Supplementary Information

Construction of IMiDs-based Azides Library as a Kit for PROTAC Research

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Contents of Supporting Information

1. General methods.

Chemical Materials

All chemicals were obtained from commercial suppliers (Adamas and Alfa), and used without further purification, unless otherwise indicated. HPLC preparation was performed on SHIMADZU LC-20AP instrument with original column. All new compounds were characterized by ^{1}H NMR, HRMS or ^{13}C NMR. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE III 500 MHZ (operating at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR), chemical shifts were reported in ppm relative to the residual d_6-DMSO (δ 2.50 ppm ^{1}H, δ 39.52 ppm ^{13}C), and coupling constants (*J*) are given in Hz. Multiplicities of signals are described as follows: s --- singlet, br. s --- broad singlet, d --- doublet, t --- triplet, m --- multiple. High Resolution Mass spectra were recorded on AB Triple 4600 spectrometer with acetonitrile and water as solvent. Compound **DAS-6-2-2-6-CRBN** and **dBET1** were synthesized respectively as reported (G. E. Winter, D. L. Buckley, J. Paulk and J. E. Bradner, *Science*, 2015, **348**, 1376; A. C. Lai, M. Toure, C. M. Crews *etc*. *Angew. Chem. Int. Ed*. 2016, **55**, 807.).

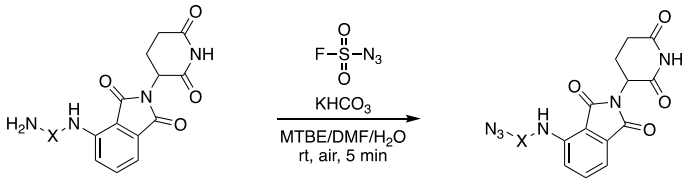
Cell lines and cell culture. The human chronic myelogenous leukemia cell line K562 and the human biphenotypic B-myelomonocytic leukemia cell line MV-4-11 were purchased from American Type Culture Collection. All these cells were cultured according to the provider's instructions and maintained at 37 °C in a humidified atmosphere containing 5% CO_2 in air.

Cell Growth Inhibition. For cell growth experiments, 4000 ~ 15000 cells/well in 100 μL were seeded into a 96-well tissue culture plate. Then compounds were diluted in the corresponding medium and then 3 ~ 5-fold serially diluted in to each well. Cells were incubated for 3 days at 37 °C in an atmosphere of 5% CO_2. Cell growth was evaluated

utilizing CCK-8 assay (CK04, Dojindo Molecular Technologies, MD), incubated for 2~4 h in the cell culture incubator, and read at 450 nm in a Microporous plate detection system (Perkin Elmer Envision, California). The readings were normalized to the DMSO-treated cells and fitted using a nonlinear regression analysis with the GraphPad Prism 6 software to obtain the IC_{50} value for each compound.

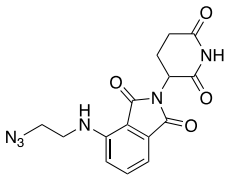
Western Blotting. 0.3×10^6 cells/ml were plated in 24- well plates and treated with compounds at the indicated concentrations and times. Cells were collected, washed with cold 1 x PBS, and lysed in 1x SDS buffer containing protease inhibitor cocktails (#539134, Merck). Protein in cell lysate was quantified by detergent compatible Bradford assay kit (#23246, Thermo). Primary antibodies used in this study include c-ABL antibody (#2862, Cell Signaling Technology) and BRD4 Antibody (#13440S, Cell Signaling Technology). The Millipose Immobilon Western Chemiluminescence Substrate was used for signal development. Blots were imaged in an Amersham Imager 600 (GE Healthcare).

2. Efficient construction of IMiDs-based azides Library via one-step conversion.

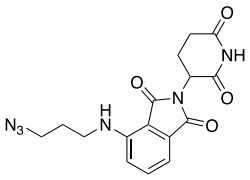


X = (CH_2)n or (PEG)n
1

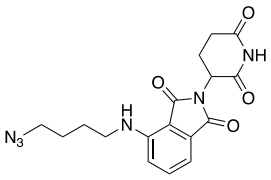
X = (CH_2)n or (PEG)n
2



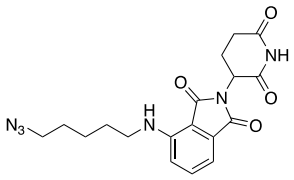
2a, 89%[a]



2b, 68%[a]



2c, 60%[a]



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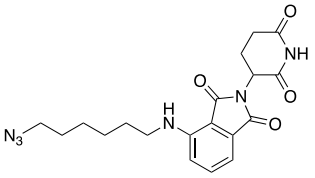
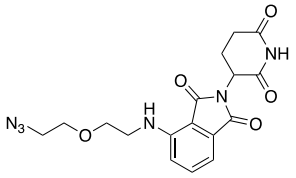
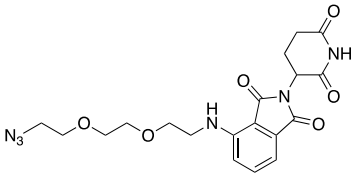


2e, 66%[a]



2f, 70%[a]



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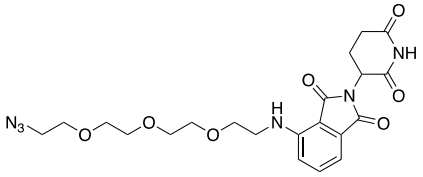
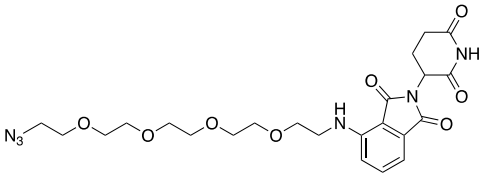


2h, 60%[a]



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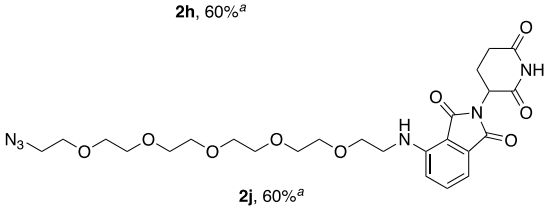
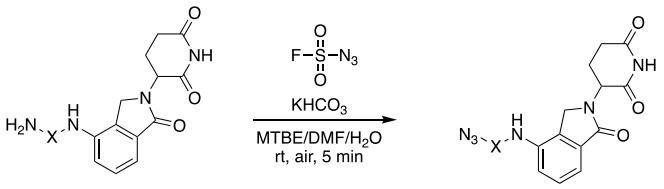


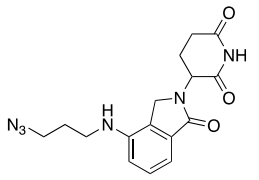
2j, 60%[a]

[a] Isolated yield.

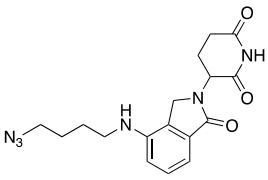


X = (CH_2)n or (PEG)n
3

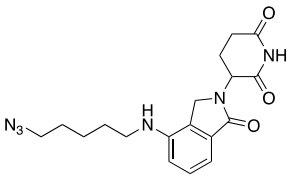
X = (CH_2)n or (PEG)n
4



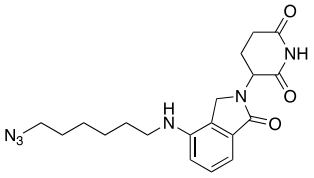
4a, 58%[a]



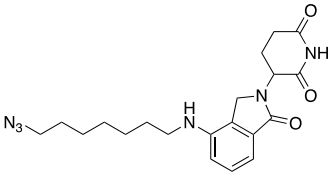
4b, 50%[a]



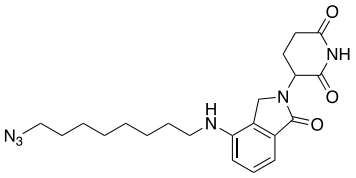
4c, 51%[a]



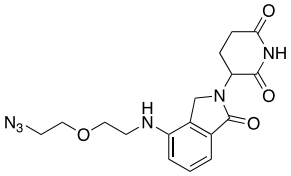
4d, 56%[a]



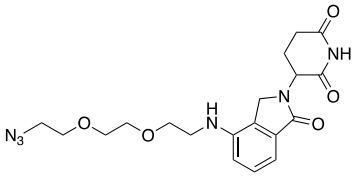
4e, 58%[a]



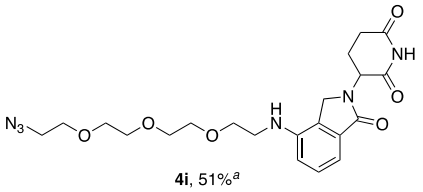
4f, 45%[a]



4g, 50%[a]



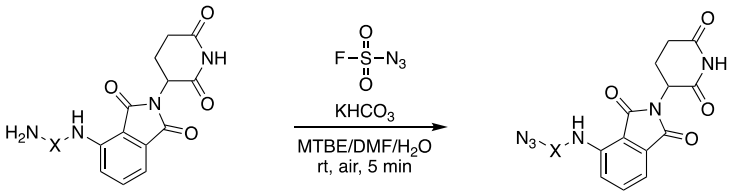
4h, 49%[a]



4i, 51%[a]

[a] Isolated yield

3. General procedure for the synthesis of compounds 2.



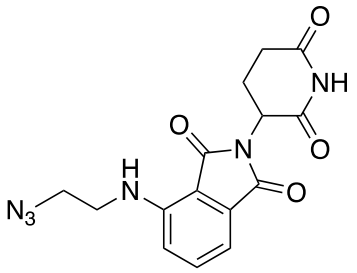
X = (CH_2)n or (PEG)n
1

X = (CH_2)n or (PEG)n
2

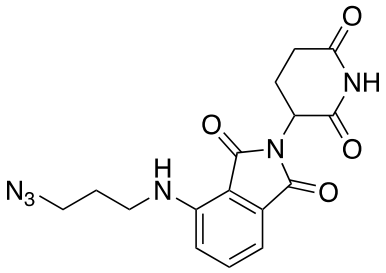
To a stirred solution of **1** (1.0 equiv, TFA salt) in DMF were added FSO_2N_3 solution (0.5 M in MTBE; 1.0 equiv) and $KHCO_3$ aqueous solution (3.0 M, 4.0 equiv). Then the resulting mixture was stirred at room temperature for 5 min. LC-MS showed the reaction was complete. The reaction mixture was filtered and purified by prep-HPLC (eluent: with

10%-100% (v1: v2) acetonitrile in water). The collections were concentrated in vacuo to remove most of the solvent and then lyophilized to afford the azide products **2**.

4. Characterization data of products 2.

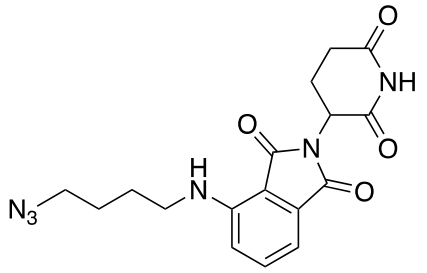


4-((2-azidoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2a). TFA salt of **1a** (51 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow solid, 36 mg, 89% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.60 (dd, J = 8.6, 7.1 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.73 (t, J = 5.8 Hz, 1H), 5.06 (dd, J = 12.8, 5.4 Hz, 1H), 3.62-3.52(m, 4H), 2.95-2.85 (m, 1H), 2.64 – 2.52 (m, 2H), 2.09-1.99 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.5, 169.3, 167.7, 146.6, 136.8, 132.7, 117.9, 111.4, 110.0, 50.5, 49.1, 41.8, 31.5, 22.6. HRMS (ESI) m/z: calcd for $C_{15}H_{15}N_6O_4^+$ $[M + H]^+$, 343.1149; found, 343.1151.

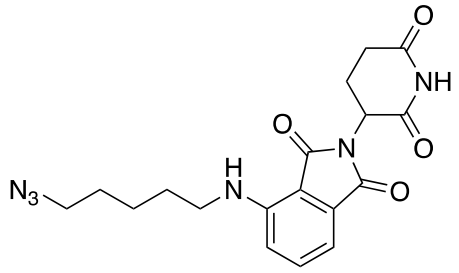


4-((3-azidopropyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2b). TFA salt of **1b** (46 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow solid, 25 mg, 68% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.08 (s, 1H), 7.59 (dd, J = 8.6, 7.1 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H),

7.04 (d, J = 7.0 Hz, 1H), 6.67 (t, J = 6.1 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 3.45 (t, J = 6.6 Hz, 2H), 3.40-3.36 (m, 2H), 2.85-2.95 (m, 1H), 2.61 – 2.52 (m, 2H), 1.98-2.05 (m, 1H), 1.85-1.80 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.6, 169.3, 167.8, 146.7, 136.8, 132.7, 117.6, 111.0, 109.8, 49.0, 49.0, 31.5, 28.4, 22.6. (The missing signal is presumably under d_6-DMSO signals). HRMS (ESI) m/z: calcd for $C_{16}H_{17}N_6O_4^+$ $[M + H]^+$, 357.1306; found, 357.1305.

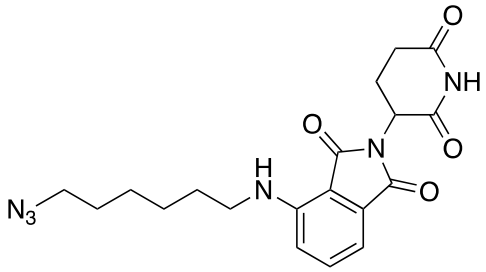


4-((4-azidobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2c). TFA salt of **1c** (47 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow solid, 23 mg, 60% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 7.58 (dd, J = 8.6, 7.0 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.61 (t, J = 6.1 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 3. 34 – 3. 37 (m, 4H), 2.94 – 2.82 (m, 1H), 2.62 – 2.52 (m, 2H), 2.06-1.98 (m, 1H), 1.66-1.57 (m, 4H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 146.8, 136.7, 132.7, 117.7, 110.9, 109.6, 50.8, 49.0, 41.8, 31.5, 26.4, 26.2, 22.6. HRMS (ESI) m/z: calcd for $C_{17}H_{19}N_6O_4^+$ $[M + H]^+$, 371.1462; found, 371.1463.

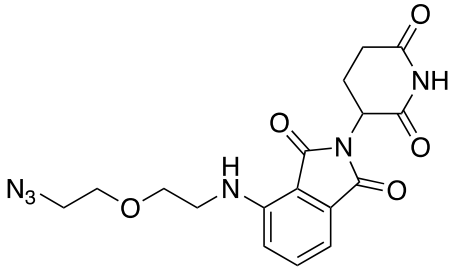


4-((5-azidopentyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2d). TFA salt of **1d** (49 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow solid, 20 mg, 50% yield) ^{1}H NMR (500

MHz, DMSO-d_6) δ 10.93 (s, 1H), 7.58 (dd, J = 8.6, 7.1 Hz, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.56 (t, J = 6.0 Hz, 1H), 5.05 (dd, J = 12.7, 5.4 Hz, 1H), 3.35 (d, J = 6.9 Hz, 2H), 3.33 – 3.27 (m, 2H), 2.93-2.84 (m, 1H), 2.63 – 2.52 (m, 2H), 1.98 - 2.07 (m, 1H), 1.54 -1.65 (m, 4H), 1.44 – 1.35 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 146.9, 136.8, 132.7, 117.7, 110.9, 109.5, 51.0, 49.0, 42.2, 31.4, 28.7, 28.5, 24.0, 22.6. HRMS (ESI) m/z: calcd for $C_{18}H_{21}N_6O_4^+$ [M + H]$^+$, 385.1619; found, 385.1619.

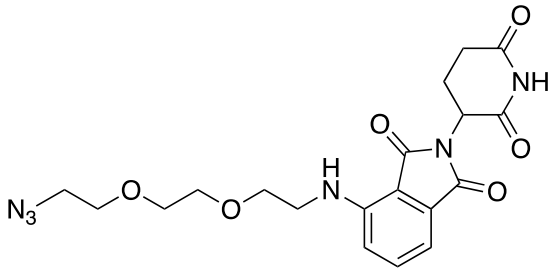


4-((6-azidohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2e). TFA salt of **1e** (46 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow solid, 25 mg, 66% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.02 (d, J = 5.0 Hz, 1H), 6.54 (t, J = 6.3 Hz, 1H), 5.05 (dd, J = 12.7, 5.2 Hz, 1H), 3.34 -3.28(m, 4H), 2.93 – 2.82 (m, 1H), 2.65 – 2.50 (m, 2H), 2.08 – 1.98 (m, 1H), 1.61-1.49 (m, 4H), 1.4-1.32 (m, 4H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 146.9, 136.8, 132.7, 117.7, 110.9, 109.5, 51.0, 49.0, 42.2, 31.5, 29.0, 28.6, 26.4, 26.3, 22.6. HRMS (ESI) m/z: calcd for $C_{19}H_{23}N_6O_4^+$ [M + H]$^+$, 399.1775; found, 399.1777.

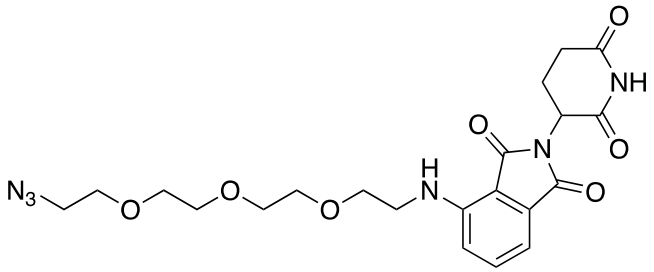


4-((2-(2-azidoethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2f). TFA salt of **1f** (46 mg) was used. The crude product was purified by prep-HPLC

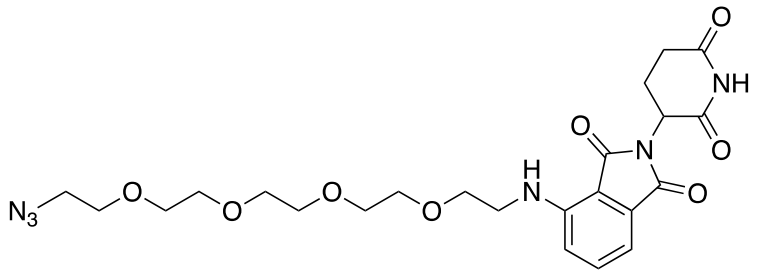
(eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow solid, 26 mg, 70% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.58 (dd, J = 8.6, 7.1 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.63 (t, J = 6.0 Hz, 1H), 5.05 (dd, J = 12.8, 5.4 Hz, 1H), 3.68-3.62 (m, 4H), 3.51-3.48 (m, 2H), 3.44 – 3.38 (m, 2H), 2.94-2.84 z(m, 1H), 2.62 – 2.52 (m, 2H), 2.05-1.97 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.2, 109.8, 69.6, 69.4, 50.5, 49.0, 42.2, 31.4, 22.6. HRMS (ESI) m/z: calcd for $C_{17}H_{19}N_6O_5^+$ $[M + H]^+$, 387.1411; found, 387.1416.



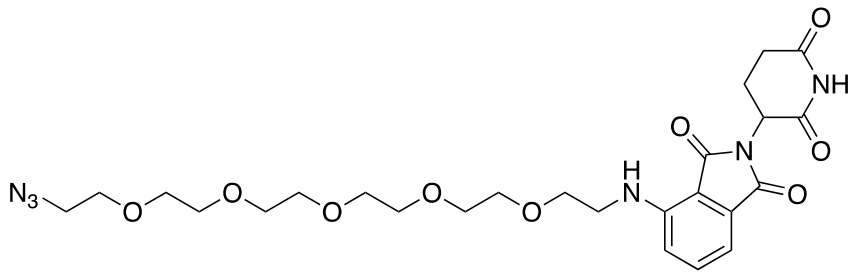
4-((2-(2-(2-azidoethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2g). TFA salt of **1g** (46 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow solid, 25 mg, 65% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.07 (s, 1H), 7.58 (dd, J = 8.6, 7.1 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.61 (t, J = 5.9 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 3.63 (t, J = 5.4 Hz, 2H), 3.62 – 3.55 (m, 6H), 3.47 (q, J = 5.5 Hz, 2H), 3.39 – 3.33 (m, 2H), 2.95-2.85(m, 1H), 2.62 – 2.52 (m, 2H), 2.05-1.98 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.6, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.2, 109.7, 70.3, 70.2, 69.8, 69.4, 50.5, 49.0, 42.2, 31.5, 22.6. HRMS (ESI) m/z: calcd for $C_{19}H_{23}N_6O_6^+$ $[M + H]^+$, 431.1674; found, 431.1677.



4-((2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2h). TFA salt of **1h** (53 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow oil, 27 mg, 60% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.58 (dd, J = 8.6, 7.1 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.60 (t, J = 5.8 Hz, 1H), 5.05 (dd, J = 12.8, 5.4 Hz, 1H), 3.62 (t, J = 5.4 Hz, 2H), 3.60 – 3.51 (m, 10H), 3.49-3.45 (m, 2H), 3.39 – 3.34 (m, 2H), 2.95-2.85 (m, 1H), 2.66 – 2.52 (m, 2H), 2.04-1.97(m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.5, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.2, 109.7, 70.3, 70.3, 70.3, 70.2, 69.7, 69.4, 50.5, 49.0, 42.2, 31.5, 22.6. HRMS (ESI) m/z: calcd for $C_{21}H_{27}N_6O_7^+$ $[M + H]^+$, 475.1936; found, 475.1943.

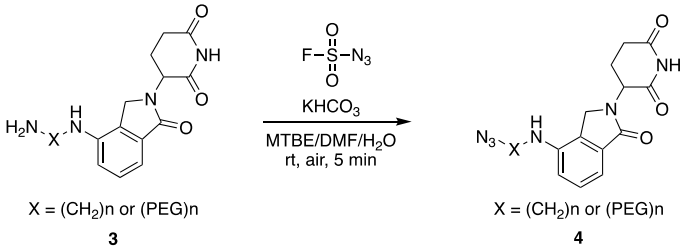


4-((14-azido-3,6,9,12-tetraoxatetradecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2i). TFA salt of **1i** (51 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow oil, 28 mg, 64% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.58 (dd, J = 8.6, 7.1 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 6.60 (t, J = 5.9 Hz, 1H), 5.05 (dd, J = 12.8, 5.4 Hz, 1H), 3.62 (t, J = 5.5 Hz, 2H), 3.59 – 3.55 (m, 4H), 3.55 – 3.50 (m, 10H), 3.47 (q, J = 5.6 Hz, 2H), 3.37 (t, J = 5.0 Hz, 2H), 2.84 - 2.92(m, 1H), 2.66 – 2.56 (m, 2H), 2.07 – 1.99 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.5, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.2, 109.7, 70.30, 70.29, 70.27, 70.25, 70.2, 69.7, 69.4, 50.5, 49.0, 42.2, 31.5, 22.6. (Two signals are presumably overlapped.) HRMS (ESI) m/z: calcd for $C_{23}H_{31}N_6O_8^+$ $[M + H]^+$, 519.2198; found, 519.2192.



4-((17-azido-3,6,9,12,15-pentaoxaheptadecyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (2j). TFA salt of **1j** (54 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (yellow oil, 28 mg, 60% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.59 (dd, J = 8.6, 7.1 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 7.1 Hz, 1H), 6.61 (t, J = 5.8 Hz, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 3.62 (t, J = 5.5 Hz, 2H), 3.60 – 3.57 (m, 2H), 3.59 – 3.55 (m, 2H), 3.55-3.52 (m, 6H), 3.51 – 3.48 (m, 8H), 3.47 (d, J = 5.7 Hz, 2H), 3.40 – 3.37 (m, 2H), 2.94 -2.84 m, 1H), 2.64 – 2.51 (m, 2H), 2.05-1.98 m,1H); ^{13}C NMR (126 MHz, DMSO) δ 173.3, 170.5, 169.4, 167.8, 146.9, 136.7, 132.6, 117.9, 111.2, 109.7, 70.3, 70.3, 70.3, 70.2, 70.2, 69.7, 69.4, 50.5, 49.1, 49.0, 42.2, 31.5, 22.6. HRMS (ESI) m/z: calcd for $C_{25}H_{35}N_6O_9^+$ $[M + H]^+$, 563.2460; found, 563.2465.

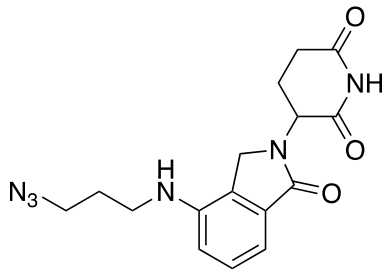
5. General procedure for the synthesis of compounds 4.



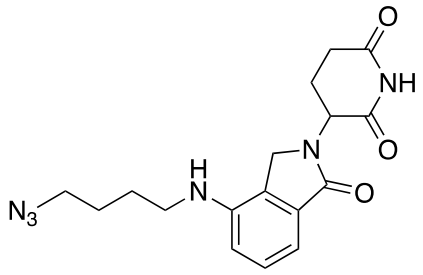
To a stirred solution of **3** (1.0 equiv, TFA salt) in DMF were added FSO_2N_3 solution (0.5 M in MTBE; 1.0 equiv) and $KHCO_3$ aqueous solution (3.0 M, 4.0 equiv). Then the resulting mixture was stirred at room temperature for 5 min. LC-MS showed the reaction was complete. The reaction mixture was filtered and purified by prep-HPLC (eluent: with

10%-100% (v1: v2) acetonitrile in water). The collections were concentrated in vacuo to remove most of the solvent and then lyophilized to afford the azide products **4**.

6. Characterization data of products 4.

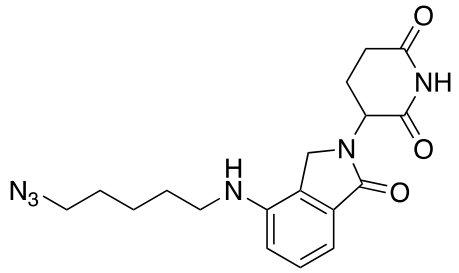


3-(4-((3-azidopropyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4a). TFA salt of **3a** (47 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (light yellow solid, 54 mg, 58% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.30 (t, J = 7.7 Hz, 1H), 6.95 (dd, J = 7.5, 0.8 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 5.66 (t, J = 5.6 Hz, 1H), 5.12 (dd, J = 13.3, 5.2 Hz, 1H), 4.24 (d, J = 17.1 Hz, 1H), 4.13 (d, J = 17.1 Hz, 1H), 3.47 (t, J = 6.8 Hz, 2H), 3.22-3.18 (m, 2H), 2.99-2.89 (m, 1H), 2.66-2.58 (m, 1H), 2.38 – 2.23 (m, 1H), 2.09-1.99 (m, 1H), 1.86-1.81 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.3, 144.0, 132.6, 129.7, 127.1, 112.2, 110.7, 52.0, 49.0, 46.2, 31.7, 28.2, 23.3. (The missing signal is presumably under d_6-DMSO signals). HRMS (ESI) m/z: calcd for $C_{16}H_{19}N_6O_3^+$ $[M + H]^+$, 343.1513; found, 343.1512.

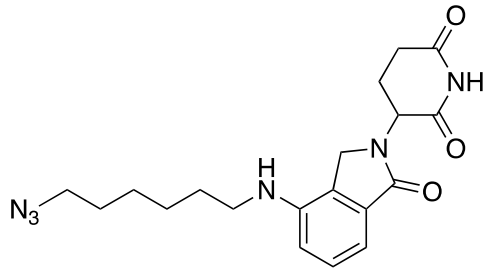


3-(4-((4-azidobutyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4b). TFA salt of **3b** (52 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-

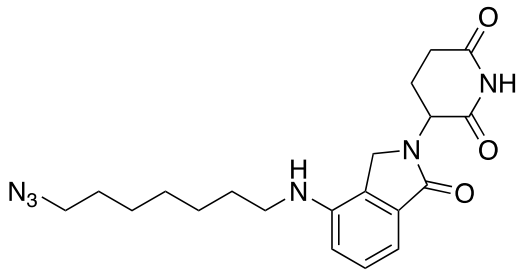
100% (v1: v2) acetonitrile in water). (light yellow solid, 21 mg, 50% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.93 (d, J = 6.7 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 5.62 (t, J = 5.6 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.23 (d, J = 17.1 Hz, 1H), 4.13 (d, J = 17.1 Hz, 1H), 3.41 – 3.35 (m, 2H), 3.15 (d, J = 5.9 Hz, 2H), 2.98-2.88(m, 1H), 2.66-2.58(m, 1H), 2.37 – 2.21 (m, 1H), 2.09-1.98 (m, 1H), 1.68-1.59 (m, 4H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.4, 144.1, 132.5, 129.7, 127.0, 112.3, 110.5, 52.0, 51.0, 46.2, 42.6, 31.7, 26.5, 26.2, 23.3. HRMS (ESI) m/z: calcd for $C_{17}H_{21}N_6O_3^+$ $[M + H]^+$, 357.1670; found, 357.1674.



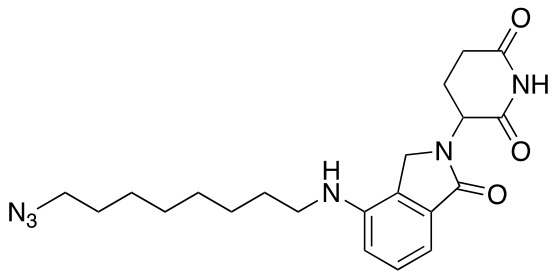
3-(4-((5-azidopentyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4c). TFA salt of **3c** (39 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (light yellow solid, 16 mg, 51% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.28 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 5.58 (s, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 4.12 (d, J = 17.2 Hz, 1H), 3.39-3.35(m, 2H), 3.15 – 3.07 (m, 2H), 2.96-2.89 (m, 1H), 2.67 – 2.57 (m, 1H), 2.38 – 2.23 (m, 1H), 2.08-2.01 (m, 1H), 1.63-1.56 (m, 4H), 1.47 – 1.38 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.4, 144.2, 132.5, 129.7, 126.9, 112.2, 110.4, 52.0, 51.1, 46.2, 43.0, 31.7, 28.6, 28.5, 24.3, 23.3. HRMS (ESI) m/z: calcd for $C_{18}H_{23}N_6O_3^+$ $[M + H]^+$, 371.1826; found, 371.1832.



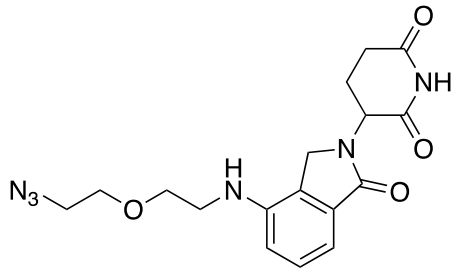
3-(4-((6-azidohexyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4d). TFA salt of **3d** (44 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (light yellow solid, 20 mg, 56% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.28 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 5.56 (t, J = 5.6 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 4.12 (d, J = 17.1 Hz, 1H), 3.38-3.35 (m, 2H), 3.16 – 3.08 (m, 2H), 2.98-2.88 (m, 1H), 2.67-2.58 (m, 1H), 2.39 – 2.22 (m, 1H), 2.08-2.01 (m, 1H), 1.62-1.57 (m, 4H), 1.44 – 1.34 (m, 4H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.4, 144.2, 132.5, 129.7, 126.9, 112.2, 110.4, 51.9, 51.1, 46.2, 43.1, 31.7, 28.9, 28.7, 26.6, 26.5, 23.3. HRMS (ESI) m/z: calcd for $C_{19}H_{25}N_6O_3^+$ $[M + H]^+$, 385.1983; found, 385.1979.



3-(4-((7-azidoheptyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4e). TFA salt of **3e** (44 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (light yellow solid, 21 mg, 58% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.28 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 5.55 (t, J = 5.6 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 4.12 (d, J = 17.1 Hz, 1H), 3.30-3.32 (m, 2H) 3.14 – 3.08 (m, 2H), 2.96-2.87 (m, 1H), 2.65 – 2.58 (m, 1H), 2.37 – 2.24 (m, 1H), 2.06-1.99 (m, 1H), 1.59 – 1.51 (m, 4H), 1.43-1.35 m, 4H), 1.35-1.29 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.4, 144.3, 132.5, 129.7, 126.9, 112.2, 110.4, 52.0, 51.1, 46.2, 43.2, 31.7, 28.9, 28.9, 28.7, 27.0, 26.6, 23.3. HRMS (ESI) m/z: calcd for $C_{20}H_{27}N_6O_3^+$ $[M + H]^+$, 399.2139; found, 399.2136.

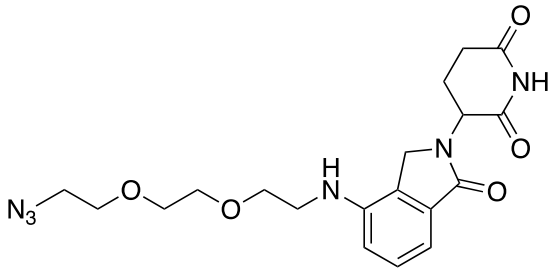


3-(4-((8-azidooctyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4f). TFA salt of **3f** (40 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (light yellow solid, 15 mg, 45% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.28 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.74 (d, J = 8.1 Hz, 1H), 5.55 (t, J = 5.5 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.22 (d, J = 17.2 Hz, 1H), 4.12 (d, J = 17.1 Hz, 1H), 3.30 (s, 2H) , 3.14 – 3.08 (m, 2H), 2.97-2.89 (m, 1H), 2.68-2.57(m, 1H), 2.37 – 2.24 (m, 1H), 2.06-1.98 (m, 1H), 1.60-1.49 (m, 4H), 1.41 – 1.27 (m, 8H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.4, 144.3, 132.5, 129.7, 126.9, 112.2, 110.4, 51.9, 51.1, 46.2, 43.2, 31.7, 29.3, 29.0, 29.0 28.7, 27.0, 26.6, 23.3. HRMS (ESI) m/z: calcd for $C_{21}H_{29}N_6O_3^+$ $[M + H]^+$, 413.2296; found, 413.2291.

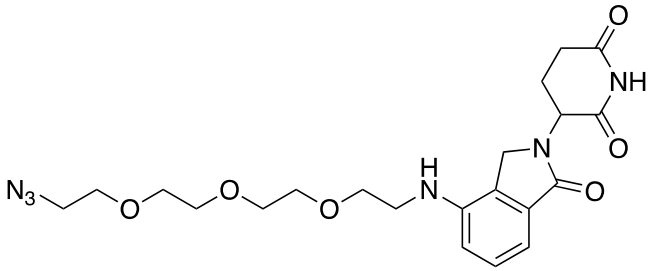


3-(4-((2-(2-azidoethoxy)ethyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4g). TFA salt of **3g** (49 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (light yellow solid, 20 mg, 50% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.95 (d, J = 6.7 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 5.57 (t, J = 5.8 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.23 (d, J = 17.1 Hz, 1H), 4.12 (d, J = 17.1 Hz, 1H), 3.67 – 3.61 (m, 4H), 3.44 – 3.38 (m, 2H), 3.37-3.33 (m, 2H), 2.98-2.88(m, 1H), 2.68-2.58 (m, 1H), 2.37 – 2.22 (m, 1H), 2.08-1.98 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.3, 144.0, 132.6, 129.7, 127.0,

112.4, 110.8, 69.7, 69.3, 52.0, 50.5, 46.1, 43.0, 31.7, 23.3. HRMS (ESI) m/z: calcd for $C_{17}H_{21}N_6O_4^+$ $[M + H]^+$, 373.1619; found, 373.1615.



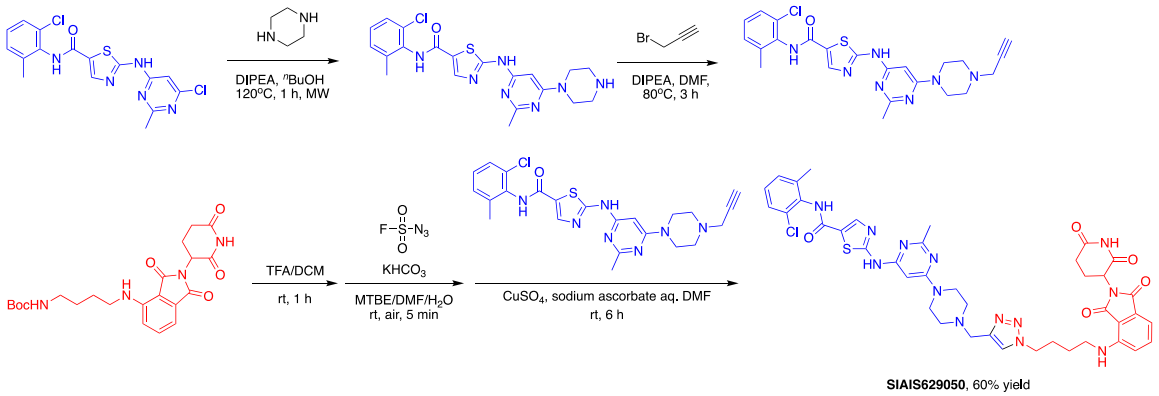
3-(4-((2-(2-(2-azidoethoxy)ethoxy)ethyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4h). TFA salt of **3h** (49 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (light yellow solid, 20 mg, 49% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.81 (d, J = 7.3 Hz, 1H), 5.57 (t, J = 5.8 Hz, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.23 (d, J = 17.1 Hz, 1H), 4.12 (d, J = 17.1 Hz, 1H), 3.63 – 3.55 (m, 8H), 3.40 – 3.31 (m, 4H), 2.97-2.88 (m, 1H), 2.67-2.56 (m, 1H), 2.36 – 2.25 (m, 1H), 2.06-1.98 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.3, 144.0, 132.6, 129.7, 127.0, 112.5, 110.8, 70.2, 70.1, 69.8, 69.4, 52.0, 50.5, 46.2, 43.0, 31.7, 23.3. HRMS (ESI) m/z: calcd for $C_{19}H_{25}N_6O_5^+$ $[M + H]^+$, 417.1881; found, 417.1876.



3-(4-((2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethyl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (4i). TFA salt of **3i** (47 mg) was used. The crude product was purified by prep-HPLC (eluent: with 10%-100% (v1: v2) acetonitrile in water). (light yellow solid, 20 mg, 51% yield) ^{1}H NMR (500 MHz, DMSO-d_6) δ ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.29 (t, J = 7.7 Hz, 1H), 6.94 (d, J = 7.3 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.67-5.47 (m, 1H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.23 (d, J = 17.1 Hz, 1H),

4.12 (d, J = 17.1 Hz, 1H), 3.61 – 3.56 (m, 4H), 3.56 – 3.52 (m, 8H), 3.38 – 3.35 (m, 4H), 2.96-2.89 (m, 1H), 2.65 – 2.58 (m, 1H), 2.39 – 2.21 (m, 1H), 2.07-1.97 (m, 1H); ^{13}C NMR (126 MHz, DMSO) δ 173.4, 171.7, 169.3, 143.9, 132.6, 129.7, 127.1, 112.6, 110.9, 70.3, 70.3, 70.2, 70.2, 69.7, 69.3, 52.0, 50.5, 46.2, 43.1, 31.7, 23.3. HRMS (ESI) m/z: calcd for $C_{21}H_{29}N_6O_6^+$ $[M + H]^+$, 461.2143; found, 461.2147.

7. Procedure for the synthesis of compound SIAIS629050.



The preparation of dasatinib derivative N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(4-(prop-2-yn-1-yl)piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide:

A solution of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (1.0 g, 2.54 mmol, 1.0 equiv)), piperazine (1.31 g, 15.21 mmol, 6.0 equiv) and DIPEA (4.9 g, 38.0 mmol, 15 equiv) in ^{n}BuOH (8 mL) was flushed with N_2 and then microwaved at 120°C for 1 h. LCMS showed the reaction was complete. The reaction mixture was cooled to room temperature and a large amount of white solid was precipitated. The mixture was filtered. The filter cake was washed with ^{n}BuOH for three times and dried in vacuo to afford N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (0.9 g, 80% yield) as a white solid. The white solid (0.45g, 1.0 mmol, 1.0 equiv) was dissolved in DMF (5 mL). 3-bromoprop-1-yne (238 mg, 2.0 mmol, 2.0 equiv) and DIPEA (388 mg, 3.0 mmol, 3.0 equiv) were added. The resulting mixture was stirred at 80°C for 3 h. LCMS showed

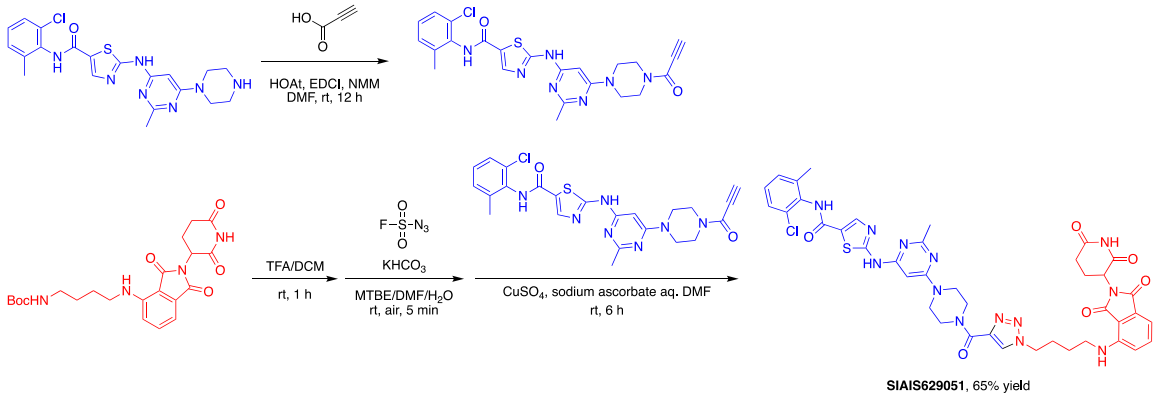
the reaction was complete. The reaction mixture was cooled to rt and purified by reverse ISCO to afford N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(4-(prop-2-yn-1-yl)piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (294 mg, 61% yield) as a light yellow solid.

The preparation of compound SIAIS629050:

To a stirred solution of tert-butyl (4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)carbamate (13 mg, 0.03 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (0.2 mL). The resulting mixture was stirred at room temperature for 1 h, then concentrated in vacuo. The residue was dissolved in DMF (2 mL), then FSO_2N_3 solution (0.5 M in MTBE, 1.0 equiv) and $KHCO_3$ aqueous solution (3.0 M, 4.0 equiv) were added. The resulting mixture was stirred at room temperature for 5 min, followed by the addition of prepared N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(4-(prop-2-yn-1-yl)piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (14.5 mg, 1.0 equiv), $CuSO_4$ aqueous solution (1 M , 3 equiv) and sodium ascorbate aqueous solution (1 M, 1.5 equiv). Then the resulting mixture was stirred at room temperature for 6 h. When the reaction was complete, the reaction mixture was filtered and purified by prep-HPLC (eluent: with 10% - 100% (v1: v2) acetonitrile in water) . The collections were concentrated in vacuo to remove most of the solvent and then lyophilized to afford the target compound **SIAIS629050 N-(2-chloro-6-methylphenyl)-2-((6-(4-((1-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)-1H-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide** (15 mg, 60% yield over 3 steps) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 10.01 (s, 1H), 8.36 (s, 1H), 8.29 (s, 1H), 7.61 – 7.54 (m, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.29-7.23(m, 2H), 7.10 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.20 (s, 1H), 5.04 (dd, J = 12.8, 5.4 Hz, 1H), 4.52 – 4.43 (m, 4H), 4.40 – 4.30 (m, 2H), 3.46-3.40 (m, 2H), 3.34 (t, J = 7.1 Hz, 4H), 3.18-3.03 (m, 2H), 2.95-2.82 (m, 1H), 2.63 – 2.54 (m, 1H), 2.54-2.50 (m, 1H), 2.45 (s, 3H), 2.23 (s, 3H), 2.09-1.98 (m, 1H), 1.97-1.89 (m, 2H), 1.60 -1.58(m, 2H). ^{13}C NMR (126

MHz, DMSO-d_6) δ 172.9, 170.2, 169.0, 167.4, 161.7, 159.9, 157.2, 146.4, 138.9, 136.4, 136.2, 133.5, 132.5, 132.3, 129.1, 128.3, 127.1, 117.3, 110.6, 109.2, 83.7, 49.9, 49.7, 49.4, 48.7, 48.6, 41.2, 40.9, 31.0, 27.2, 25.7, 22.2, 18.6, 18.4. (The missing signals are presumably overlapped or under d_6-DMSO signals). HRMS (ESI) m/z: calcd for $C_{40}H_{43}ClN_{13}O_5S^+$ $[M + H]^+$, 852.2914; found, 852.2901.

8. Procedure for the synthesis of compound SIAIS629051.



The preparation of dasatinib derivative N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(4-propioloylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide:

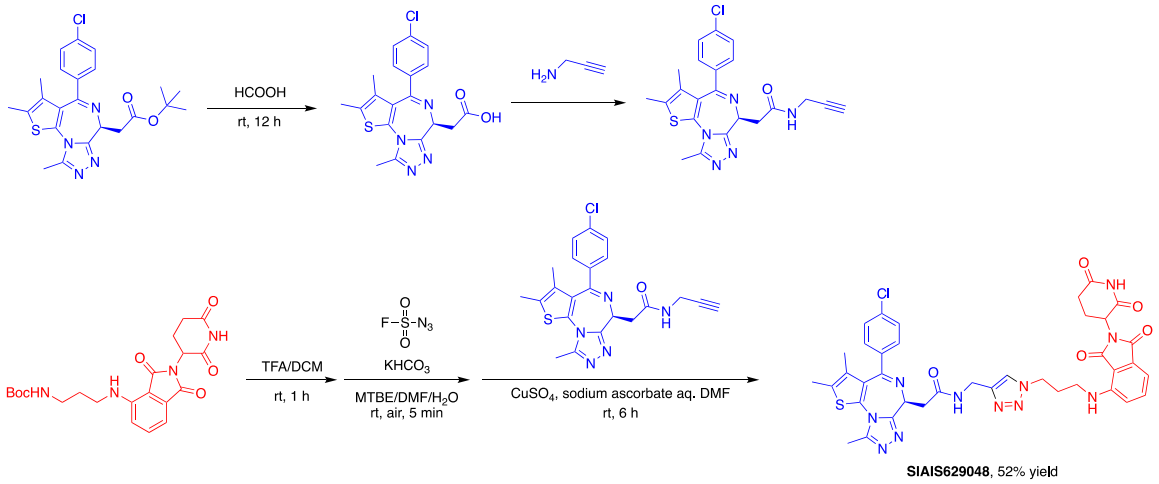
A solution of N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (0.45 g, 1.0 mmol, 1.0 equiv), propiolic acid (70 mg, 1.0 mmol, 1.0 equiv), HOAt (272 mg, 2.0 mmol, 2.0 equiv), EDCI (383 mg, 2.0 mmol, 2.0 equiv) and NMM (506 mg, 5.0 mmol, 5.0 equiv) in DMF (5 mL) was stirred at rt for 12 h. LCMS showed the reaction was complete. The reaction mixture was purified by reverse ISCO to afford N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(4-propioloylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (377 mg, 76% yield) as a light yellow solid.

The preparation of compound SIAIS629051:

To a stirred solution of tert-butyl (4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)carbamate (13 mg, 0.03 mmol, 1.0 equiv) in DCM (1

mL) was added TFA (0.2 mL). The resulting mixture was stirred at room temperature for 1 h, then concentrated in vacuo. The residue was dissolved in DMF (2 mL), then FSO_2N_3 solution (0.5 M in MTBE, 1.0 equiv) and $KHCO_3$ aqueous solution (3.0 M, 4.0 equiv) were added. The resulting mixture was stirred at room temperature for 5 min, followed by the addition of prepared N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(4-propioloylpiperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (14.9 mg, 1.0 equiv), $CuSO_4$ aqueous solution (1 M , 3 equiv) and sodium ascorbate aqueous solution (1 M, 1.5 equiv). Then the resulting mixture was stirred at room temperature for 6 h. When the reaction was complete, the reaction mixture was filtered and purified by prep-HPLC (eluent: with 10% - 100% (v1: v2) acetonitrile in water) . The collections were concentrated in vacuo to remove most of the solvent and then lyophilized to afford the target compound **SIAIS629051 N-(2-chloro-6-methylphenyl)-2-((6-(4-(1-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)-1H-1,2,3-triazole-4-carbonyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide** (17 mg, 65% yield over 3 steps) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.08 (s, 1H), 10.15 (s, 1H), 8.63 (s, 1H), 8.36 (s, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 7.32 – 7.21 (m, 2H), 7.09 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 7.0 Hz, 1H), 6.35 (s, 1H), 5.04 (dd, J = 12.7, 5.4 Hz, 1H), 4.47 (t, J = 7.0 Hz, 2H), 4.22 (s, 2H), 3.77 (s, 6H), 3.34 (t, J = 7.0 Hz, 2H), 2.91 – 2.80 (m, 1H), 2.63-2.58 (m, 1H), 2.55 (s, 3H), 2.54 -2.50 (m, 1H), 2.24 (s, 3H), 2.10-1.98 (m, 1H), 1.96-1.90 (m, 2H), 1.60 -1.50 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.9, 170.2, 168.9, 167.4, 159.8, 146.3, 142.8, 138.8, 136.3, 133.4, 132.5, 132.3, 129.1, 128.9, 128.4, 127.1, 117.3, 110.6, 109.2, 83.8, 56.1, 49.4, 48.6, 41.2, 31.0, 27.1, 25.6, 22.2, 18.6, 18.4. (The missing signals are presumably overlapped or under d_6-DMSO signals). HRMS (ESI) m/z: calcd for $C_{40}H_{41}ClN_{13}O_6S^+$ $[M + H]^+$, 866.2707; found, 866.2673.

9. Procedure for the synthesis of compound SIAIS629048.



The preparation of JQ-1 derivative:

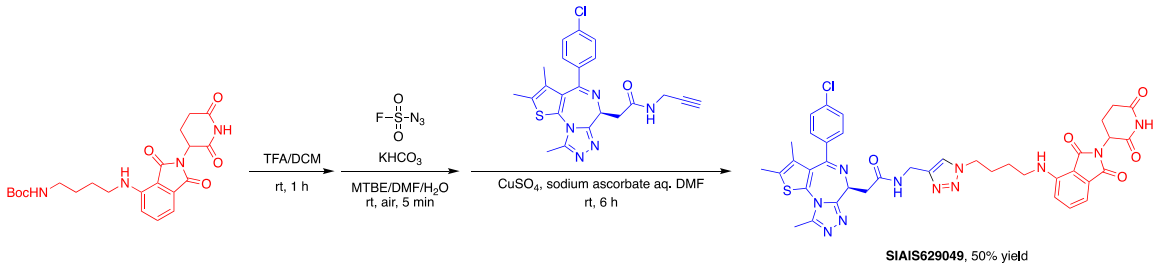
A solution of tert-butyl (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (1.0 g, 2.14 mmol, 1.0 equiv) in TFA/DCM (1 mL/5 mL) was stirred at rt for 2 h. LCMS showed the reaction was complete. The reaction mixture was concentrated in vacuo and the residue was lyophilized to afford (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (840 mg, 96% yield) as a white solid.

The preparation of compound SIAIS629048:

To a stirred solution of tert-butyl (3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)carbamate (21 mg, 0.05 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (0.2 mL). The resulting mixture was stirred at room temperature for 1 h, then concentrated in vacuo. The residue was dissolved in DMF (2 mL), then FSO_2N_3 solution (0.5 M in MTBE, 1.0 equiv) and $KHCO_3$ aqueous solution (3.0 M, 4.0 equiv) were added. The resulting mixture was stirred at room temperature for 5 min, followed by the addition of prepared (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(prop-2-yn-1-yl)acetamide (21.9 mg, 1.0 equiv), $CuSO_4$ aqueous solution (1 M , 3 equiv) and sodium ascorbate aqueous solution (1

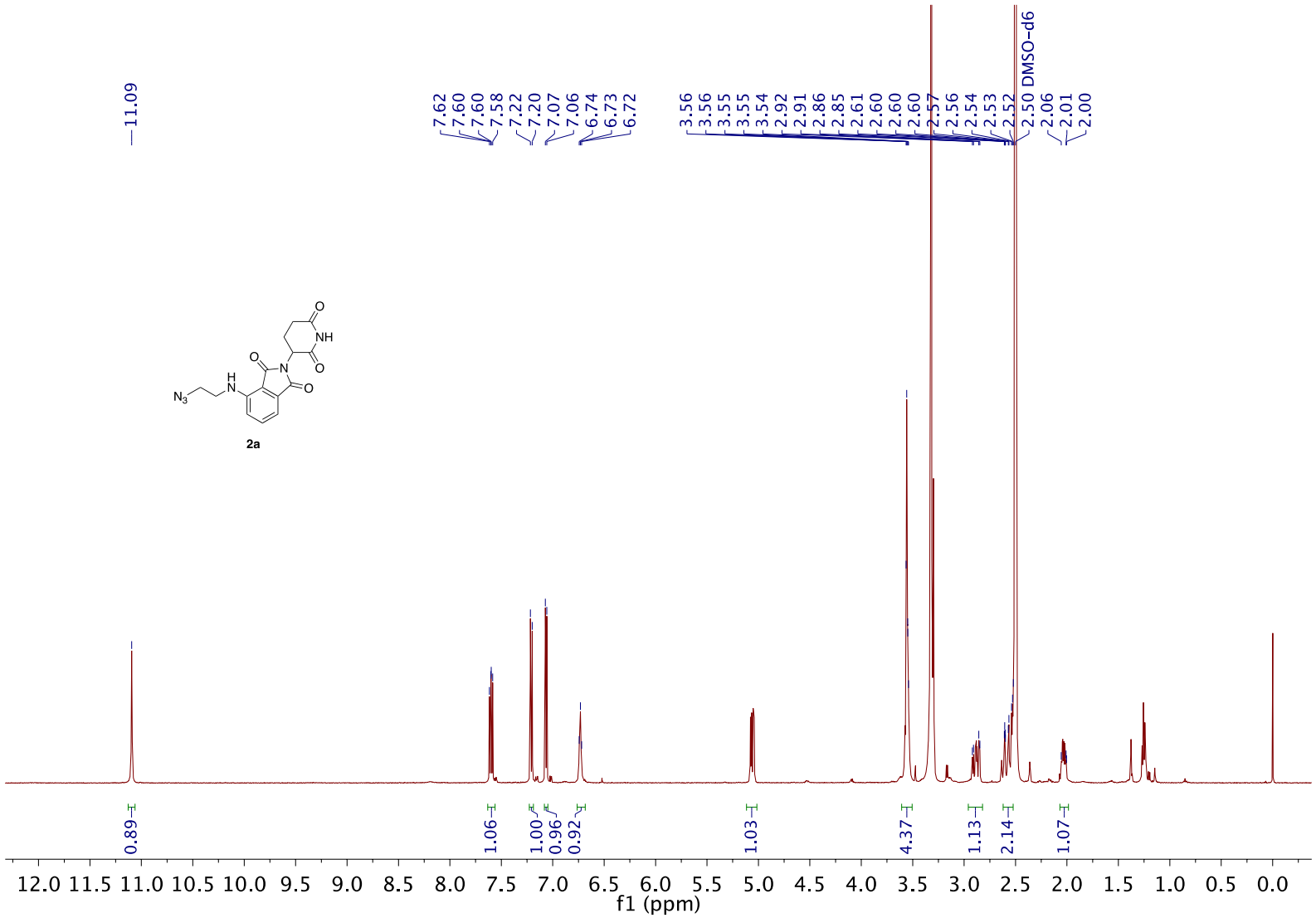
M, 1.5 equiv). Then the resulting mixture was stirred at room temperature for 6 h. When the reaction was complete, the reaction mixture was filtered and purified by prep-HPLC (eluent: with 10% - 100% (v1: v2) acetonitrile in water) . The collections were concentrated in vacuo to remove most of the solvent and then lyophilized to afford the target compound **SIAIS629048 2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-((1-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)-1H-1,2,3-triazol-4-yl)methyl)acetamide** (20 mg, 52% yield over 3 steps) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.10 (s, 1H), 8.74 (t, J = 5.7 Hz, 1H), 8.01 (s, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 7.4 Hz, 2H), 6.70 (t, J = 6.2 Hz, 1H), 5.05 (dd, J = 12.7, 5.4 Hz, 1H), 4.52 (t, J = 7.2 Hz, 1H), 4.41 (t, J = 7.0 Hz, 2H), 4.36 (d, J = 5.6 Hz, 2H), 3.38 -3.2 (m, 4H), 2.93 – 2.82 (m, 1H), 2.64 -2.59 (m, 1H),2.57 (s, 3H), 2.53 (m, 1H), 2.39 (s, 3H), 2.14-2.06 (m, 2H), 2.05-1.99 (m, 1H), 1.58 (s,1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.9, 170.1, 169.7, 168.8, 167.4, 163.2, 155.1, 150.0, 146.1, 145.2, 136.8, 136.3, 135.3, 132.3, 130.7, 130.2, 129.9, 129.6, 128.5, 123.0, 117.1, 110.7, 109.4, 53.9, 48.6, 47.1, 37.6, 34.3, 31.0, 29.3, 22.2, 14.1, 12.7, 11.3. (The missing signals are presumably overlapped or under d_6-DMSO signals). HRMS (ESI) m/z: calcd for $C_{38}H_{37}ClN_{11}O_5S^+$ $[M + H]^+$, 794.2383; found, 794.2383.

10. Procedure for the synthesis of compound SIAIS629049.



To a stirred solution of tert-butyl (4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)carbamate (23 mg, 0.05 mmol, 1.0 equiv) in DCM (1

mL) was added TFA (0.2 mL). The resulting mixture was stirred at room temperature for 1 h, then concentrated in vacuo. The residue was dissolved in DMF (2 mL), then FSO_2N_3 solution (0.5 M in MTBE, 1.0 equiv) and $KHCO_3$ aqueous solution (3.0 M, 4.0 equiv) were added. The resulting mixture was stirred at room temperature for 5 min, followed by the addition of prepared (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(prop-2-yn-1-yl)acetamide (21.9 mg, 1.0 equiv), $CuSO_4$ aqueous solution (1 M , 3 equiv) and sodium ascorbate aqueous solution (1 M, 1.5 equiv). Then the resulting mixture was stirred at room temperature for 6 h. When the reaction was complete, the reaction mixture was filtered and purified by prep-HPLC (eluent: with 10% - 100% (v1: v2) acetonitrile in water) . The collections were concentrated in vacuo to remove most of the solvent and then lyophilized to afford the target compound **SIAIS629049 2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-((1-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butyl)-1H-1,2,3-triazol-4-yl)methyl)acetamide** (21 mg, 50% yield over 3 steps) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.73 (t, J = 5.7 Hz, 1H), 7.96 (s, 1H), 7.60 – 7.53 (m, 1H), 7.46 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 7.0 Hz, 1H), 6.61 (t, J = 6.0 Hz, 1H), 5.04 (dd, J = 12.8, 5.5 Hz, 1H), 4.52 (t, J = 7.2 Hz, 1H), 4.40 - 4.34(m, 4H), 3.32 – 3.23 (m, 4H), 2.92 – 2.81 (m, 1H), 2.59 (s, 3H), 2.57 – 2.55 (m, 1H), 2.53 -2.50 (m, 1H), 2.39 (s, 3H), 2.05 – 1.97 (m, 1H), 1.91-1.86 (m, 2H), 1.61 (s, 3H), 1.58 -1.49 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.9, 170.2, 169.7, 168.9, 167.4, 163.1, 146.3, 145.0, 136.8, 136.3, 135.3, 132.3, 132.3, 130.8, 130.3, 129.9, 129.6, 128.5, 122.9, 117.2, 110.5, 109.2, 53.9, 49.0, 48.6, 41.2, 37.6, 34.3, 31.0, 27.2, 25.7, 22.2, 14.1, 12.7, 11.3. (The missing signals are presumably overlapped or under d_6-DMSO signals.) HRMS (ESI) m/z: calcd for $C_{39}H_{39}ClN_{11}O_5S^+$ $[M + H]^+$, 808.2539; found, 808.2510.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2.85
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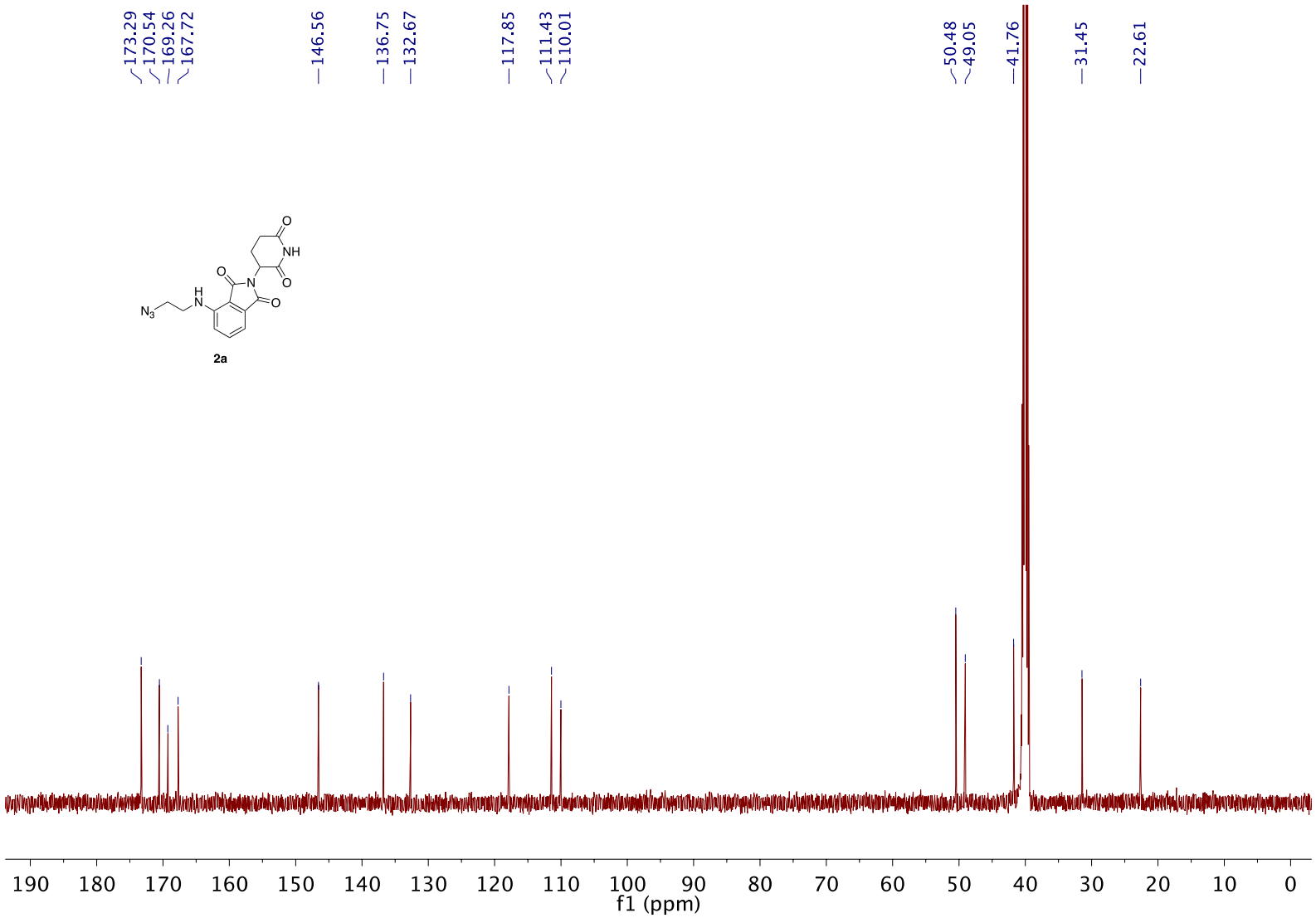
2.60
2.60
2.57
2.56
2.54
2.53
2.52
2.50 DMSO-d6
2.06
2.01
2.00
0.89
1.06
1.00
0.96
0.92
1.03
4.37
1.13
2.14
1.07
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

2a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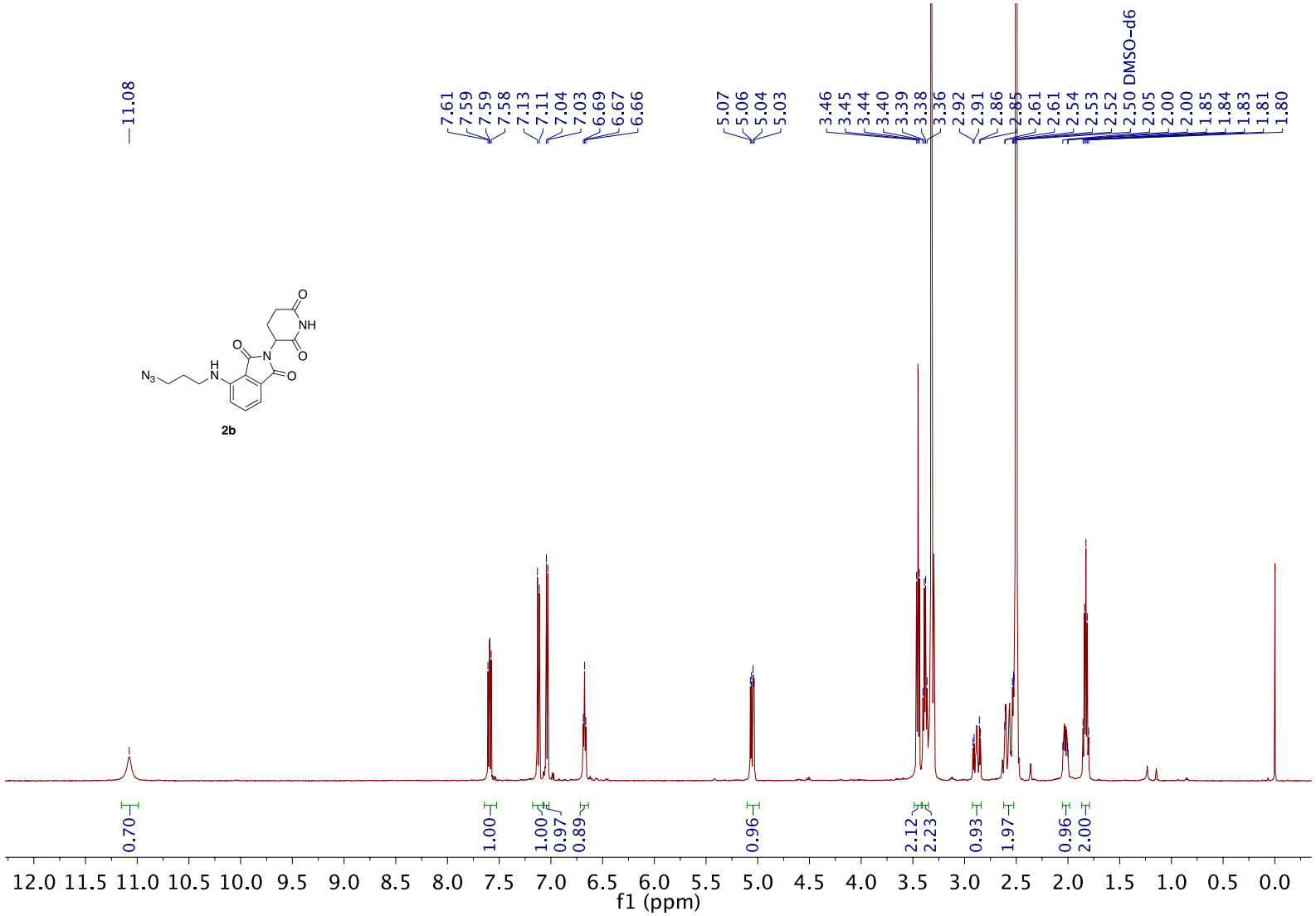
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1.81
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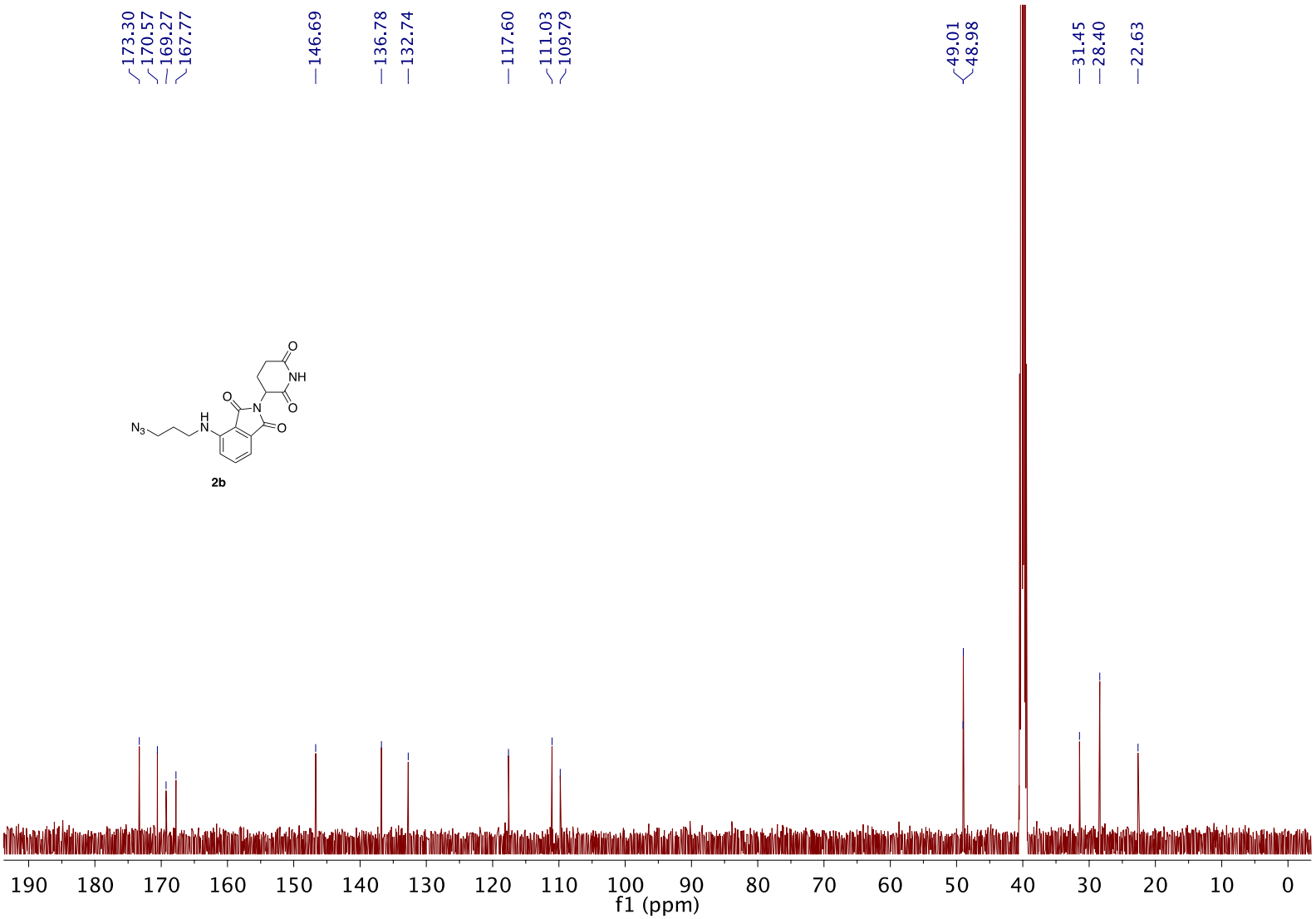
1.00
1.00
0.97
0.89
0.96
2.12
2.23
0.93
1.97
0.96
2.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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31.45
28.40
22.63
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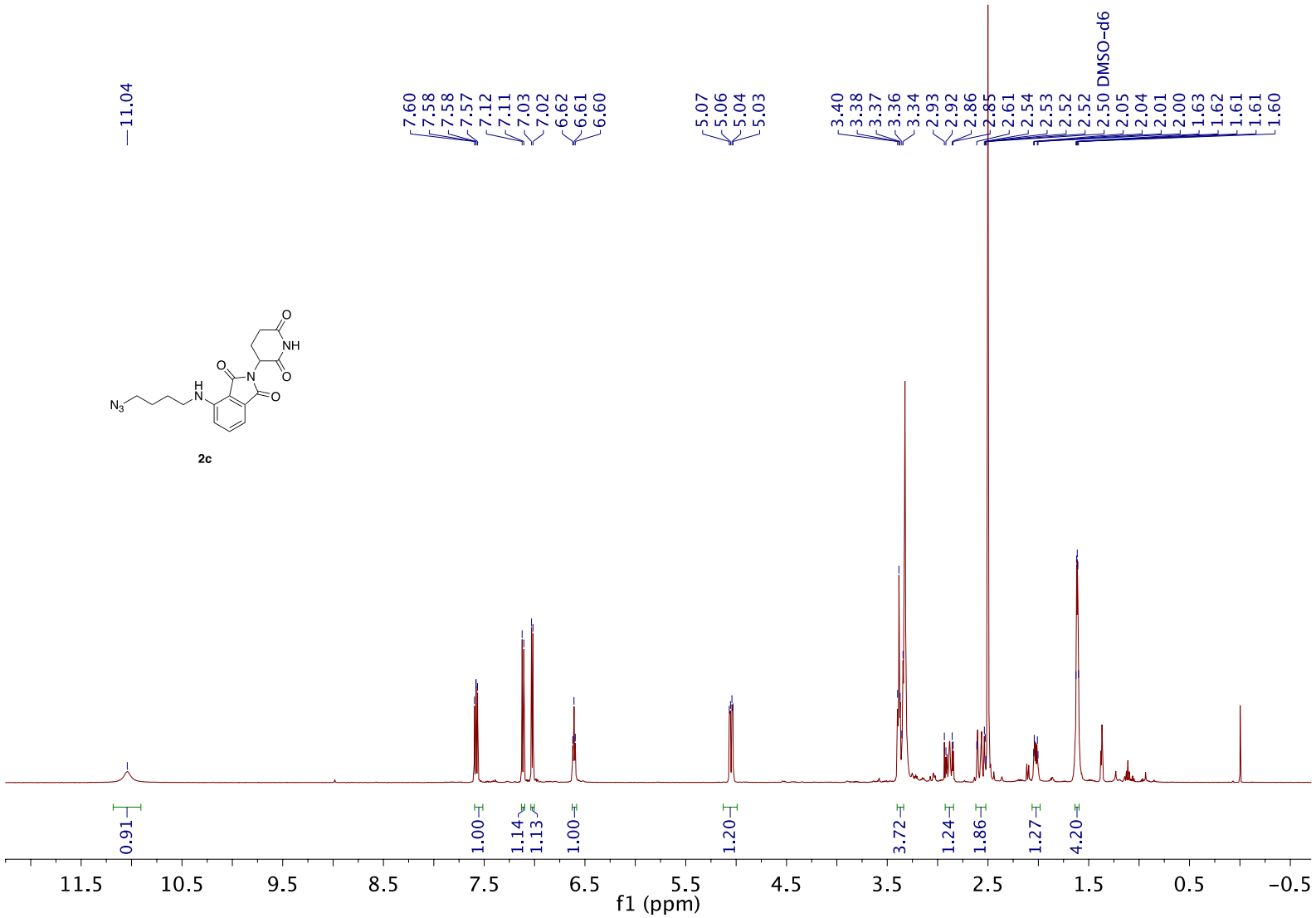
f1 (ppm)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5.06
5.04
5.03
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3.37
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2.85
2.61
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2.53
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2.52
2.50 DMSO-d6
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2.04
2.01
2.00
1.63
1.62
1.61
1.61
1.60
0.91
1.00
1.14
1.13
1.00
1.20
3.72
1.24
1.86
1.27
4.20
11.5
10.5
9.5
8.5
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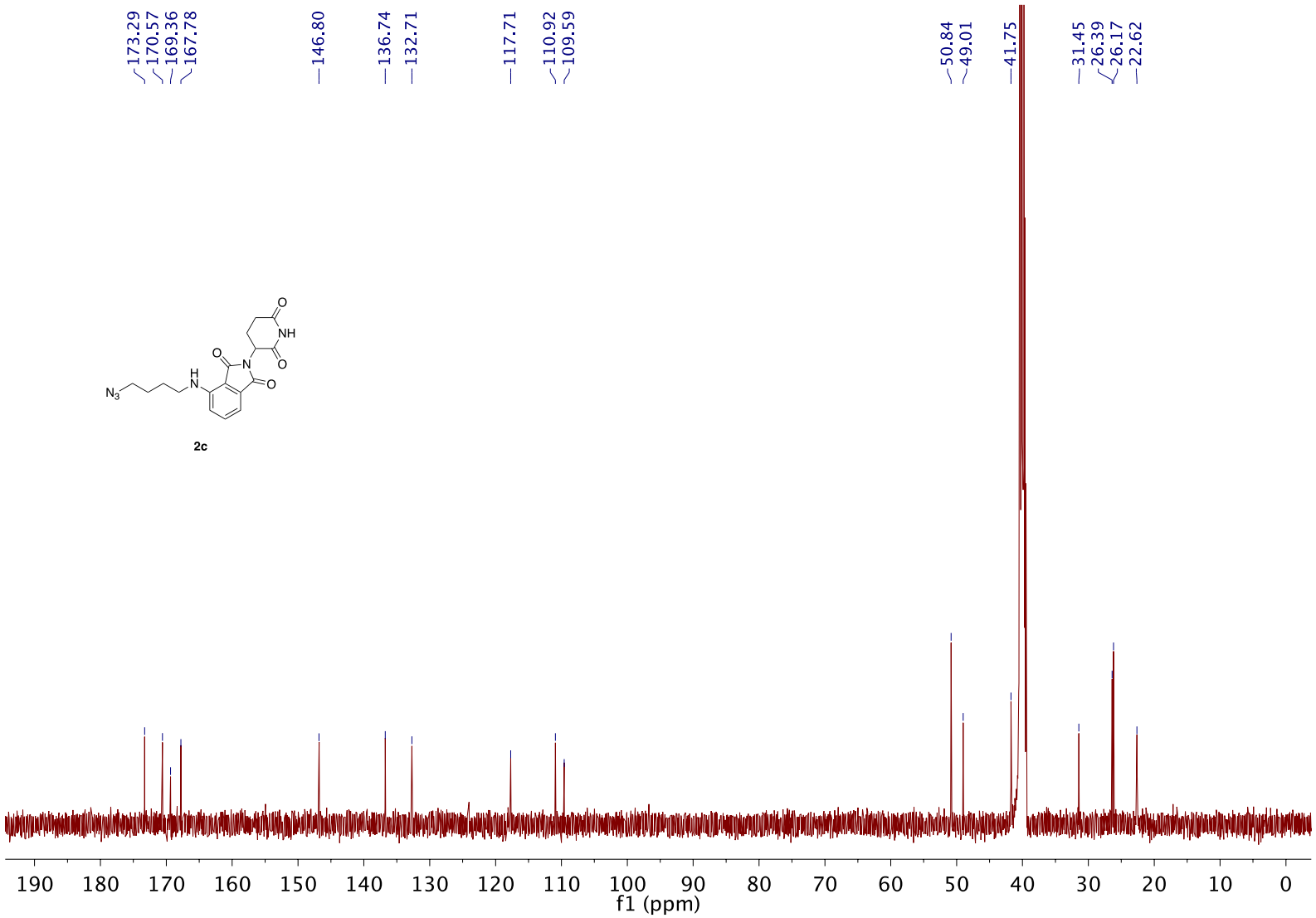
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

2c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31.45
26.39
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N
H
N3
2c
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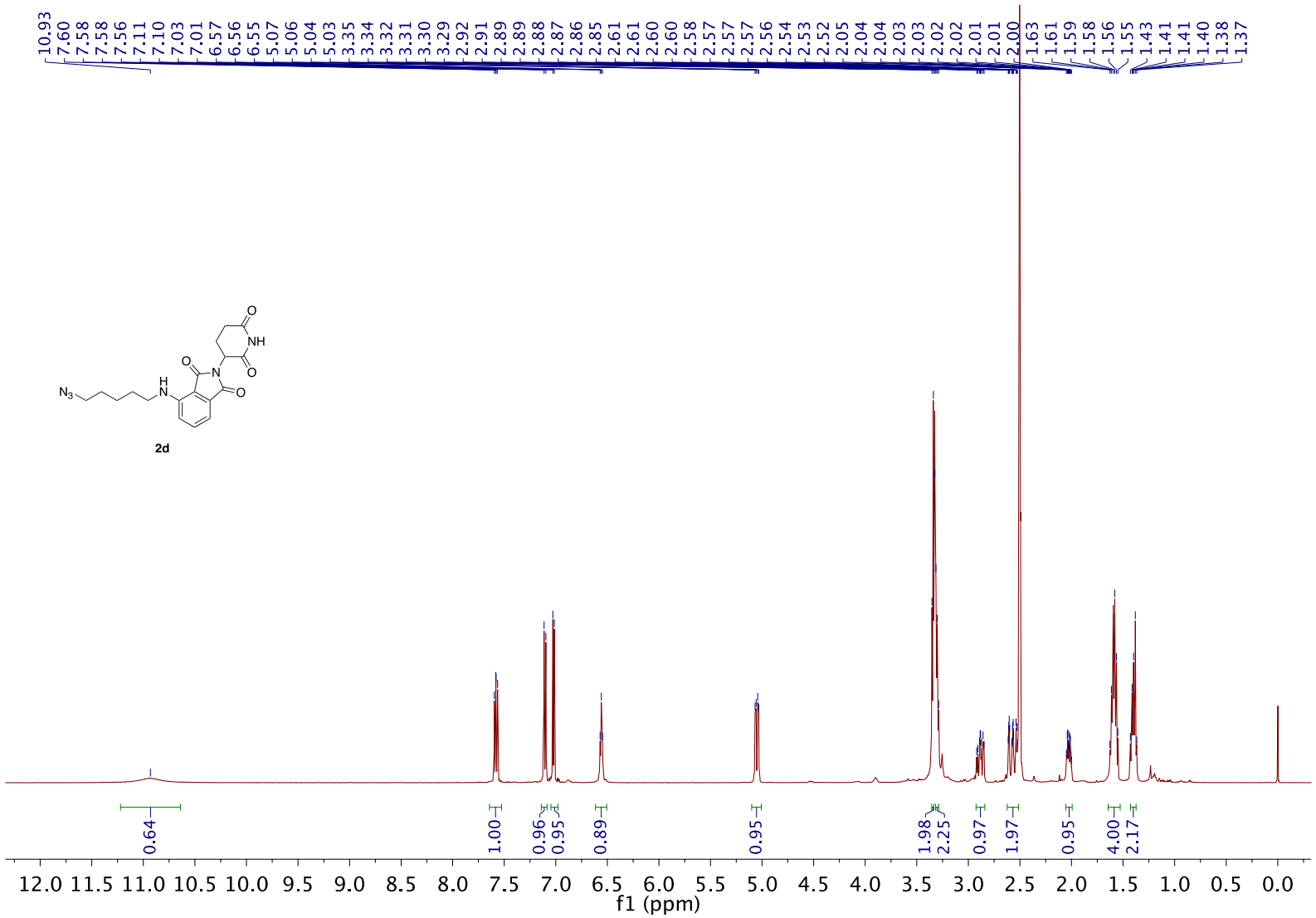
f1 (ppm)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5.04
5.03
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3.34
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3.31
3.30
3.29
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2.58
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2.57
2.57
2.56
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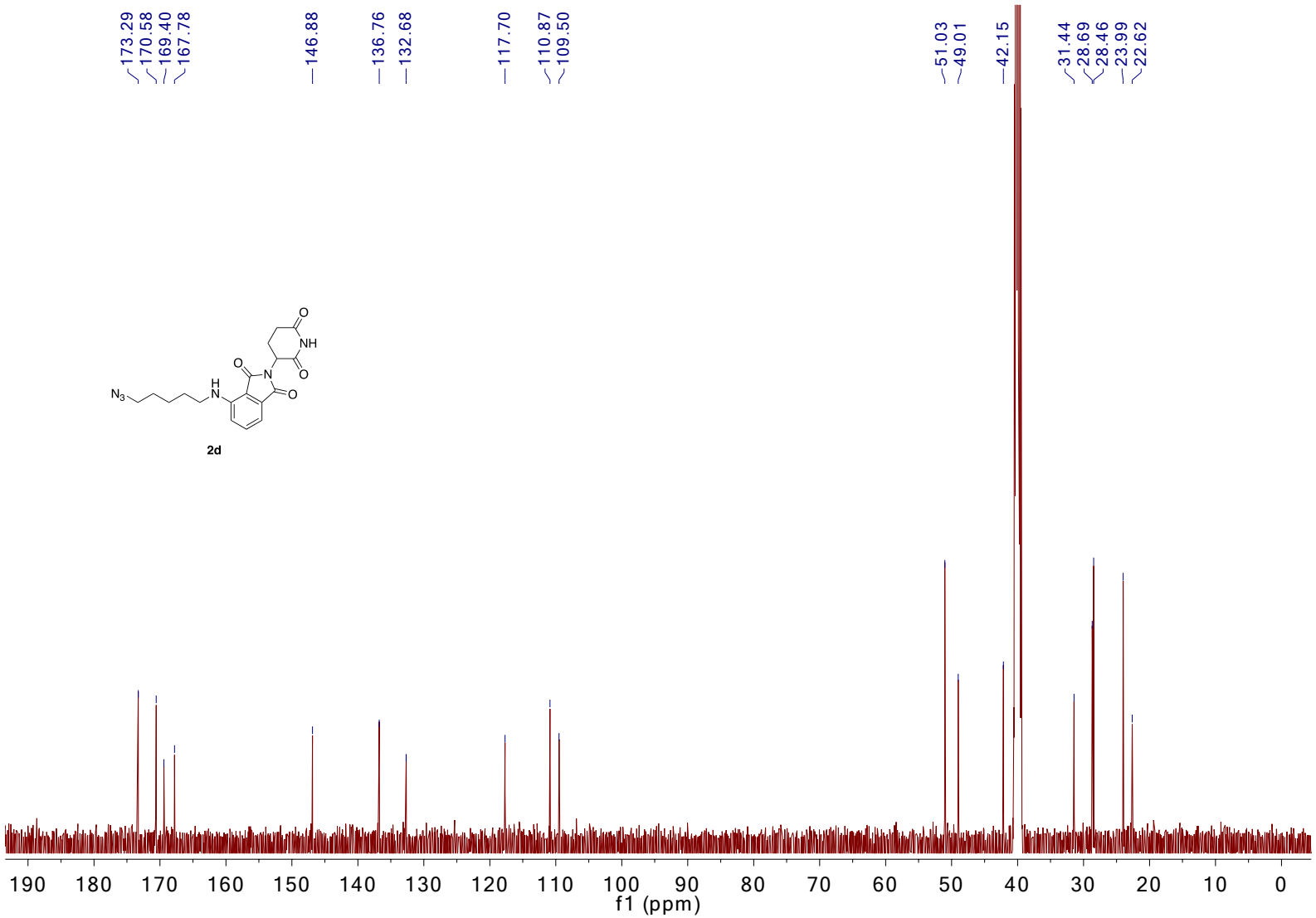
2.53
2.52
2.05
2.04
2.04
2.03
2.03
2.02
2.02
2.01
2.01
2.00
1.63
1.61
1.59
1.58
1.56
1.55
1.43
1.41
1.41
1.40
1.38
1.37
O
NH
O
O
N
H
N
O
O
N3
2d
0.64
1.00
0.96
0.95
0.89
0.95
1.98
2.25
0.97
1.97
0.95
4.00
2.17
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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49.01
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28.46
23.99
22.62
2d
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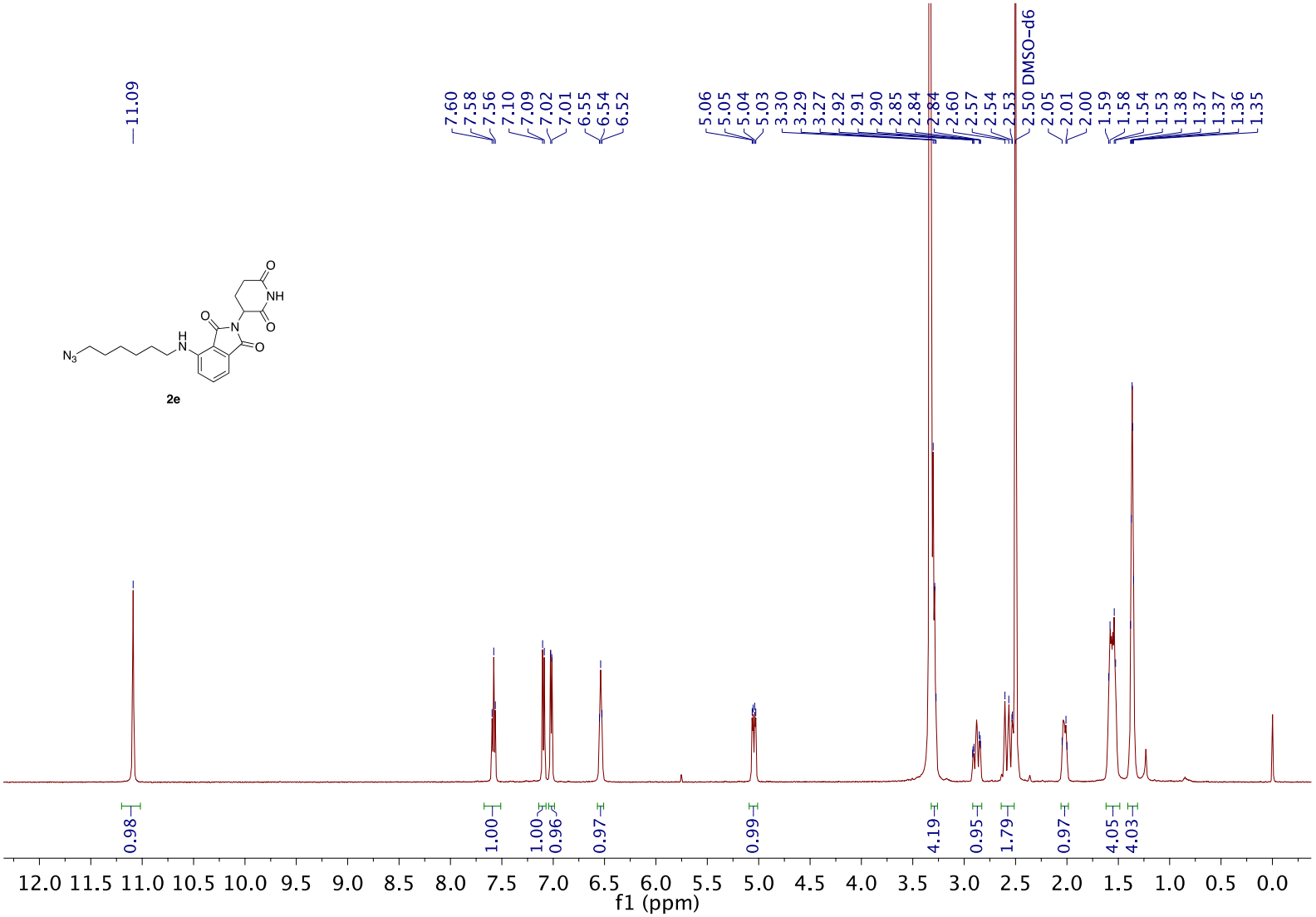
f1 (ppm)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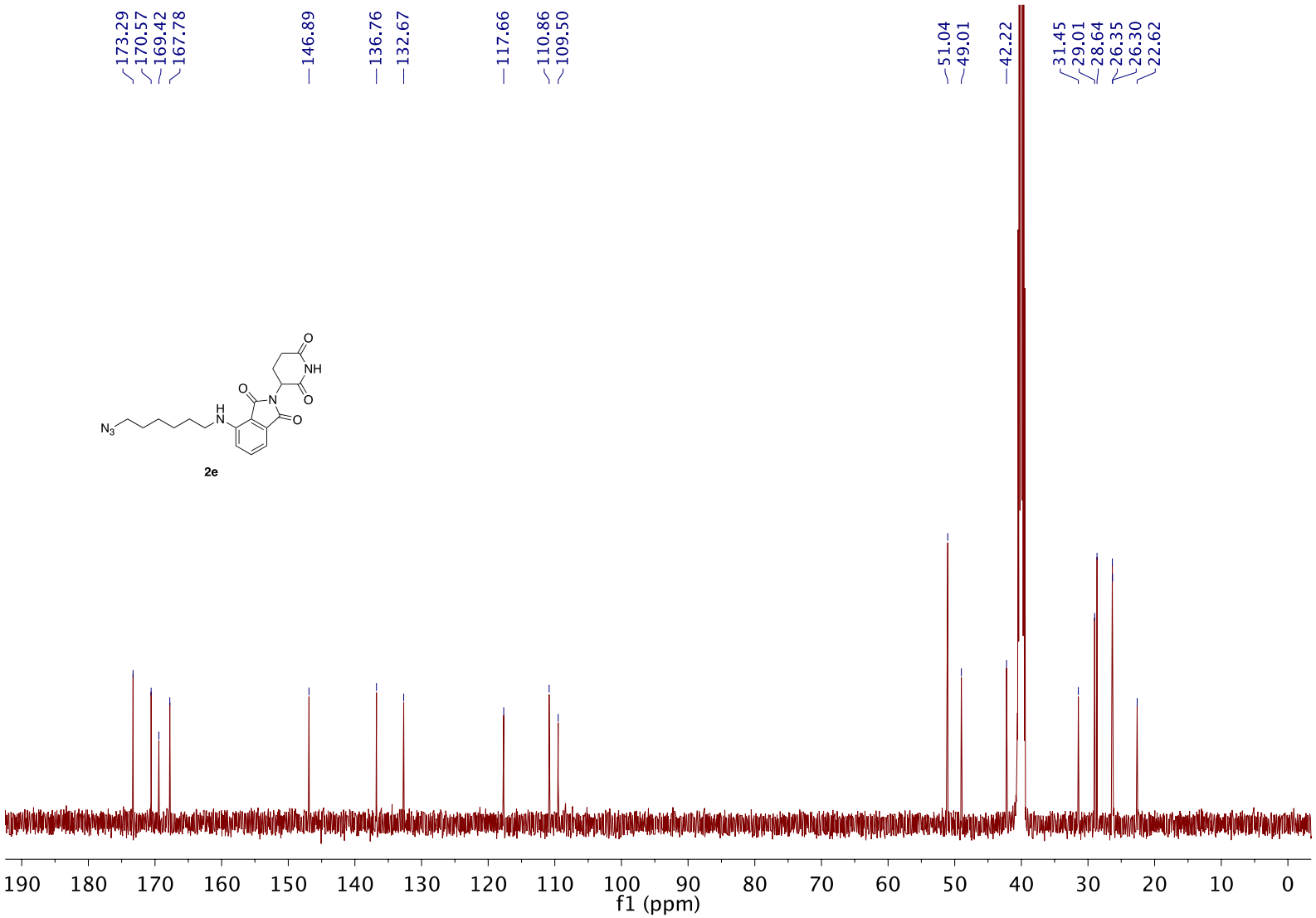
6.52
5.06
5.05
5.04
5.03
3.30
3.29
3.27
2.92
2.91
2.90
2.85
2.84
2.84
2.60
2.57
2.54
2.53
2.50 DMSO-d6
2.05
2.01
2.00
1.59
1.58
1.54
1.53
1.38
1.37
1.37
1.36
1.35
0.98
1.00
1.00
0.96
0.97
0.99
4.19
0.95
1.79
0.97
4.05
4.03
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

2e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109.50
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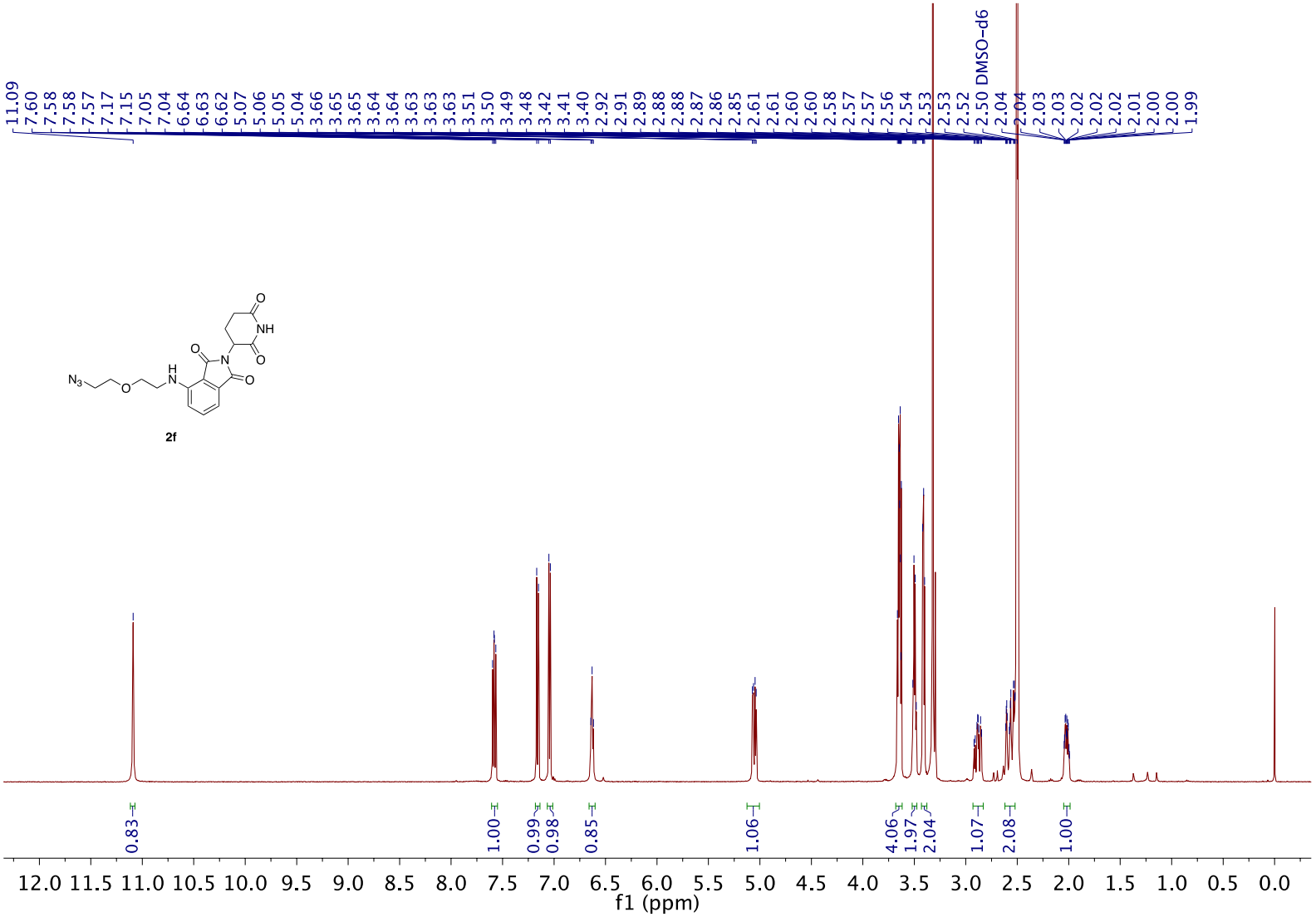
49.01
42.22
31.45
29.01
28.64
26.35
26.30
22.62
2e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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6.63
6.62
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5.04
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3.41
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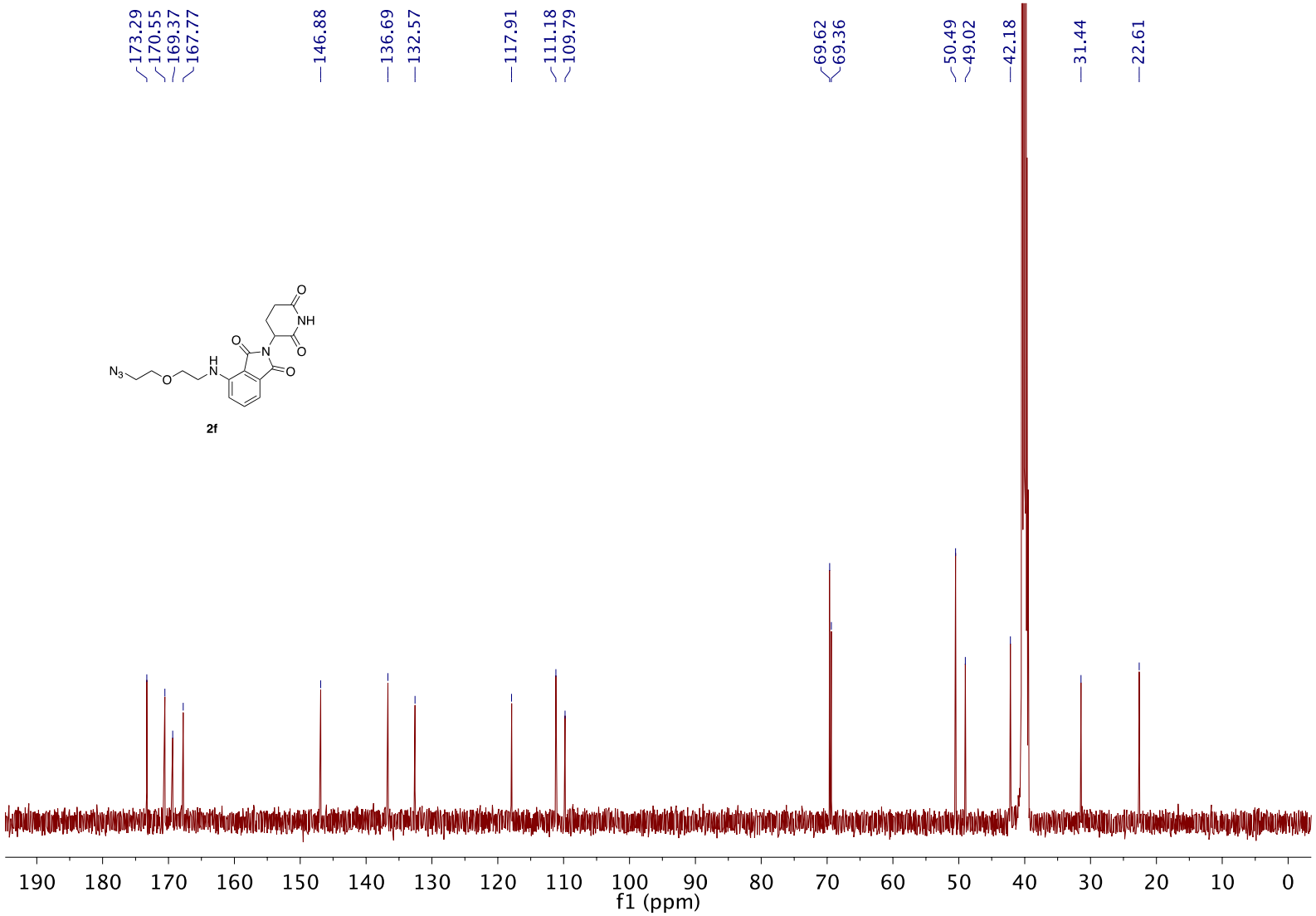
2.89
2.88
2.88
2.87
2.86
2.85
2.61
2.61
2.60
2.60
2.58
2.57
2.57
2.56
2.54
2.53
2.53
2.52
2.50 DMSO-d6
2.04
2.04
2.03
2.03
2.02
2.02
2.02
2.01
2.00
2.00
1.99
0.83
1.00
0.99
0.98
0.85
1.06
4.06
1.97
2.04
1.07
2.08
1.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

2f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69.62
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42.18
31.44
22.61
2f
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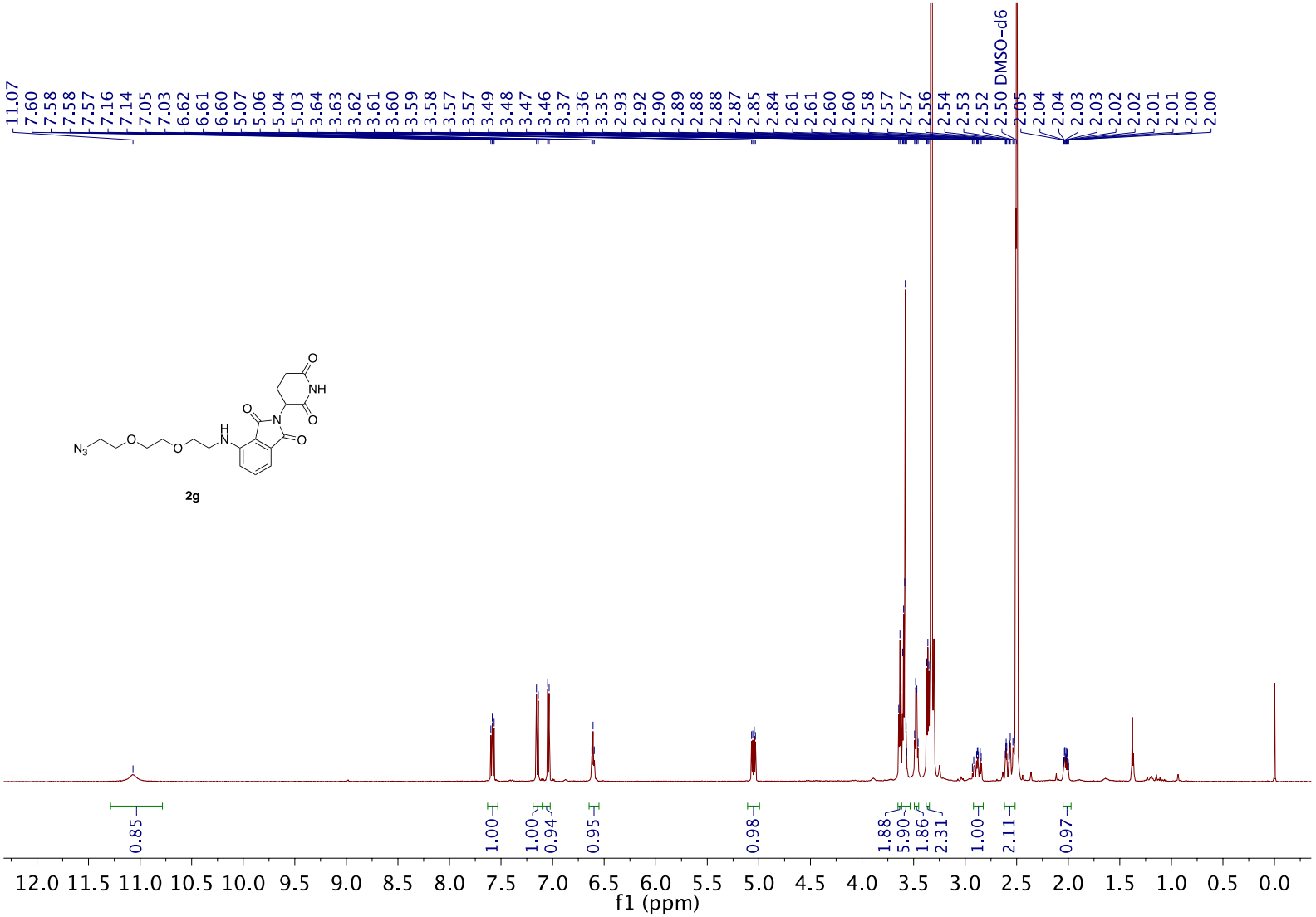
f1 (ppm)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5.06
5.04
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3.63
3.62
3.61
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3.57
3.57
3.49
3.48
3.47
3.46
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3.36
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2.87
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2.04
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2.03
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2.02
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1.00
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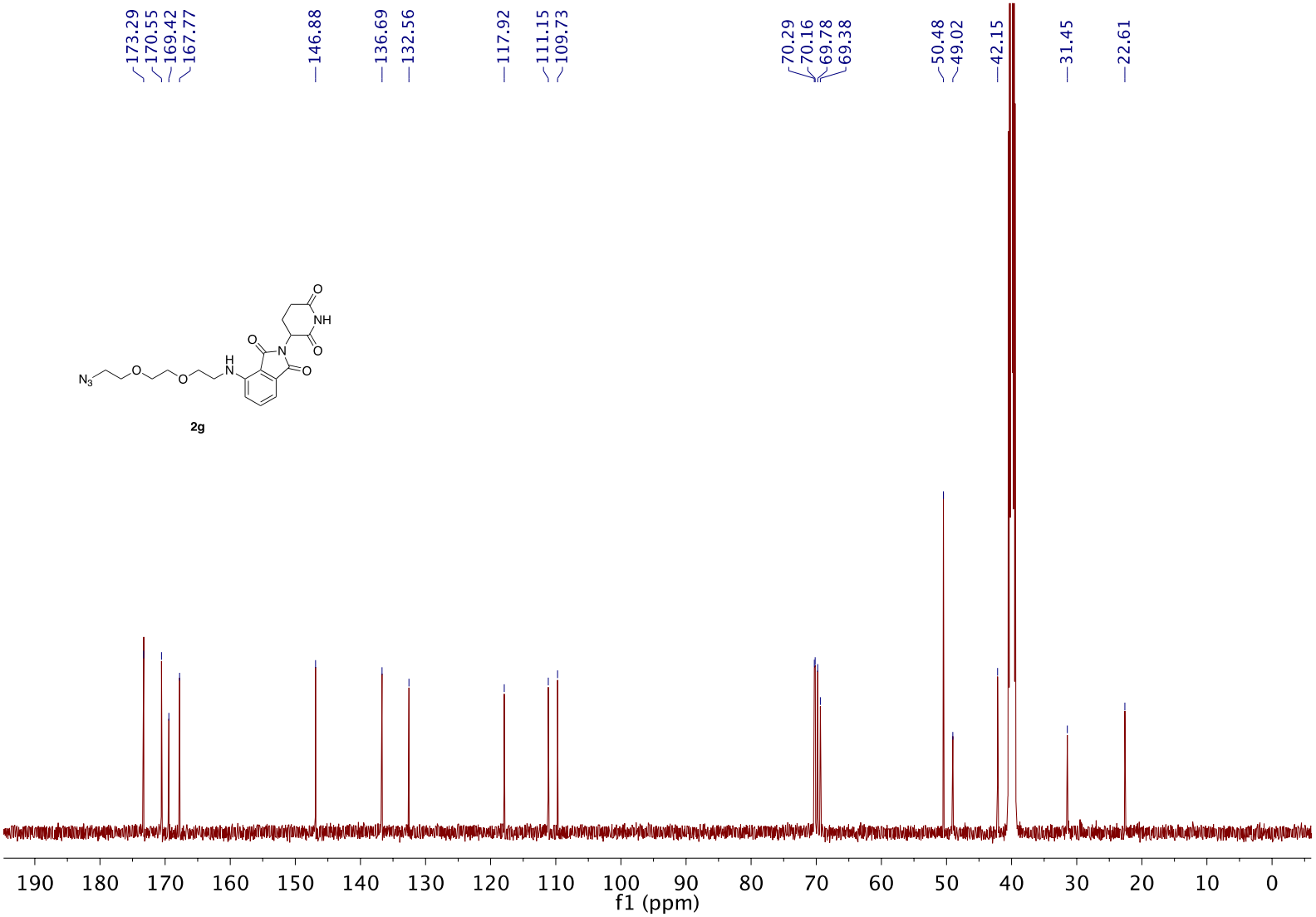
0.95
0.98
1.88
5.90
1.86
2.31
1.00
2.11
0.97
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

2g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70.16
69.78
69.38
50.48
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42.15
31.45
22.61
2g
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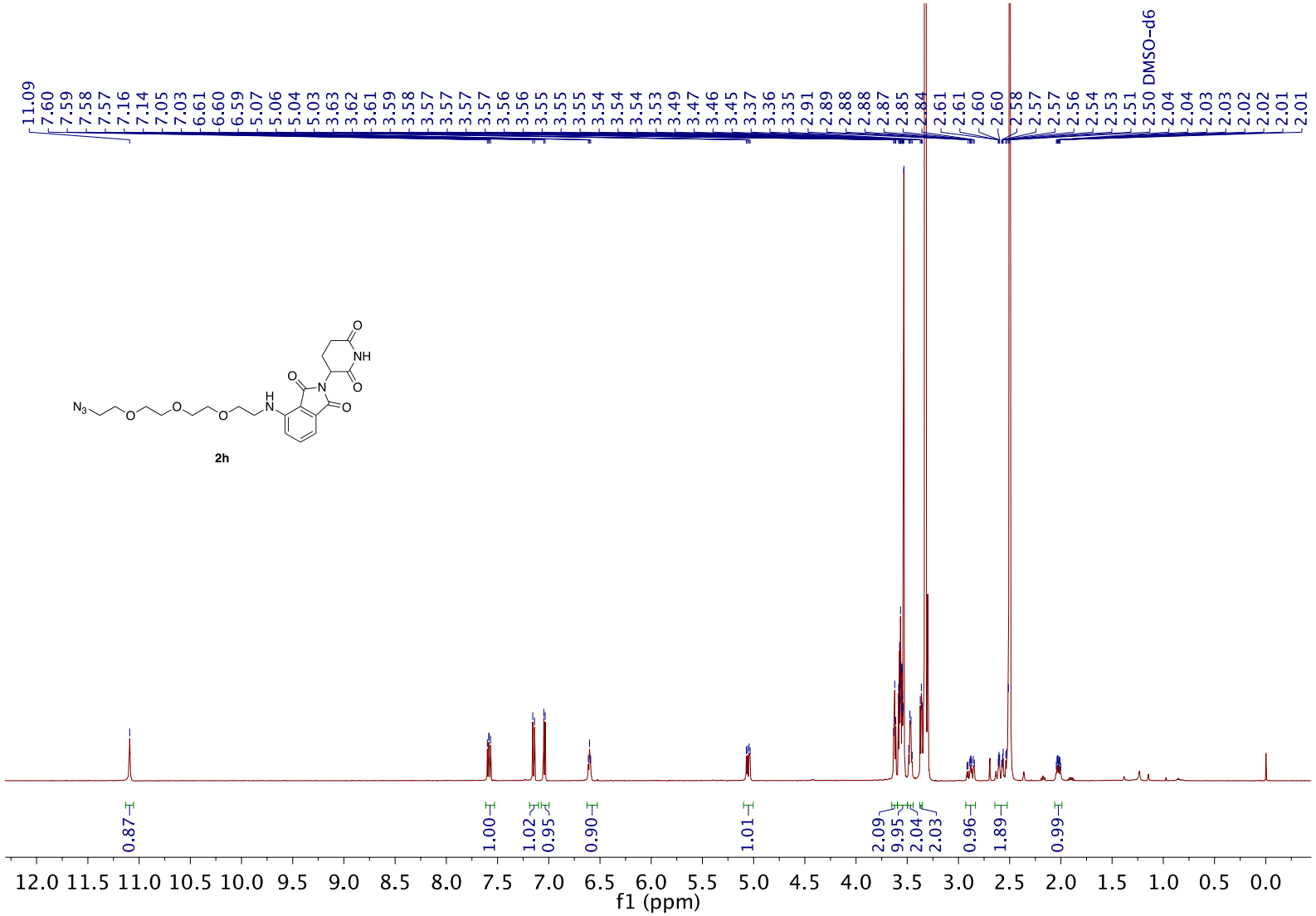
f1 (ppm)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7.03
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5.07
5.06
5.04
5.03
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3.62
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3.46
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2.04
2.03
2.03
2.02
2.02
2.01
2.01
2h
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1.02
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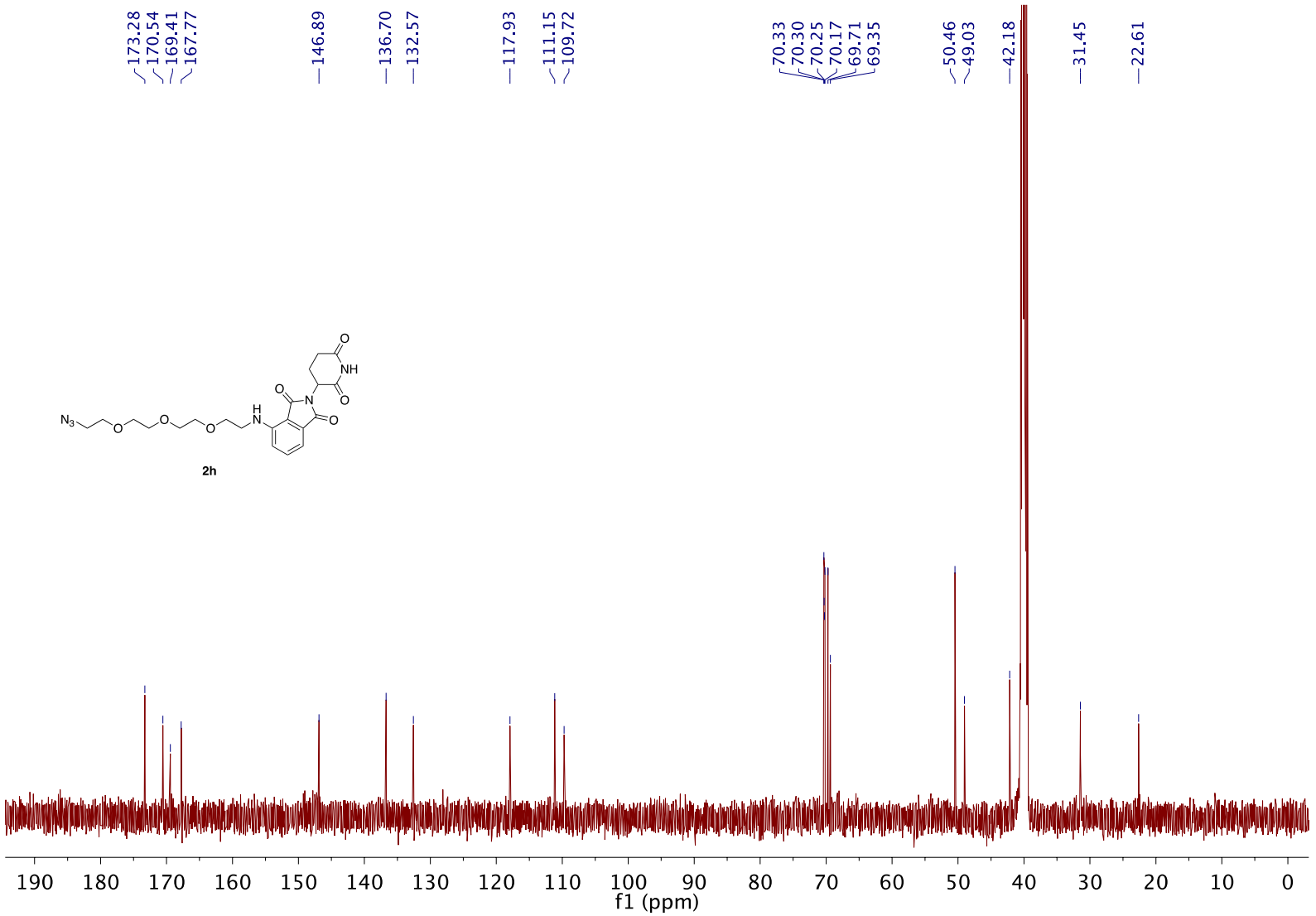
0.90
1.01
2.09
9.95
2.04
2.03
0.96
1.89
0.99
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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69.71
69.35
50.46
49.03
42.18
31.45
22.61
2h
190
180
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110
100
90
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50
40
30
20
10
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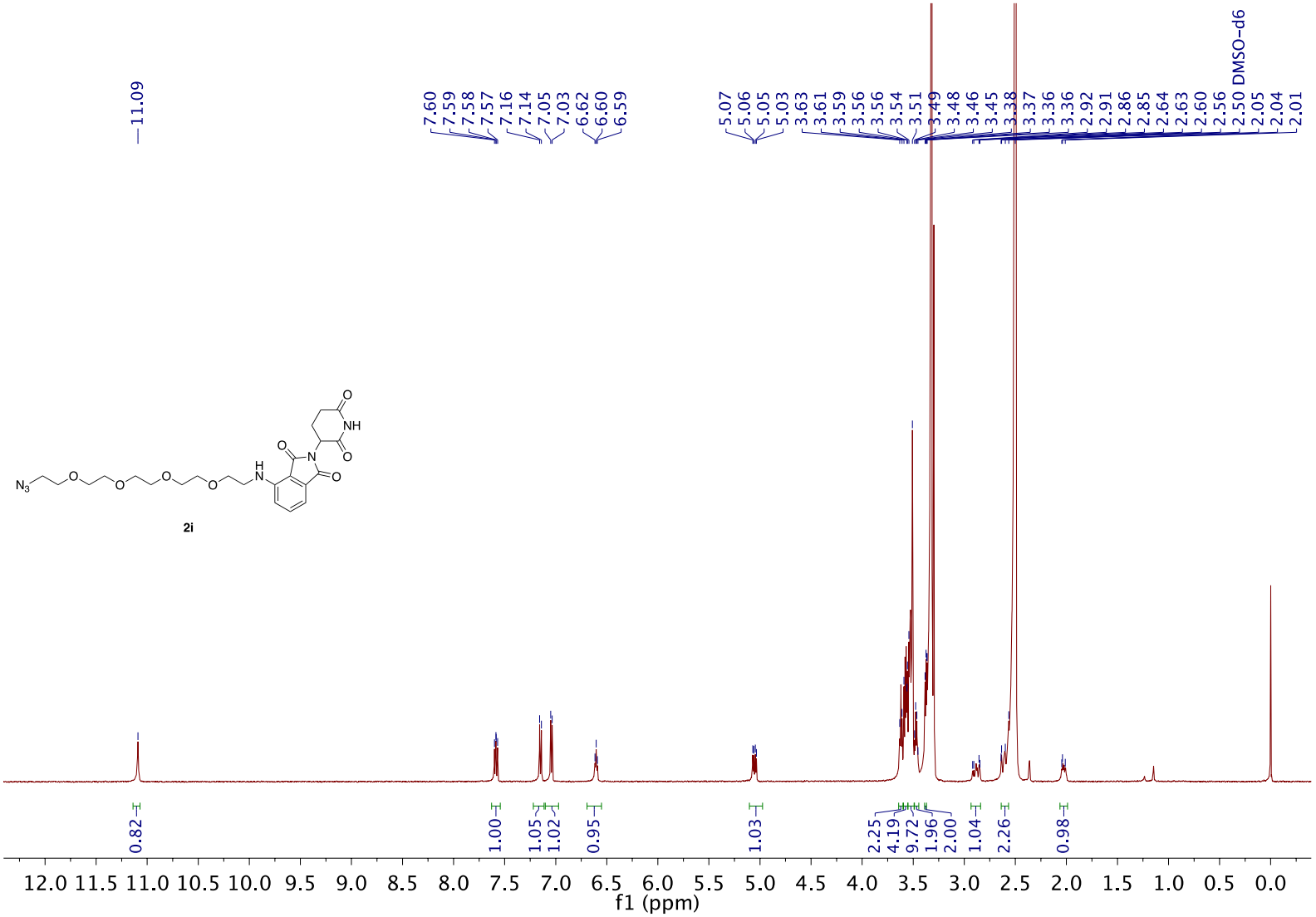
f1 (ppm)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5.03
3.63
3.61
3.59
3.56
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3.54
3.51
3.49
3.48
3.46
3.45
3.38
3.37
3.36
3.36
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2.91
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2.63
2.60
2.56
2.50 DMSO-d6
2.05
2.04
2.01
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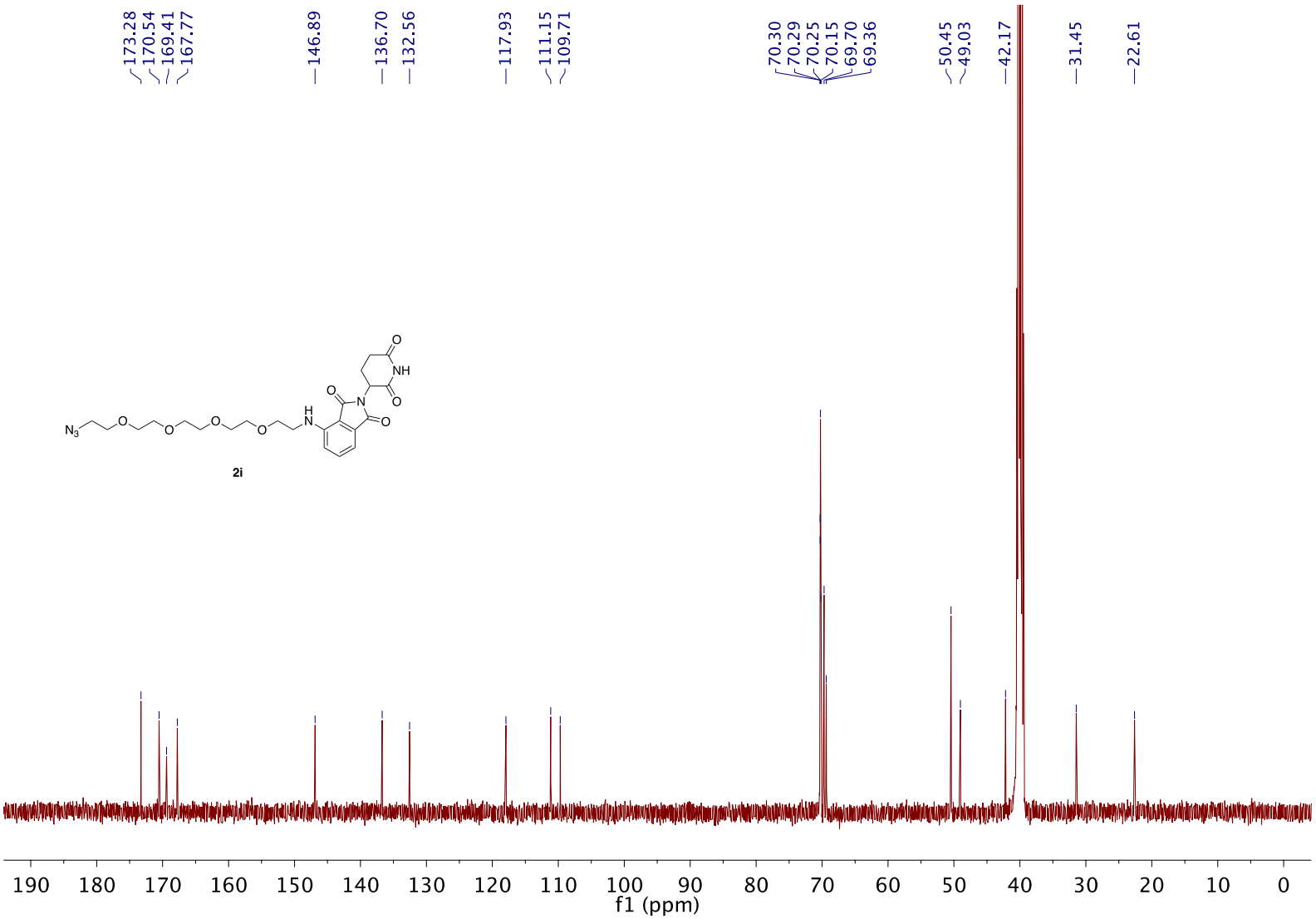
1.00
1.05
1.02
0.95
1.03
2.25
4.19
9.72
1.96
2.00
1.04
2.26
0.98
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

2i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109.71
70.30
70.29
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70.15
69.70
69.36
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42.17
31.45
22.61
2i
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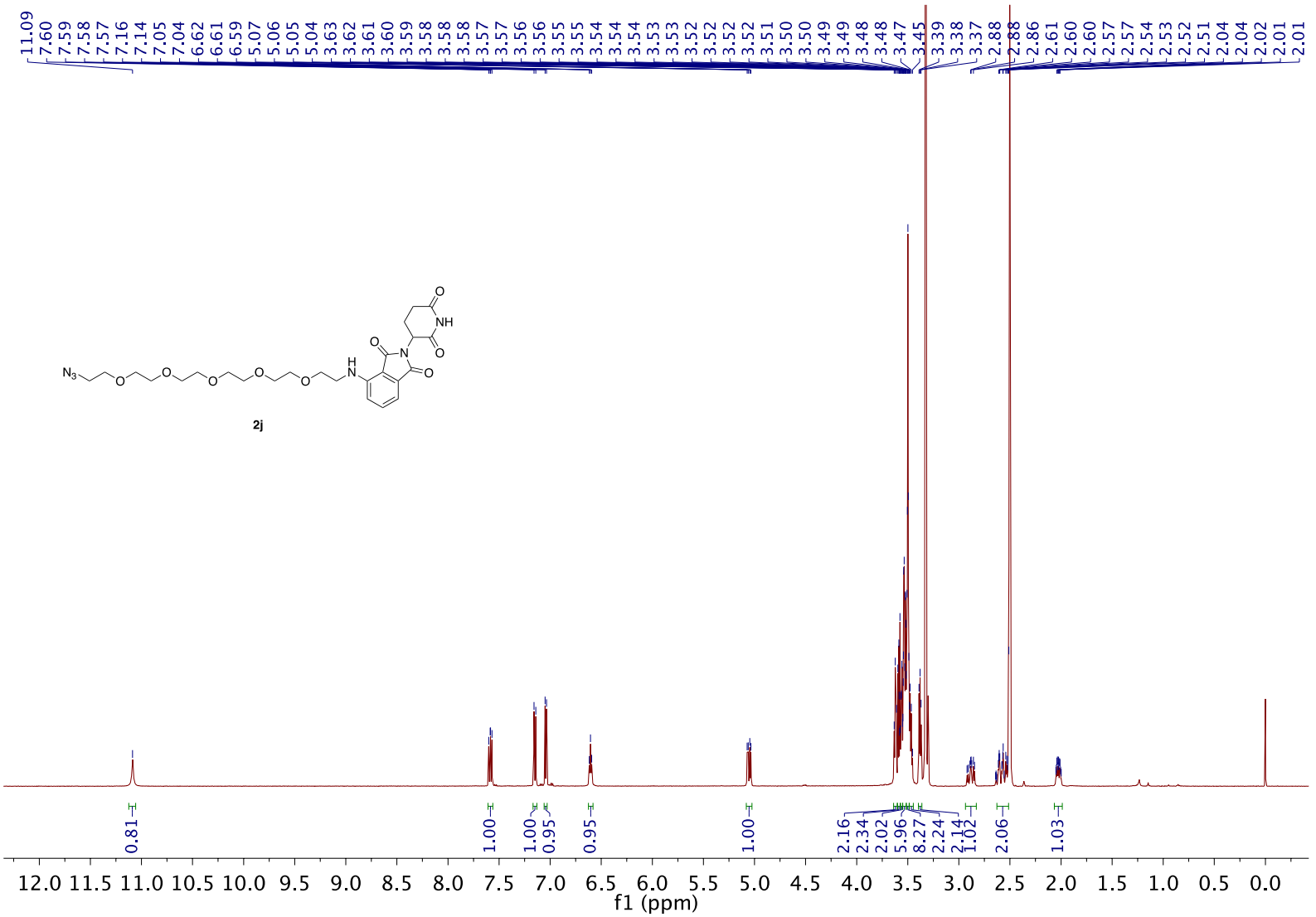
f1 (ppm)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3.38
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2.57
2.54
2.53
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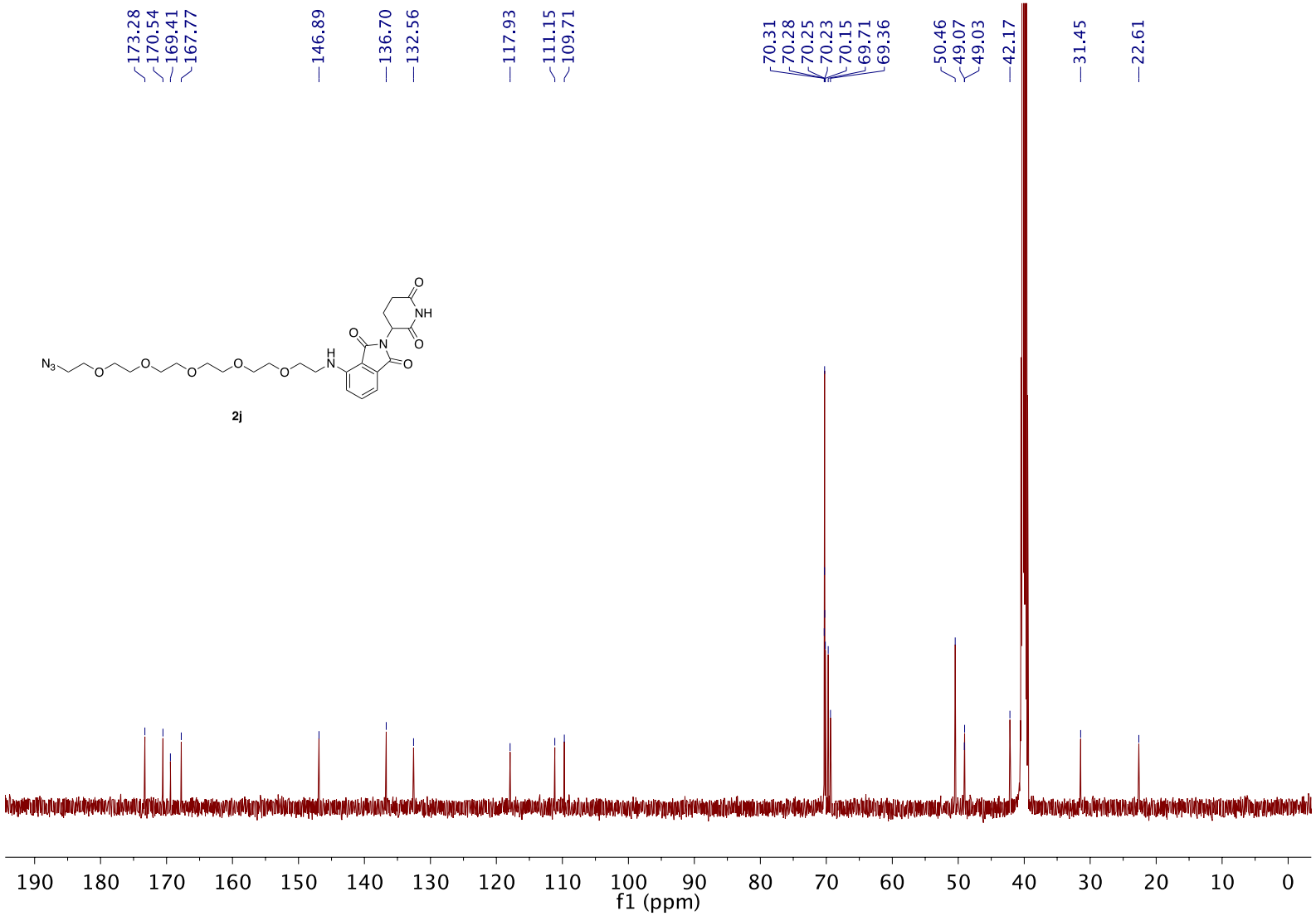
2.04
2.02
2.01
2.01
O
NH
O
O
N
O
H
N
O
N3
O
O
O
O
O
2j
0.81
1.00
1.00
0.95
0.95
1.00
2.16
2.34
2.02
5.96
8.27
2.24
2.14
1.02
2.06
1.03
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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70.28
70.25
70.23
70.15
69.71
69.36
50.46
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42.17
31.45
22.61
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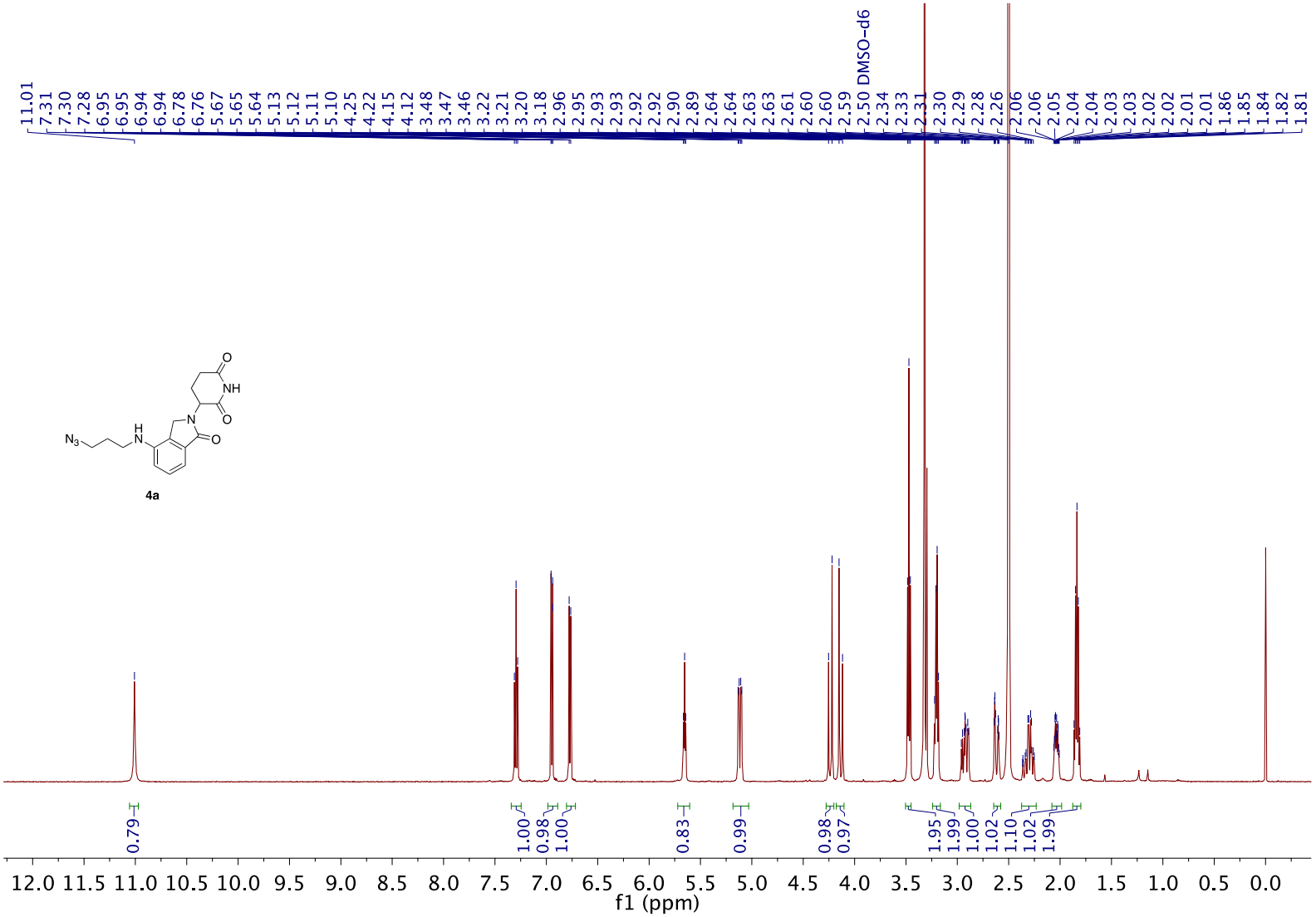
f1 (ppm)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6.76
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5.12
5.11
5.10
4.25
4.22
4.15
4.12
3.48
3.47
3.46
3.22
3.21
3.20
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2.95
2.93
2.93
2.92
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2.90
2.89
2.64
2.64
2.63
2.63
2.61
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2.50 DMSO-d6
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2.28
2.26
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2.06
2.05
2.04
2.04
2.03
2.03
2.02
2.02
2.01
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1.81
O
NH
O
N
H
N
O
N3
4a
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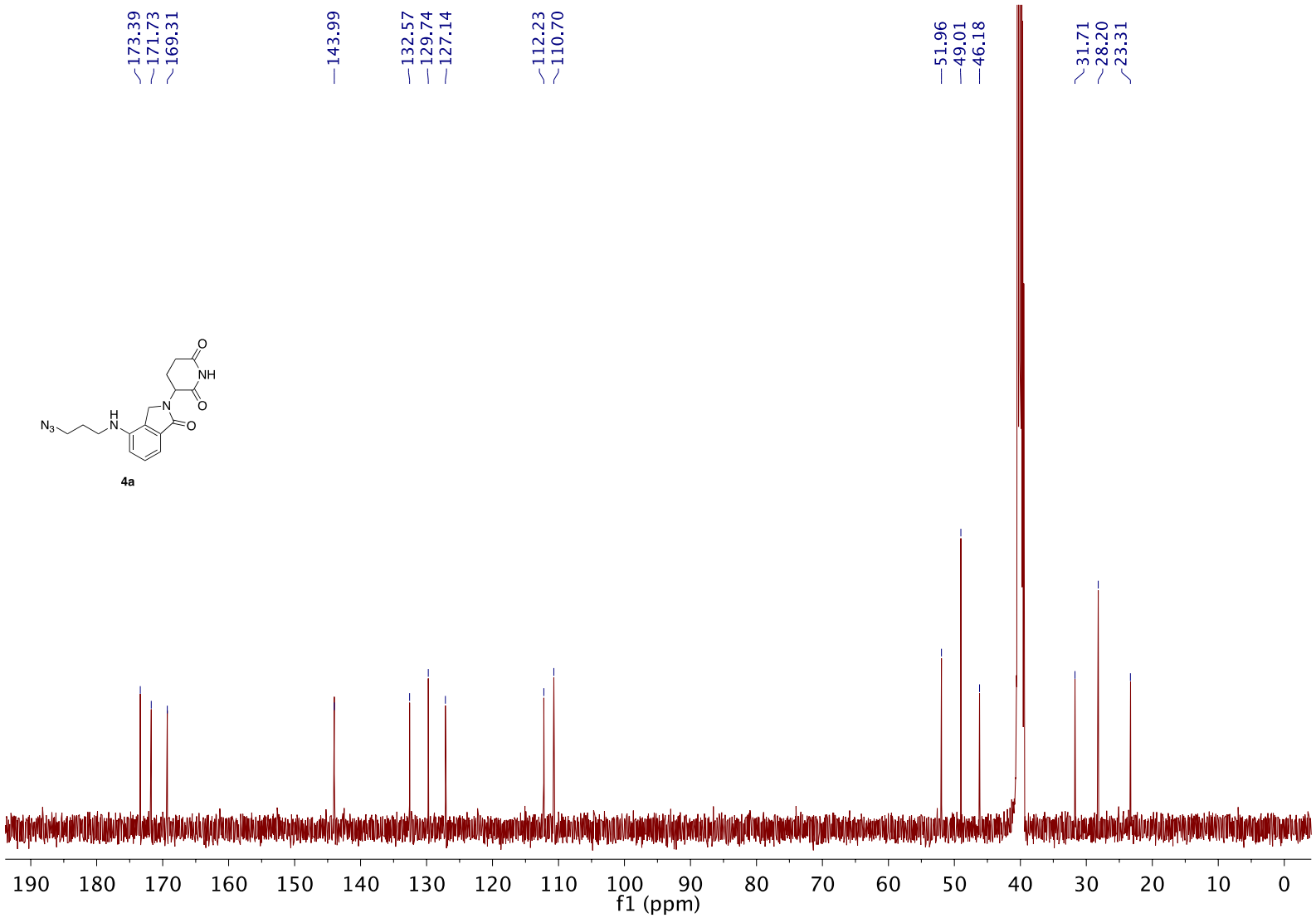
0.98
1.00
0.83
0.99
0.98
0.97
1.95
1.99
1.00
1.02
1.10
1.02
1.99
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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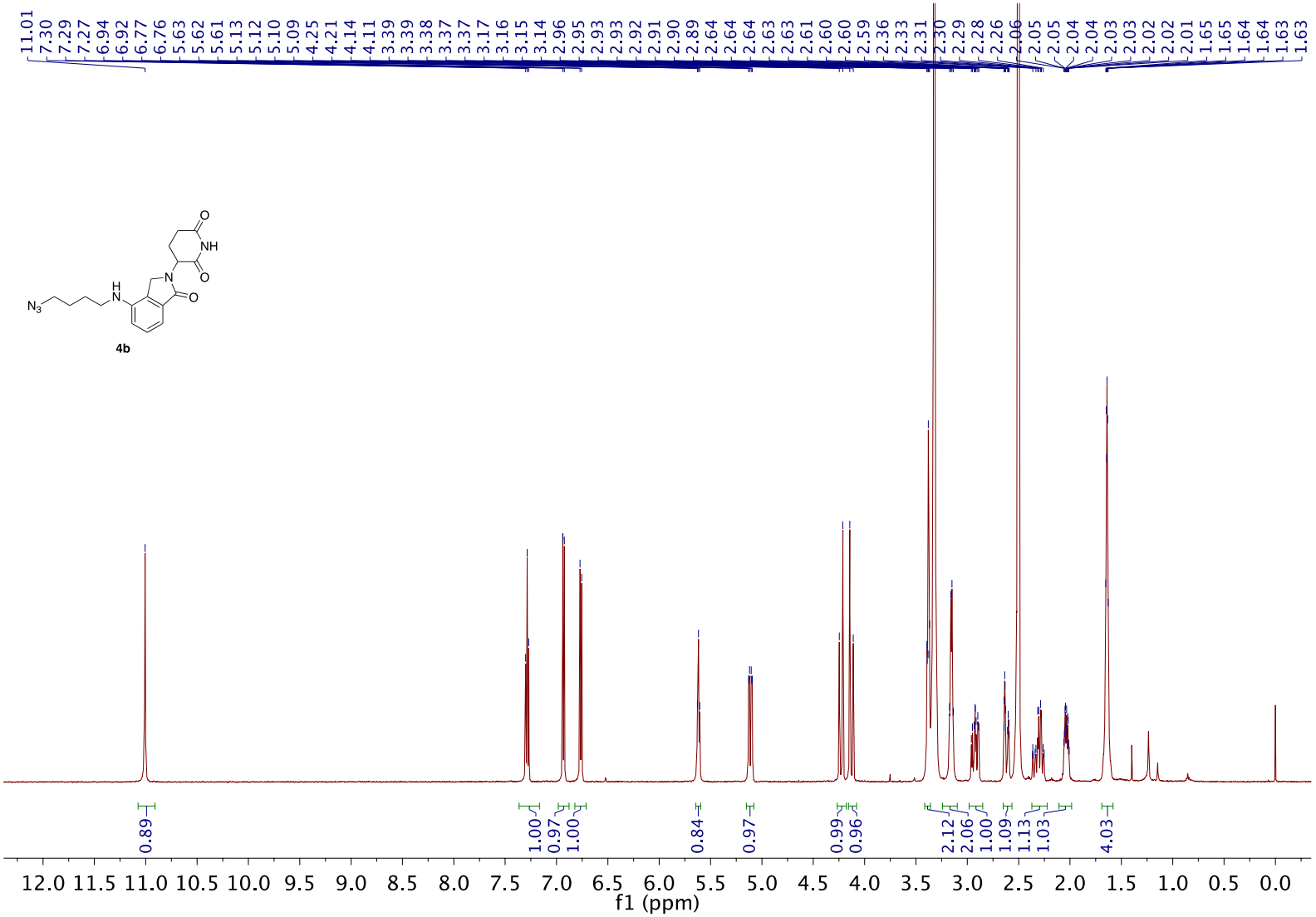
127.14
112.23
110.70
51.96
49.01
46.18
31.71
28.20
23.31
O
NH
O
N
H
N
O
N3
4a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.27
6.94
6.92
6.77
6.76
5.63
5.62
5.61
5.13
5.12
5.10
5.09
4.25
4.21
4.14
4.11
3.39
3.39
3.38
3.37
3.37
3.17
3.16
3.15
3.14
2.96
2.95
2.93
2.93
2.92
2.91
2.90
2.89
2.64
2.64
2.64
2.63
2.63
2.61
2.60
2.60
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2.33
2.31
2.30
2.29
2.28
2.26
2.06
2.05
2.05
2.04
2.04
2.03
2.03
2.02
2.02
2.01
1.65
1.65
1.64
1.64
1.63
1.63
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NH
O
N
O
H
N
N3
4b
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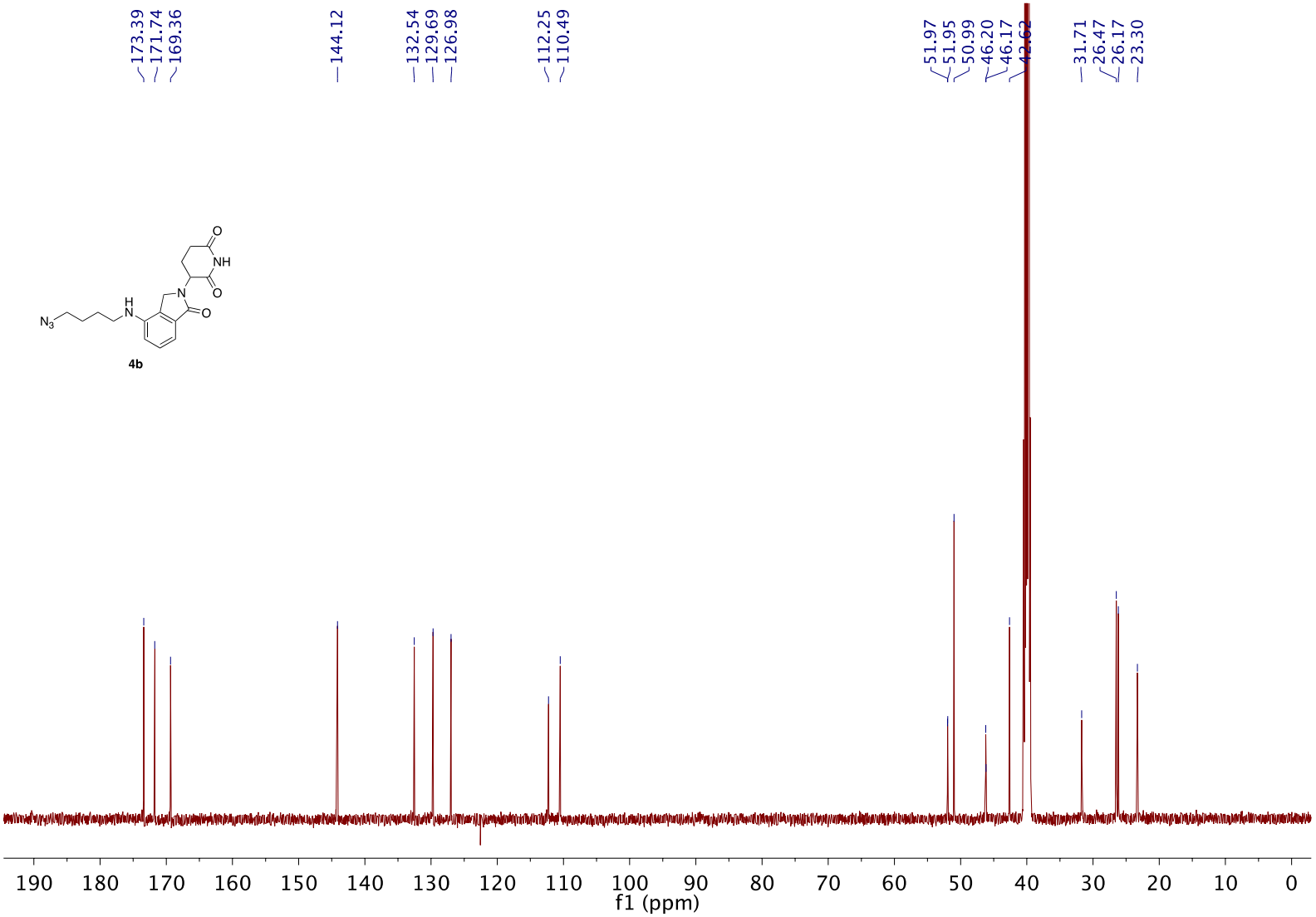
1.00
0.97
1.00
0.84
0.97
0.99
0.96
2.12
2.06
1.00
1.09
1.13
1.03
4.03
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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112.25
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51.95
50.99
46.20
46.17
42.62
31.71
26.47
26.17
23.30
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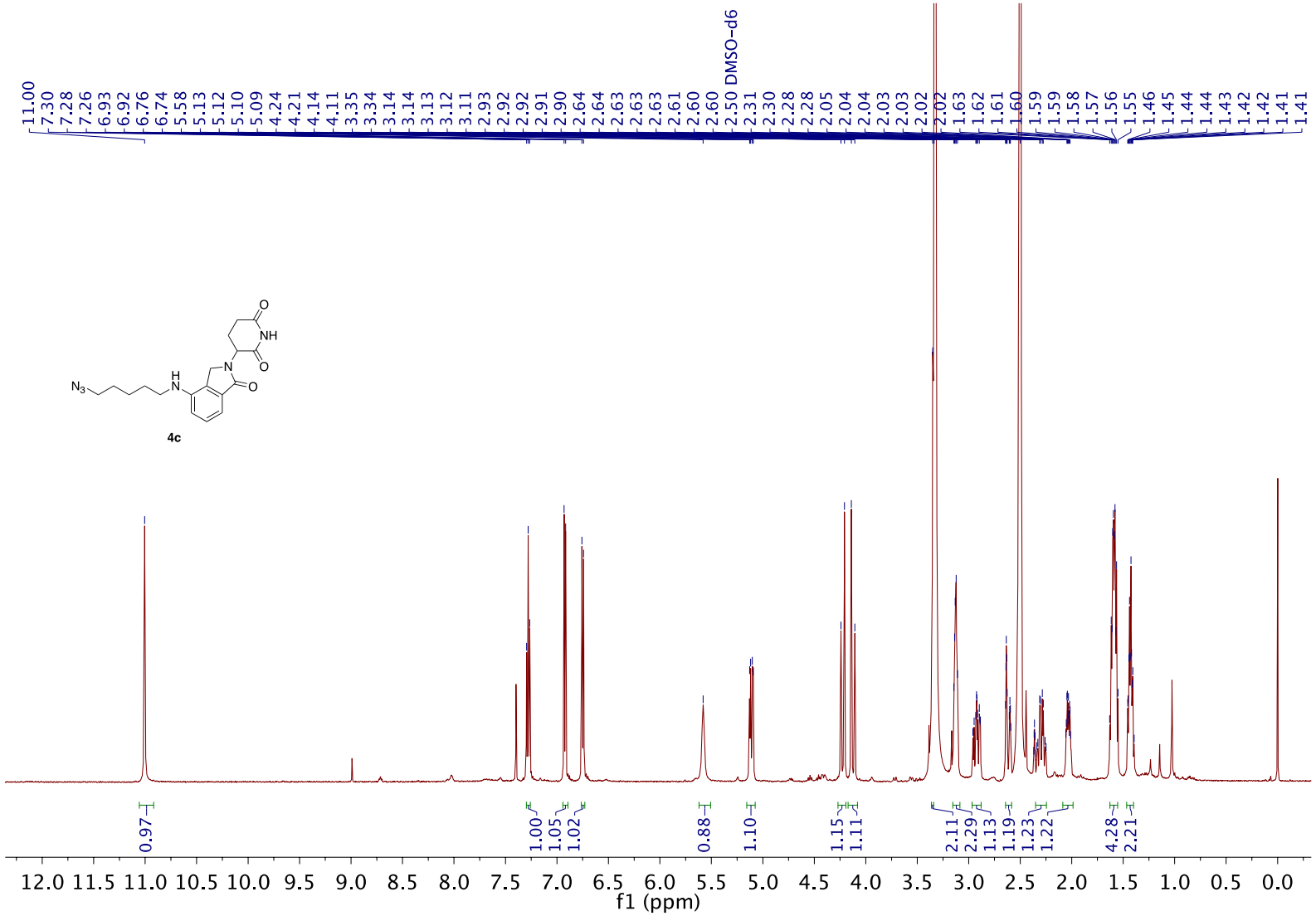
NH
O
N
O
H
N
N3
4b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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6.92
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6.74
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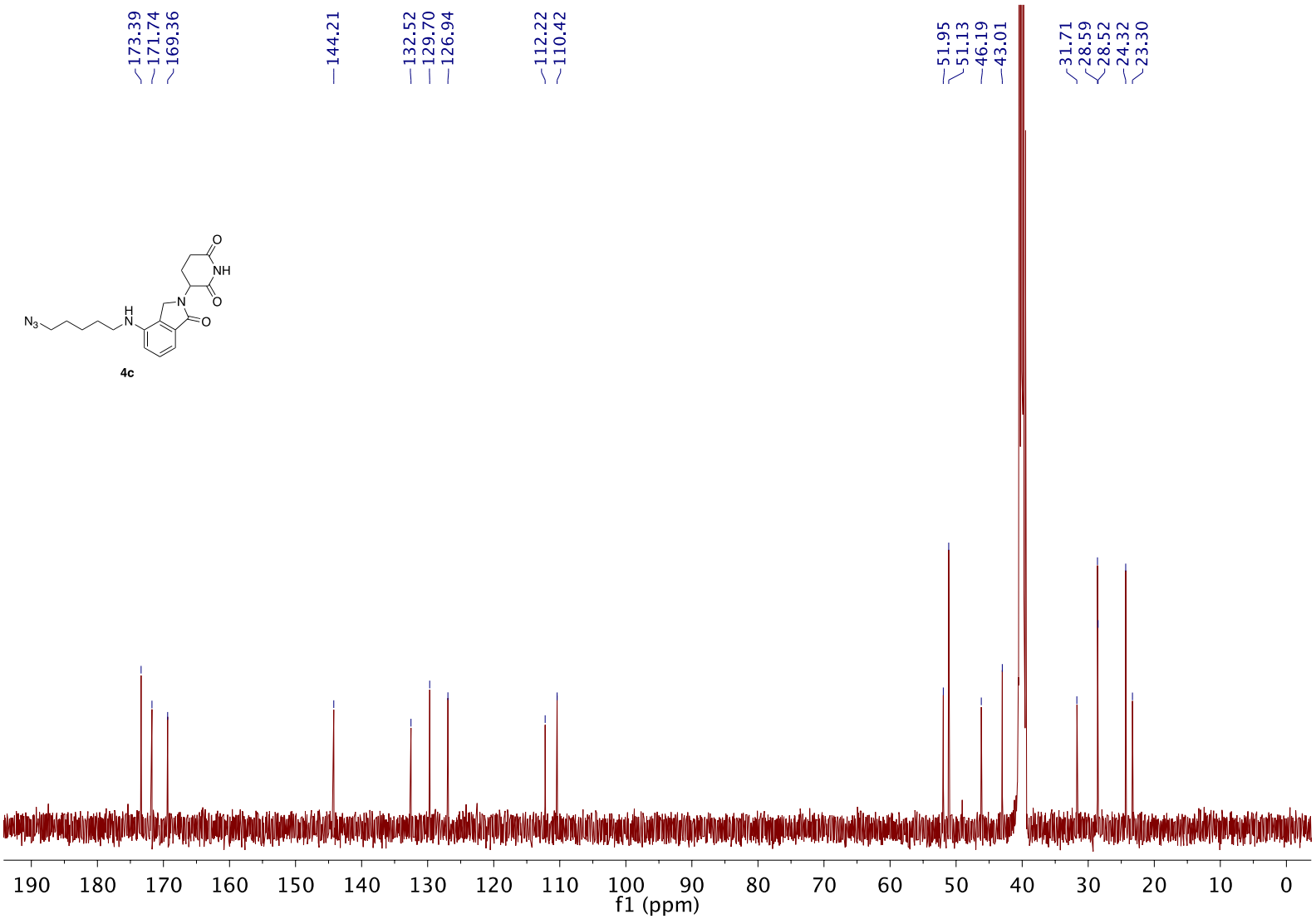
5.13
5.12
5.10
5.09
4.24
4.21
4.14
4.11
3.35
3.34
3.14
3.14
3.13
3.12
3.11
2.93
2.92
2.92
2.91
2.90
2.64
2.64
2.63
2.63
2.63
2.61
2.60
2.60
2.50 DMSO-d6
2.31
2.30
2.28
2.28
2.05
2.04
2.04
2.03
2.03
2.02
2.02
2.02
1.63
1.62
1.61
1.60
1.59
1.59
1.58
1.57
1.56
1.55
1.46
1.45
1.44
1.44
1.43
1.42
1.42
1.41
1.41
O
NH
O
N
O
H
N
N3
4c
0.97
1.00
1.05
1.02
0.88
1.10
1.15
1.11
2.11
2.29
1.13
1.19
1.23
1.22
4.28
2.21
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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112.22
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51.13
46.19
43.01
31.71
28.59
28.52
24.32
23.30
O
NH
O
N
H
N
O
N3
4c
190
180
170
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130
120
110
100
90
80
70
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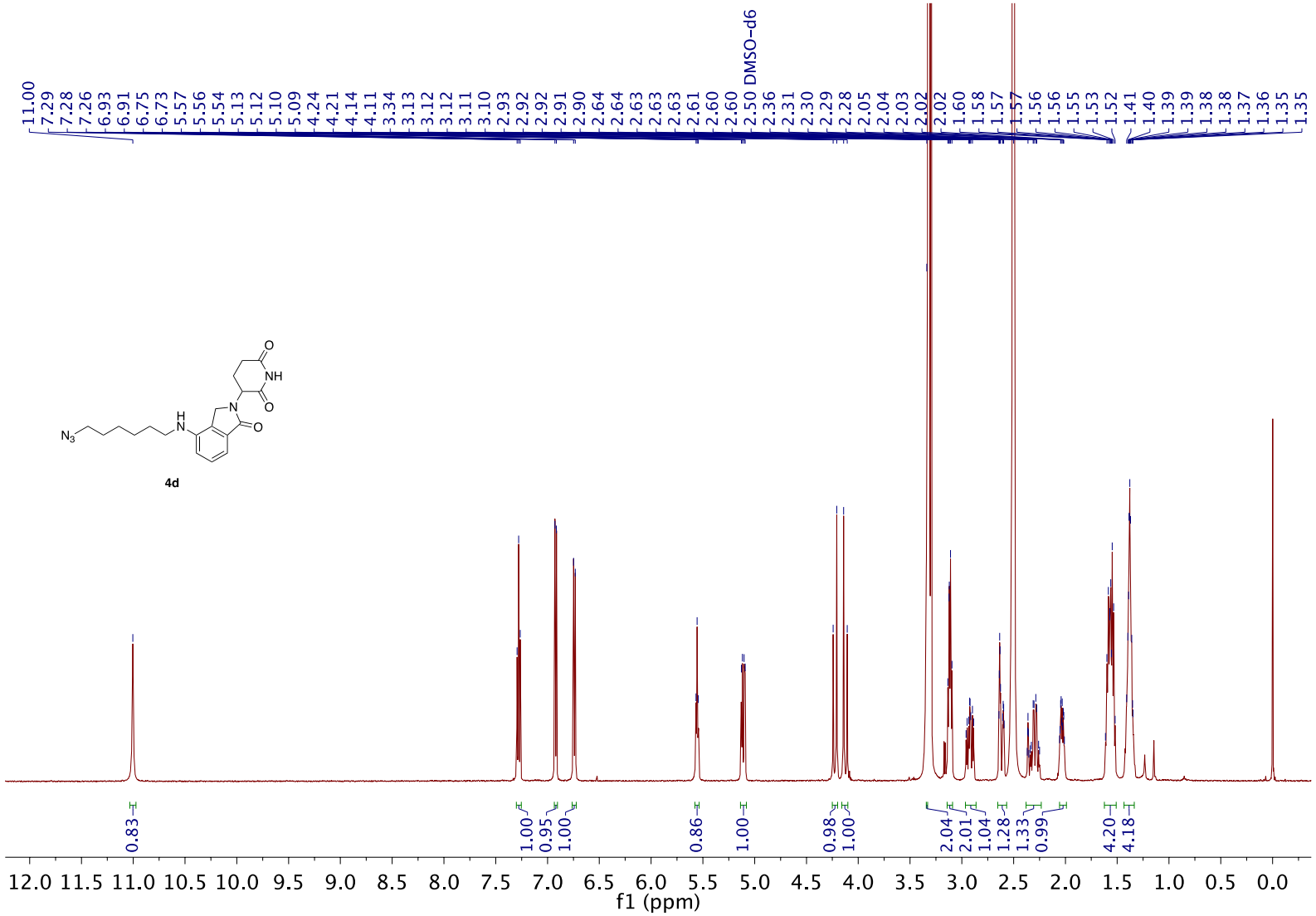
50
40
30
20
10
0
f1 (ppm)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5.56
5.54
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5.12
5.10
5.09
4.24
4.21
4.14
4.11
3.34
3.13
3.12
3.12
3.11
3.10
2.93
2.92
2.92
2.91
2.90
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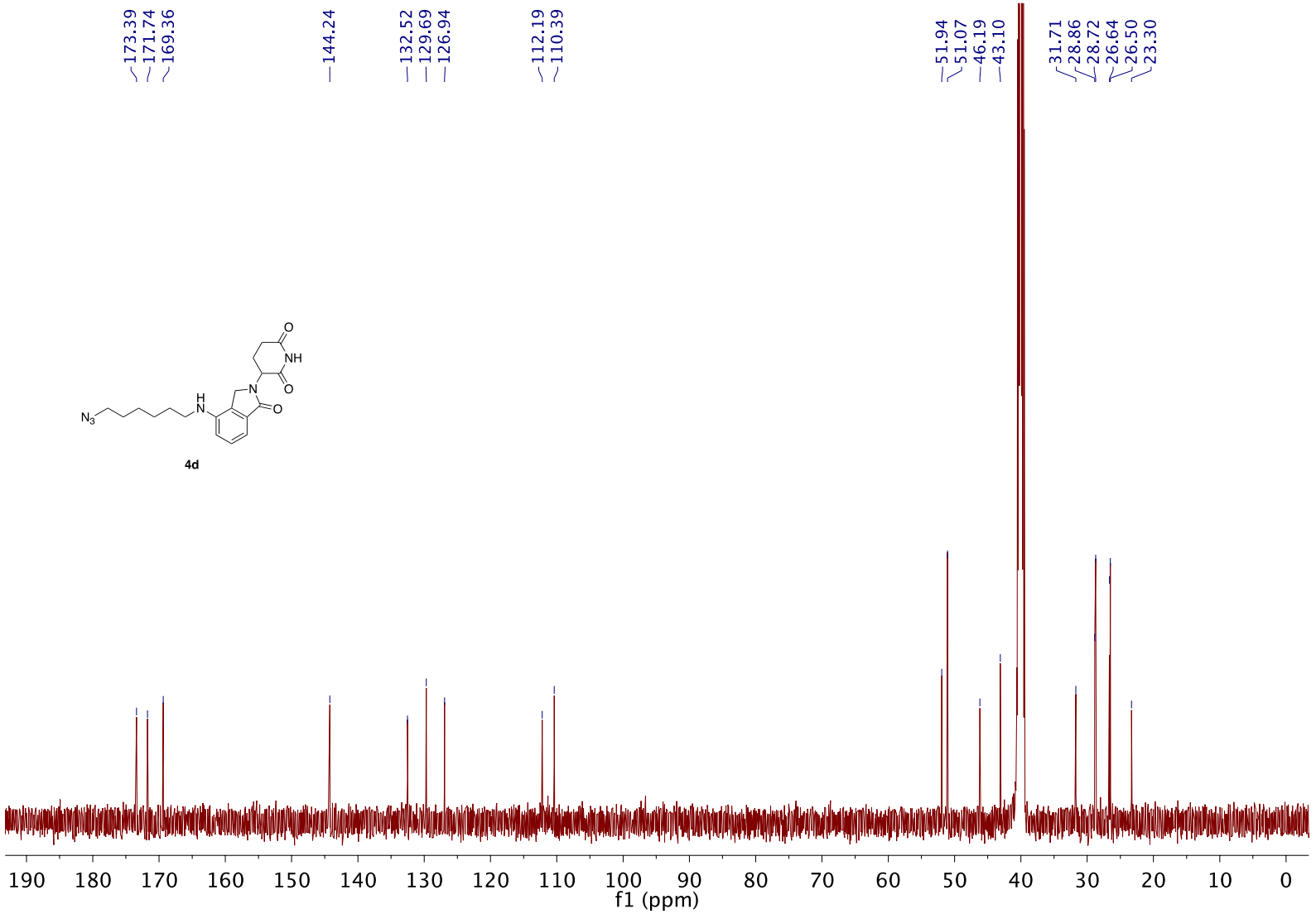
2.64
2.63
2.63
2.63
2.61
2.60
2.60
2.50 DMSO-d6
2.36
2.31
2.30
2.29
2.28
2.05
2.04
2.03
2.02
2.02
1.60
1.58
1.57
1.57
1.56
1.56
1.55
1.53
1.52
1.41
1.40
1.39
1.39
1.38
1.38
1.37
1.36
1.35
1.35
O
NH
O
N
O
H
N
N3
4d
0.83
1.00
0.95
1.00
0.86
1.00
0.98
1.00
2.04
2.01
1.04
1.28
1.33
0.99
4.20
4.18
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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129.69
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112.19
110.39
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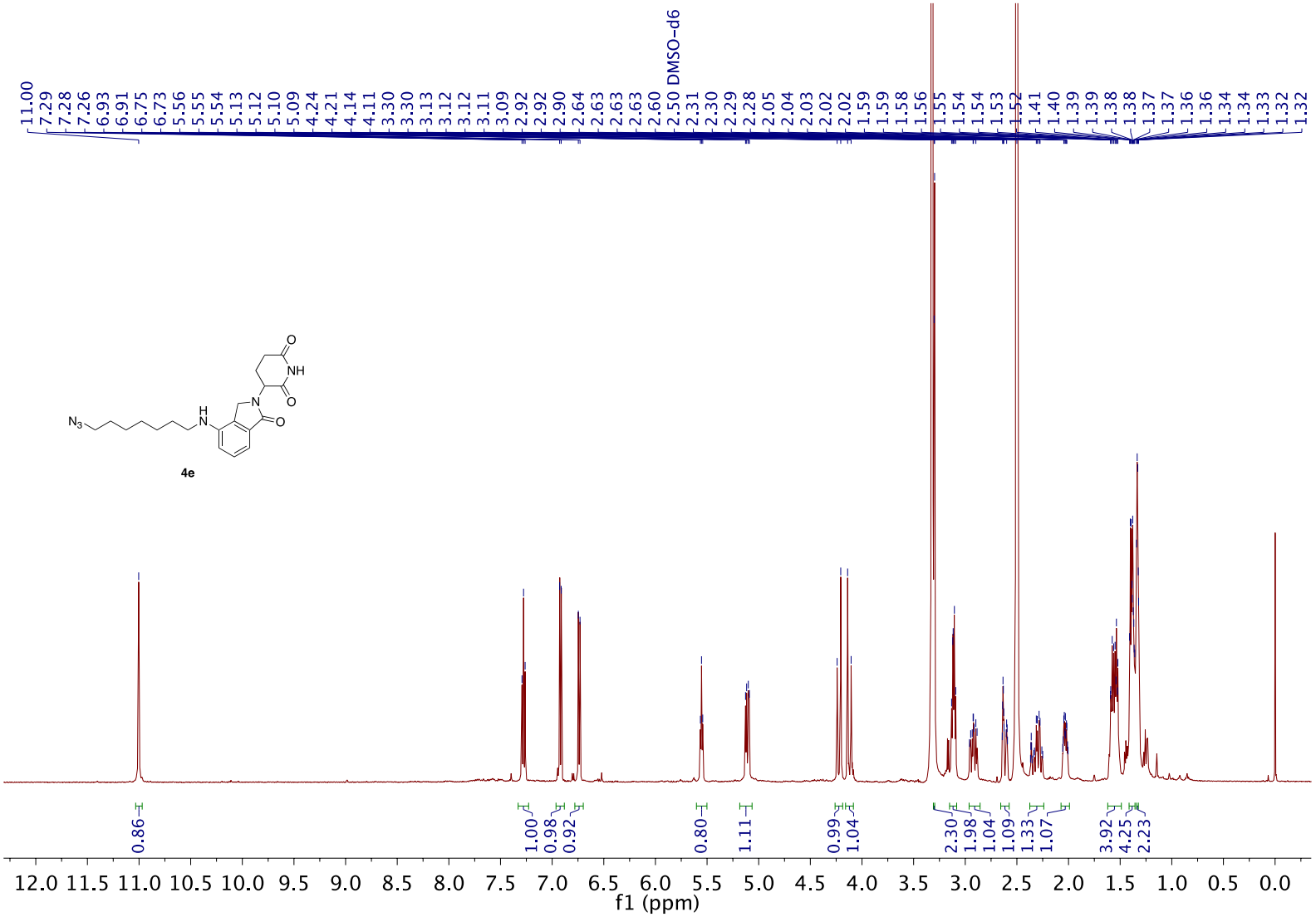
43.10
31.71
28.86
28.72
26.64
26.50
23.30
4d
f1 (ppm)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5.54
5.13
5.12
5.10
5.09
4.24
4.21
4.14
4.11
3.30
3.30
3.13
3.12
3.12
3.11
3.09
2.92
2.92
2.90
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2.63
2.63
2.63
2.60
2.50 DMSO-d6
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2.29
2.28
2.05
2.04
2.03
2.02
2.02
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1.59
1.58
1.56
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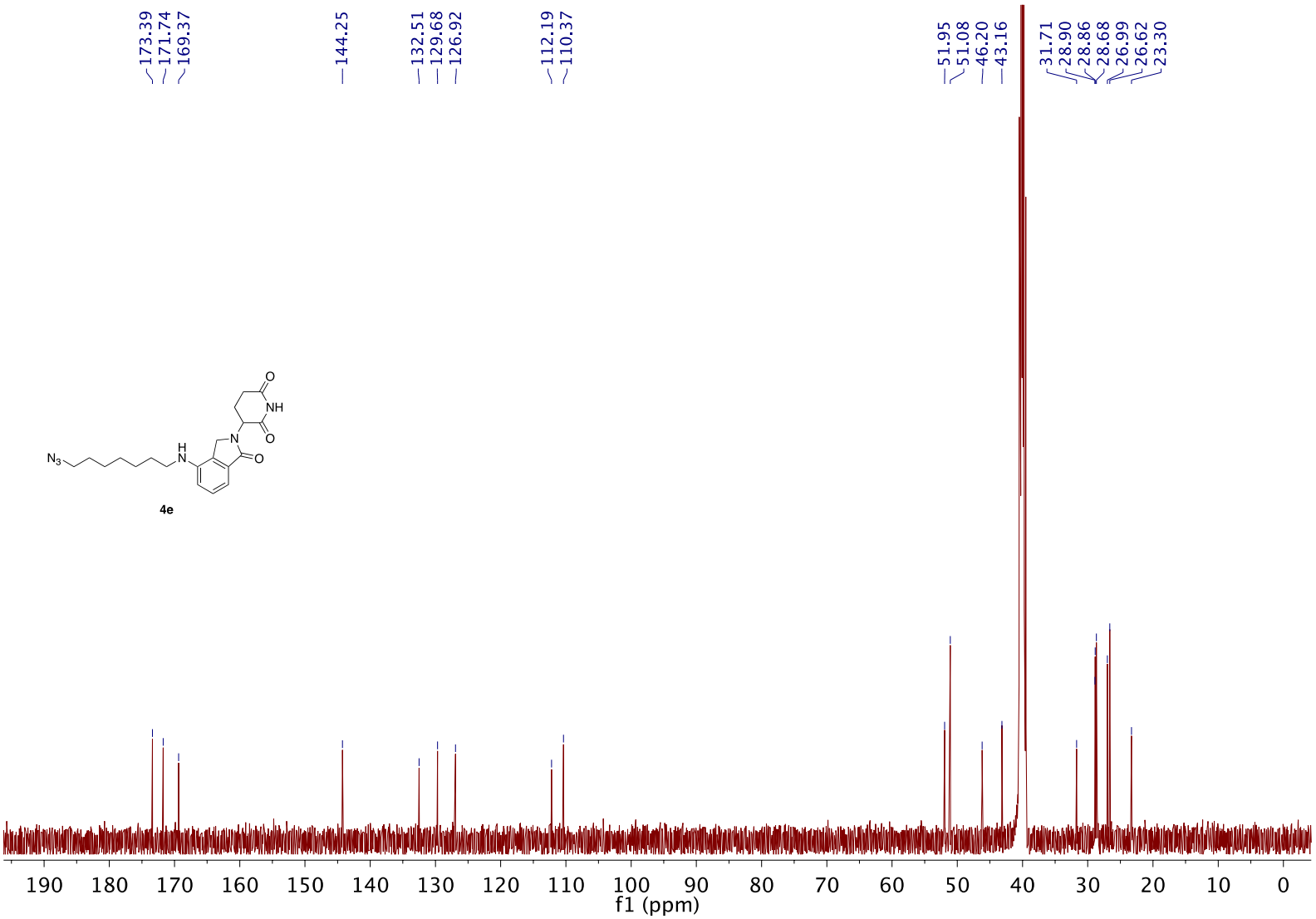
1.54
1.54
1.53
1.52
1.41
1.40
1.39
1.39
1.38
1.38
1.37
1.37
1.36
1.36
1.34
1.34
1.33
1.32
1.32
O
NH
O
N
O
H
N
O
N3
4e
0.86
1.00
0.98
0.92
0.80
1.11
0.99
1.04
2.30
1.98
1.04
1.09
1.33
1.07
3.92
4.25
2.23
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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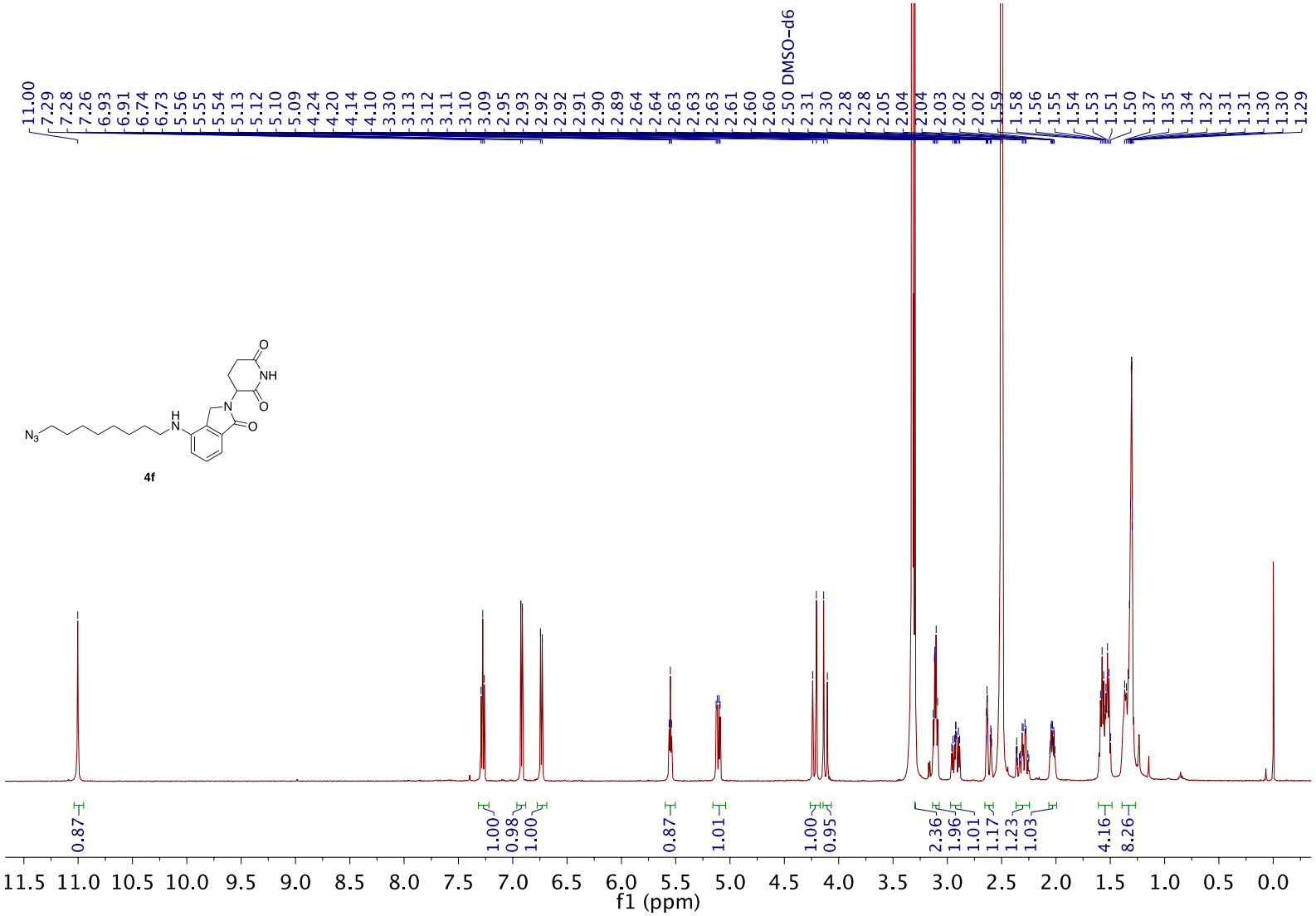
51.95
51.08
46.20
43.16
31.71
28.90
28.86
28.68
26.99
26.62
23.30
O
NH
O
N
H
N
O
N3
4e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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5.54
5.13
5.12
5.10
5.09
4.24
4.20
4.14
4.10
3.30
3.13
3.12
3.11
3.10
3.09
2.95
2.93
2.92
2.92
2.91
2.90
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2.63
2.63
2.63
2.61
2.60
2.60
2.50 DMSO-d6
2.31
2.30
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2.28
2.05
2.04
2.04
2.03
2.02
2.02
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1.58
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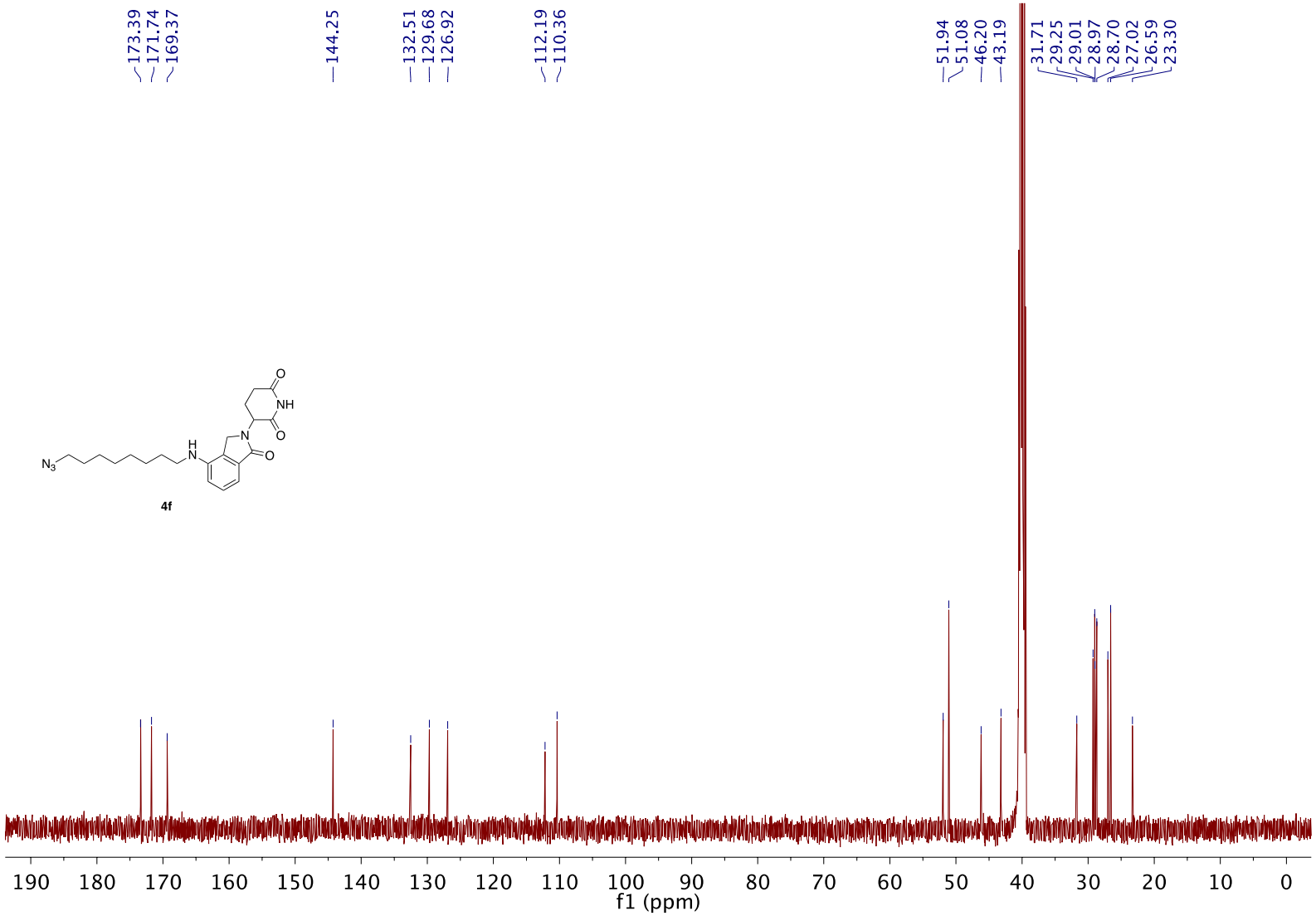
1.54
1.53
1.51
1.50
1.37
1.35
1.34
1.32
1.31
1.31
1.30
1.30
1.29
O
NH
O
N
O
H
N
N3
4f
0.87
1.00
0.98
1.00
0.87
1.01
1.00
0.95
2.36
1.96
1.01
1.17
1.23
1.03
4.16
8.26
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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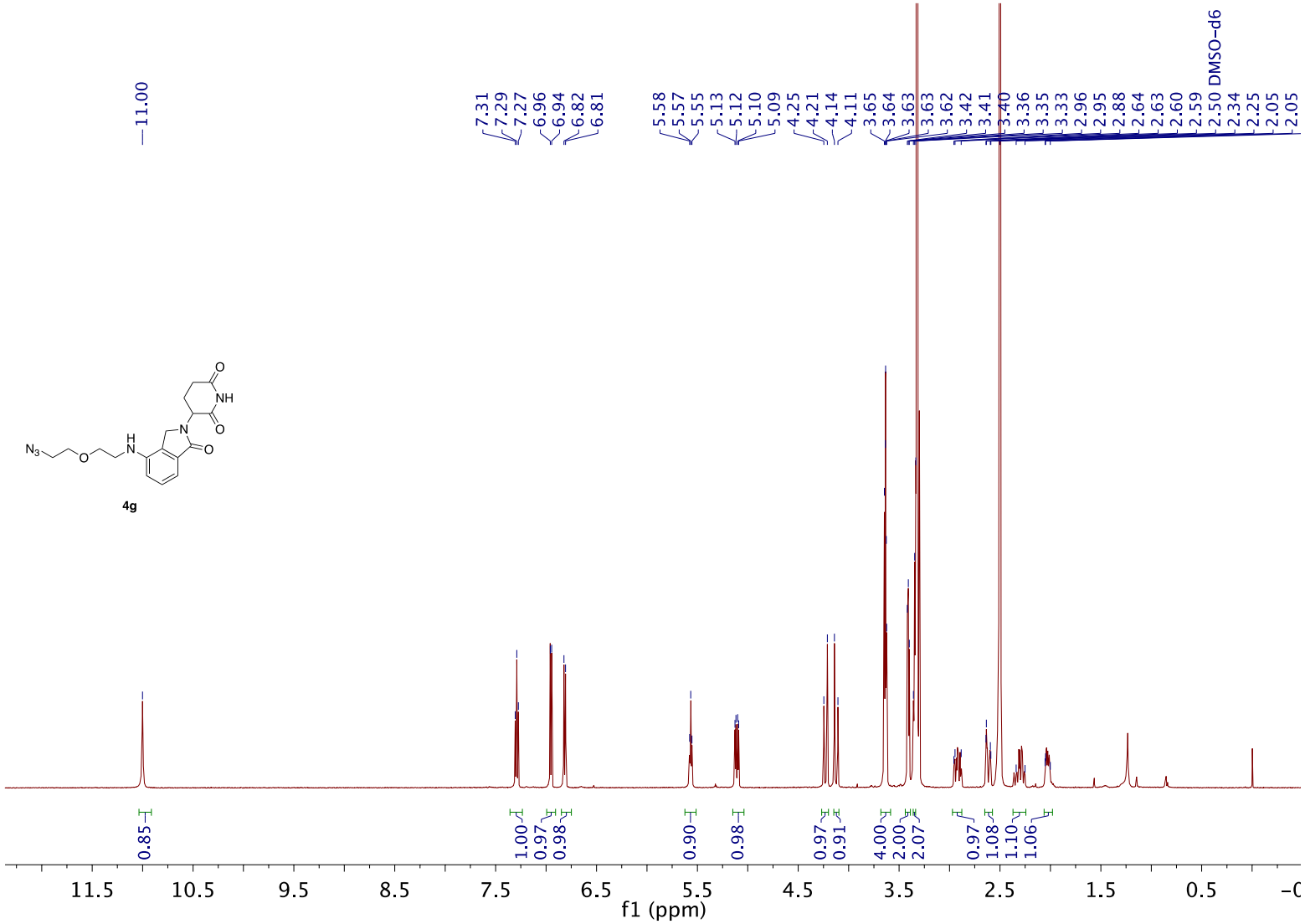
144.25
132.51
129.68
126.92
112.19
110.36
51.94
51.08
46.20
43.19
31.71
29.25
29.01
28.97
28.70
27.02
26.59
23.30
O
NH
O
N
H
N
O
N3
4f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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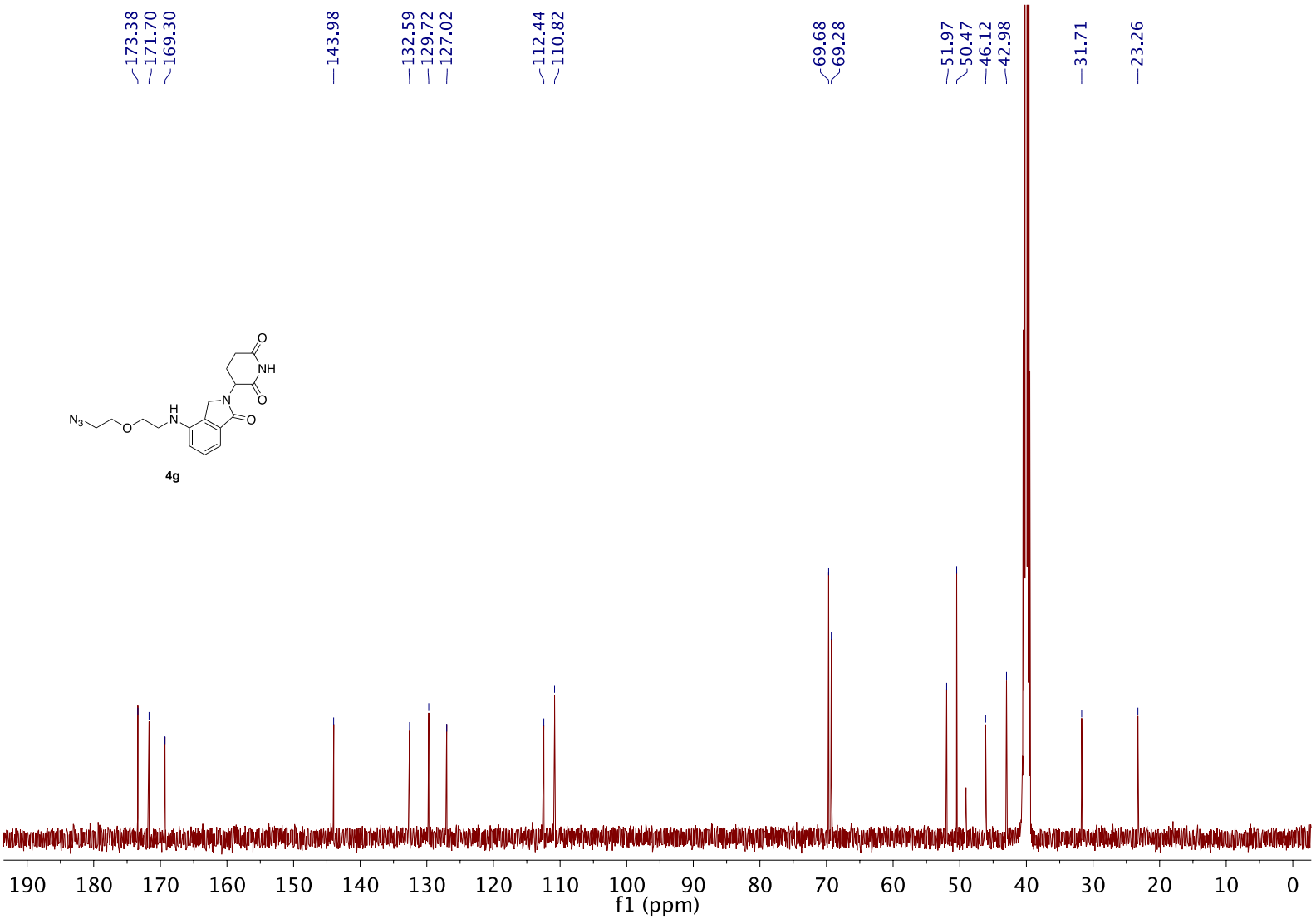
5.13
5.12
5.10
5.09
4.25
4.21
4.14
4.11
3.65
3.64
3.63
3.63
3.62
3.42
3.41
3.40
3.36
3.35
3.33
2.96
2.95
2.88
2.64
2.63
2.60
2.59
2.50 DMSO-d6
2.34
2.25
2.05
2.05
0.85
1.00
0.97
0.98
0.90
0.98
0.97
0.91
4.00
2.00
2.07
0.97
1.08
1.10
1.06
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

4g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69.28
51.97
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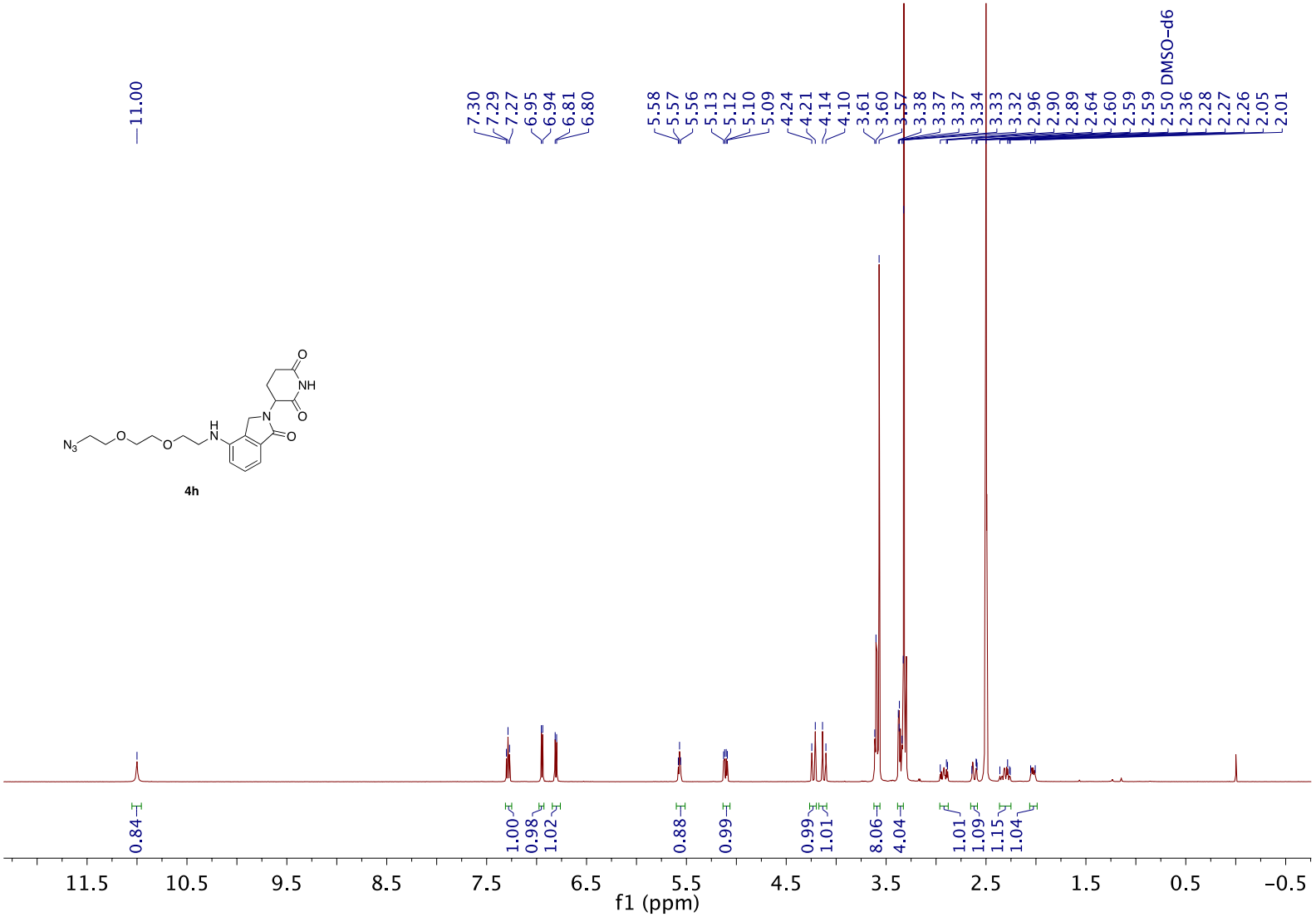
46.12
42.98
31.71
23.26
O
NH
O
N
O
H
N
O
N3
O
4g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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5.56
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5.12
5.10
5.09
4.24
4.21
4.14
4.10
3.61
3.60
3.57
3.38
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3.37
3.34
3.33
3.32
2.96
2.90
2.89
2.64
2.60
2.59
2.59
2.50 DMSO-d6
2.36
2.28
2.27
2.26
2.05
2.01
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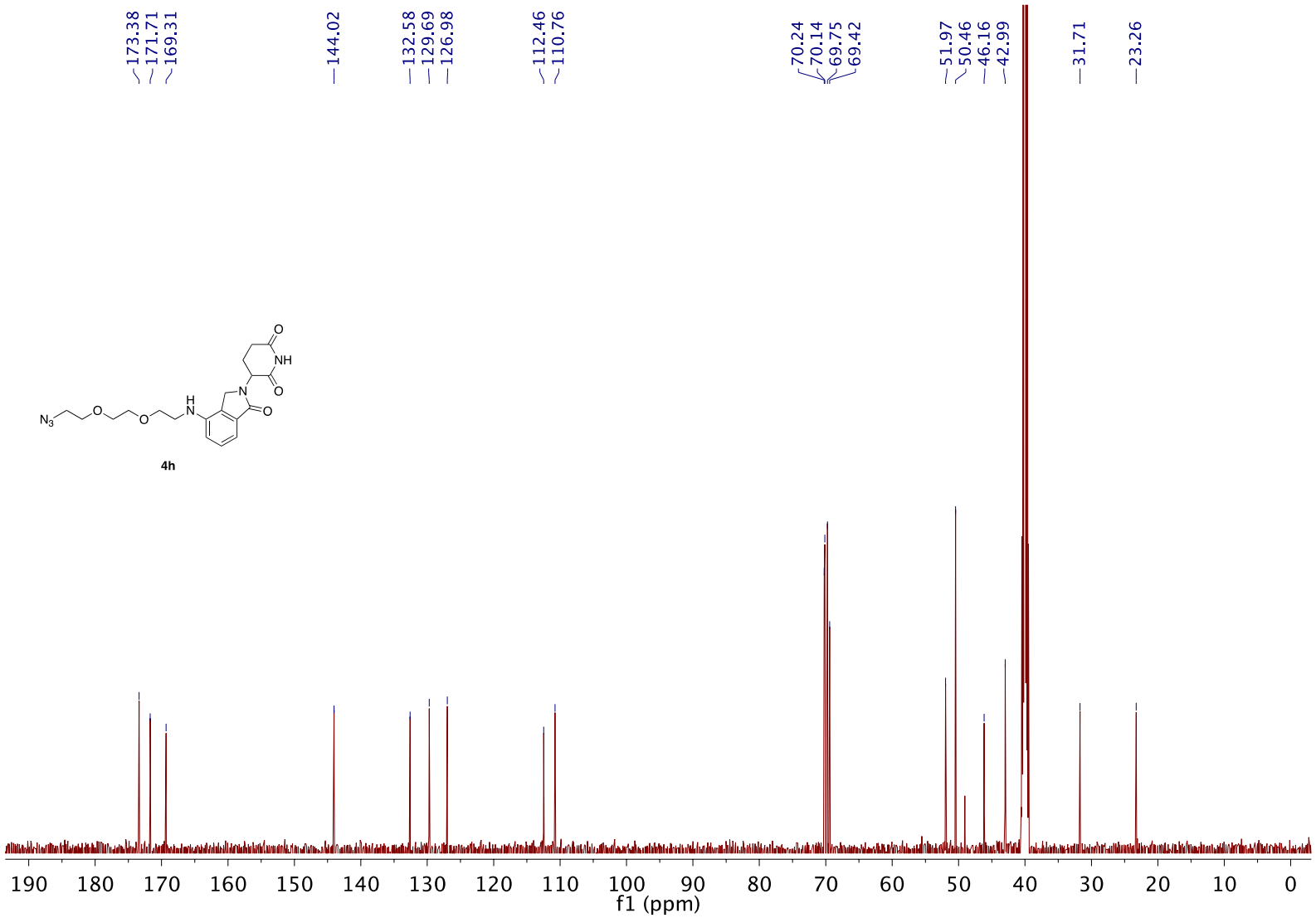
1.00
0.98
1.02
0.88
0.99
0.99
1.01
8.06
4.04
1.01
1.09
1.15
1.04
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
f1 (ppm)

4h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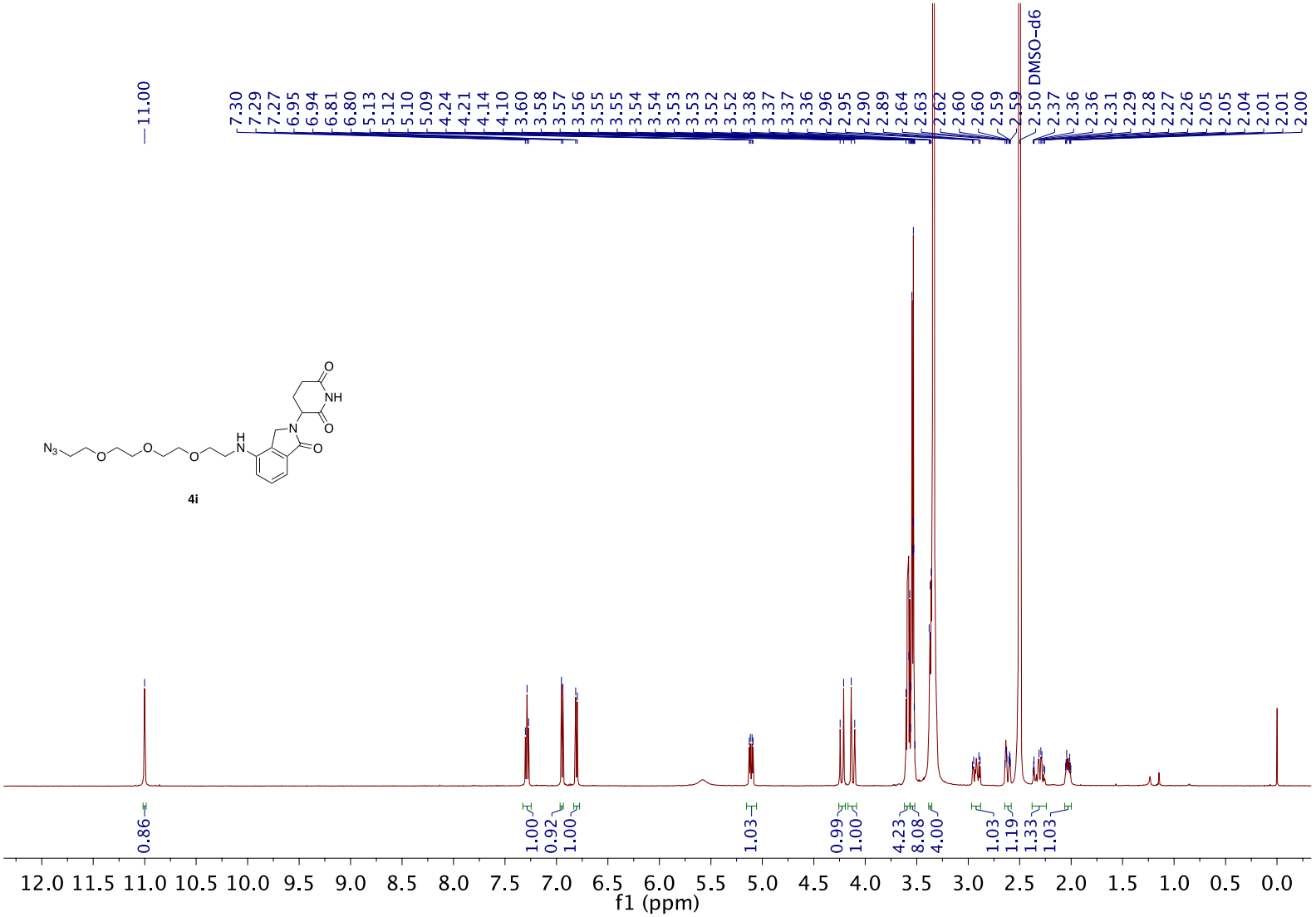
70.14
69.75
69.42
51.97
50.46
46.16
42.99
31.71
23.26
4h
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.29
7.27
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5.10
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4.24
4.21
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3.52
3.52
3.38
3.37
3.37
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2.96
2.95
2.90
2.89
2.64
2.63
2.62
2.60
2.60
2.59
2.59
2.50 DMSO-d6
2.37
2.36
2.36
2.31
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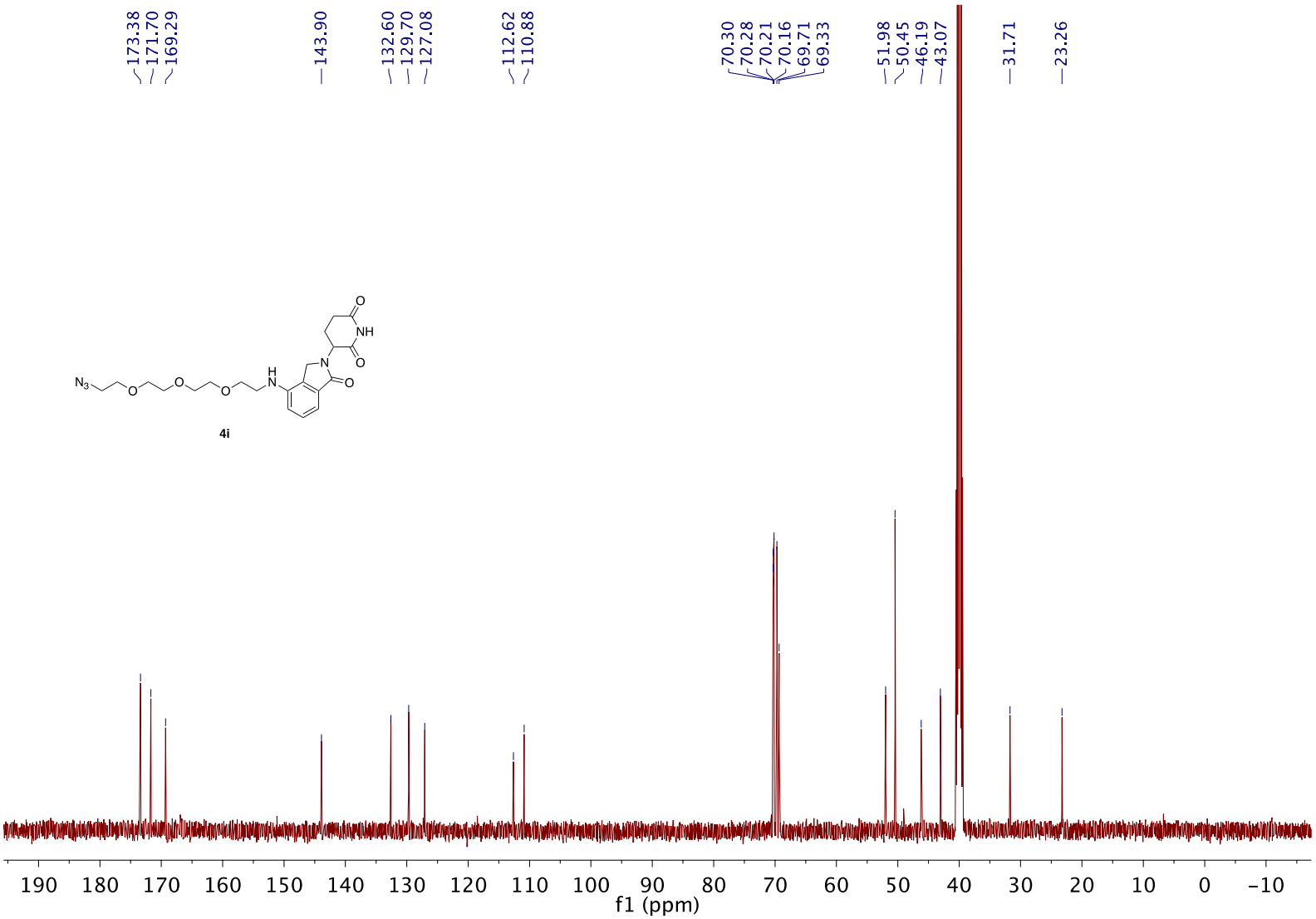
2.28
2.27
2.26
2.05
2.05
2.04
2.01
2.01
2.00
0.86
1.00
0.92
1.00
1.03
0.99
1.00
4.23
8.08
4.00
1.03
1.19
1.33
1.03
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

4i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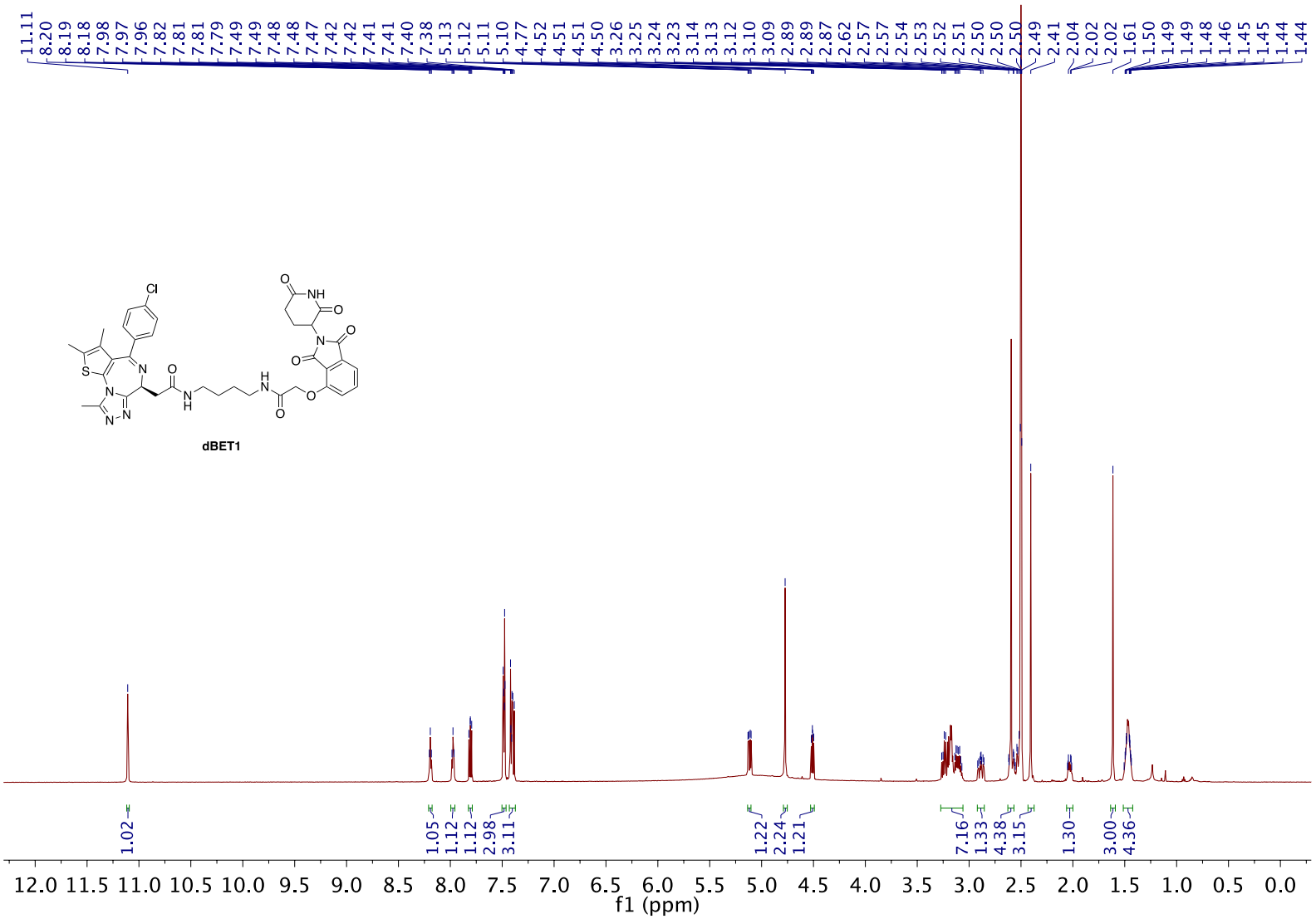
143.90
132.60
129.70
127.08
112.62
110.88
70.30
70.28
70.21
70.16
69.71
69.33
51.98
50.45
46.19
43.07
31.71
23.26
4i
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)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7.48
7.48
7.47
7.42
7.42
7.41
7.41
7.40
7.38
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5.12
5.11
5.10
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4.51
4.51
4.50
3.26
3.25
3.24
3.23
3.14
3.13
3.12
3.10
3.09
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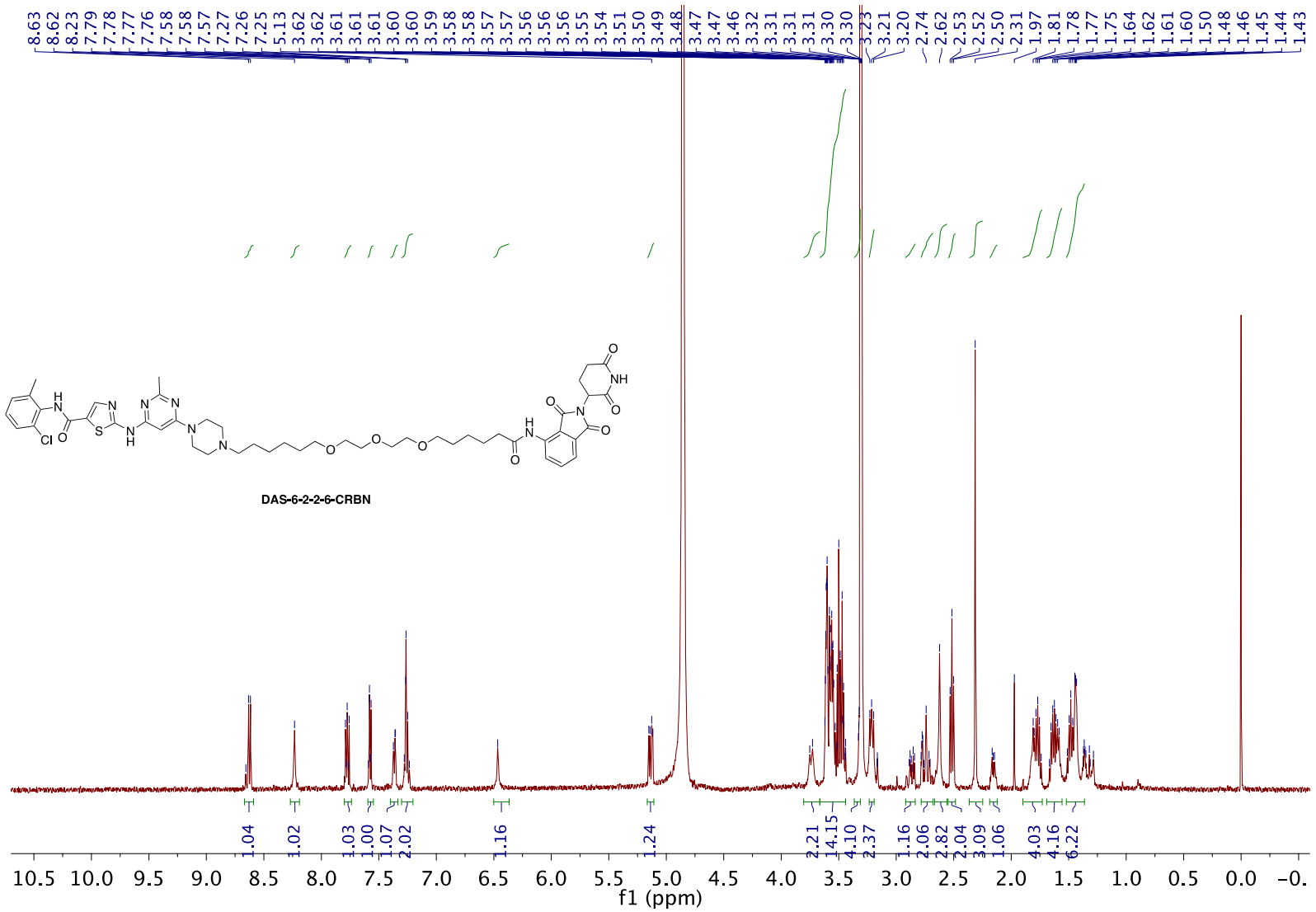
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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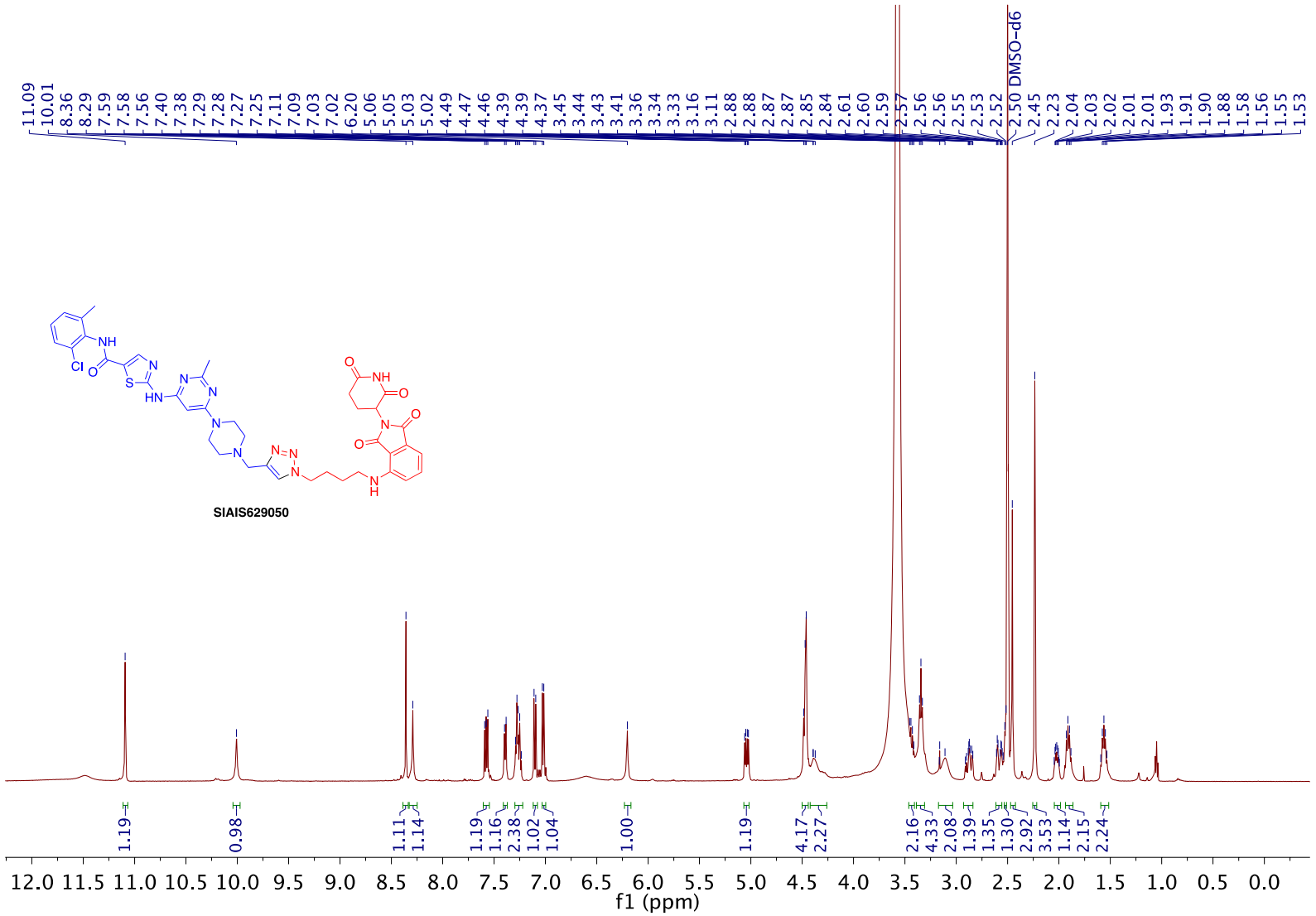
DAS-6-2-2-6-CRBN
1.04 1.02 1.03 1.00 1.07 2.02 1.16 1.24 2.21 14.15 4.10 2.37 1.16 2.06 2.82 2.04 3.09 1.06 4.03 4.16 6.22
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)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7.40
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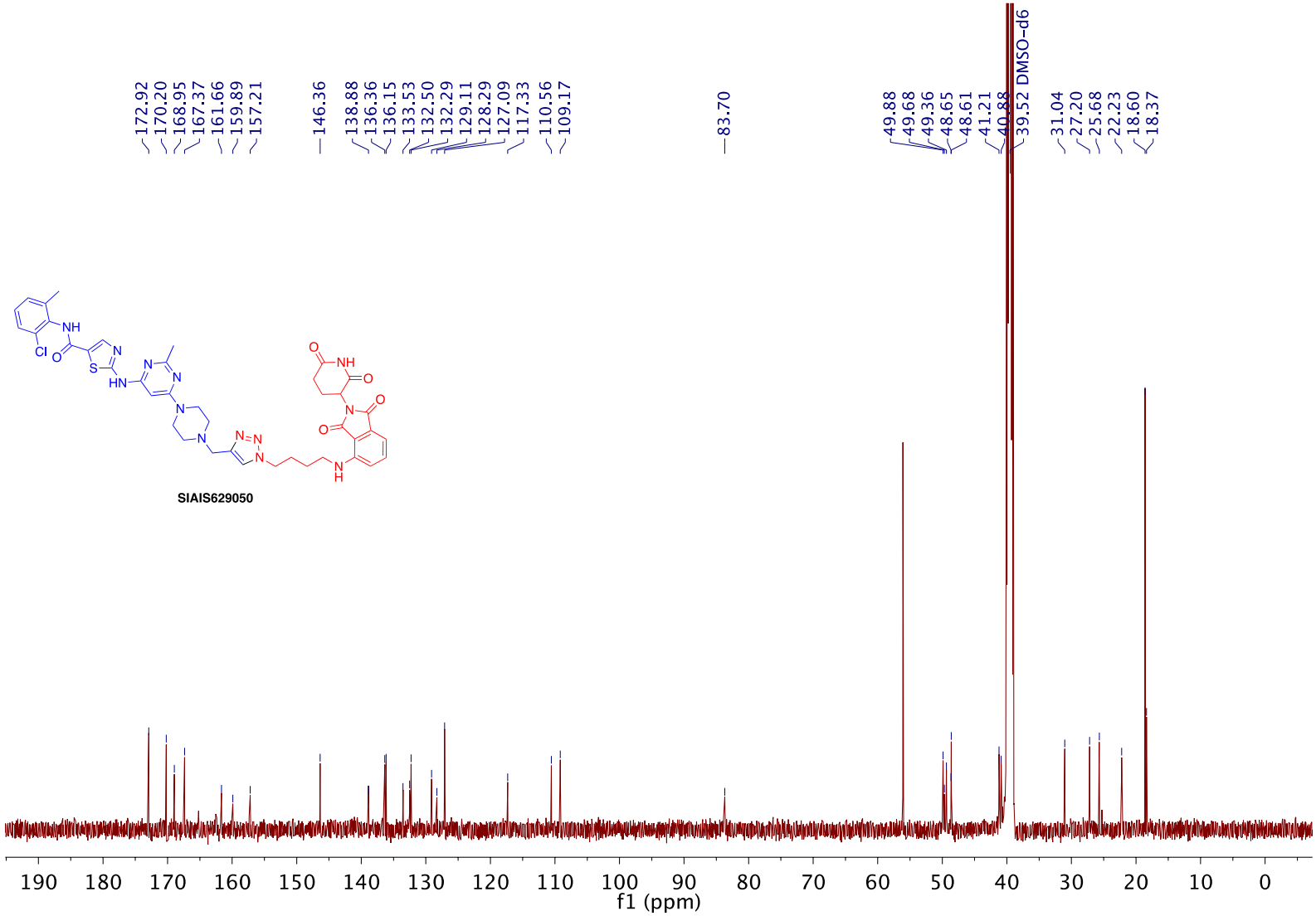
7.29
7.28
7.27
7.25
7.11
7.09
7.03
7.02
6.20
5.06
5.05
5.03
5.02
4.49
4.47
4.46
4.39
4.39
4.37
3.45
3.44
3.43
3.41
3.36
3.34
3.33
3.16
3.11
2.88
2.88
2.87
2.87
2.85
2.84
2.61
2.60
2.59
2.57
2.56
2.56
2.55
2.53
2.52
2.50 DMSO-d6
2.45
2.23
2.04
2.03
2.02
2.01
2.01
1.93
1.91
1.90
1.88
1.58
1.56
1.55
1.53
SIAIS629050
1.19
0.98
1.11
1.14
1.19
1.16
2.38
1.02
1.04
1.00
1.19
4.17
2.27
2.16
4.33
2.08
1.39
1.35
1.30
2.92
3.53
1.14
2.15
2.24
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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159.89
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146.36
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132.50
132.29
129.11
128.29
127.09
117.33
110.56
109.17
83.70
49.88
49.68
49.36
48.65
48.61
41.21
40.88
39.52 DMSO-d6
31.04
27.20
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18.60
18.37
SIAIS629050
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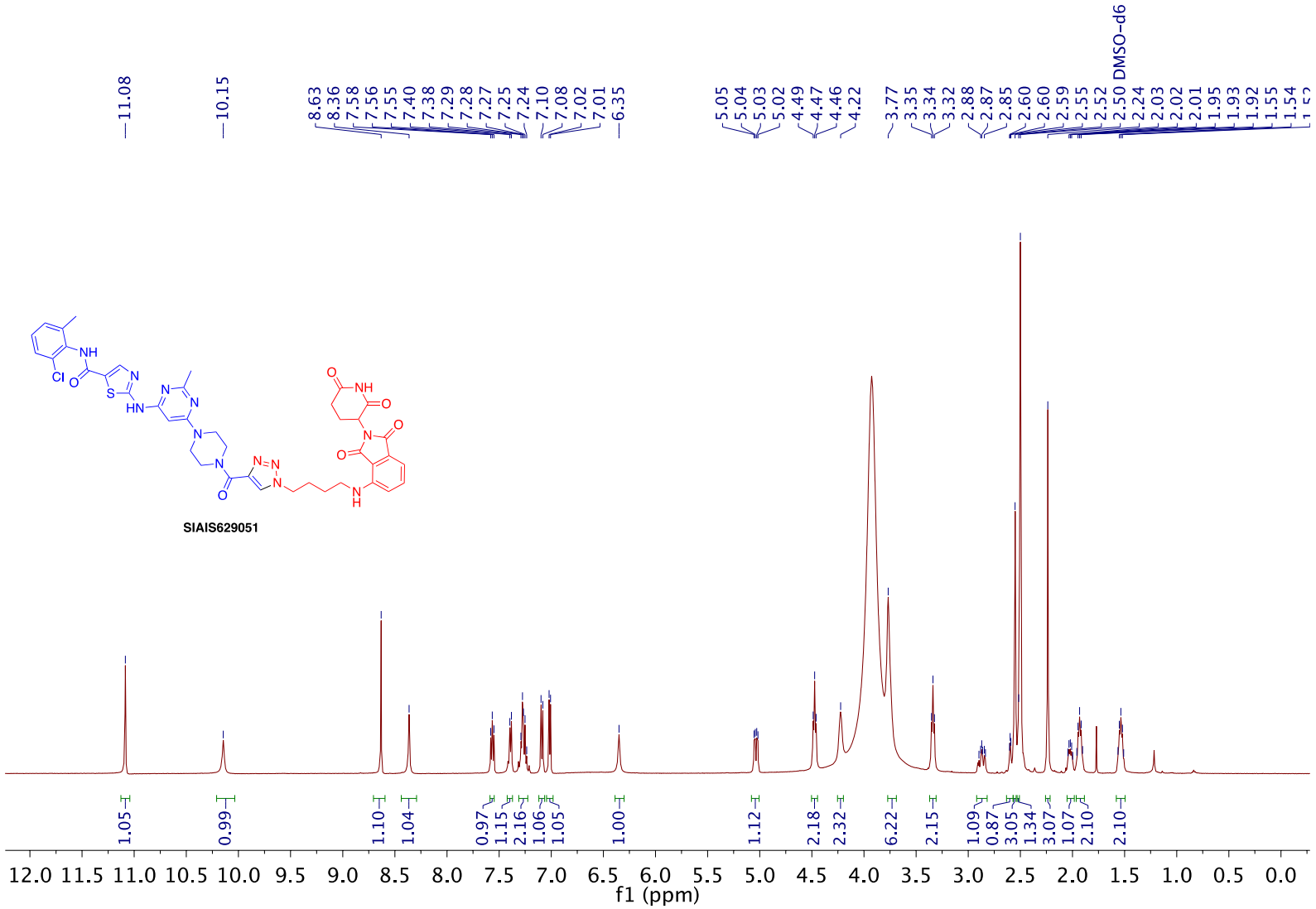
f1 (ppm)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7.40
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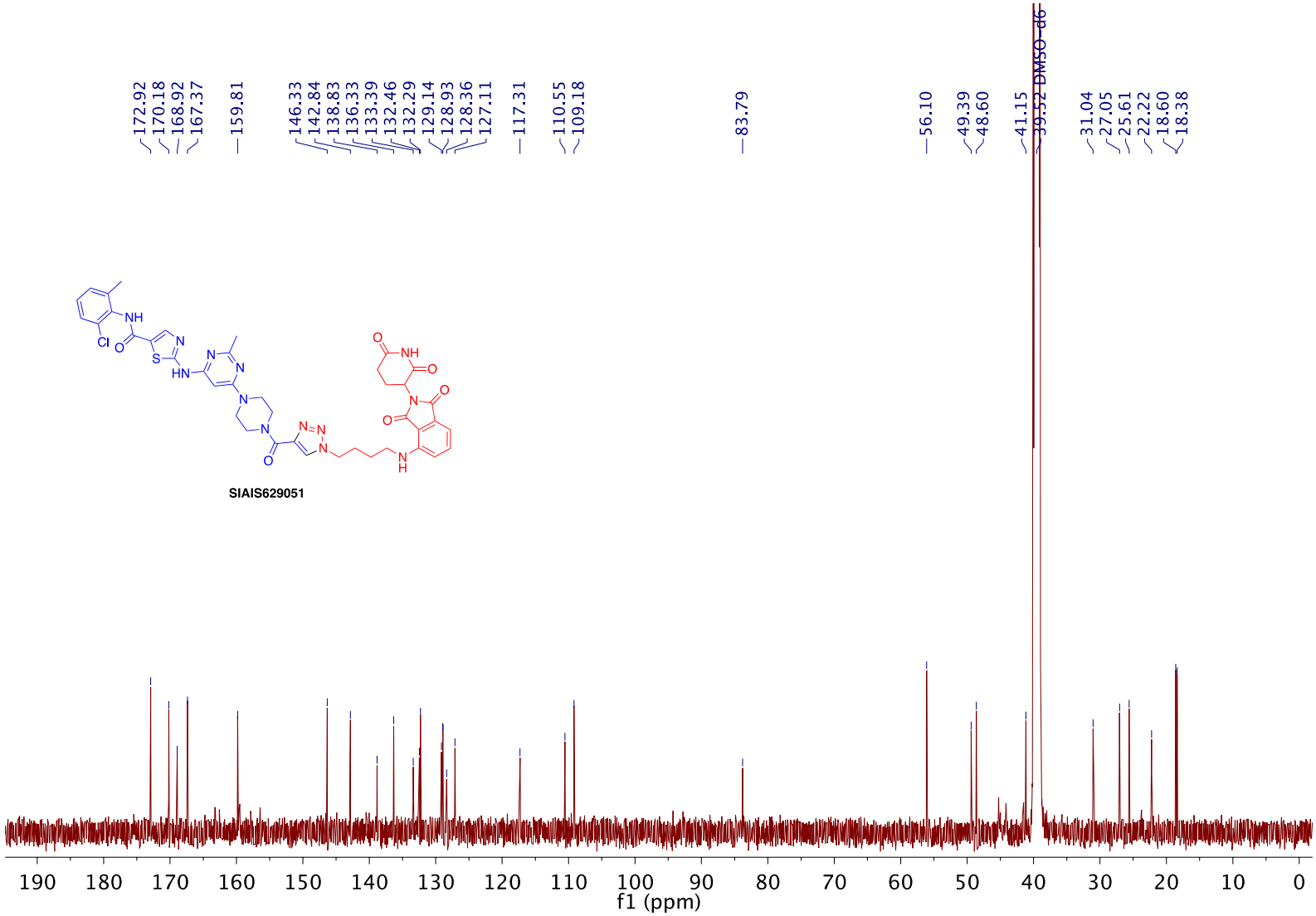
7.29
7.28
7.27
7.25
7.24
7.10
7.08
7.02
7.01
6.35
5.05
5.04
5.03
5.02
4.49
4.47
4.46
4.22
3.77
3.35
3.34
3.32
2.88
2.87
2.85
2.60
2.60
2.59
2.55
2.52
2.50 DMSO-d6
2.24
2.03
2.02
2.01
1.95
1.93
1.92
1.55
1.54
SIAIS629051
1.05
0.99
1.10
1.04
0.97
1.15
2.16
1.06
1.05
1.00
1.12
2.18
2.32
6.22
2.15
1.09
0.87
3.05
1.34
3.07
1.07
2.10
2.10
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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129.14
128.93
128.36
127.11
117.31
110.55
109.18
83.79
56.10
49.39
48.60
41.15
39.52 DMSO-d6
31.04
27.05
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22.22
18.60
18.38
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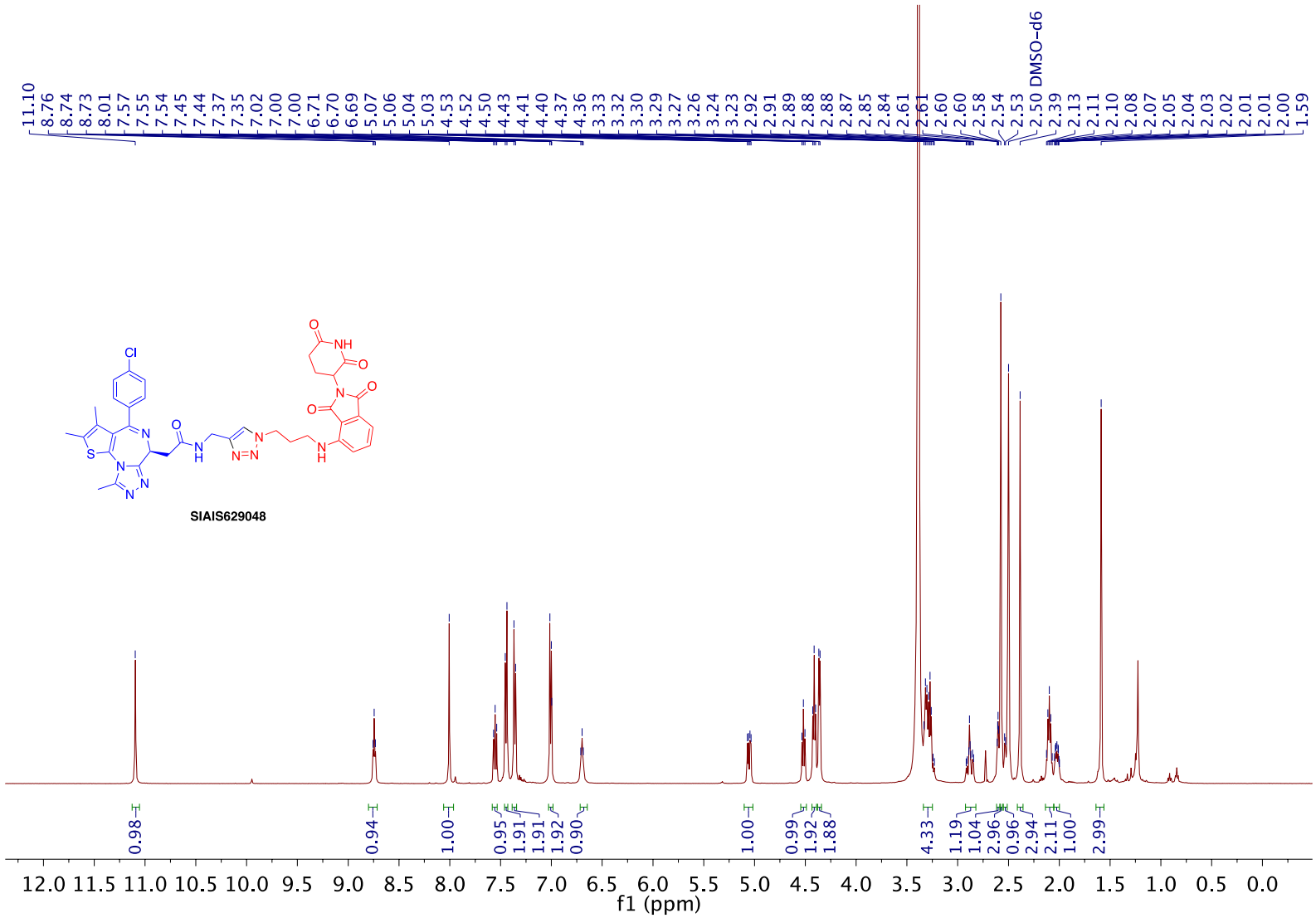
f1 (ppm)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7.54
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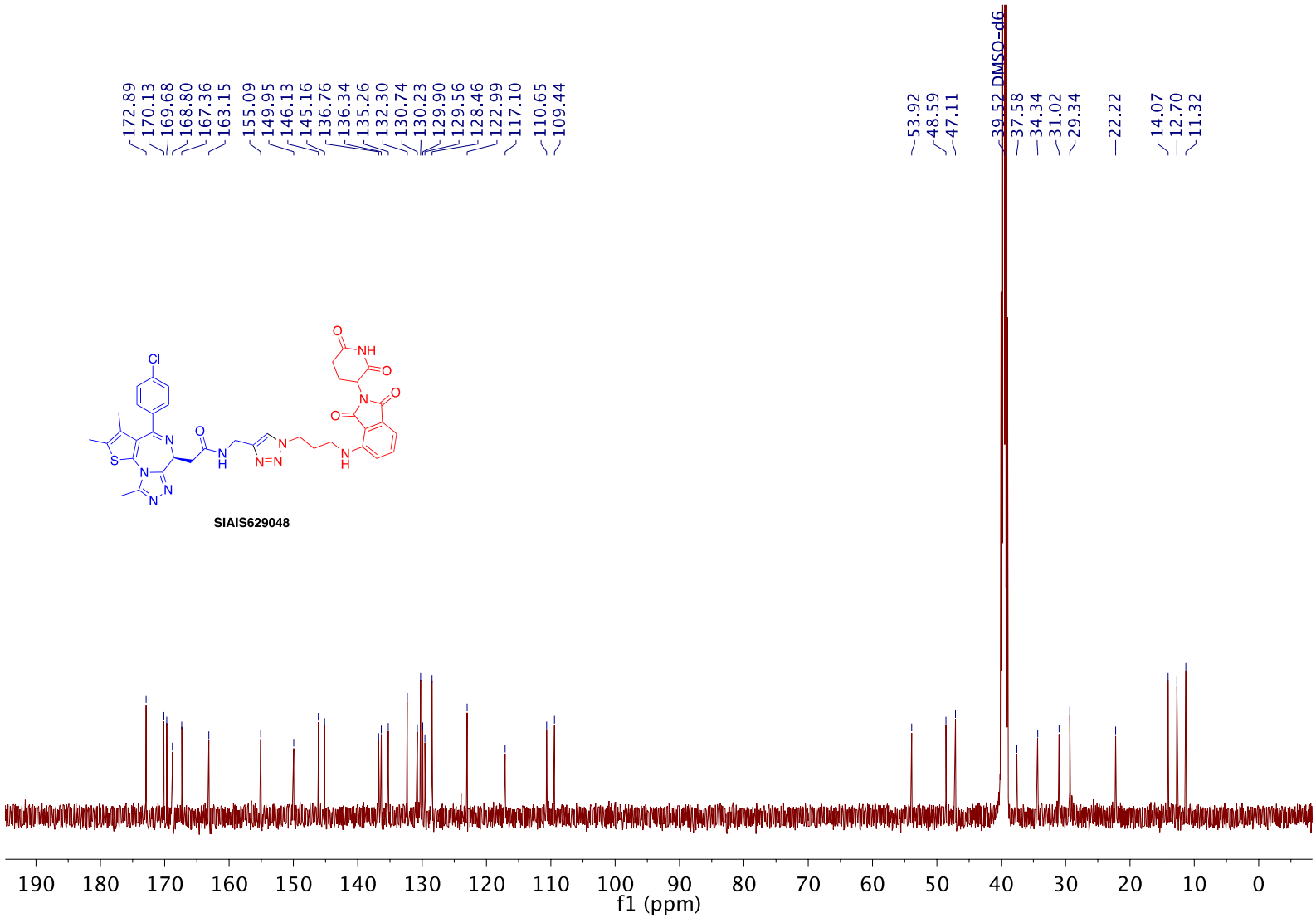
7.44
7.37
7.35
7.02
7.00
7.00
6.71
6.70
6.69
5.07
5.06
5.04
5.03
4.53
4.52
4.50
4.43
4.41
4.40
4.37
4.36
3.33
3.32
3.30
3.29
3.27
3.26
3.24
3.23
2.92
2.91
2.89
2.88
2.88
2.87
2.85
2.84
2.61
2.61
2.60
2.60
2.58
2.54
2.53
2.50 DMSO-d6
2.39
2.13
2.11
2.10
2.08
2.07
2.05
2.04
2.03
2.02
2.01
2.01
2.00
1.59
SIAIS629048
0.98
0.94
1.00
0.95
1.91
1.91
1.92
0.90
1.00
0.99
1.92
1.88
4.33
1.19
1.04
2.96
0.96
2.94
2.11
1.00
2.99
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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163.15
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149.95
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145.16
136.76
136.34
135.26
132.30
130.74
130.23
129.90
129.56
128.46
122.99
117.10
110.65
109.44
53.92
48.59
47.11
39.52 DMSO-d6
37.58
34.34
31.02
29.34
22.22
14.07
12.70
11.32
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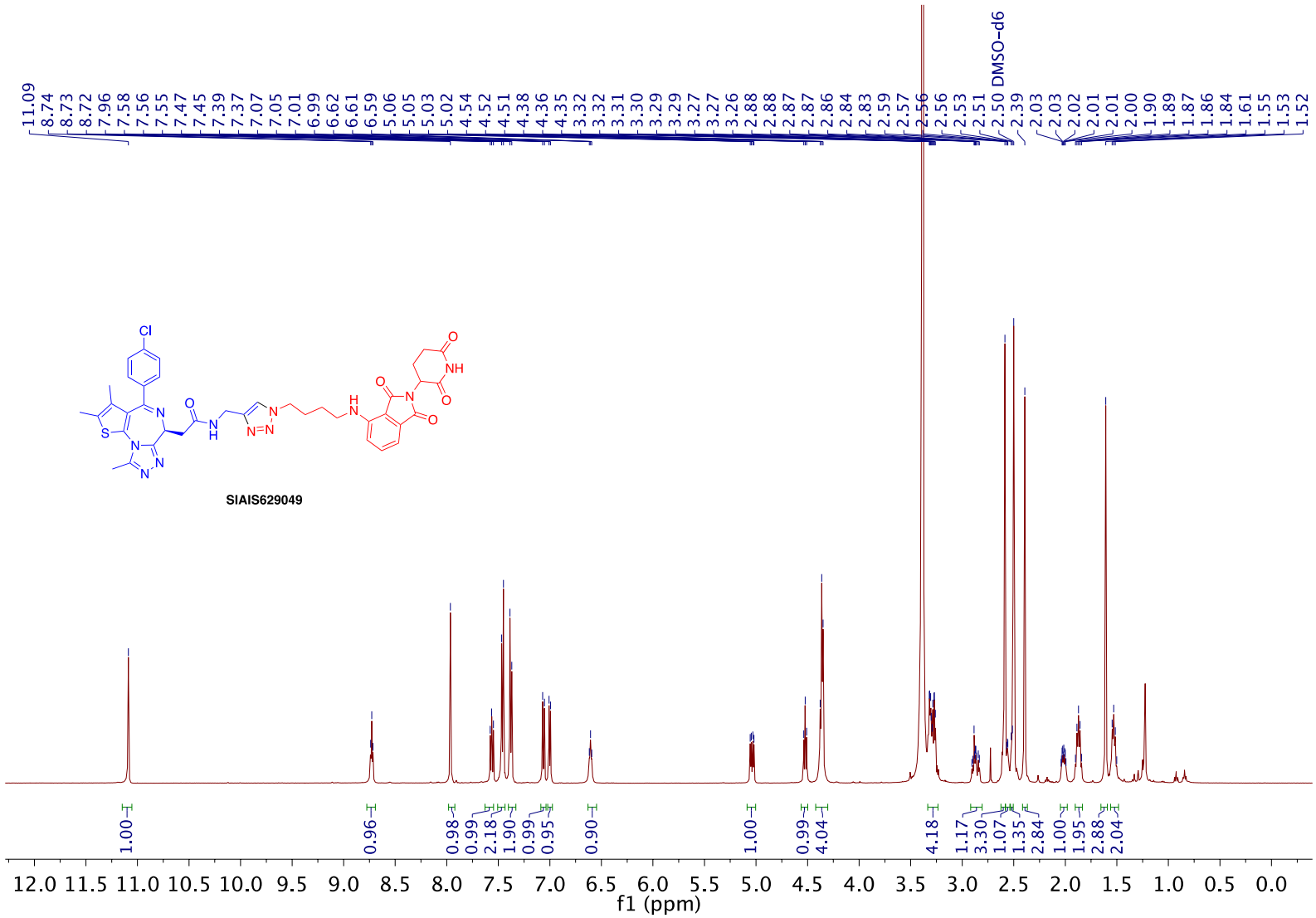
f1 (ppm)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7.39
7.37
7.07
7.05
7.01
6.99
6.62
6.61
6.59
5.06
5.05
5.03
5.02
4.54
4.52
4.51
4.38
4.36
4.35
3.32
3.32
3.31
3.30
3.29
3.29
3.27
3.27
3.26
2.88
2.88
2.87
2.87
2.86
2.84
2.83
2.59
2.57
2.56
2.56
2.53
2.51
2.50 DMSO-d6
2.39
2.03
2.03
2.02
2.01
2.01
2.00
1.90
1.89
1.87
1.86
1.84
1.61
1.55
1.53
1.52
SIAIS629049
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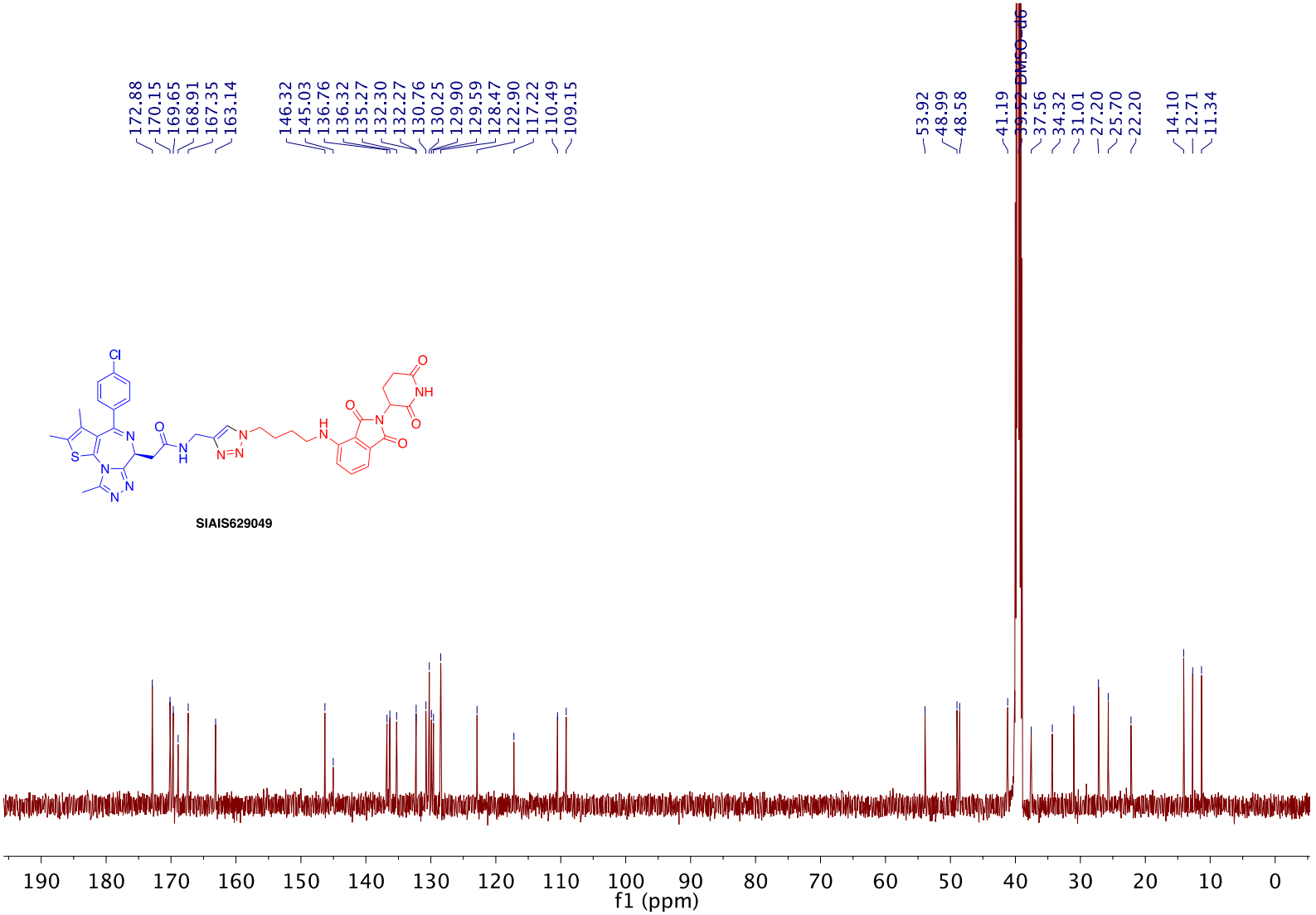
0.96
0.98
0.99
2.18
1.90
0.99
0.95
0.90
1.00
0.99
4.04
4.18
1.17
3.30
1.07
1.35
2.84
1.00
1.95
2.88
2.04
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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169.65
168.91
167.35
163.14
146.32
145.03
136.76
136.32
135.27
132.30
132.27
130.76
130.25
129.90
129.59
128.47
122.90
117.22
110.49
109.15
53.92
48.99
48.58
41.19
39.52 DMSO-d6
37.56
34.32
31.01
27.20
25.70
22.20
14.10
12.71
11.34
Cl
O
NH
N
S
H
SIAIS629049
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)