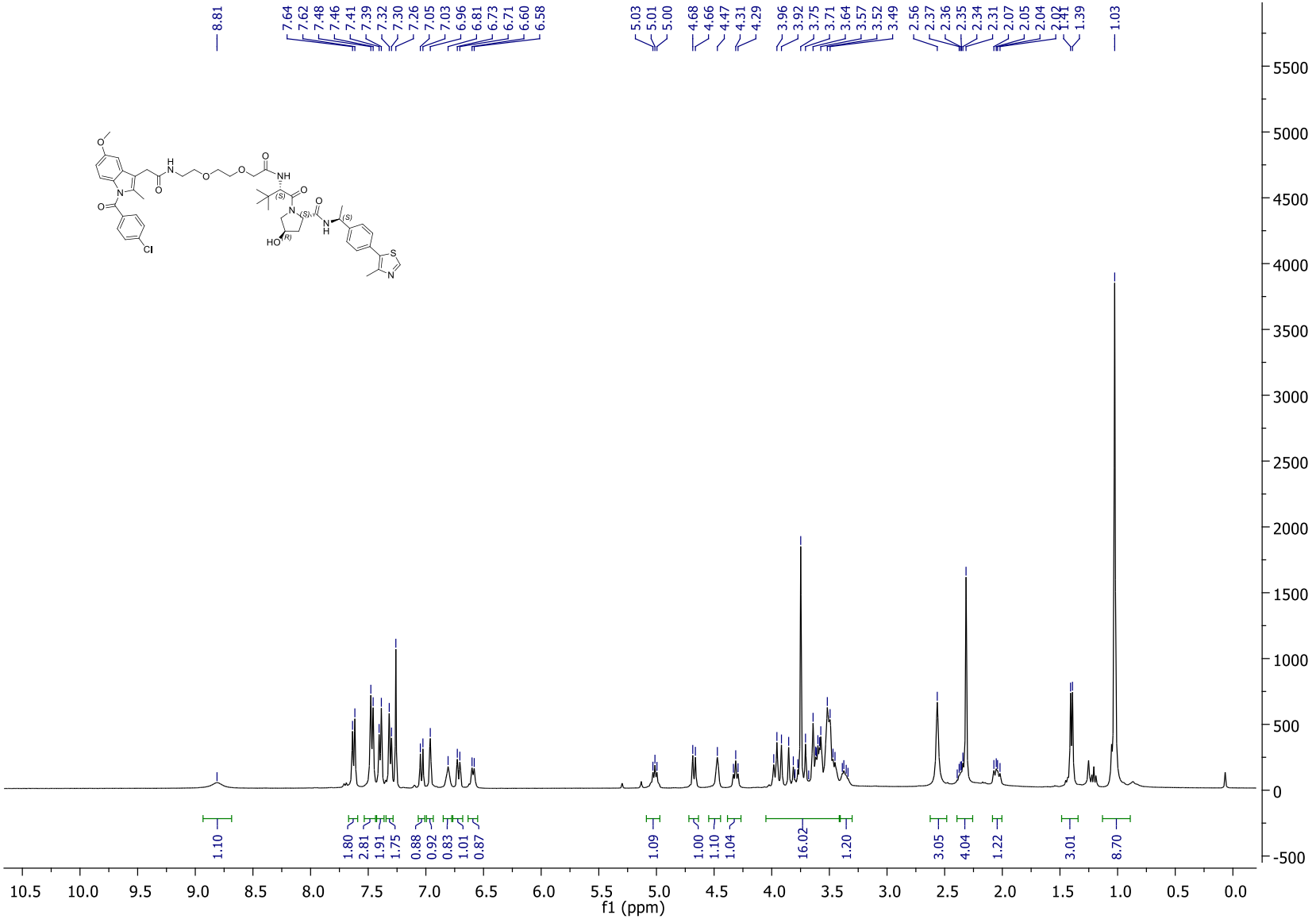
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3c.**



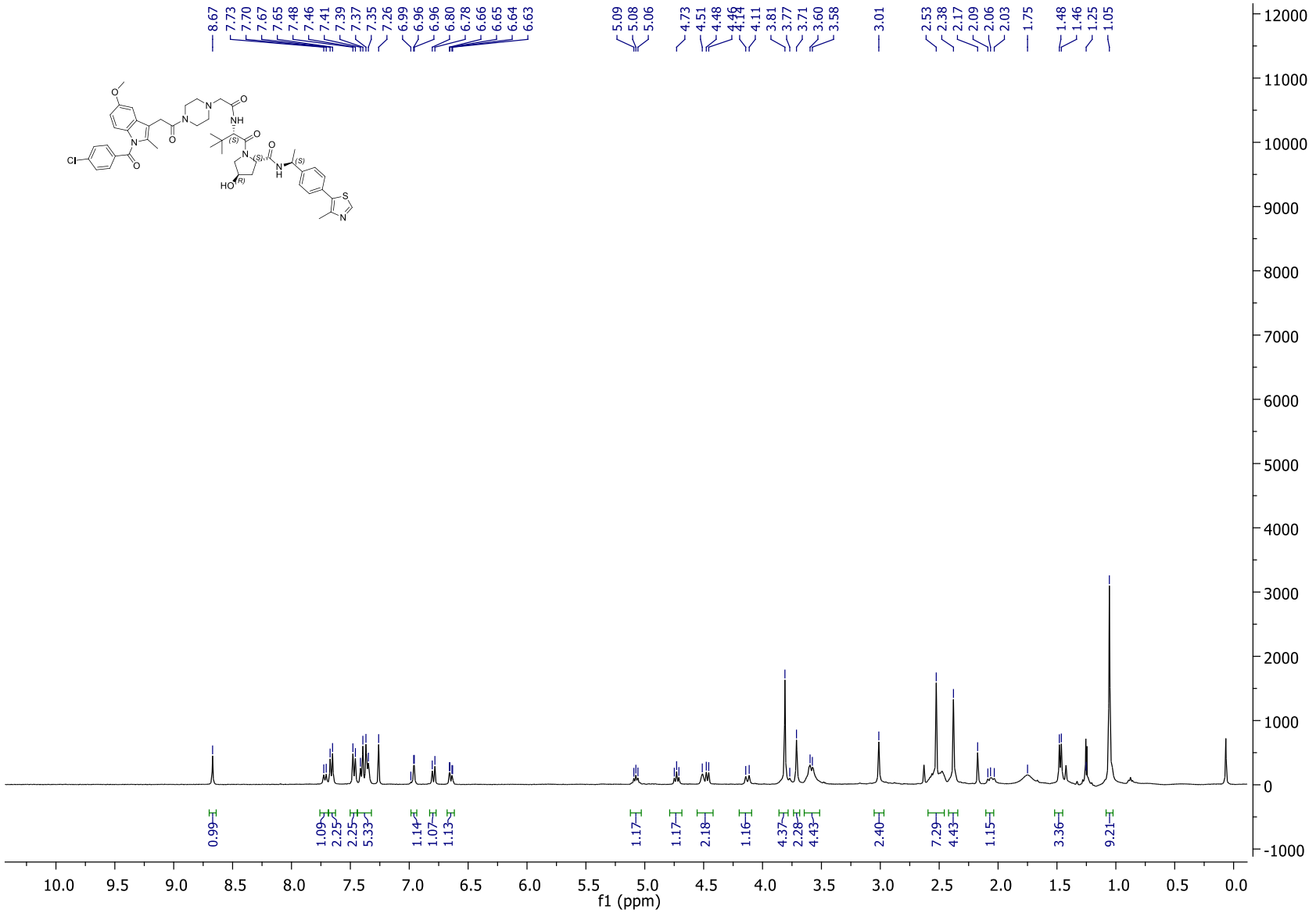
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **3c.**



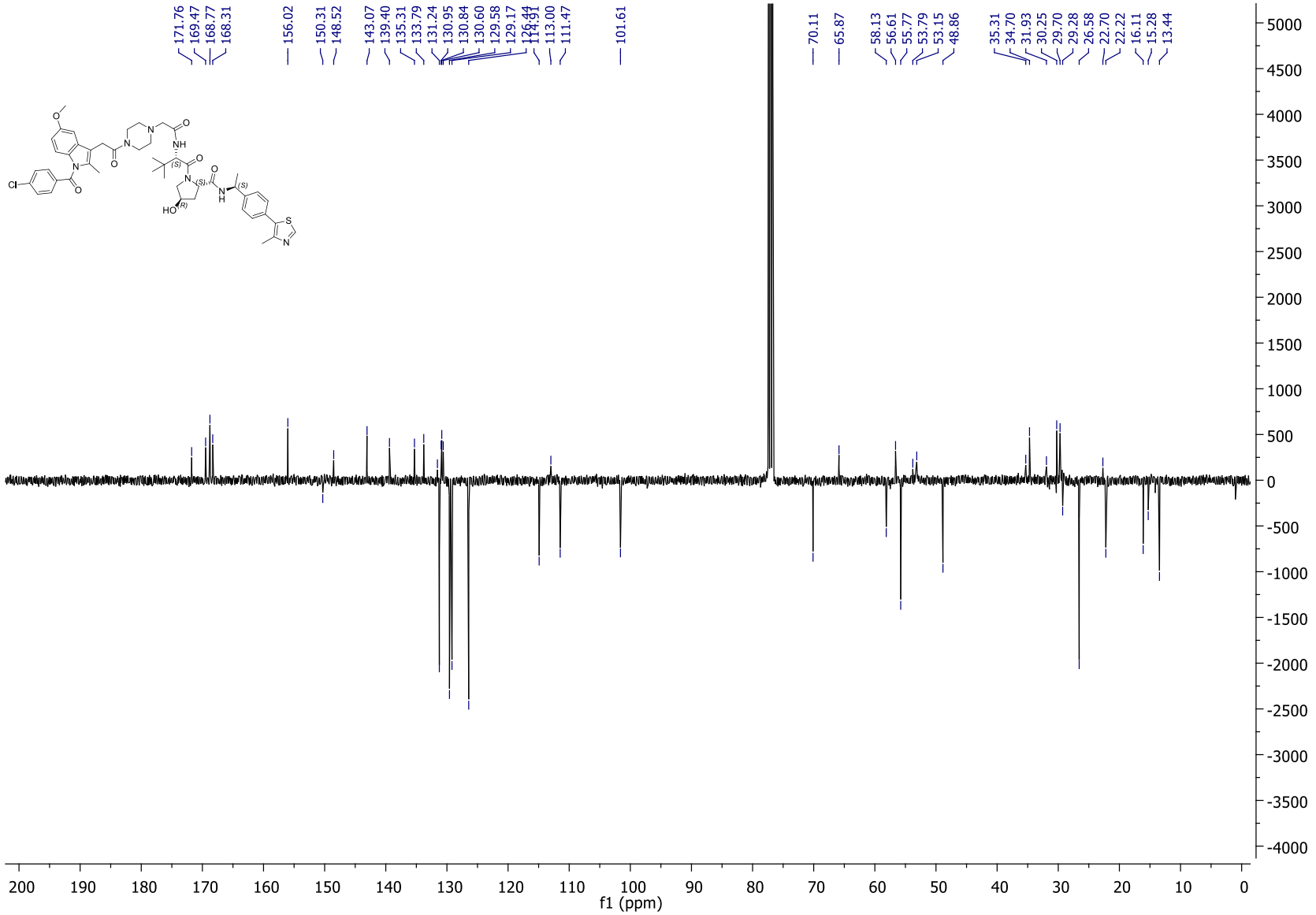
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3d.**



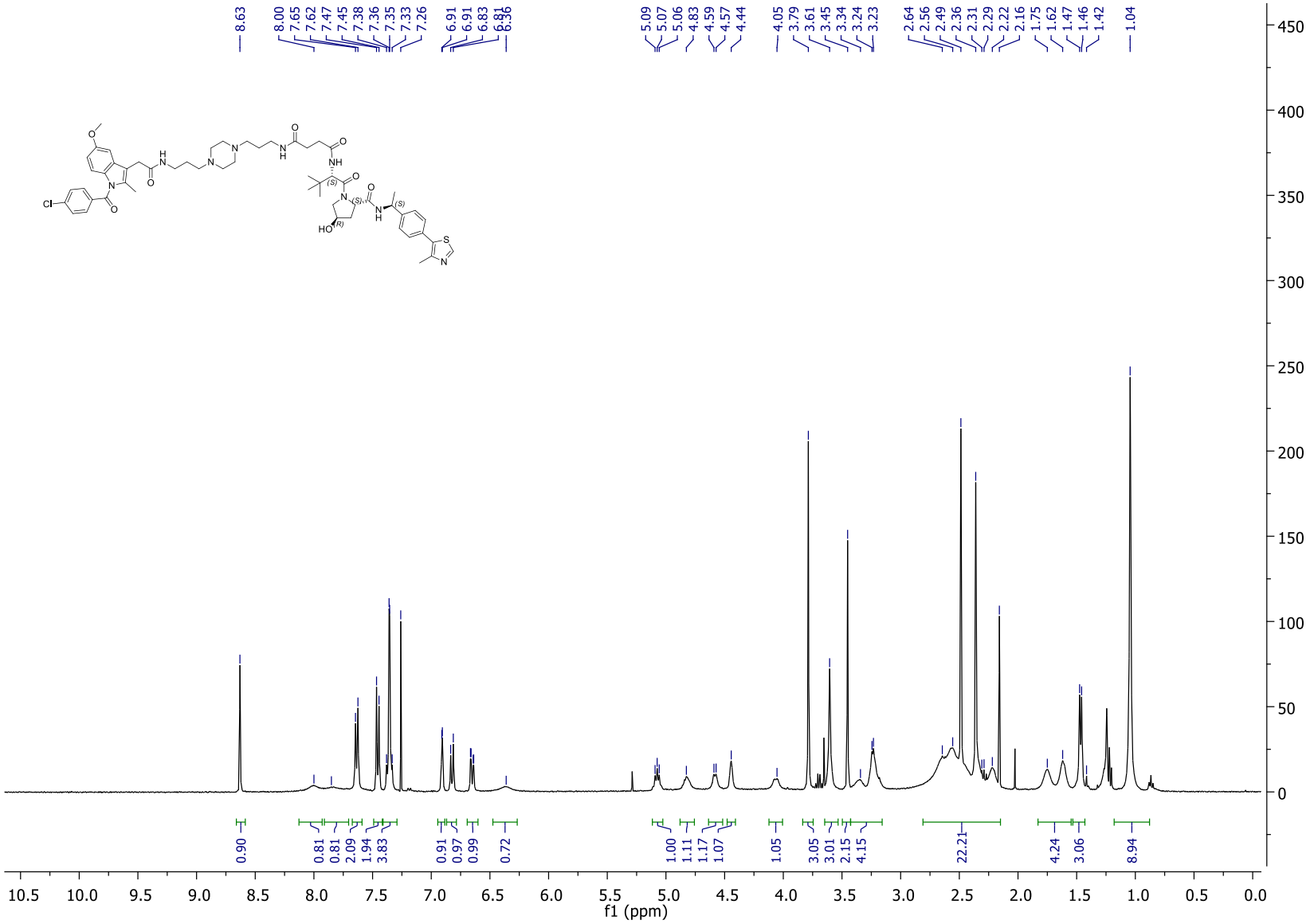
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3e.**



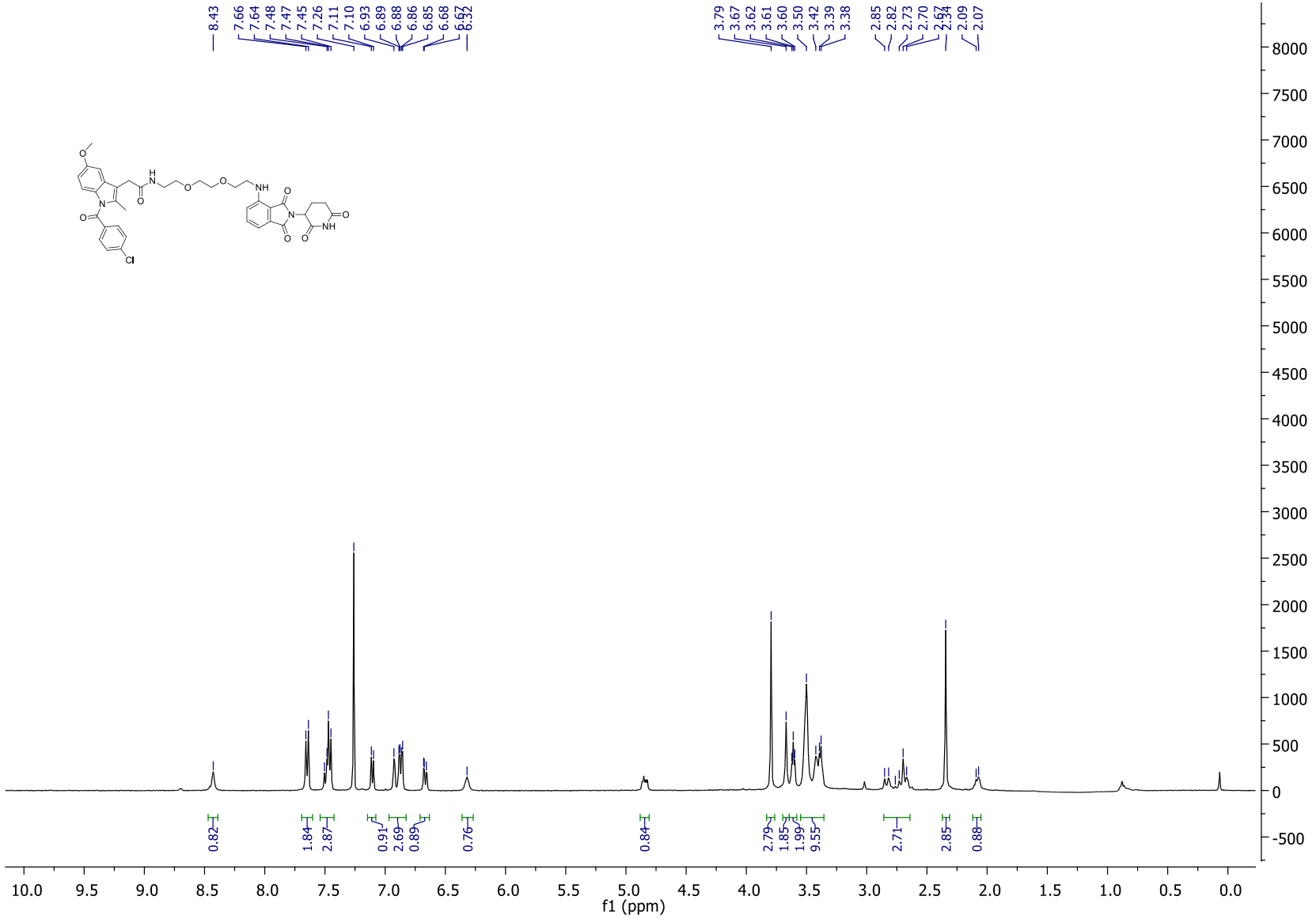
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **3e.**



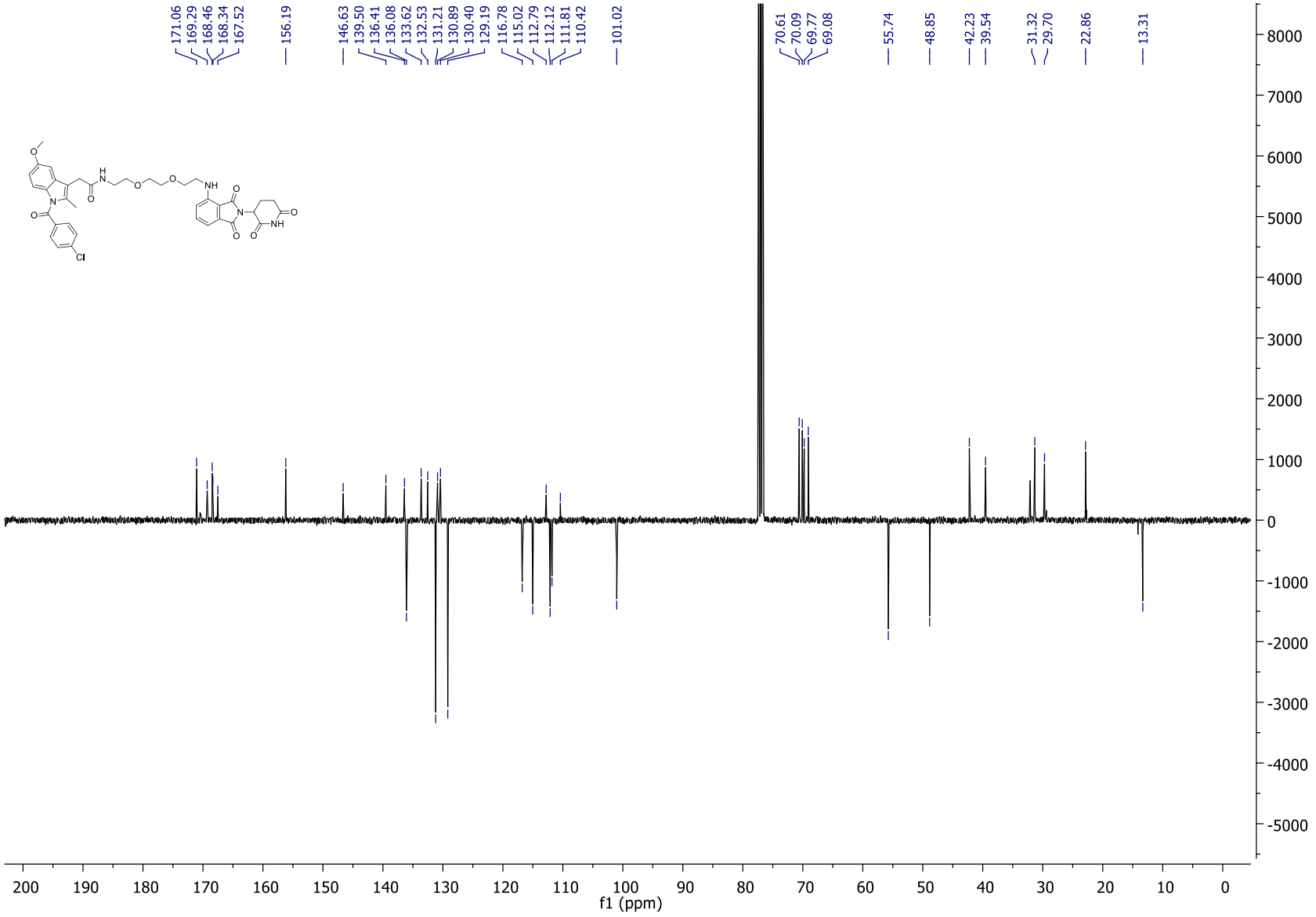
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3f.**



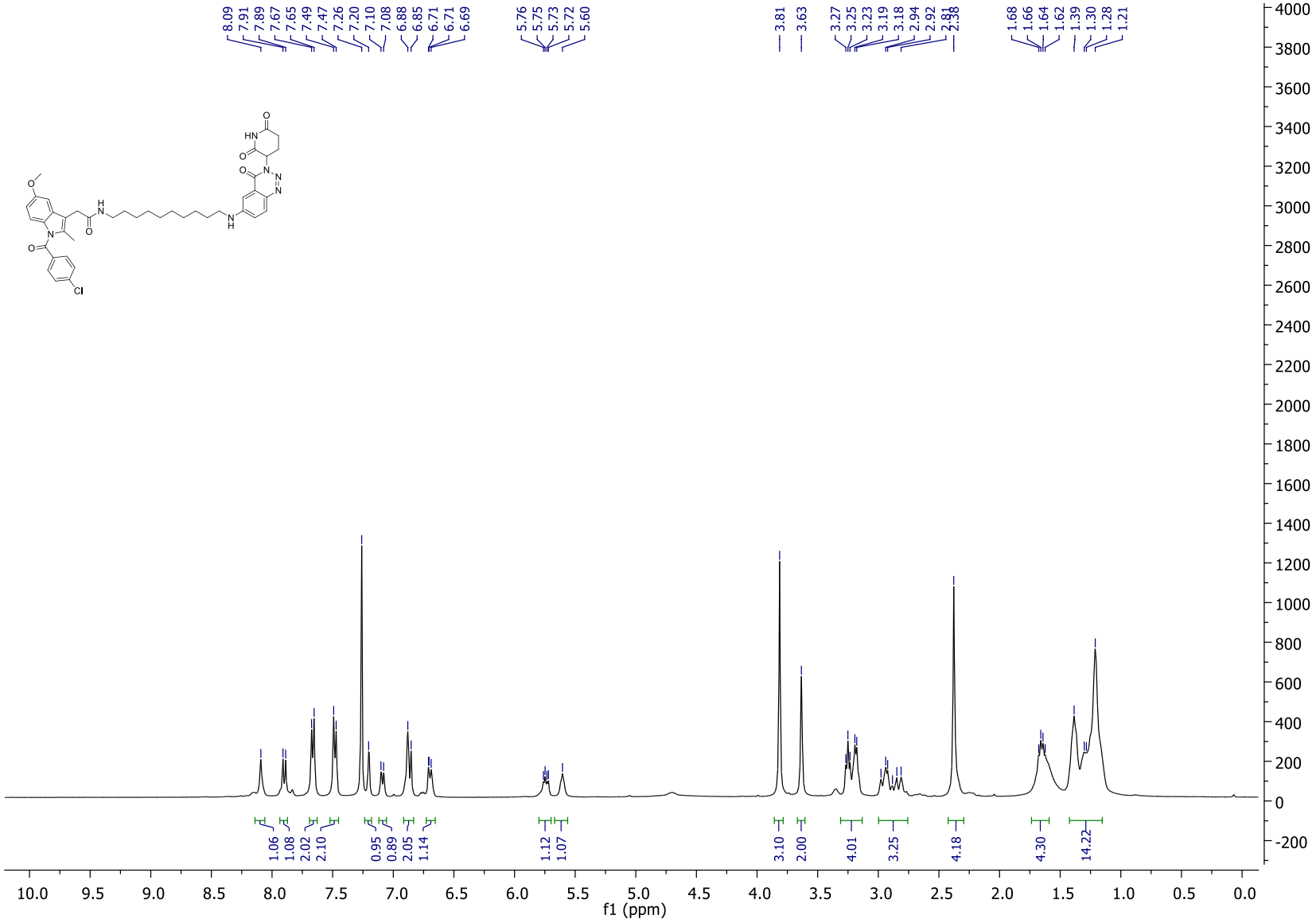
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4a.**



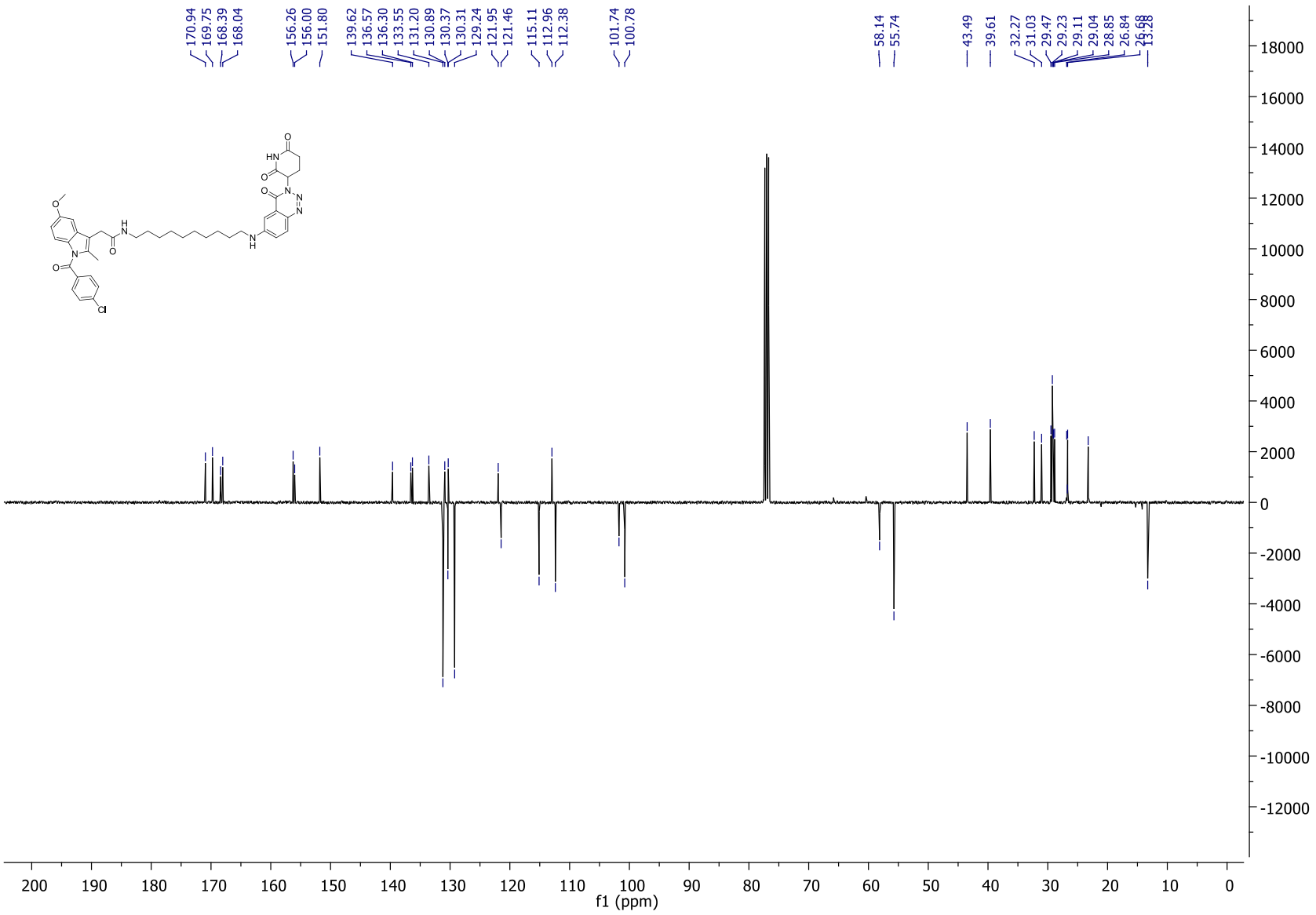
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4a.**



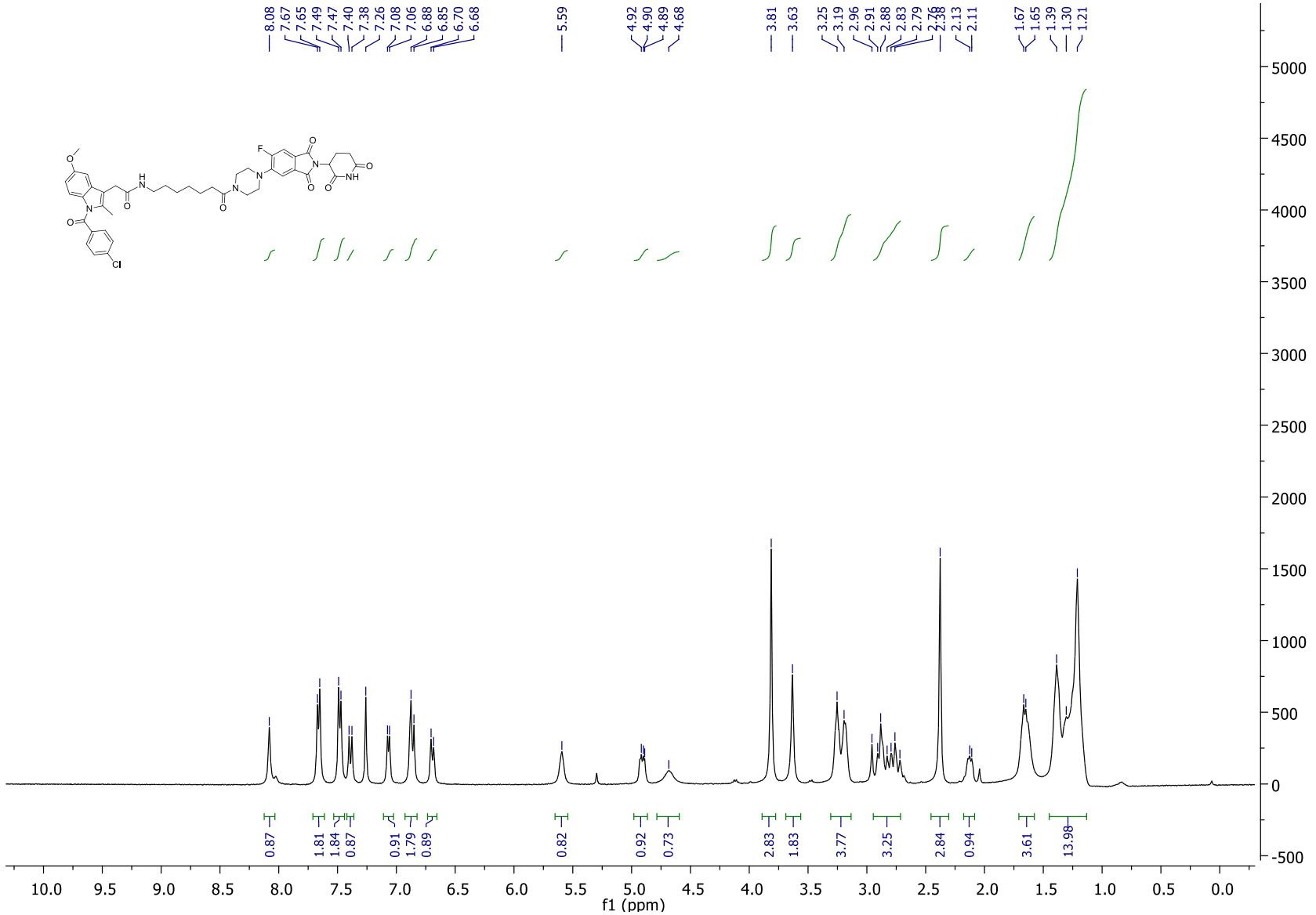
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4b.**



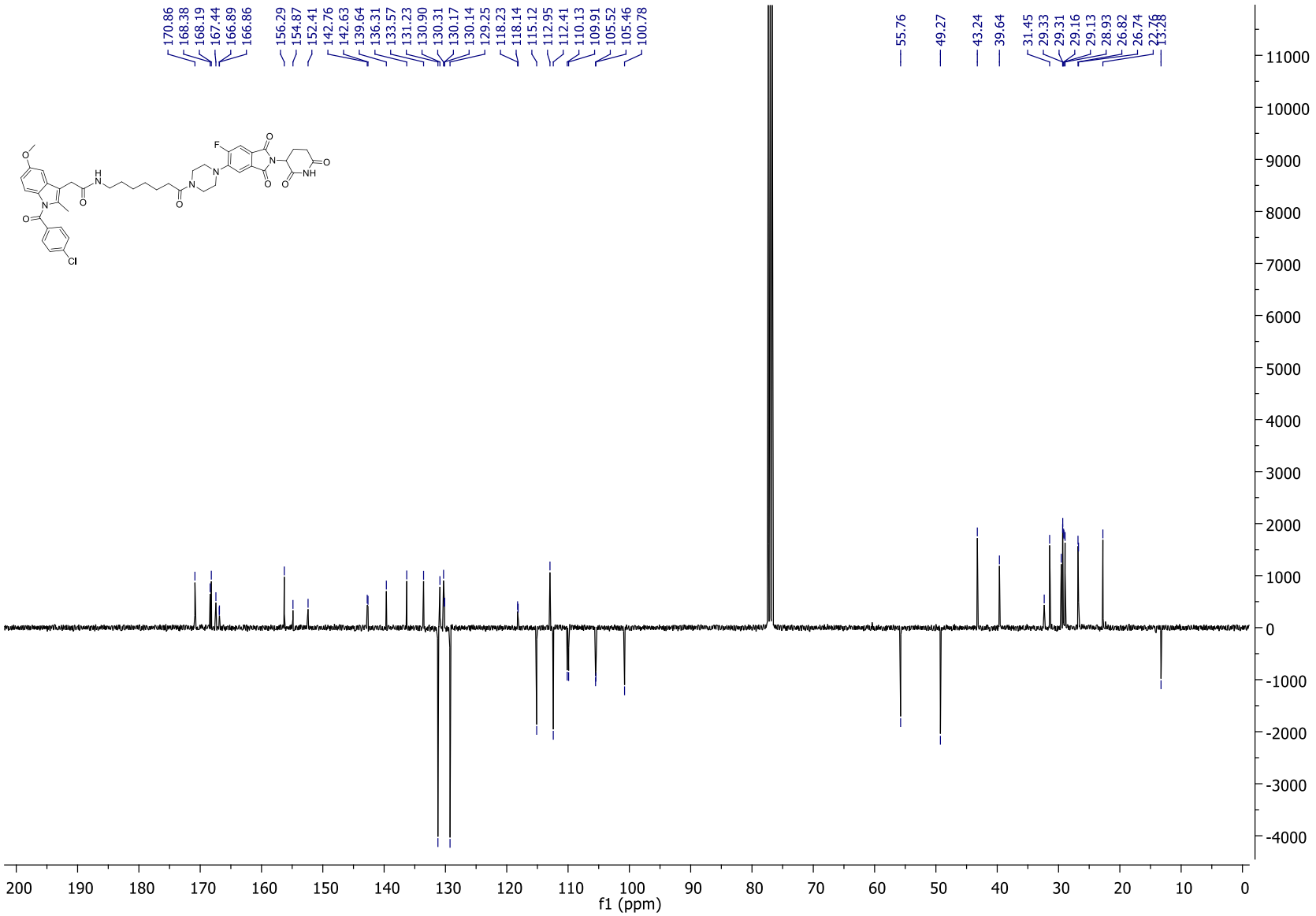
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4b.**



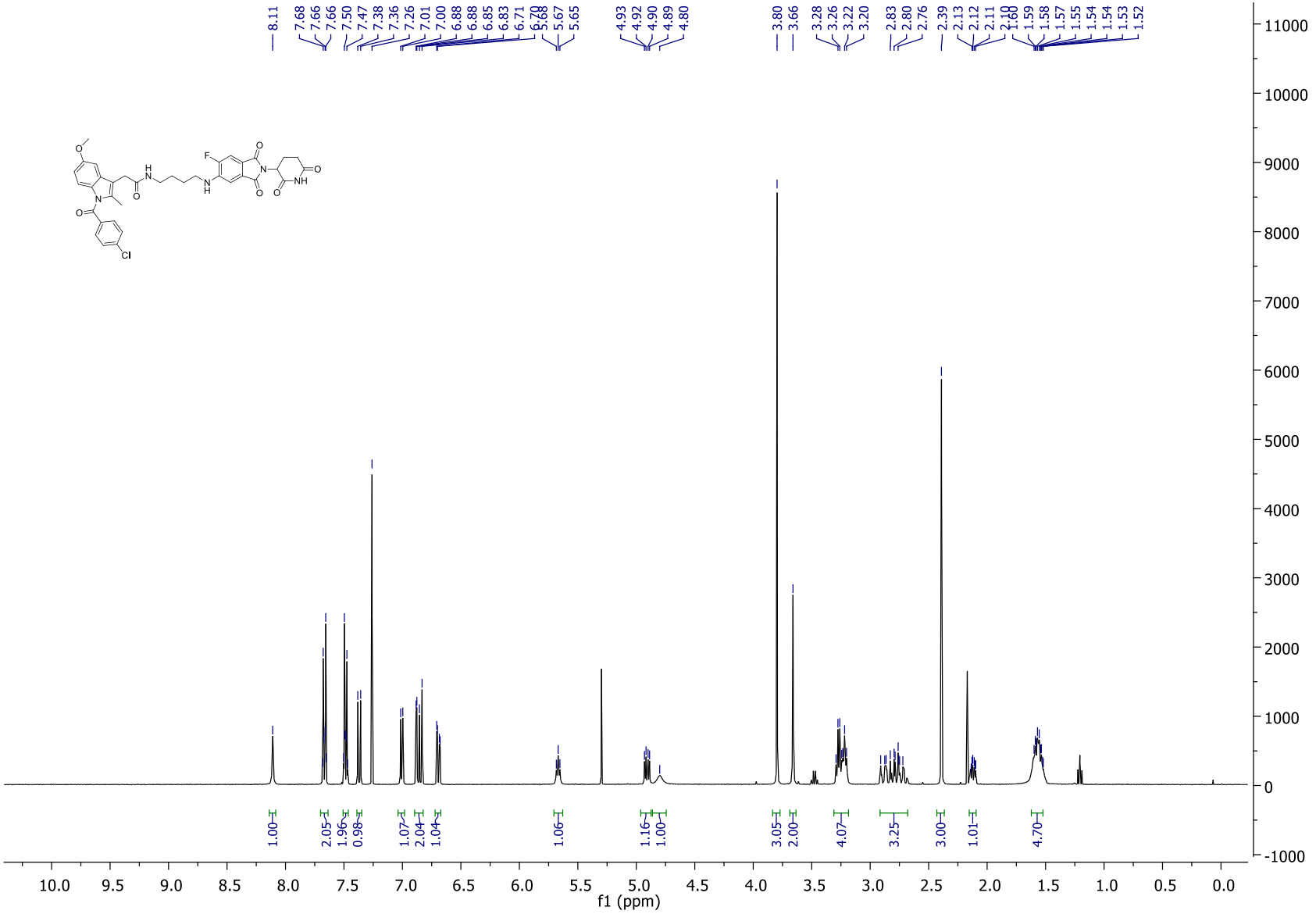
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4c.**



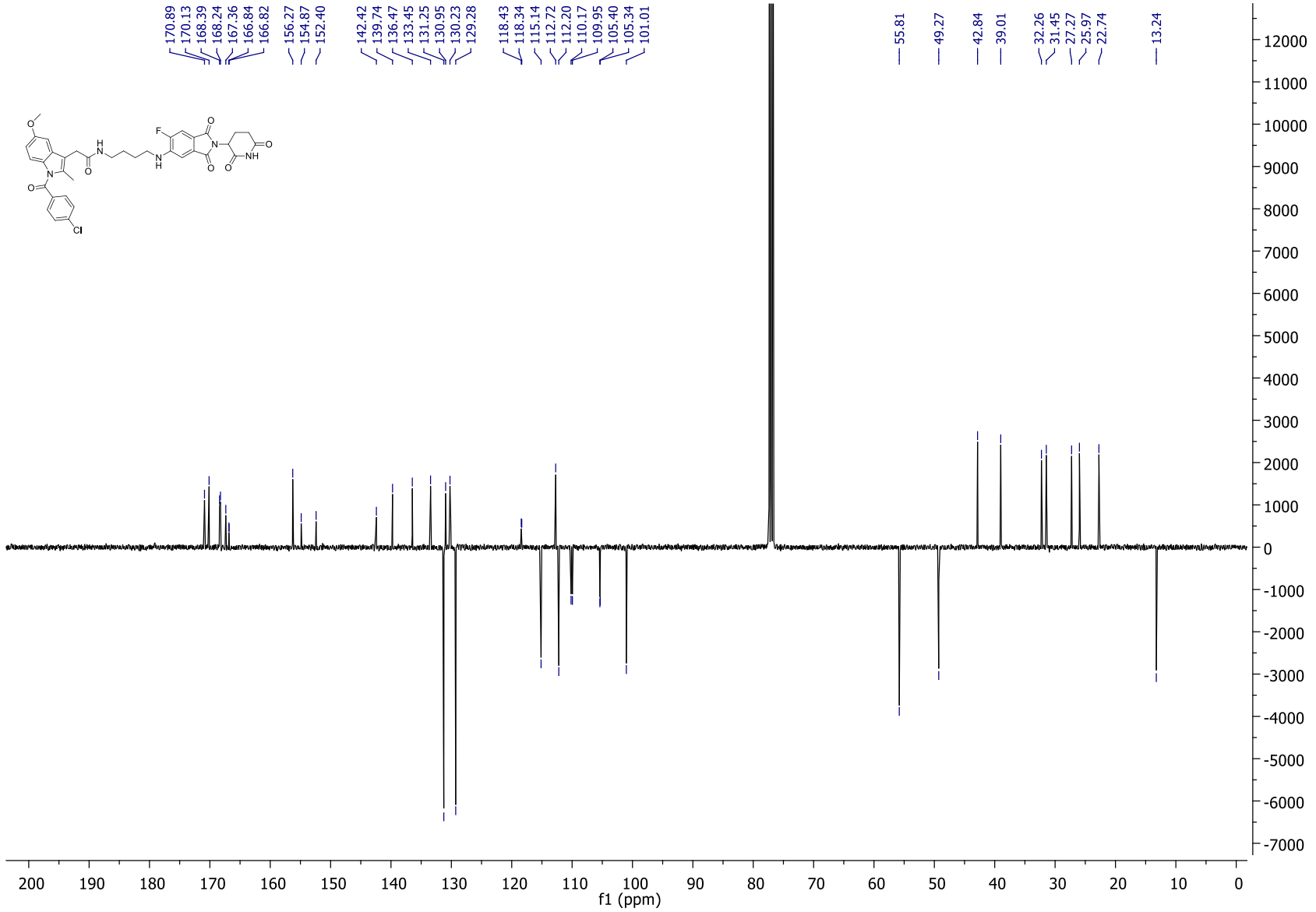
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4c.**



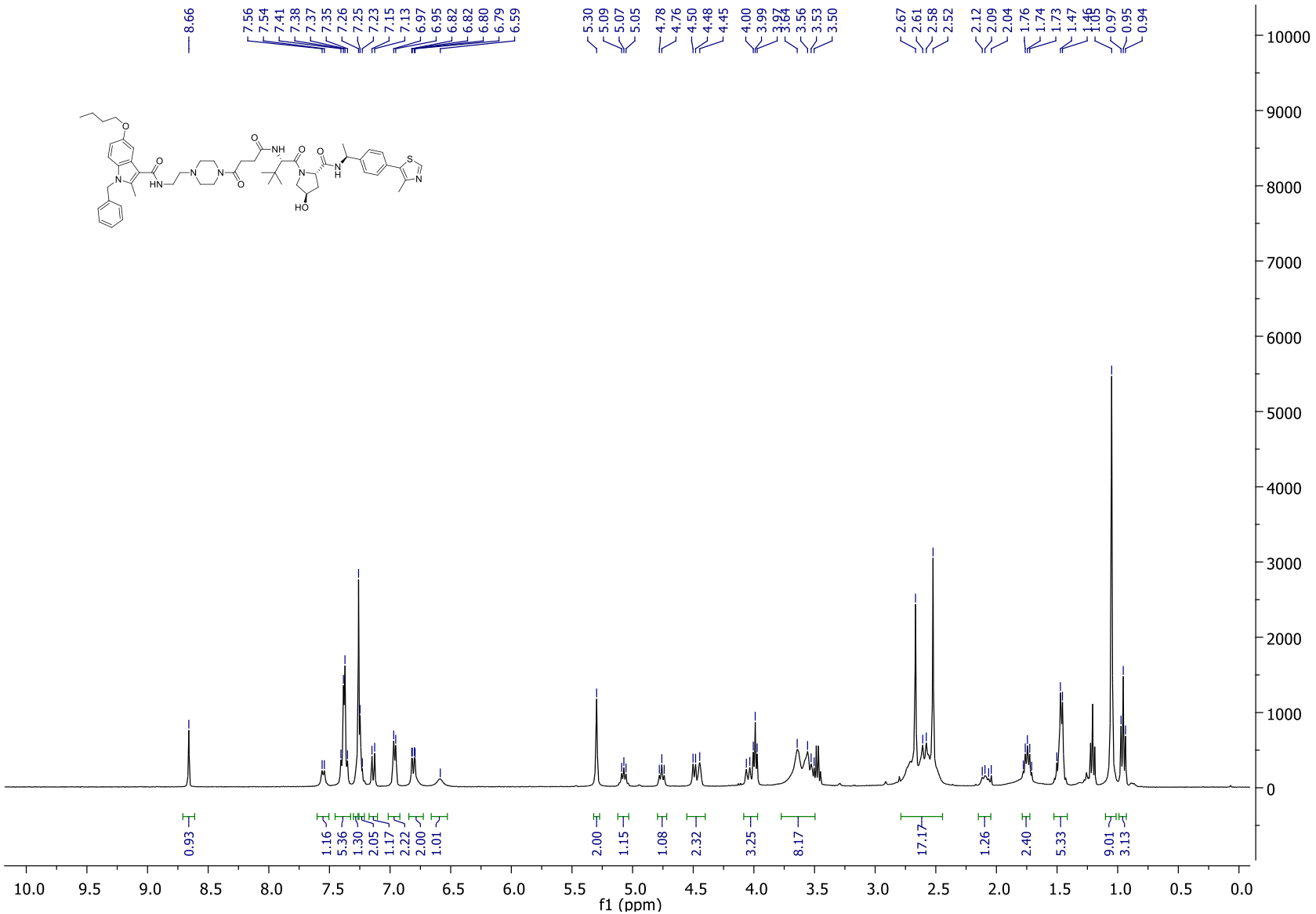
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4d.**



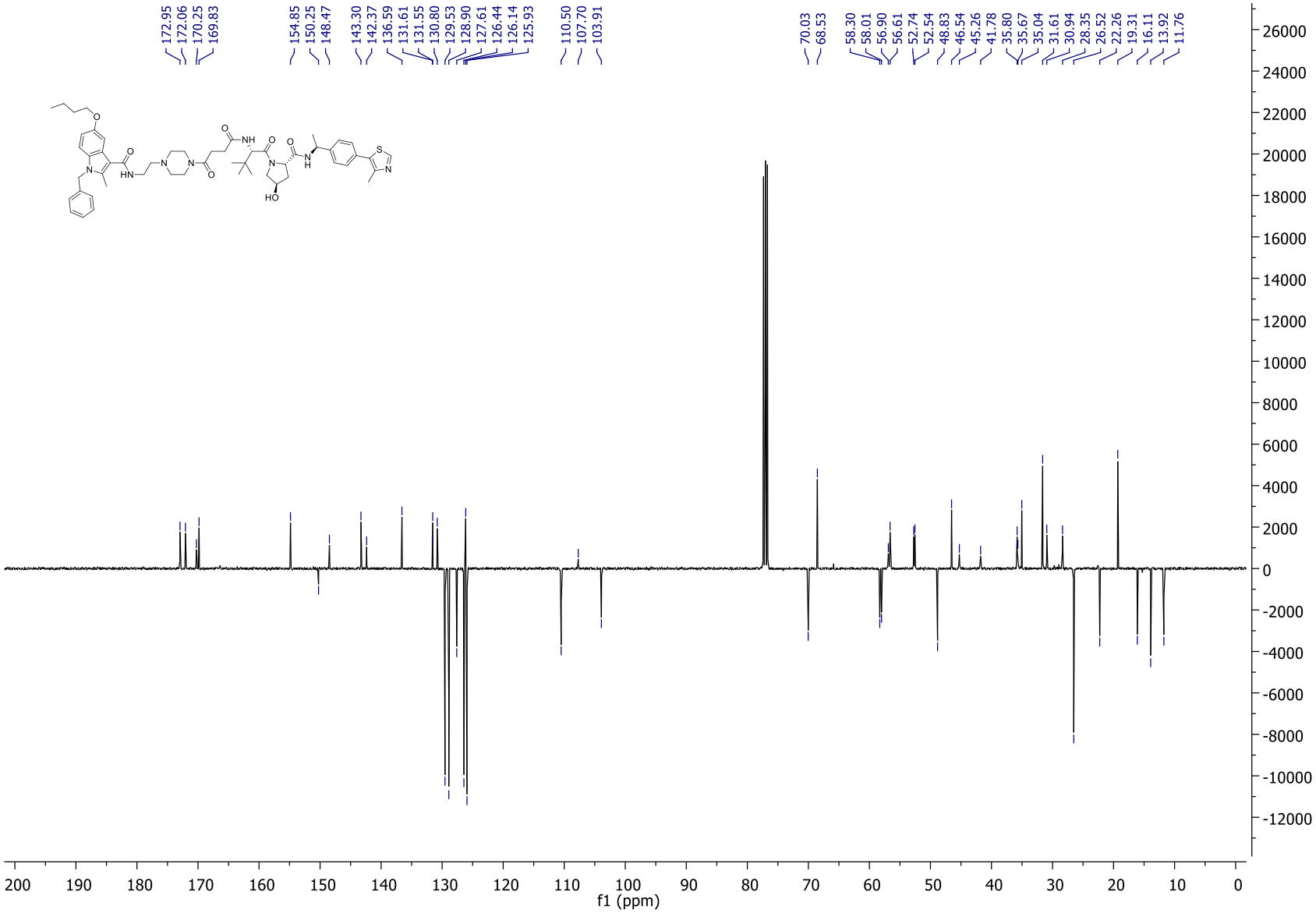
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4d.**



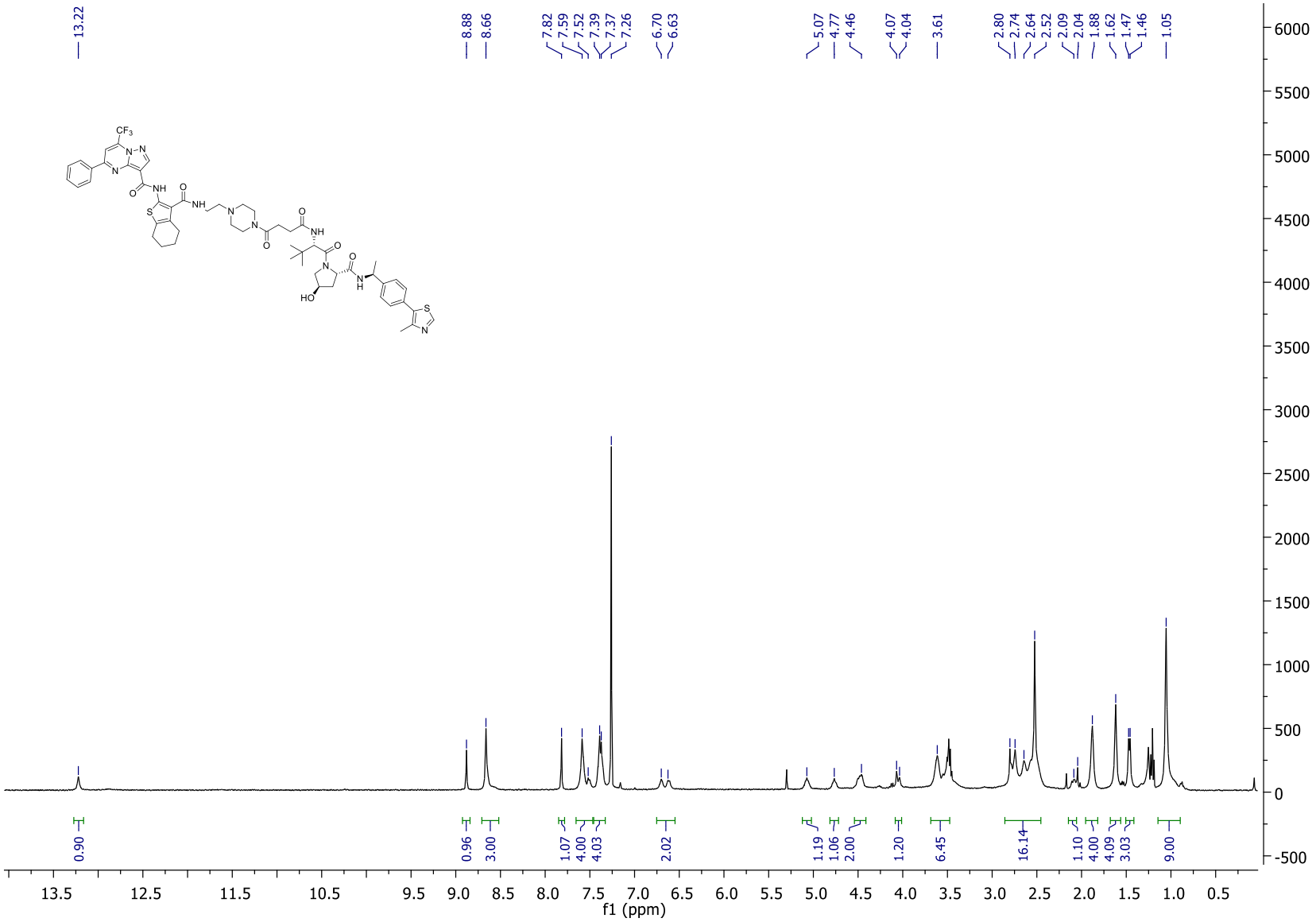
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5a.**



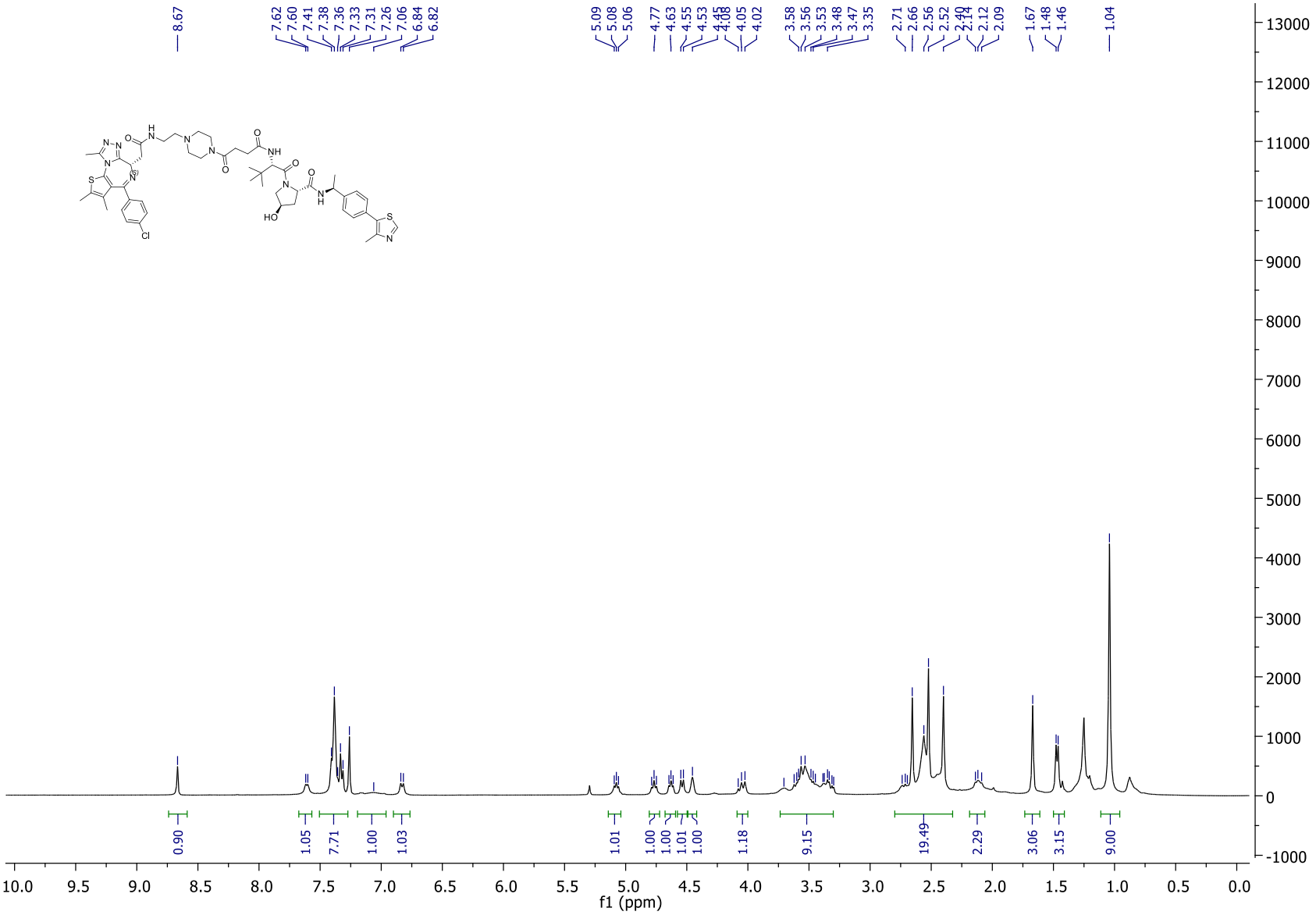
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **5a.**



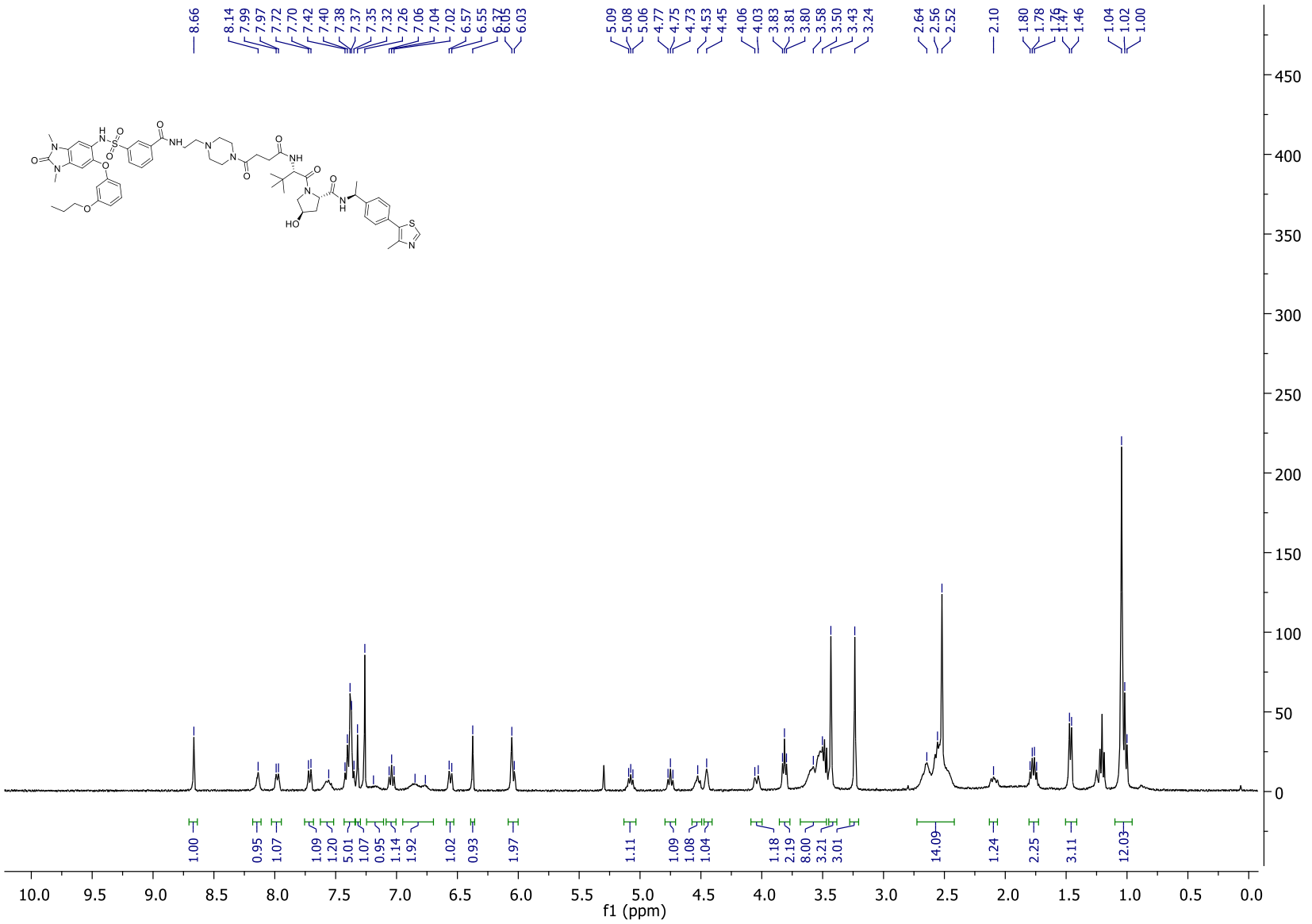
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5b.**



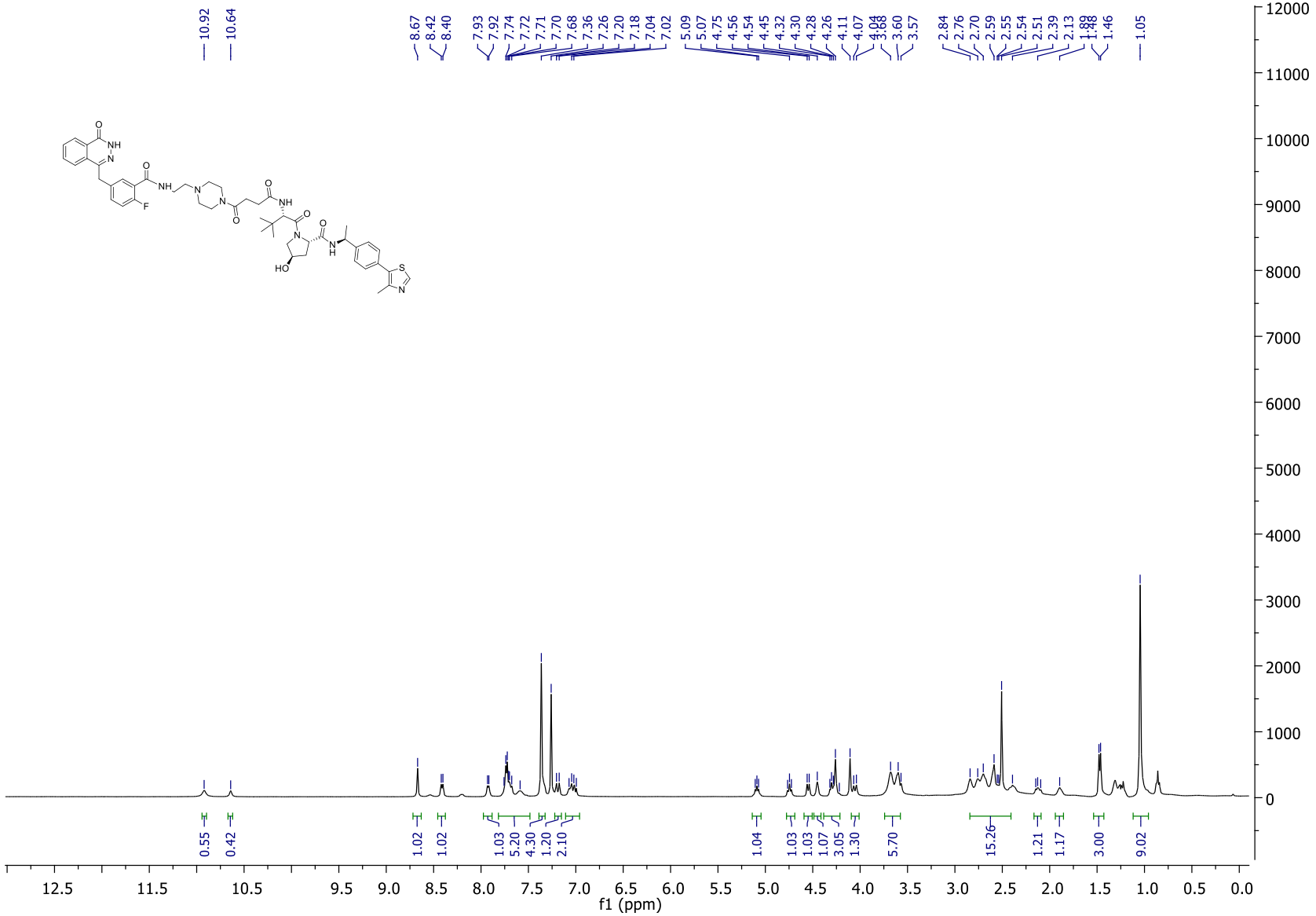
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5c.**



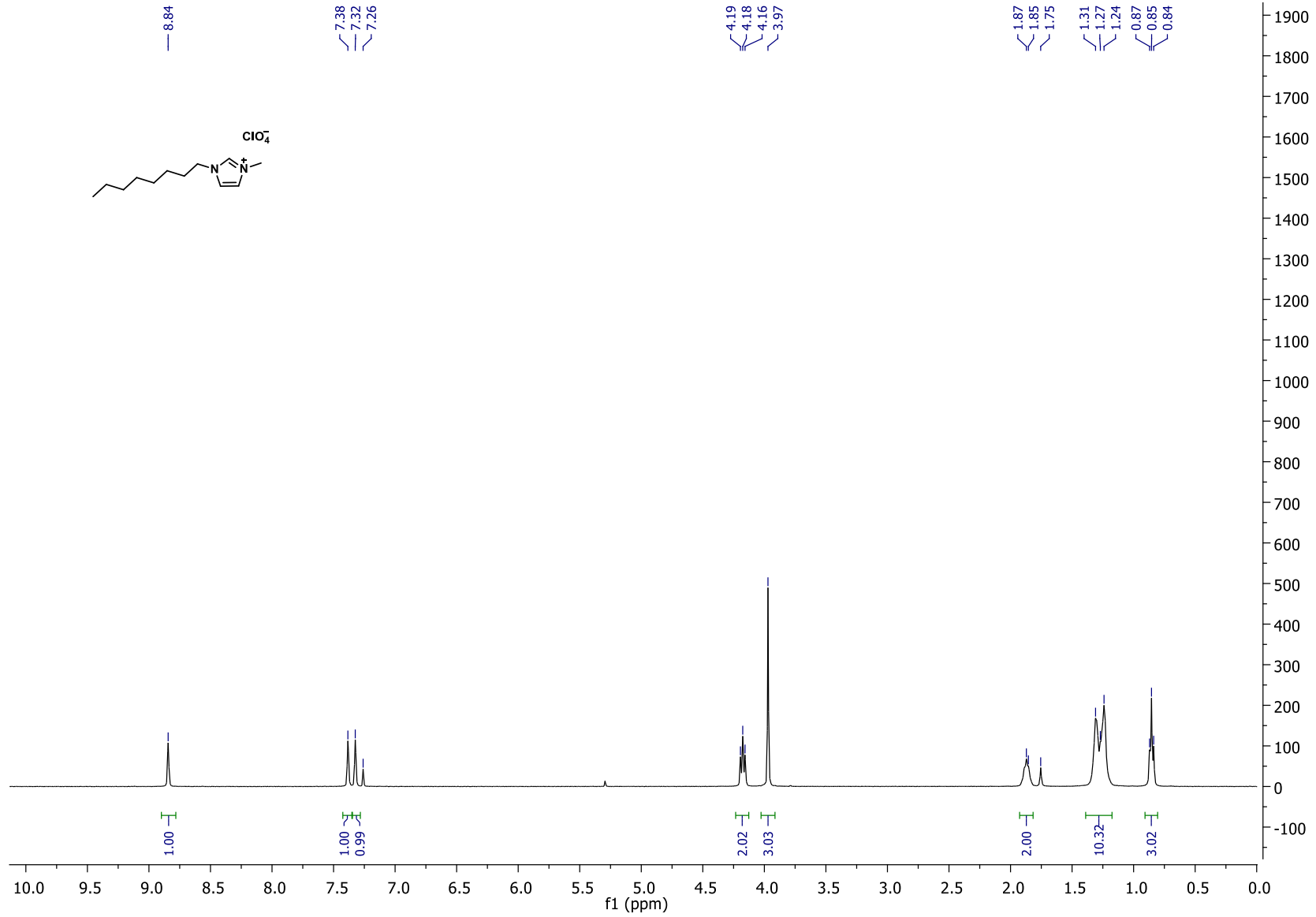
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5d.**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5e.**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **[OMIM][ClO_4]**.

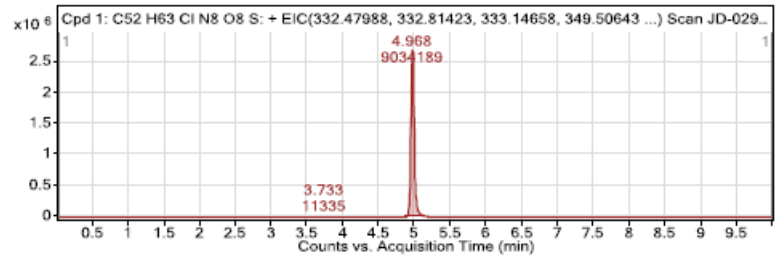


HRMS spectrum of compound **PROTAC 3a**.

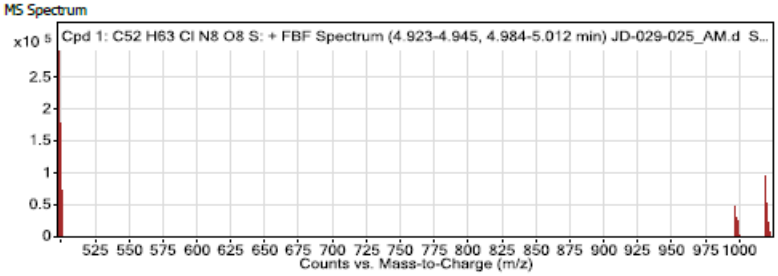
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C52 H63 Cl N8 O8 S	4.968	994.42088	292185	C52 H63 Cl N8 O8 S	994.41781	3.09	C52 H63 Cl N8 O8 S	C52 H63 Cl N8 O8 S

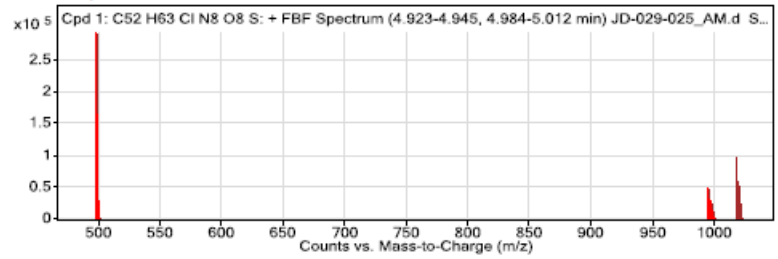
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C52 H63 Cl N8 O8 S	498.21744	4.968	Find By Formula	994.42088



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

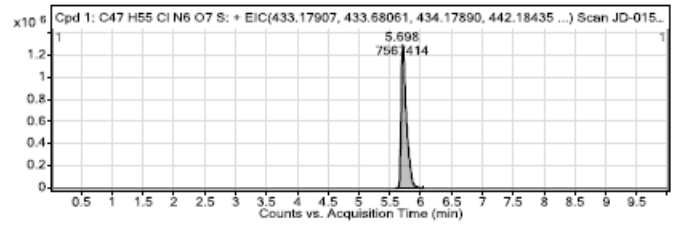
m/z	z	Abund	Formula	Ion
498.21744	2	292184.53	C52H63ClN8O8S	(M+2H)+2
498.71928	2	178787.48	C52H63ClN8O8S	(M+2H)+2
499.21781	2	162168.19	C52H63ClN8O8S	(M+2H)+2
499.71859	2	73976.98	C52H63ClN8O8S	(M+2H)+2
995.42844	1	48624.58	C52H63ClN8O8S	(M+H)+
996.43083	1	29388.76	C52H63ClN8O8S	(M+H)+
997.42813	1	26311.72	C52H63ClN8O8S	(M+H)+
1017.41096	1	96182.16	C52H63ClN8O8S	(M+Na)+
1018.41337	1	59110	C52H63ClN8O8S	(M+Na)+
1019.41096	1	52788.61	C52H63ClN8O8S	(M+Na)+

HRMS spectrum of compound **3b**.

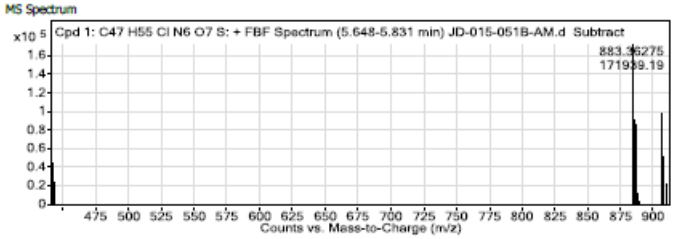
Compound Table

Compound Label	Data File	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C47 H55 Cl N6 O7 S	JD-015-051B-AM.d	5.698	882.35601	171939	C47 H55 Cl N6 O7 S	882.35415	2.11	C47 H55 Cl N6 O7 S	C47 H55 Cl N6 O7 S

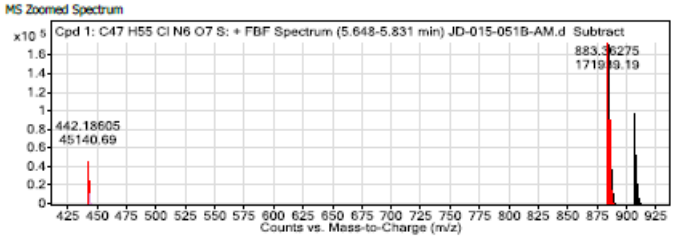
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C47 H55 Cl N6 O7 S	883.36275	5.698	Find By Formula	882.35601



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

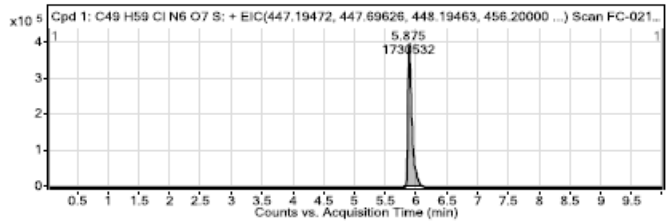
m/z	z	Abund	Formula	Ion
442.18605	2	45140.69	C47H55ClN6O7S	(M+2H)+2
442.68742	2	24522.23	C47H55ClN6O7S	(M+2H)+2
443.18587	2	23375.59	C47H55ClN6O7S	(M+2H)+2
883.36275	1	171939.19	C47H55ClN6O7S	(M+H)+
884.3662	1	92364.96	C47H55ClN6O7S	(M+H)+
885.36311	1	86414.78	C47H55ClN6O7S	(M+H)+
886.36438	1	37871.07	C47H55ClN6O7S	(M+H)+
905.34529	1	98301.53	C47H55ClN6O7S	(M+Na)+
906.34792	1	52567.24	C47H55ClN6O7S	(M+Na)+
907.34502	1	49292.28	C47H55ClN6O7S	(M+Na)+

HRMS spectrum of compound **3c**.

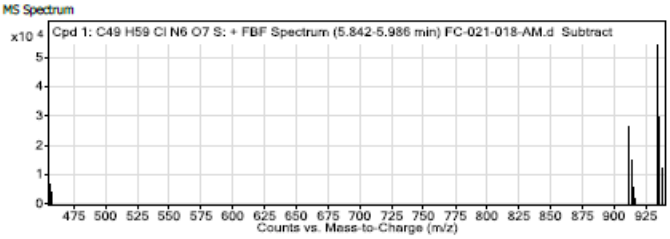
Compound Table

Compound Label	Data File	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C49 H59 Cl N6 O7 S	FC-021-018-AM.d	5.875	910.38668	26227	C49 H59 Cl N6 O7 S	910.38545	1.36	C49 H59 Cl N6 O7 S	C49 H59 Cl N6 O7 S

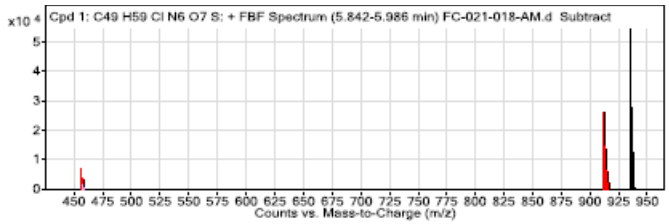
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C49 H59 Cl N6 O7 S	911.39345	5.875	Find By Formula	910.38668



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

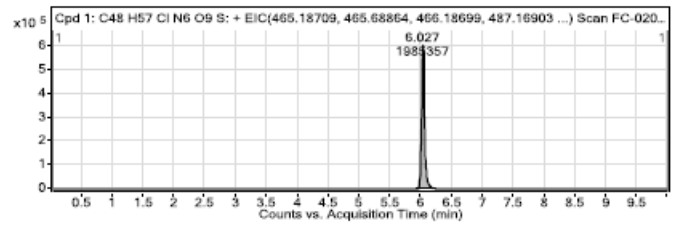
m/z	z	Abund	Formula	Ion
456.20144	2	6875.84	C49H59ClN6O7S	(M+2H)+2
911.39345	1	26226.95	C49H59ClN6O7S	(M+H)+
912.39634	1	15032.21	C49H59ClN6O7S	(M+H)+
913.3937	1	13657.29	C49H59ClN6O7S	(M+H)+
914.39477	1	6146.93	C49H59ClN6O7S	(M+H)+
933.37621	1	54372.49	C49H59ClN6O7S	(M+Na)+
934.3788	1	29792.74	C49H59ClN6O7S	(M+Na)+
935.3759	1	27977.98	C49H59ClN6O7S	(M+Na)+
936.37683	1	12472.38	C49H59ClN6O7S	(M+Na)+
937.37781	1	4264.37	C49H59ClN6O7S	(M+Na)+

HRMS spectrum of compound **3d**.

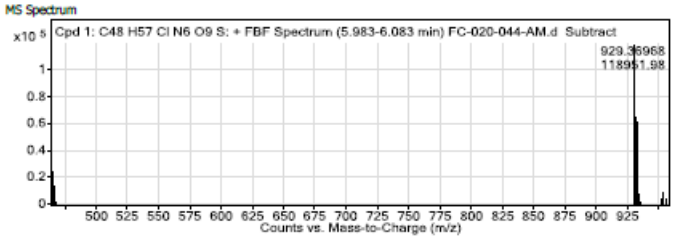
Compound Table

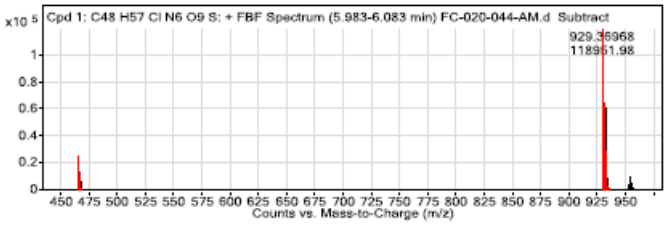
Compound Label	Data File	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C48 H57 Cl N6 O9 S	FC-020-044-AM.d	6.027	928.36302	24798	C48 H57 Cl N6 O9 S	928.35963	3.66	C48 H57 Cl N6 O9 S	C48 H57 Cl N6 O9 S

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C48 H57 Cl N6 O9 S	465.18889	6.027	Find By Formula	928.36302



MS Spectrum





MS Spectrum Peak List

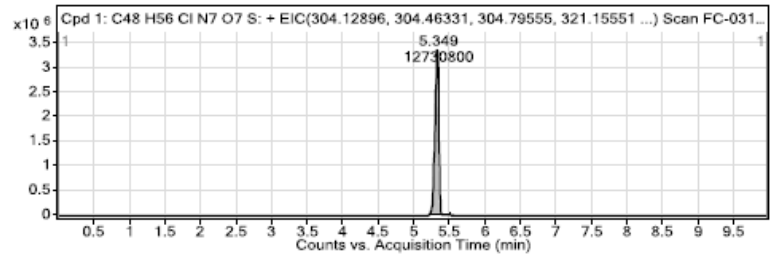
m/z	z	Abund	Formula	Ion
465.18889	2	24798.13	C48H57ClN6O9S	(M+2H)+2
465.69031	2	13926.89	C48H57ClN6O9S	(M+2H)+2
466.1888	2	13262.13	C48H57ClN6O9S	(M+2H)+2
929.36968	1	118951.98	C48H57ClN6O9S	(M+H)+
930.37273	1	65030.77	C48H57ClN6O9S	(M+H)+
931.36964	1	61329.72	C48H57ClN6O9S	(M+H)+
932.37069	1	26586.57	C48H57ClN6O9S	(M+H)+
933.37099	1	8886.37	C48H57ClN6O9S	(M+H)+
951.35119	1	4327.28	C48H57ClN6O9S	(M+Na)+
953.36063	1	9669.76	C48H57ClN6O9S	(M+Na)+

HRMS spectrum of compound **3e**.

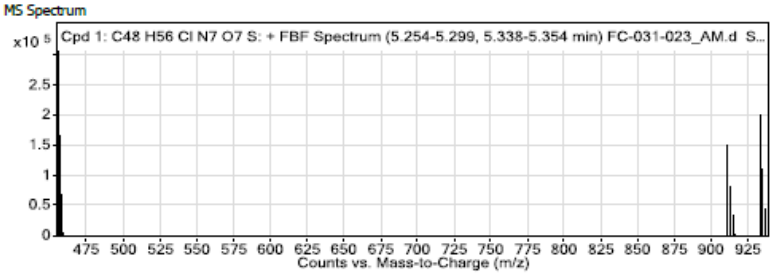
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C48 H56 Cl N7 O7 S	5.315	909.36847	201030	C48 H56 Cl N7 O7 S	909.36505	3.76	C48 H56 Cl N7 O7 S	C48 H56 Cl N7 O7 S

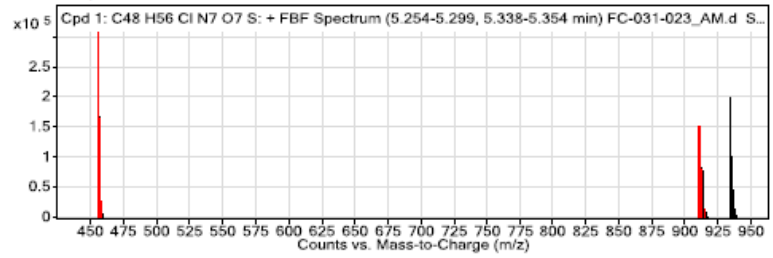
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C48 H56 Cl N7 O7 S	932.3569	5.315	Find By Formula	909.36847



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

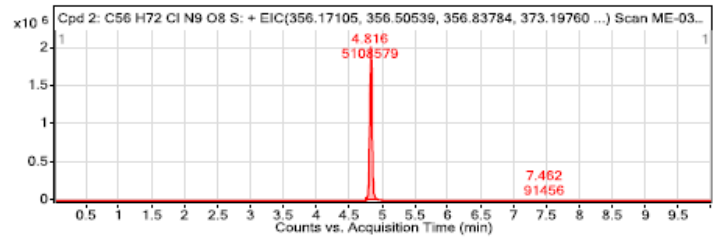
m/z	z	Abund	Formula	Ion
455.69139	2	306398.03	C48H56ClN7O7S	(M+2H)+2
456.19341	2	167854.91	C48H56ClN7O7S	(M+2H)+2
456.69202	2	159730.44	C48H56ClN7O7S	(M+2H)+2
457.19283	2	68999.56	C48H56ClN7O7S	(M+2H)+2
910.37507	1	151896.14	C48H56ClN7O7S	(M+H)+
911.37873	1	84353.55	C48H56ClN7O7S	(M+H)+
912.37566	1	78671.23	C48H56ClN7O7S	(M+H)+
932.3569	1	201029.92	C48H56ClN7O7S	(M+Na)+
933.36058	1	110964.48	C48H56ClN7O7S	(M+Na)+
934.35756	1	103203.13	C48H56ClN7O7S	(M+Na)+

HRMS spectrum of compound **3f**.

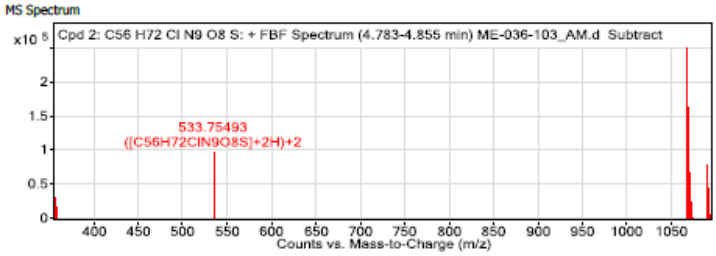
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 2: C56 H72 Cl N9 O8 S	4.816	1065.49444	80378	C56 H72 Cl N9 O8 S	1065.49131	2.94	C56 H72 Cl N9 O8 S	C56 H72 Cl N9 O8 S

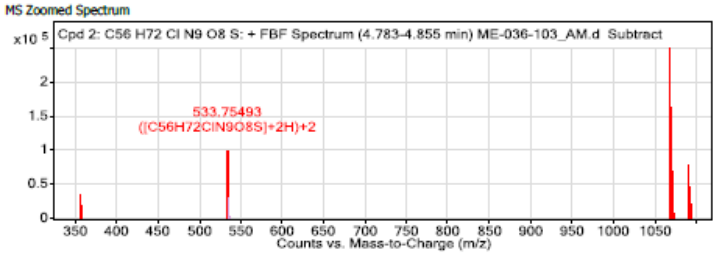
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 2: C56 H72 Cl N9 O8 S	1088.4833	4.816	Find By Formula	1065.49444



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

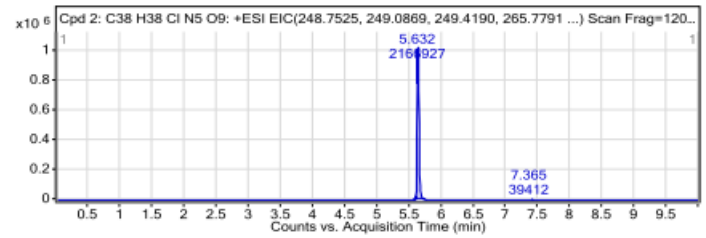
m/z	z	Abund	Formula	Ion
356.17345	3	32519.44	C56H72ClN9O8S	(M+3H)+3
533.75493	2	99267.37	C56H72ClN9O8S	(M+2H)+2
534.25669	2	64857.06	C56H72ClN9O8S	(M+2H)+2
534.75562	2	57416.65	C56H72ClN9O8S	(M+2H)+2
1066.50067	1	250044.34	C56H72ClN9O8S	(M+H)+
1067.50414	1	164170.97	C56H72ClN9O8S	(M+H)+
1068.50175	1	146343.2	C56H72ClN9O8S	(M+H)+
1069.50303	1	69081.34	C56H72ClN9O8S	(M+H)+
1088.4833	1	80377.77	C56H72ClN9O8S	(M+Na)+
1089.48591	1	51687.82	C56H72ClN9O8S	(M+Na)+

HRMS spectrum of compound **4a**.

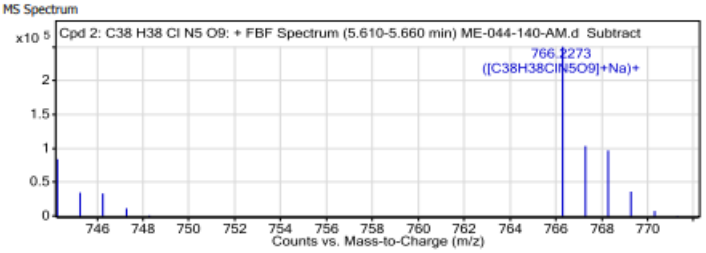
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 2: C38 H38 Cl N5 O9	5.632	743.2381	84868	C38 H38 Cl N5 O9	743.2358	3.11	C38 H38 Cl N5 O9	C38 H38 Cl N5 O9

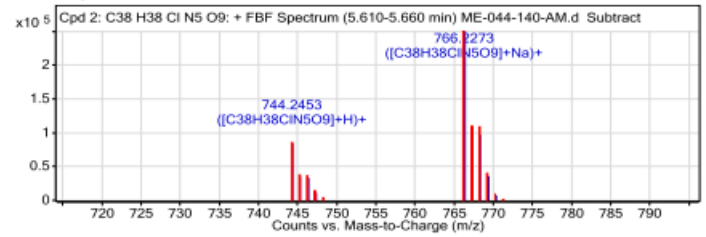
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 2: C38 H38 Cl N5 O9	744.2453	5.632	Find By Formula	743.2381



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

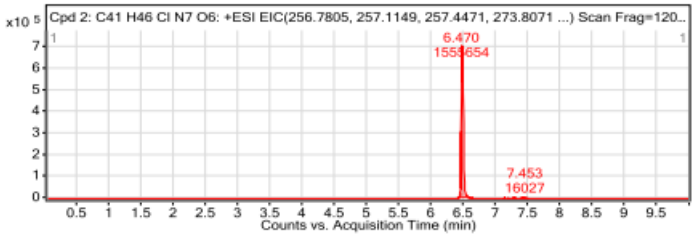
m/z	z	Abund	Formula	Ion
744.2453	1	84867.77	C38H38ClN5O9	(M+H)+
745.2482	1	35782.81	C38H38ClN5O9	(M+H)+
746.2442	1	34362.72	C38H38ClN5O9	(M+H)+
747.2466	1	12733.89	C38H38ClN5O9	(M+H)+
748.2484	1	3141.33	C38H38ClN5O9	(M+H)+
766.2273	1	250712.08	C38H38ClN5O9	(M+Na)+
767.2308	1	104694.13	C38H38ClN5O9	(M+Na)+
768.2271	1	97653.99	C38H38ClN5O9	(M+Na)+
769.2284	1	37000.9	C38H38ClN5O9	(M+Na)+
770.2307	1	9044.77	C38H38ClN5O9	(M+Na)+

HRMS spectrum of compound **4b**.

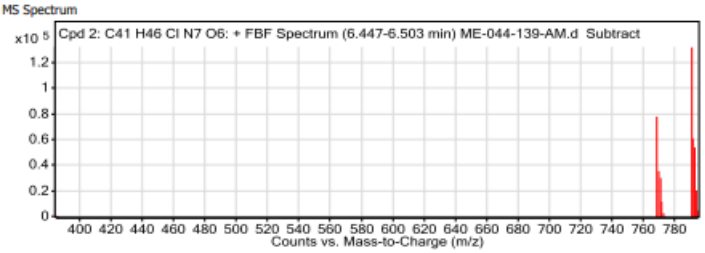
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 2: C41 H46 Cl N7 O6	6.47	767.322	78305	C41 H46 Cl N7 O6	767.3198	2.8	C41 H46 Cl N7 O6	C41 H46 Cl N7 O6

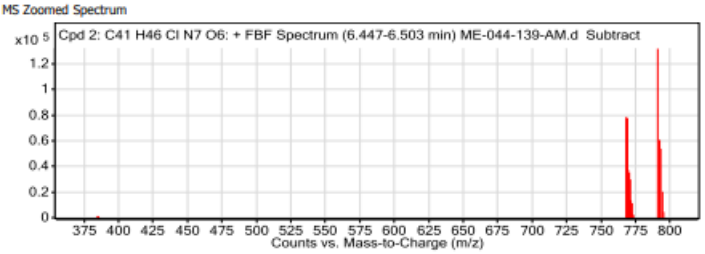
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 2: C41 H46 Cl N7 O6	768.3291	6.47	Find By Formula	767.322



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

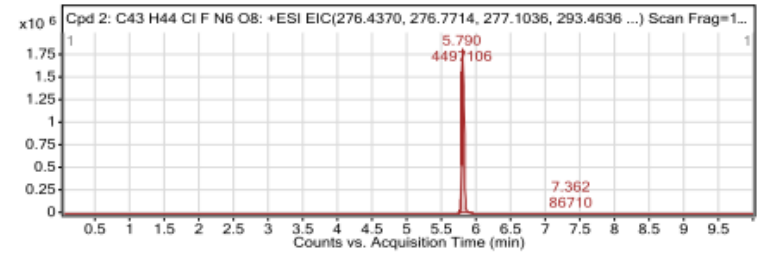
m/z	z	Abund	Formula	Ion
384.6687	2	1446.25	C41H46ClN7O6	(M+2H)+2
768.3291	1	78304.8	C41H46ClN7O6	(M+H)+
769.3319	1	36003.53	C41H46ClN7O6	(M+H)+
770.3287	1	30892.79	C41H46ClN7O6	(M+H)+
771.3297	1	12404.31	C41H46ClN7O6	(M+H)+
790.3115	1	132210.61	C41H46ClN7O6	(M+Na)+
791.3142	1	61584.04	C41H46ClN7O6	(M+Na)+
792.3107	1	54281.76	C41H46ClN7O6	(M+Na)+
793.3123	1	21130.13	C41H46ClN7O6	(M+Na)+
794.3146	1	5356.32	C41H46ClN7O6	(M+Na)+

HRMS spectrum of compound **4c**.

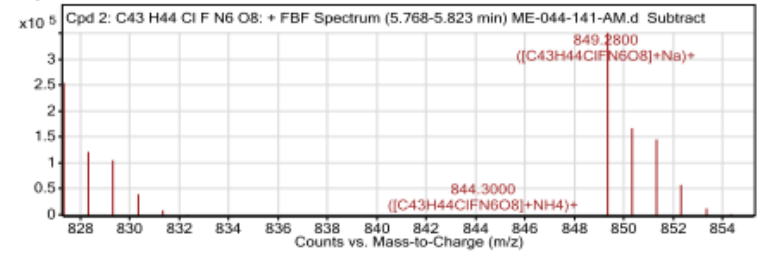
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 2: C43 H44 Cl F N6 O8	5.79	826.2913	352577	C43 H44 Cl F N6 O8	826.2893	2.34	C43 H44 Cl F N6 O8	C43 H44 Cl F N6 O8

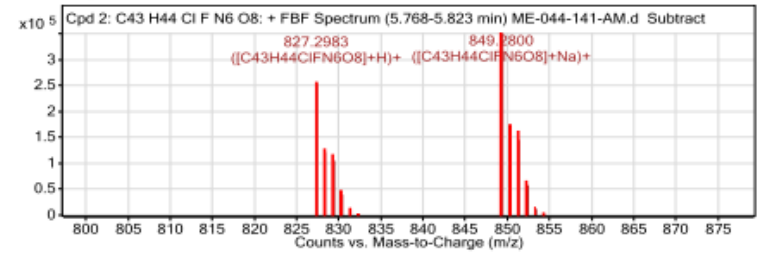
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 2: C43 H44 Cl F N6 O8	849.28	5.79	Find By Formula	826.2913



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

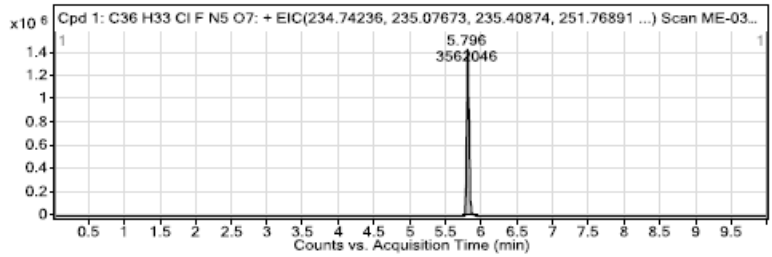
m/z	z	Abund	Formula	Ion
827.2983	1	255453.64	C43H44ClFN6O8	(M+H)+
828.302	1	122989.24	C43H44ClFN6O8	(M+H)+
829.2989	1	108017.4	C43H44ClFN6O8	(M+H)+
830.3001	1	42472.6	C43H44ClFN6O8	(M+H)+
844.3	1	329.53	C43H44ClFN6O8	(M+NH4)+
849.28	1	352576.63	C43H44ClFN6O8	(M+Na)+
850.2839	1	169403.06	C43H44ClFN6O8	(M+Na)+
851.2808	1	147595.5	C43H44ClFN6O8	(M+Na)+
852.2817	1	59192.41	C43H44ClFN6O8	(M+Na)+
853.2832	1	14819.38	C43H44ClFN6O8	(M+Na)+

HRMS spectrum of compound **4d**.

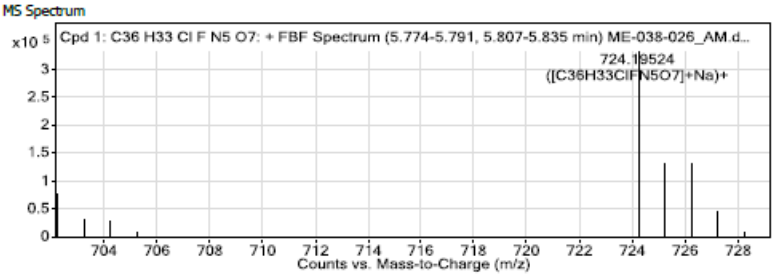
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C36 H33 Cl F N5 O7	5.796	701.20641	78517	C36 H33 Cl F N5 O7	701.20525	1.65	C36 H33 Cl F N5 O7	C36 H33 Cl F N5 O7

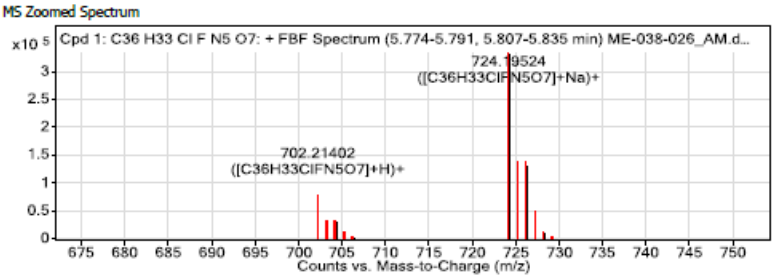
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C36 H33 Cl F N5 O7	702.21402	5.796	Find By Formula	701.20641



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

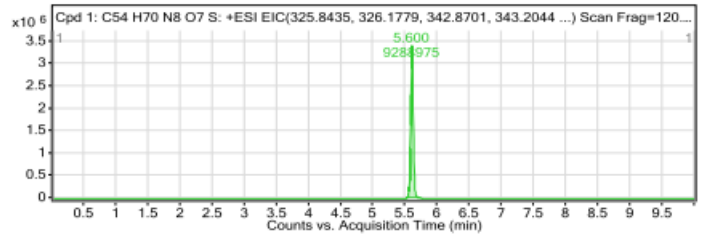
m/z	z	Abund	Formula	Ion
702.21402	1	78516.67	C36H33ClFN5O7	(M+H)+
703.2166	1	32093.21	C36H33ClFN5O7	(M+H)+
704.21238	1	31533.84	C36H33ClFN5O7	(M+H)+
705.2146	1	10723.23	C36H33ClFN5O7	(M+H)+
706.21717	1	2351.17	C36H33ClFN5O7	(M+H)+
724.19524	1	332381.94	C36H33ClFN5O7	(M+Na)+
725.19923	1	132590.22	C36H33ClFN5O7	(M+Na)+
726.19526	1	131682.41	C36H33ClFN5O7	(M+Na)+
727.19689	1	46152.17	C36H33ClFN5O7	(M+Na)+
728.19828	1	10438.37	C36H33ClFN5O7	(M+Na)+

HRMS spectrum of compound **5a**.

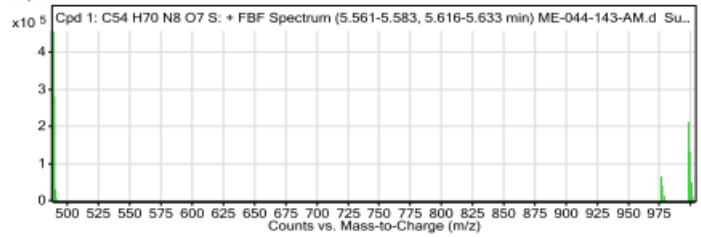
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C54 H70 N8 O7 S	5.6	974.5123	69462	C54 H70 N8 O7 S	974.5088	3.53	C54 H70 N8 O7 S	C54 H70 N8 O7 S

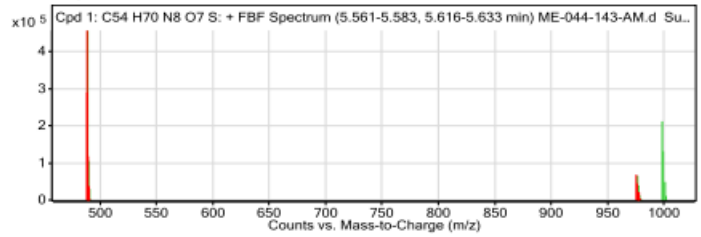
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C54 H70 N8 O7 S	975.5188	5.6	Find By Formula	974.5123



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

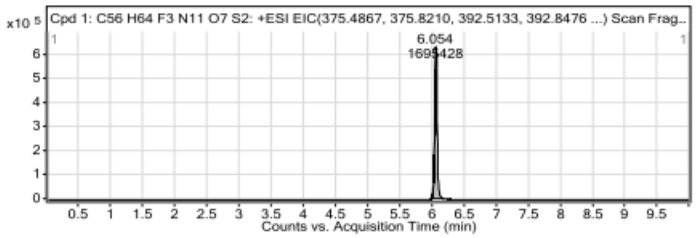
m/z	z	Abund	Formula	Ion
488.2633	2	457312.13	C54H70N8O7S	(M+2H)+2
488.7651	2	281978.75	C54H70N8O7S	(M+2H)+2
489.2664	2	108124.24	C54H70N8O7S	(M+2H)+2
489.7668	2	32794.78	C54H70N8O7S	(M+2H)+2
975.5188	1	69462.19	C54H70N8O7S	(M+H)+
976.5219	1	42891.17	C54H70N8O7S	(M+H)+
977.5236	1	16095.8	C54H70N8O7S	(M+H)+
997.5009	1	215015.28	C54H70N8O7S	(M+Na)+
998.5044	1	133789.13	C54H70N8O7S	(M+Na)+
999.5054	1	52188.84	C54H70N8O7S	(M+Na)+

HRMS spectrum of compound **5b**.

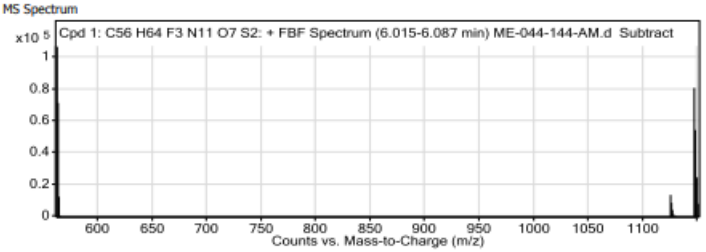
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C56 H64 F3 N11 O7 S2	6.054	1123.4417	13505	C56 H64 F3 N11 O7 S2	1123.4384	2.98	C56 H64 F3 N11 O7 S2	C56 H64 F3 N11 O7 S2

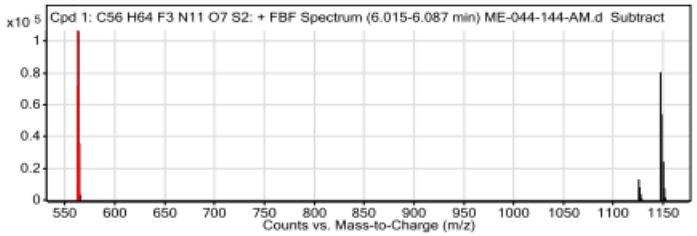
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C56 H64 F3 N11 O7 S2	1124.447	6.054	Find By Formula	1123.4417



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

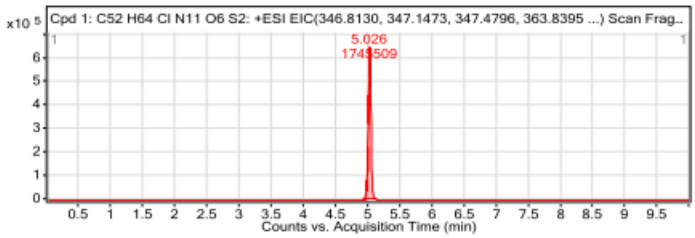
m/z	z	Abund	Formula	Ion
562.7288	2	106767.34	C56H64F3N11O7S2	(M+2H)+2
563.2302	2	71279.96	C56H64F3N11O7S2	(M+2H)+2
563.7303	2	36170.35	C56H64F3N11O7S2	(M+2H)+2
564.2302	2	12492.38	C56H64F3N11O7S2	(M+2H)+2
1124.447	1	13504.97	C56H64F3N11O7S2	(M+H)+
1125.4503	1	9060.53	C56H64F3N11O7S2	(M+H)+
1146.4297	1	80950.08	C56H64F3N11O7S2	(M+Na)+
1147.4324	1	54518.71	C56H64F3N11O7S2	(M+Na)+
1148.4328	1	24935.8	C56H64F3N11O7S2	(M+Na)+
1149.4323	1	8336.48	C56H64F3N11O7S2	(M+Na)+

HRMS spectrum of compound **5c**.

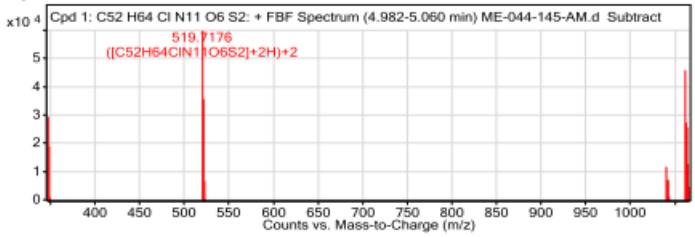
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C52 H64 Cl N11 O6 S2	5.026	1037.4204	12177	C52 H64 Cl N11 O6 S2	1037.4171	3.15	C52 H64 Cl N11 O6 S2	C52 H64 Cl N11 O6 S2

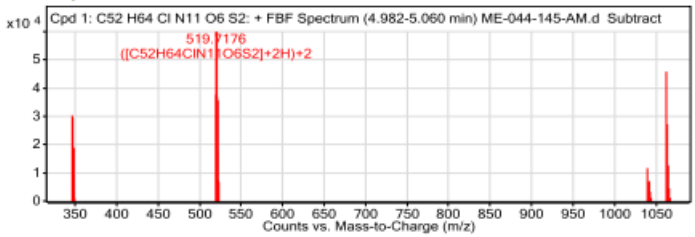
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C52 H64 Cl N11 O6 S2	1038.4252	5.026	Find By Formula	1037.4204



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

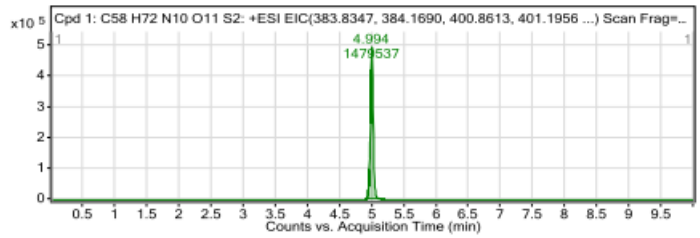
m/z	z	Abund	Formula	Ion
346.8148	3	29818.34	C52H64ClN11O6S2	(M+3H)+3
347.1491	3	18703.12	C52H64ClN11O6S2	(M+3H)+3
347.4816	3	19098.26	C52H64ClN11O6S2	(M+3H)+3
519.7176	2	60032.47	C52H64ClN11O6S2	(M+2H)+2
520.2191	2	36439.51	C52H64ClN11O6S2	(M+2H)+2
520.7178	2	35925.69	C52H64ClN11O6S2	(M+2H)+2
1038.4252	1	12177.37	C52H64ClN11O6S2	(M+H)+
1060.4079	1	46123.91	C52H64ClN11O6S2	(M+Na)+
1061.4109	1	27642.1	C52H64ClN11O6S2	(M+Na)+
1062.4076	1	26118.23	C52H64ClN11O6S2	(M+Na)+

HRMS spectrum of compound **5d**.

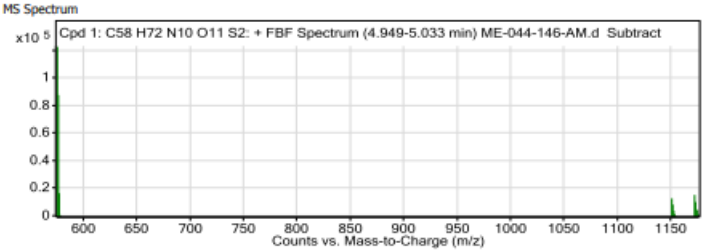
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C58 H72 N10 O11 S2	4.994	1148.4856	13116	C58 H72 N10 O11 S2	1148.4823	2.85	C58 H72 N10 O11 S2	C58 H72 N10 O11 S2

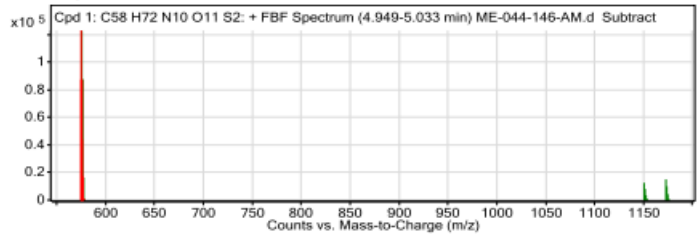
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C58 H72 N10 O11 S2	1149.4908	4.994	Find By Formula	1148.4856



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

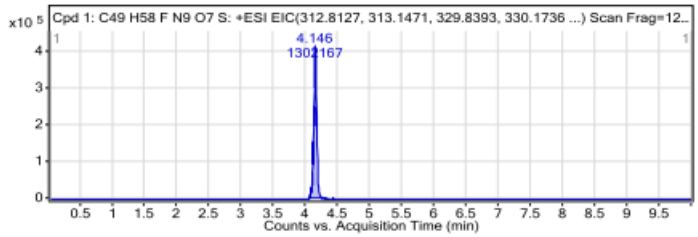
m/z	z	Abund	Formula	Ion
575.2503	2	123002.87	C58H72N10O11S2	(M+2H)+2
575.7517	2	88054.73	C58H72N10O11S2	(M+2H)+2
576.252	2	43666.48	C58H72N10O11S2	(M+2H)+2
576.7519	2	16889.85	C58H72N10O11S2	(M+2H)+2
577.2527	2	5266.69	C58H72N10O11S2	(M+2H)+2
1149.4908	1	13115.77	C58H72N10O11S2	(M+H)+
1150.4936	1	9069.57	C58H72N10O11S2	(M+H)+
1171.4731	1	15656.46	C58H72N10O11S2	(M+Na)+
1172.4762	1	10635.39	C58H72N10O11S2	(M+Na)+
1173.4765	1	5186.67	C58H72N10O11S2	(M+Na)+

HRMS spectrum of compound **5e**.

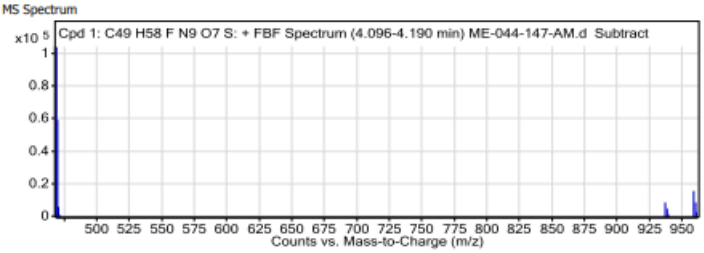
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C49 H58 F N9 O7 S	4.146	935.419	16379	C49 H58 F N9 O7 S	935.4164	2.83	C49 H58 F N9 O7 S	C49 H58 F N9 O7 S

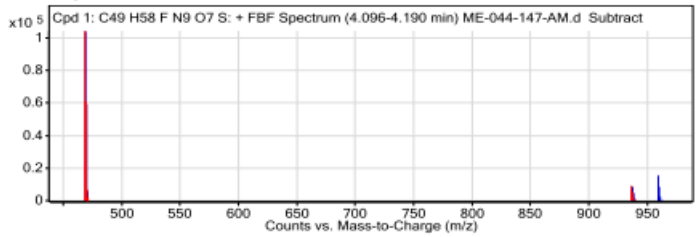
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C49 H58 F N9 O7 S	958.4065	4.146	Find By Formula	935.419



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
468.717	2	104325.62	C49H58FN9O7S	(M+2H)+2
469.2185	2	59581.66	C49H58FN9O7S	(M+2H)+2
469.7188	2	23653.47	C49H58FN9O7S	(M+2H)+2
470.2191	2	6671.06	C49H58FN9O7S	(M+2H)+2
936.4245	1	9134.8	C49H58FN9O7S	(M+H)+
937.4275	1	5207.99	C49H58FN9O7S	(M+H)+
938.4288	1	1913.74	C49H58FN9O7S	(M+H)+
958.4065	1	16379.26	C49H58FN9O7S	(M+Na)+
959.4101	1	9018.06	C49H58FN9O7S	(M+Na)+
960.41	1	3395.57	C49H58FN9O7S	(M+Na)+

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