# Supporting Information

# An Efficient Synthetic Route to *L*-γ-Methyleneglutamine and Its Amide Derivatives, and Their Selective Anticancer Activity

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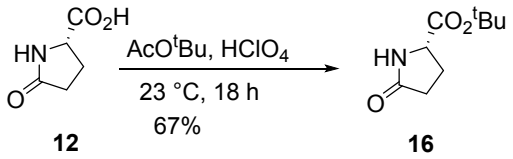
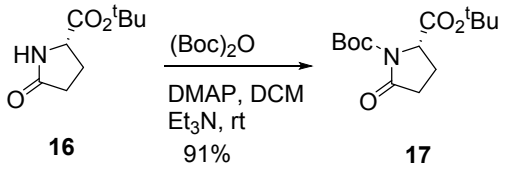



**12** **16**

tert-Butyl (S)-5-oxopyrrolidine-2-carboxylate (**16**[1]):

To the suspension of L-pyroglutamic acid (10 g, 77.5 mmol) (**12**) and tert-butyl acetate (100 mL) were added 70% $HClO_4$ (2.3 mL). The suspension was stirred overnight at rt. Diethyl ether was added to the clear reaction mixture, followed by slow addition of saturated solution of sodium bicarbonate to neutralize the acid. The reaction mixture was extracted twice with diethyl ether, dried over sodium sulfate, and evaporated *in vacuo* to afford compound **16** (9.54 g, 67 % yield) as a viscous liquid. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 4.05 (td, *J* = 8.9, 8.4, 4.6 Hz, 1H), 2.29 (qt, *J* = 17.4, 6.6 Hz, 3H), 2.17 – 1.94 (m, 1H), 1.53 – 1.23 (m, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 178.1, 171.1, 82.2, 56.1, 29.4, 27.9, 27.9, 24.8.




**16** **17**

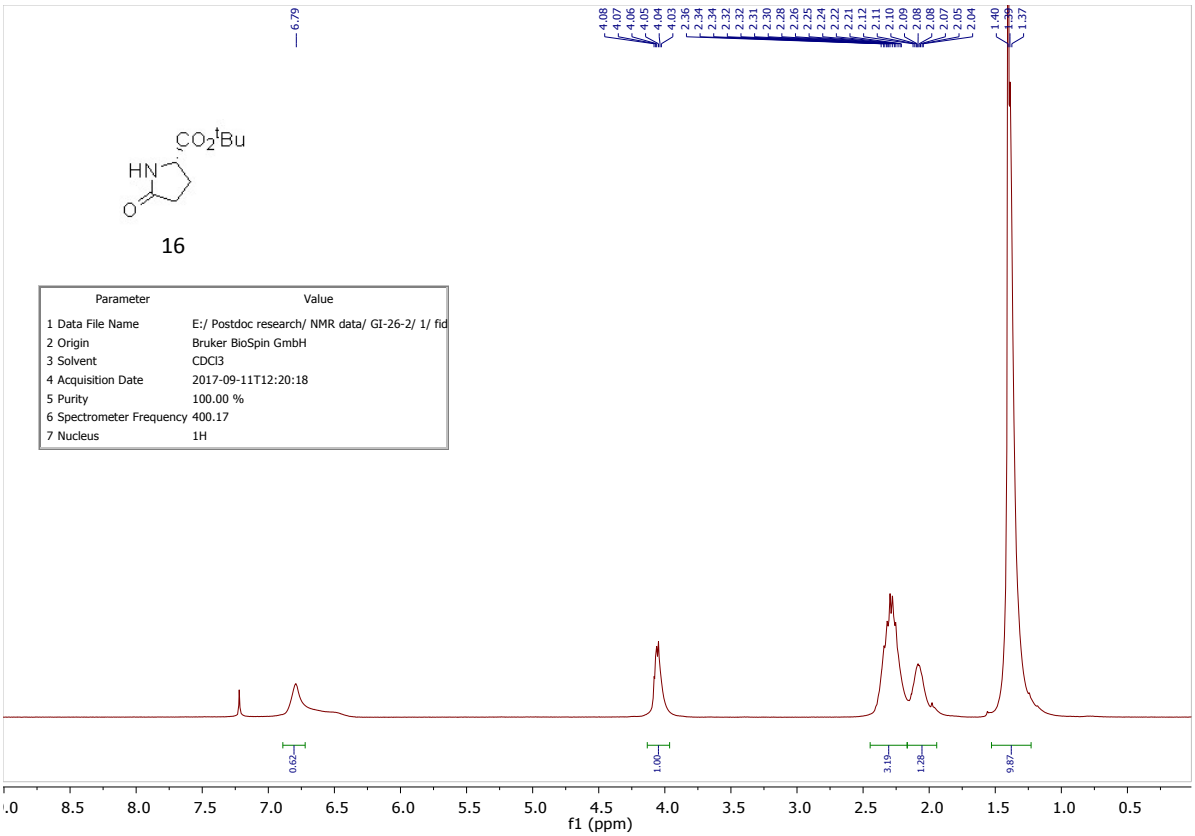
Di-tert-butyl (S)-5-oxopyrrolidine-1,2-dicarboxylate (**17**[2]):

Compound **16** (9.54 g, 51.4 mmol) was dissolved in 150 mL of anhydrous dichloromethane under argon atmosphere. 4-(Dimethylamino)pyridine (6.9 g, 56.5 mmol), $(Boc)_2O$ (12.3 g, 56.5 mmol), and $Et_3N$ (5.7 g, 56.5 mmol) were added to the reaction mixture and stirred for overnight at rt. Water (200 mL) was added to the reaction flask, and the mixture was extracted twice with ethyl acetate. The solvents were evaporated *in vacuo.* The crude compound was purified by silica column chromatography (33% ethyl acetate in hexane) to afford **17** (14.6 g, 91% yield) as a light yellow viscous liquid. $^1$H NMR (400 MHz, $CDCl_3$) δ 4.40 (dd, *J* = 9.4, 2.6 Hz, 1H), 2.52 (ddd, *J* = 17.6, 10.6, 9.5 Hz, 1H), 2.38 (ddd, *J* = 17.5, 9.4, 3.2 Hz, 1H), 2.22 (ddt, *J* = 13.5, 10.8, 9.4 Hz, 1H), 1.92 (dtt, *J* = 15.8, 6.0, 3.3 Hz, 1H), 1.41 (d, *J* = 7.1 Hz, 18H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 173.4, 170.1, 149.0, 83.0, 82.0, 59.3, 30.9, 27.7, 27.7, 21.4.

**References**

(1) Ioka, S.; Saitoh, T.; Iwano, S.; Suzuki, K.; Maki, S. A.; Miyawaki, A.; Imoto, M.; Nishiyama, S. Synthesis of Firefly Luciferin Analogues and Evaluation of the Luminescent Properties. *Chem. - A Eur. J.* **2016**, *22* (27), 9330–9337.

(2) Chiha, S.; Soicke, A.; Barone, M.; Müller, M.; Bruns, J.; Opitz, R.; Neudörfl, J.-M.; Kühne, R.; Schmalz, H.-G. Design and Synthesis of Building Blocks for PPII-Helix Secondary-Structure Mimetics: A Stereoselective Entry to 4-Substituted 5-Vinylprolines. *European J. Org. Chem.* **2018**, *2018* (4), 455–460.



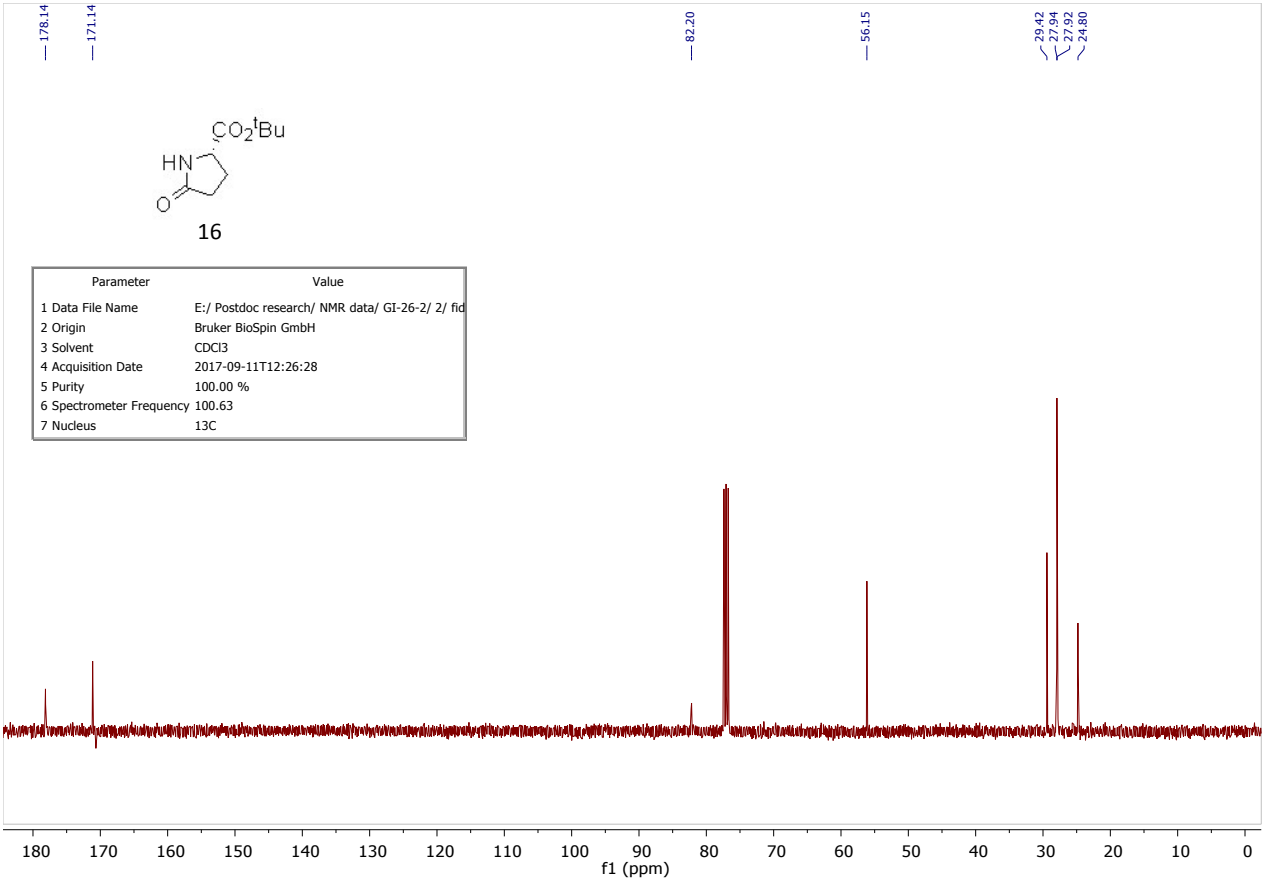
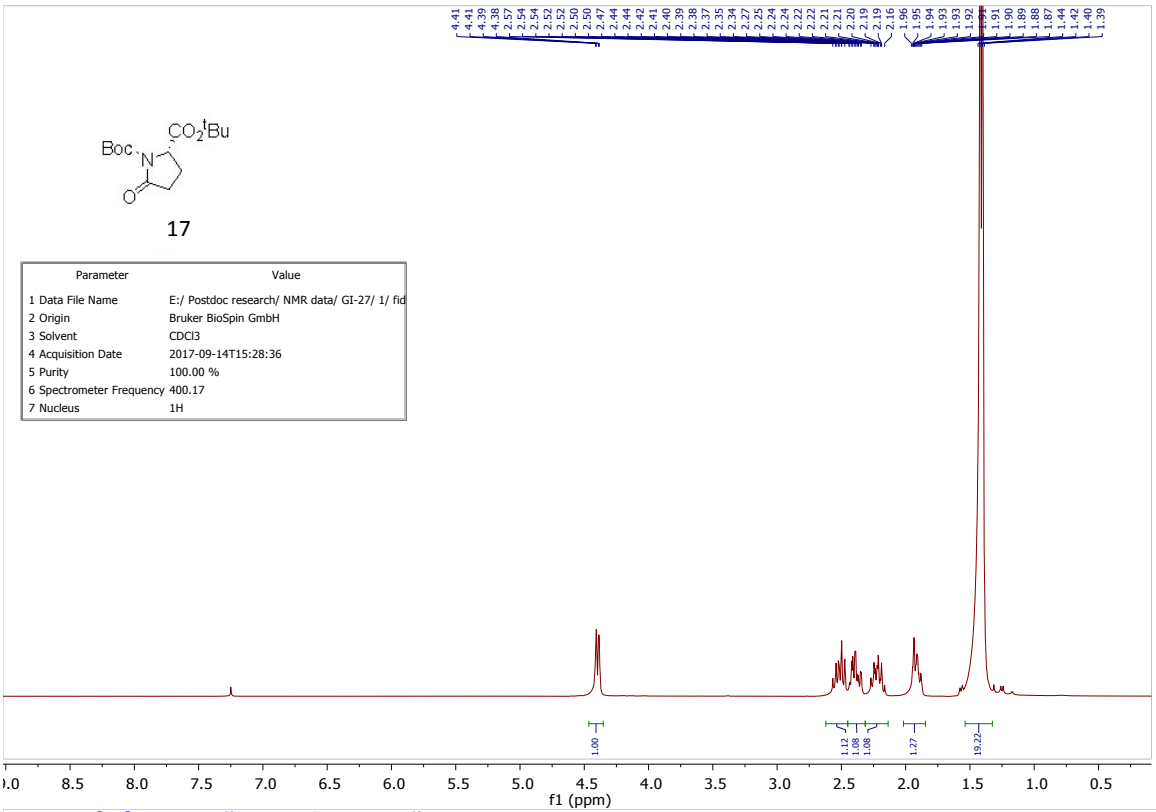




**Figure S1.** $^{1}H$ and $^{13}C$ NMR spectra of compound **16**



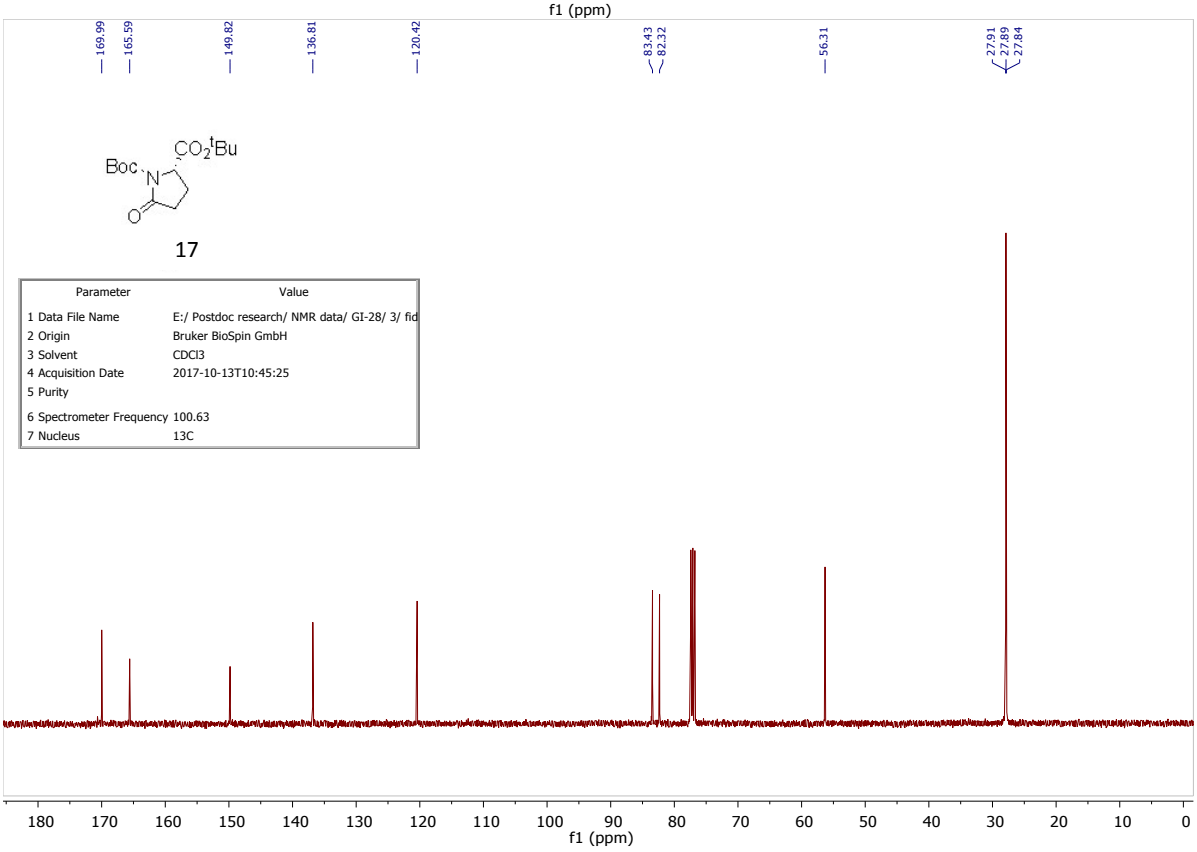
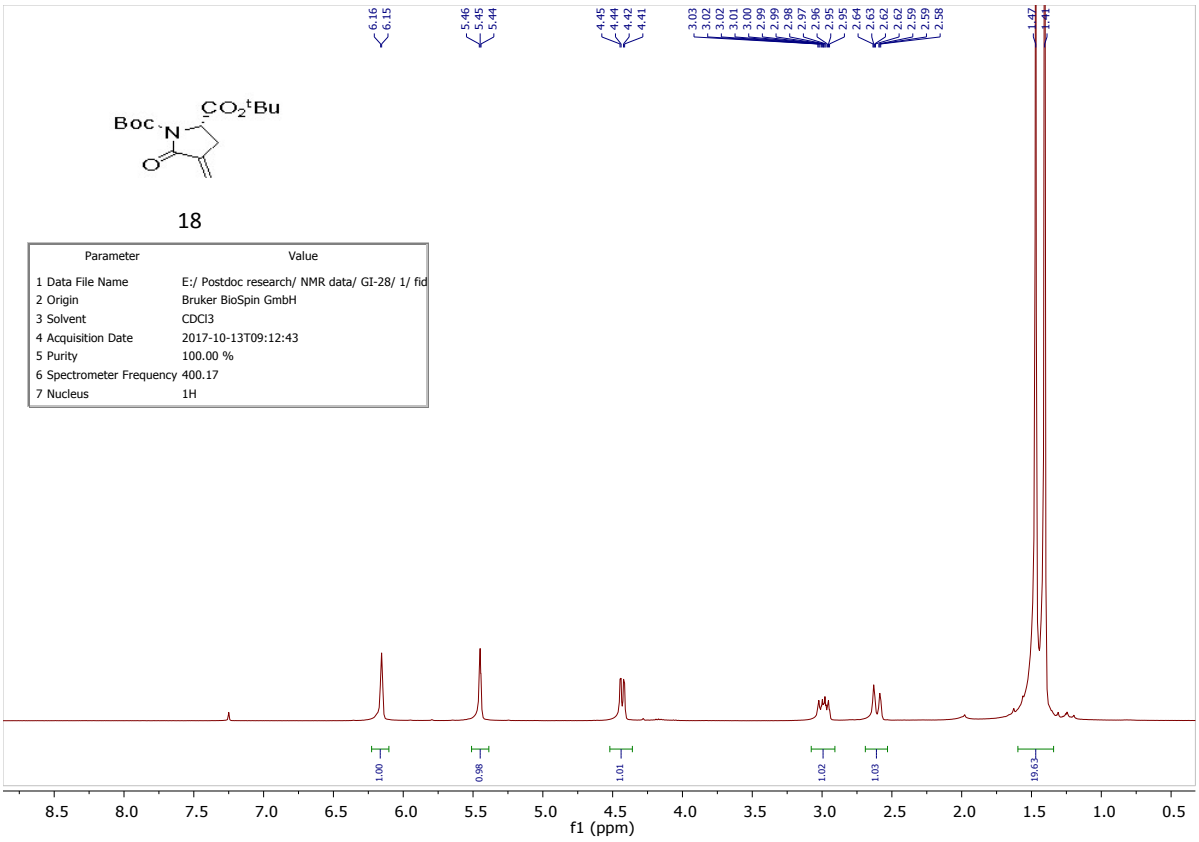




**Figure S2.** $^{1}H$ and $^{13}C$ NMR spectra of compound **17**



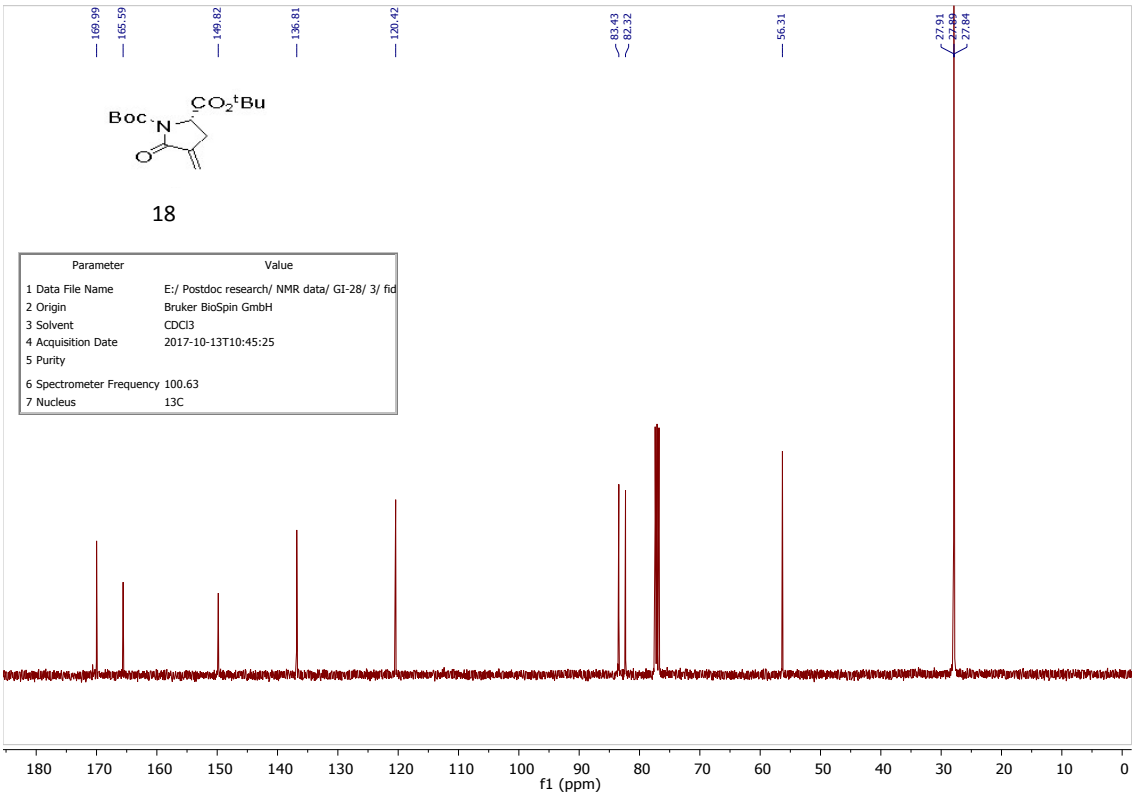
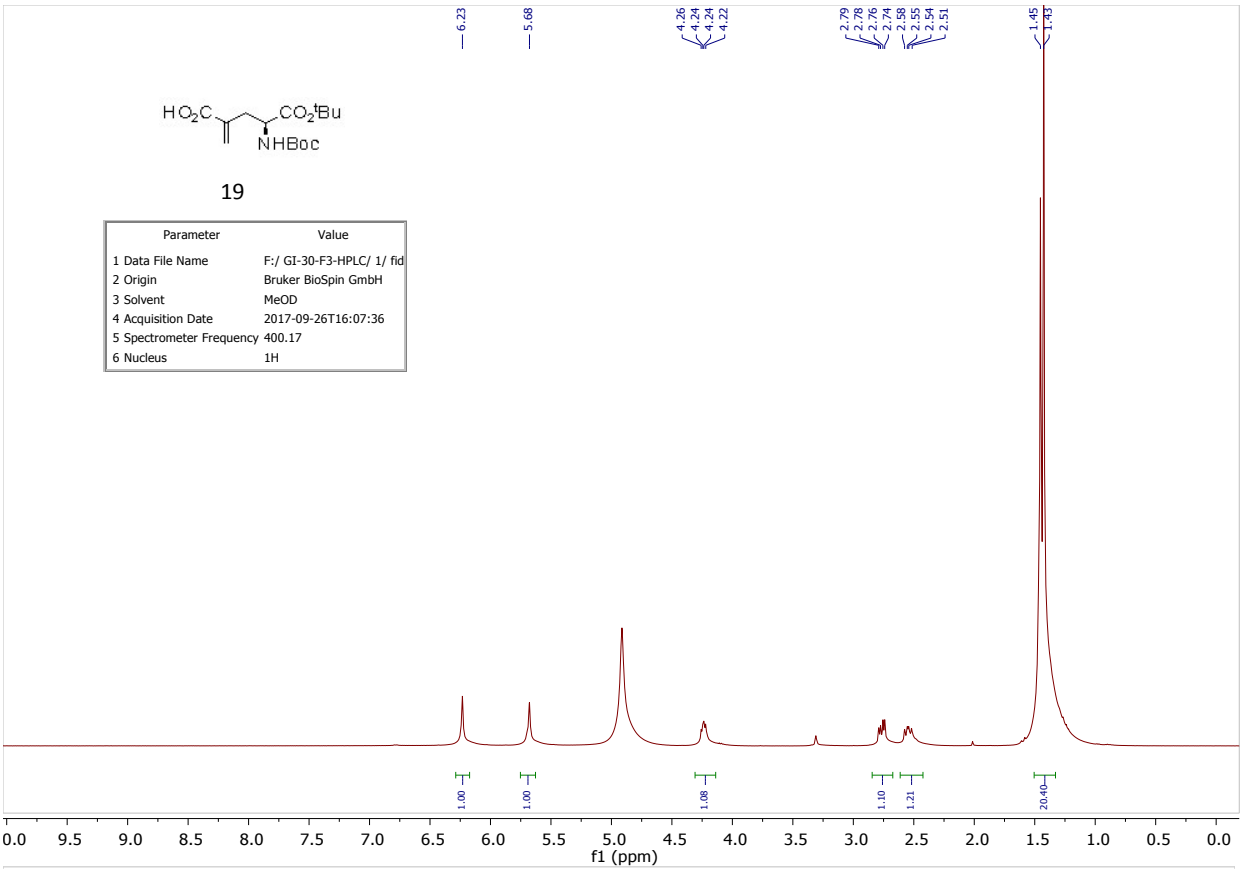




**Figure S3.** $^{1}H$ and $^{13}C$ NMR spectra of compound **18**



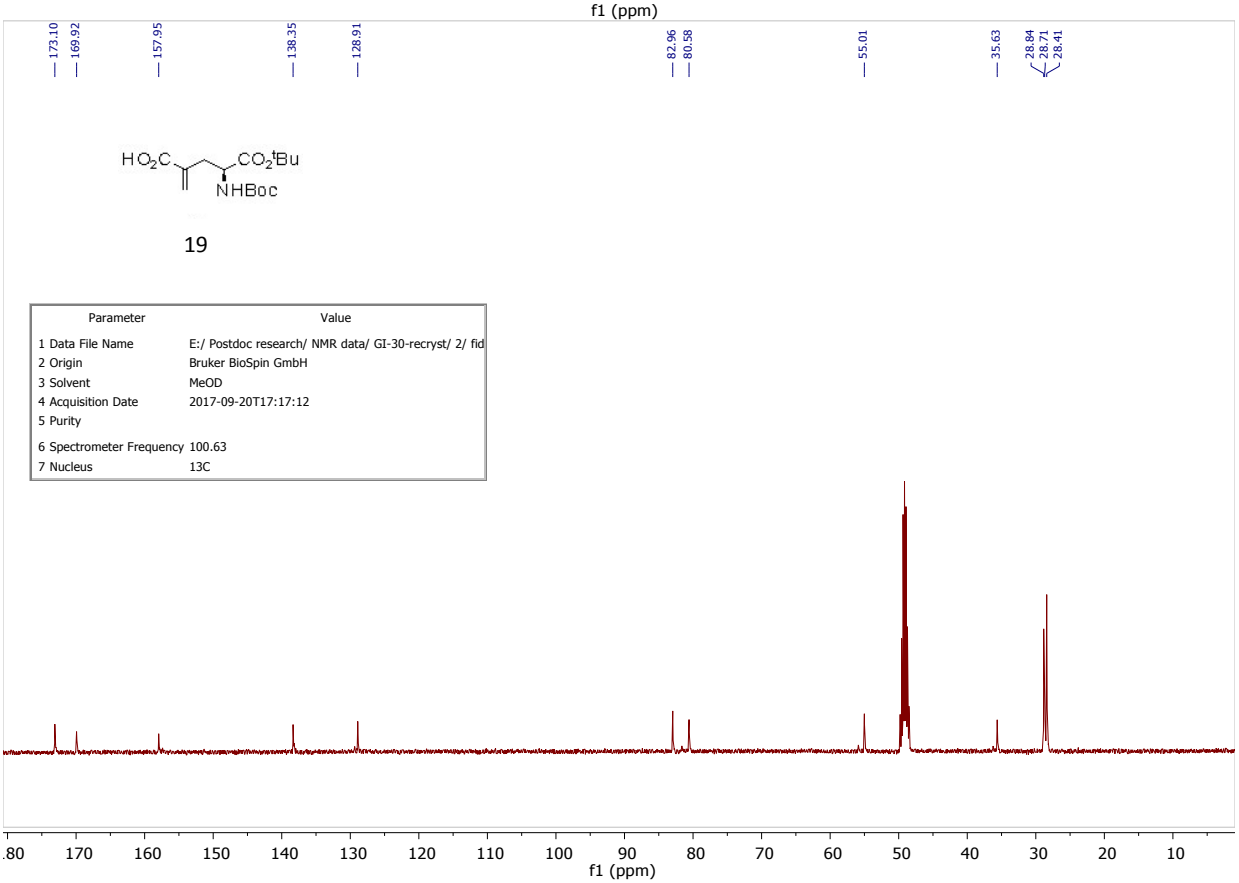
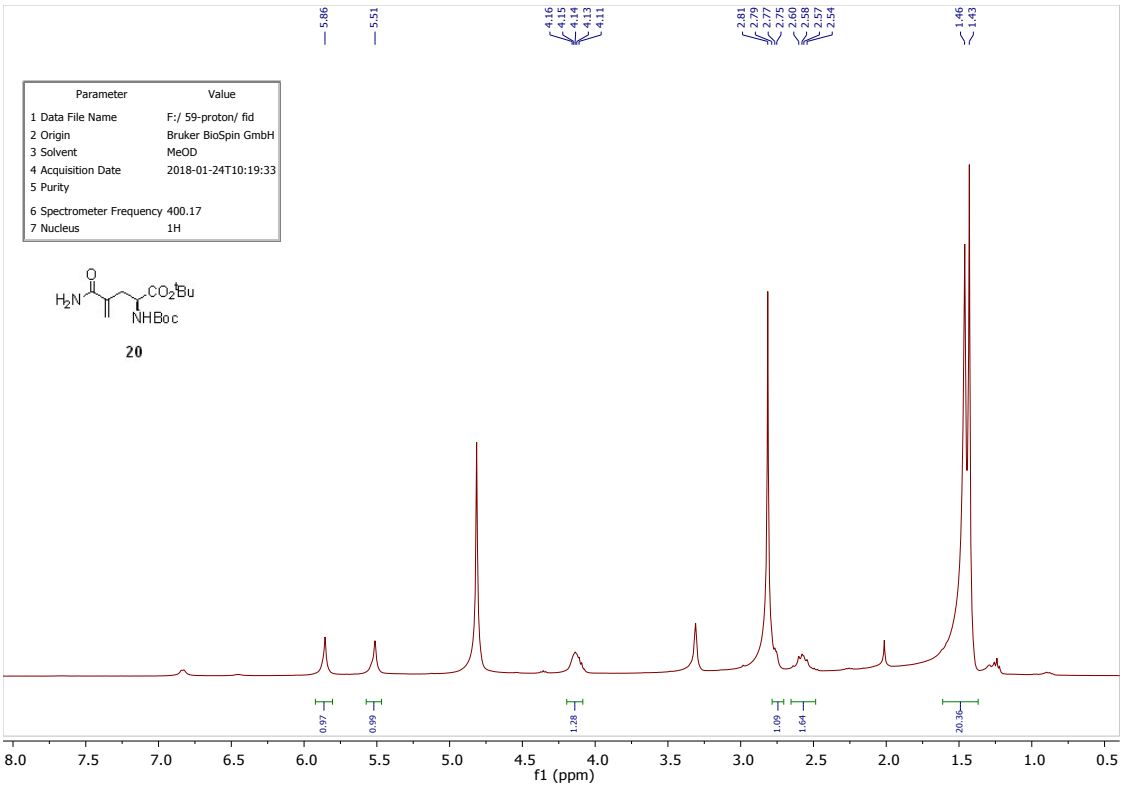




**Figure S4.** $^{1}H$ and $^{13}C$ NMR spectra of compound **19**



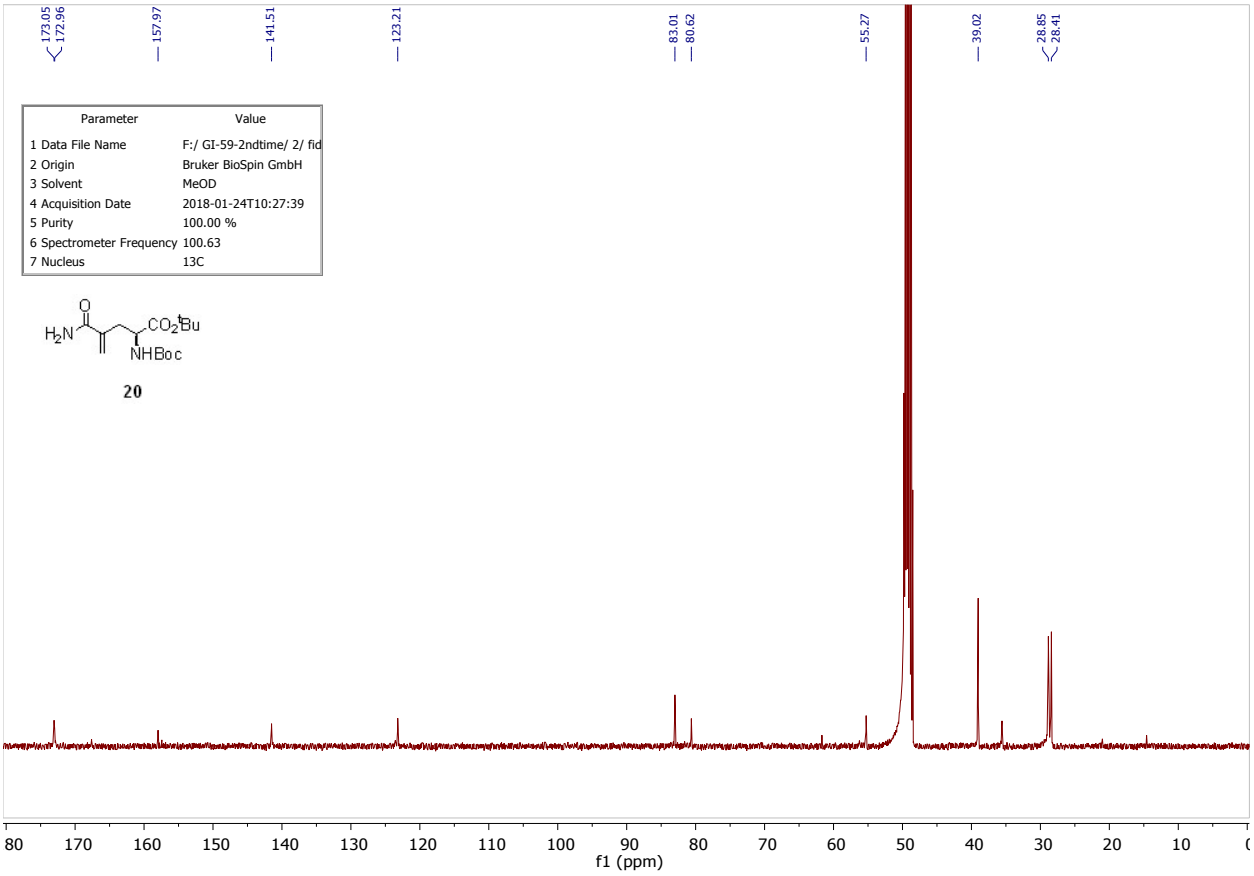
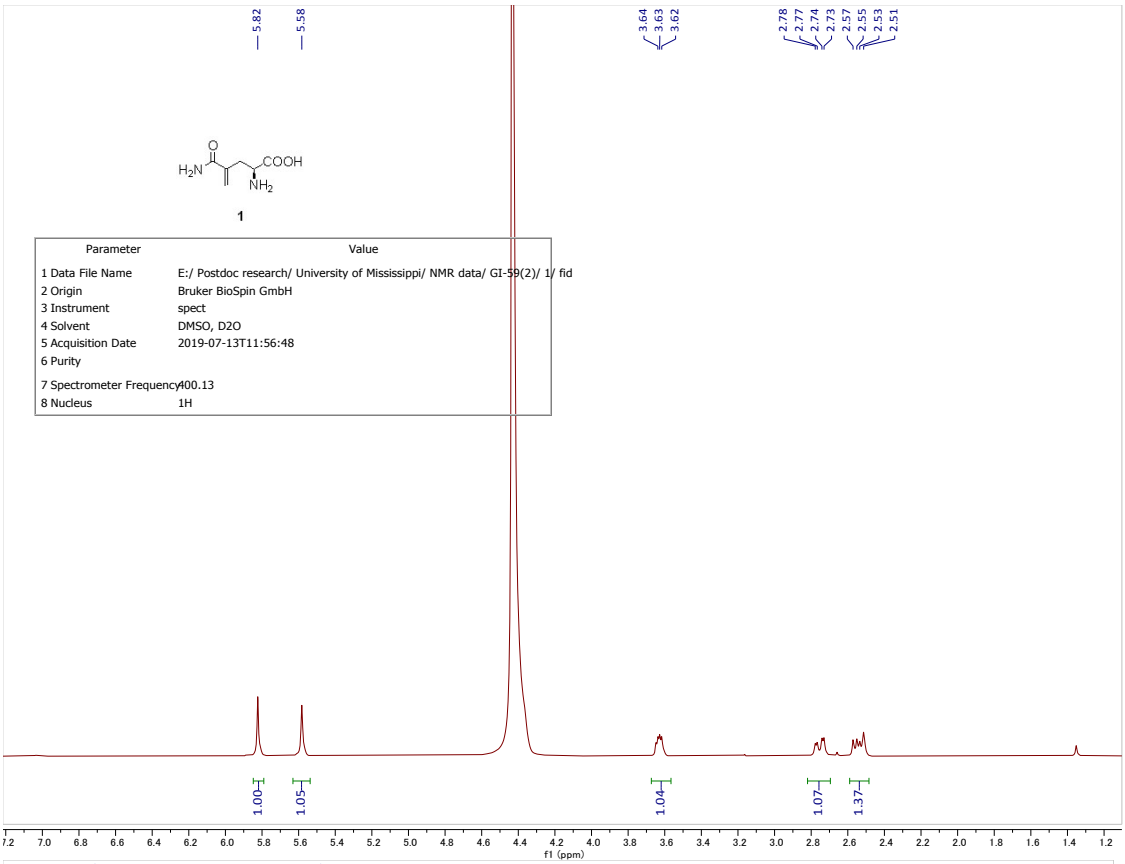




**Figure S5.** $^{1}H$ and $^{13}C$ NMR spectra of compound **20**

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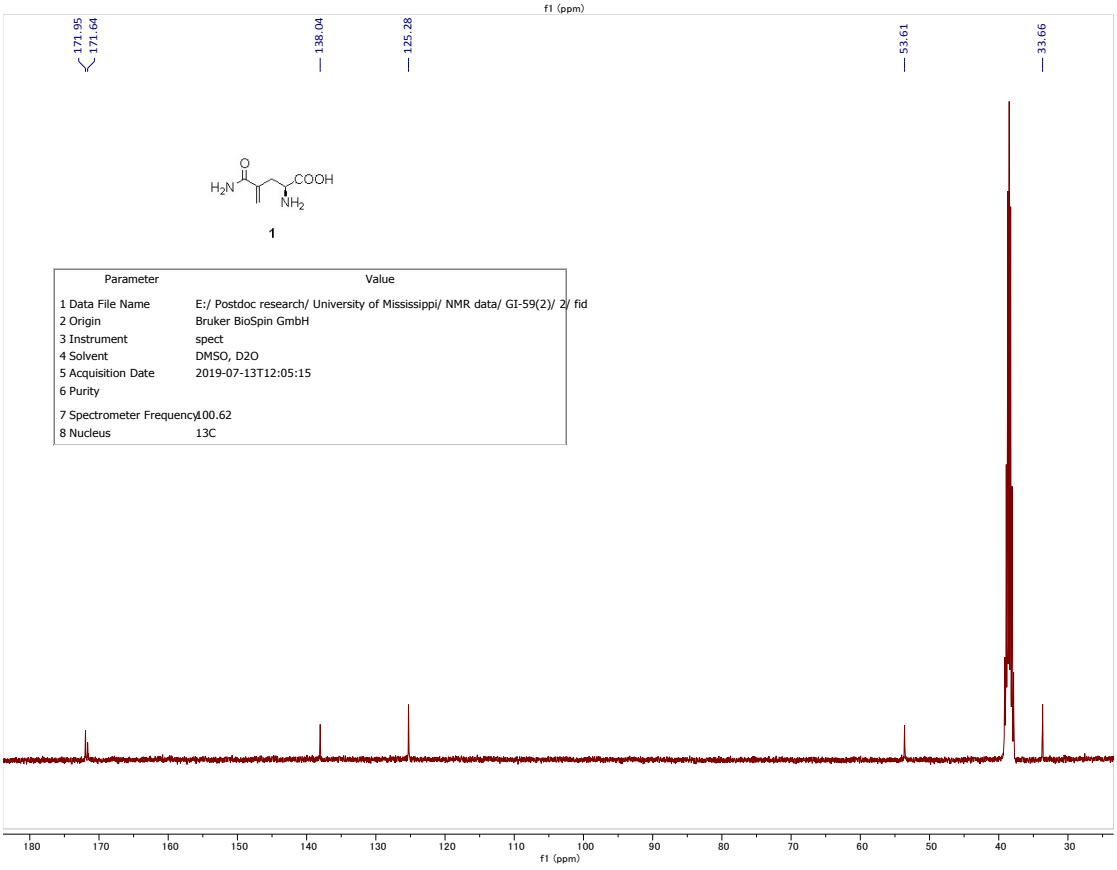


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**Figure S6.** $^{1}H$ and $^{13}C$ NMR spectra of compound **1**

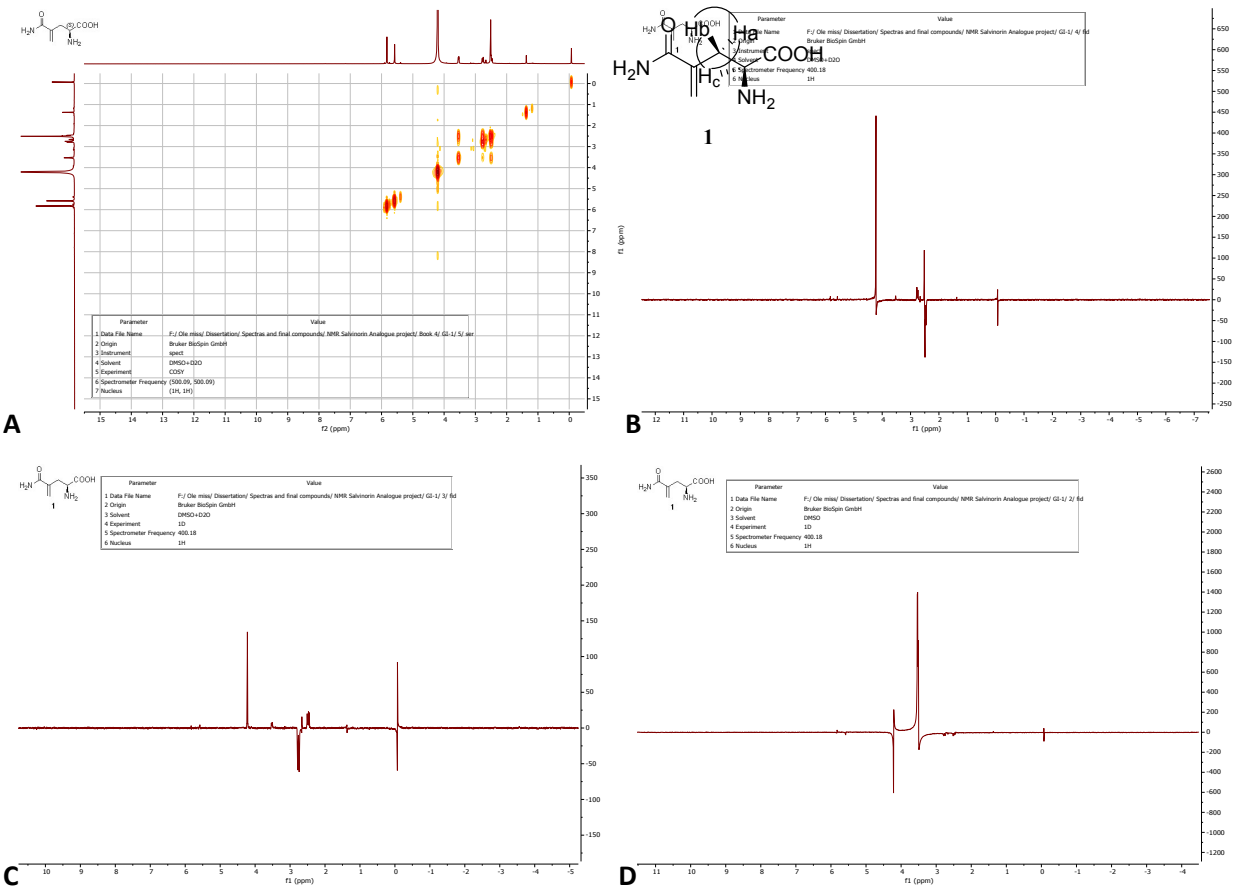



**Figure S7.** $^{1}$H-$^{1}$H COSY (**A**) and 1D NOE (**B–D**) NMR spectra of compound **1**. Chemical shifts of $H_a$, $H_b$, and $H_c$ are 2.59–2.48 ppm (m), 2.75 (dd), and 3.67–3.57 ppm (m), respectively. J values of $H_c$-$H_a$, $H_c$-$H_b$, and $H_b$-$H_a$ are 8.6 Hz, 4.5 Hz, and 14.7 Hz, respectively. $^{1}$H-$^{1}$H COSY NMR spectrum (**A**) showed a stronger correlation between $H_a$ and $H_c$ than that of $H_b$ and $H_c$. 1D NOE spectra with irradiation of $H_a$ (**B**), $H_b$ (**C**), and $H_c$ (**D**) also showed a stronger correlation between $H_a$ and $H_c$ than that of $H_b$ and $H_c$.

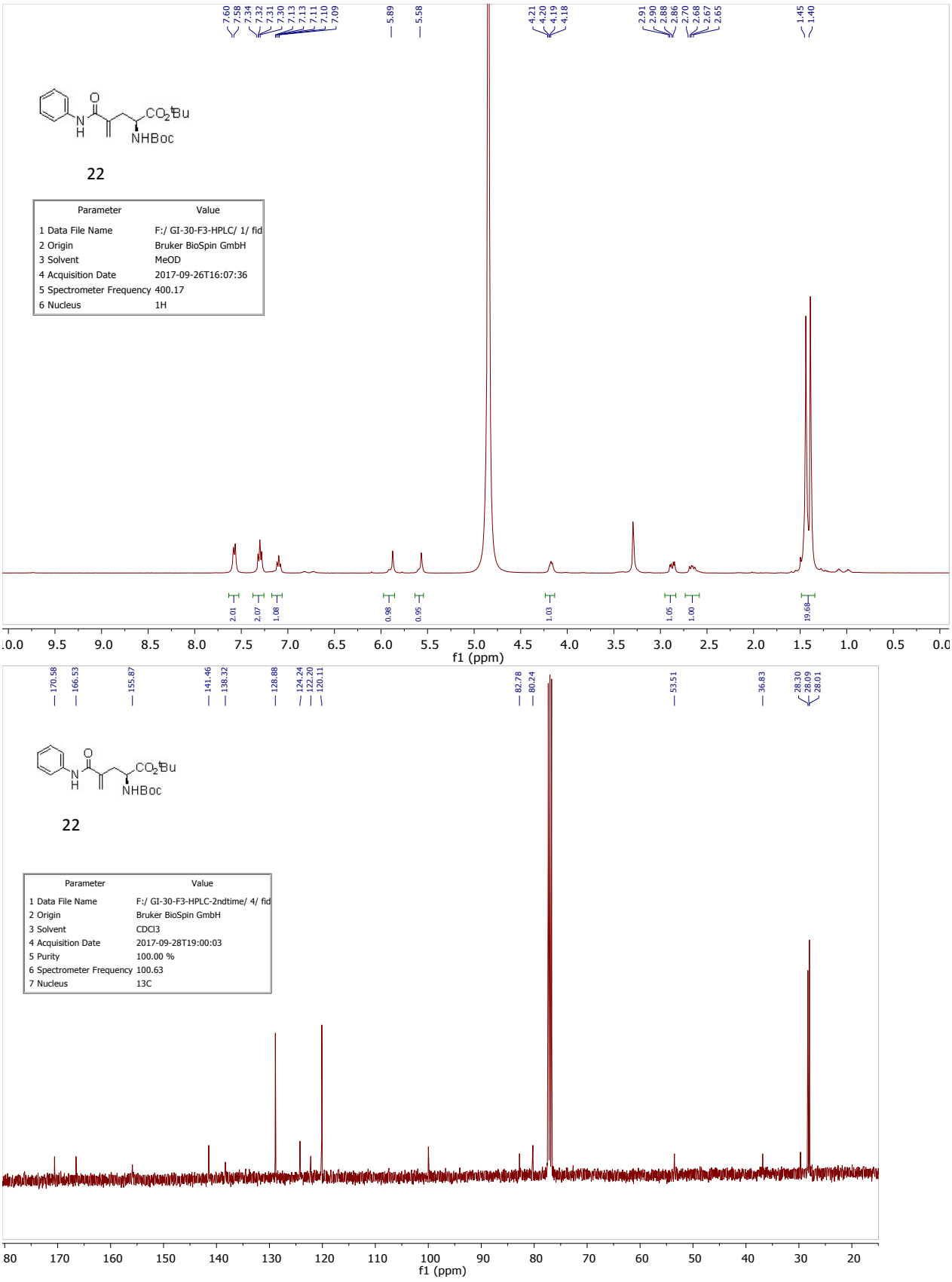
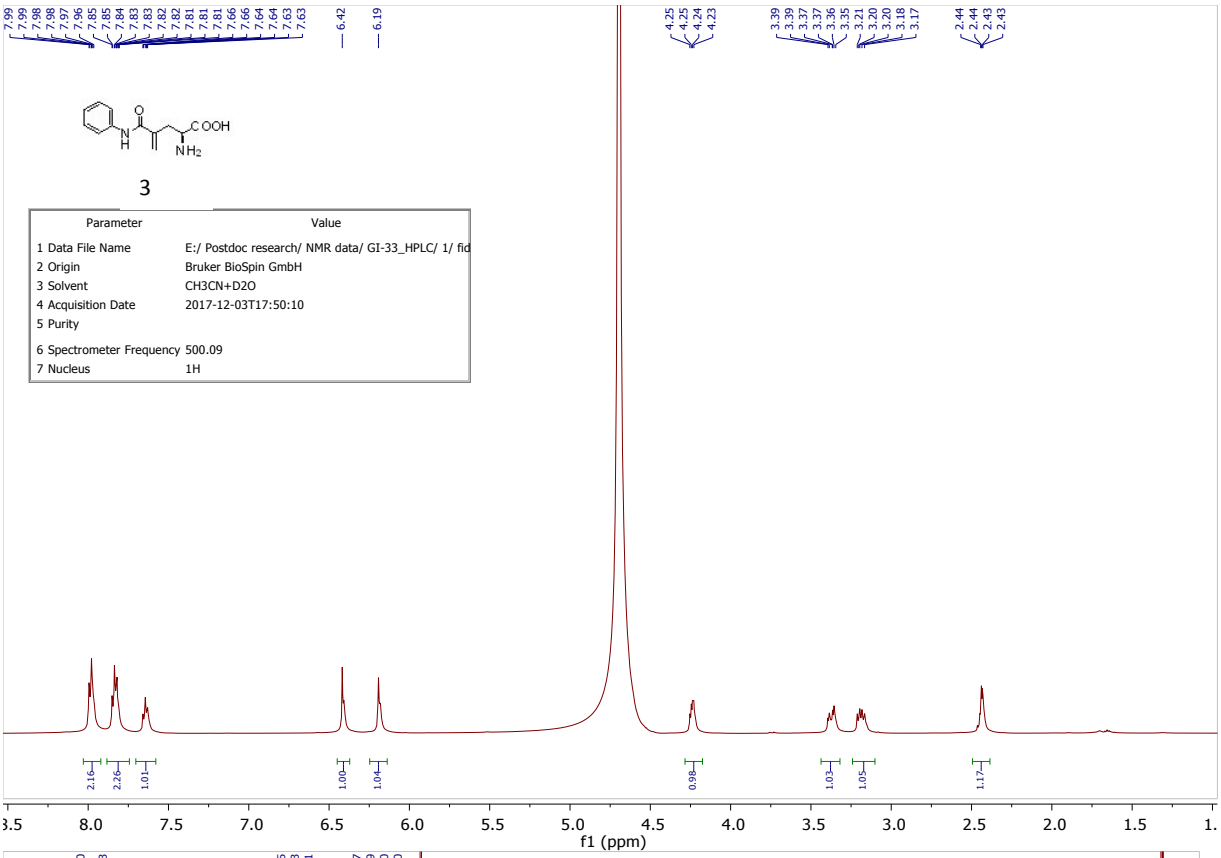



**Figure S8.** $^{1}H$ and $^{13}C$ NMR spectra of compound **22**



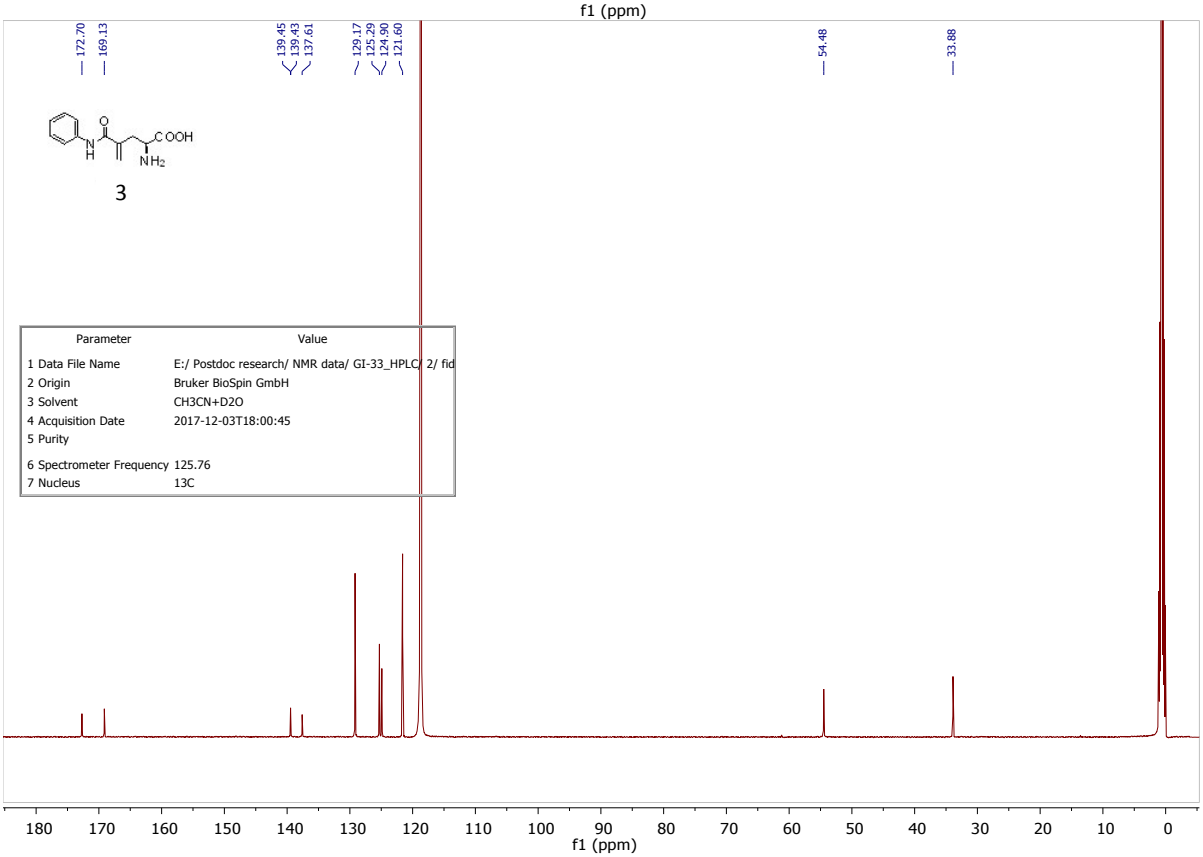




**Figure S9.** $^{1}H$ and $^{13}C$ NMR spectra of compound **3**

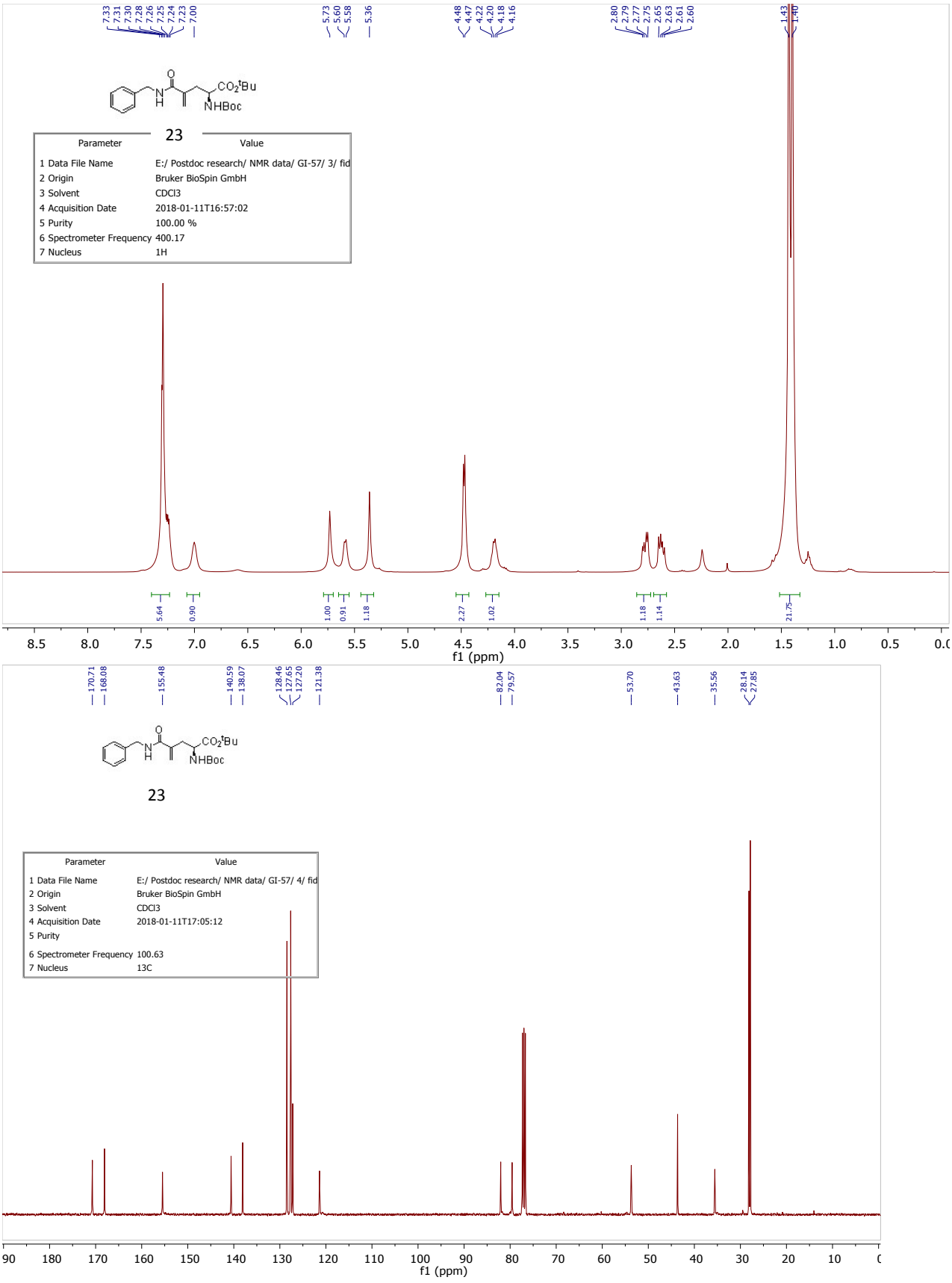



**Figure S10.** $^{1}H$ and $^{13}C$ NMR spectra of compound **23**

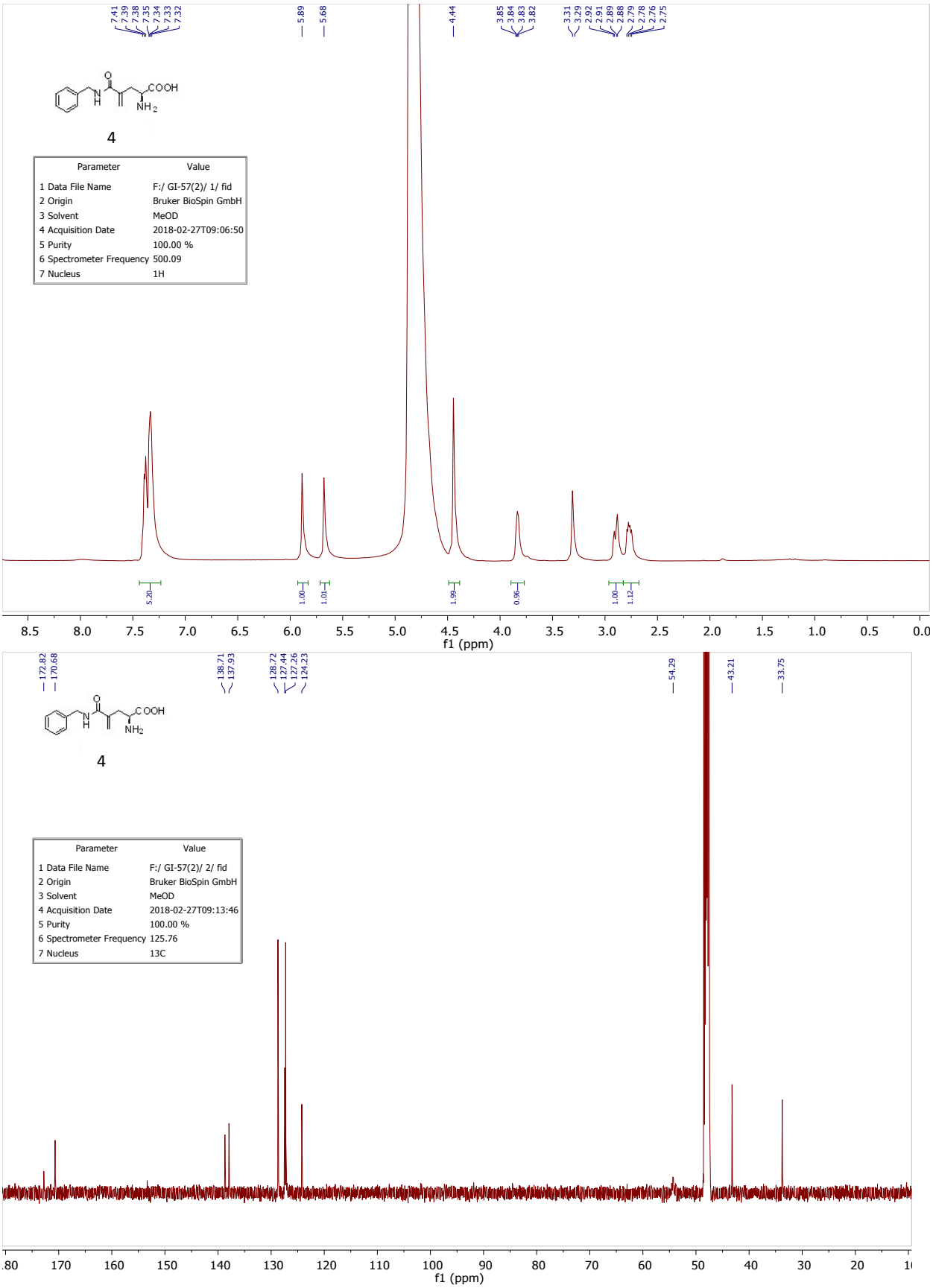



**Figure S11.** $^{1}H$ and $^{13}C$ NMR spectra of compound **4**

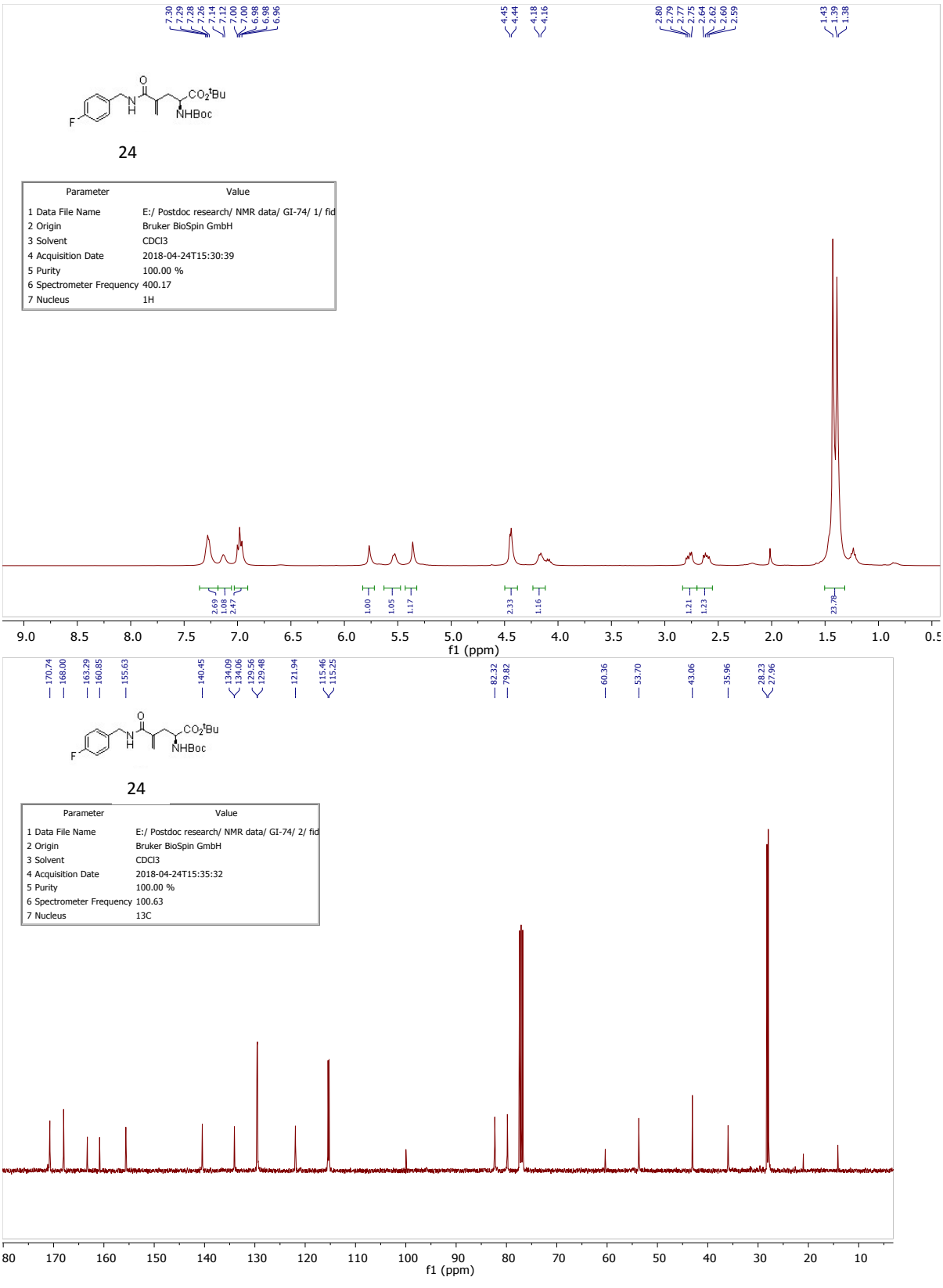



**Figure S12.** $^{1}H$ and $^{13}C$ NMR spectra of compound **24**

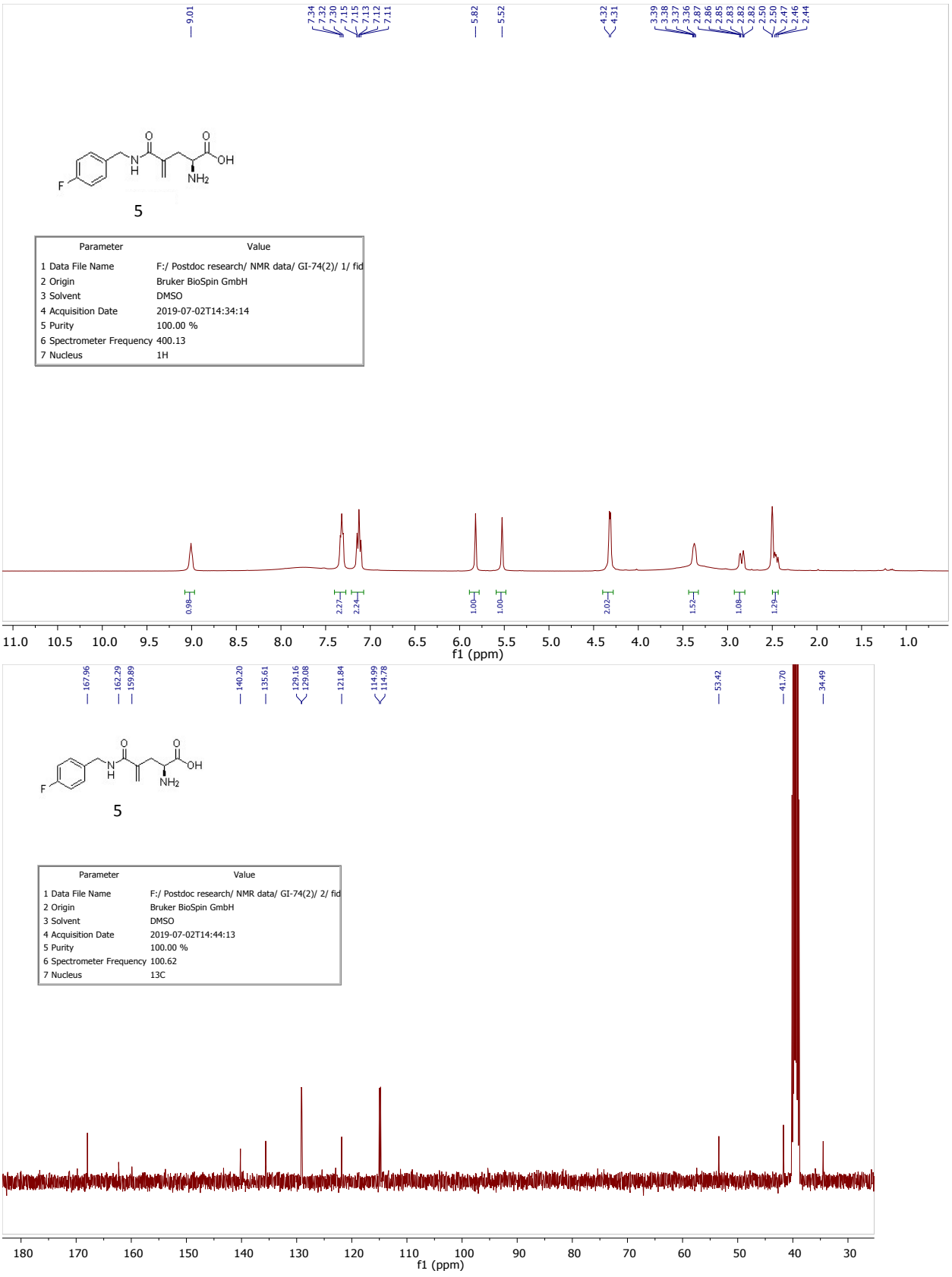



**Figure S13.** $^{1}H$ and $^{13}C$ NMR spectra of compound **5**

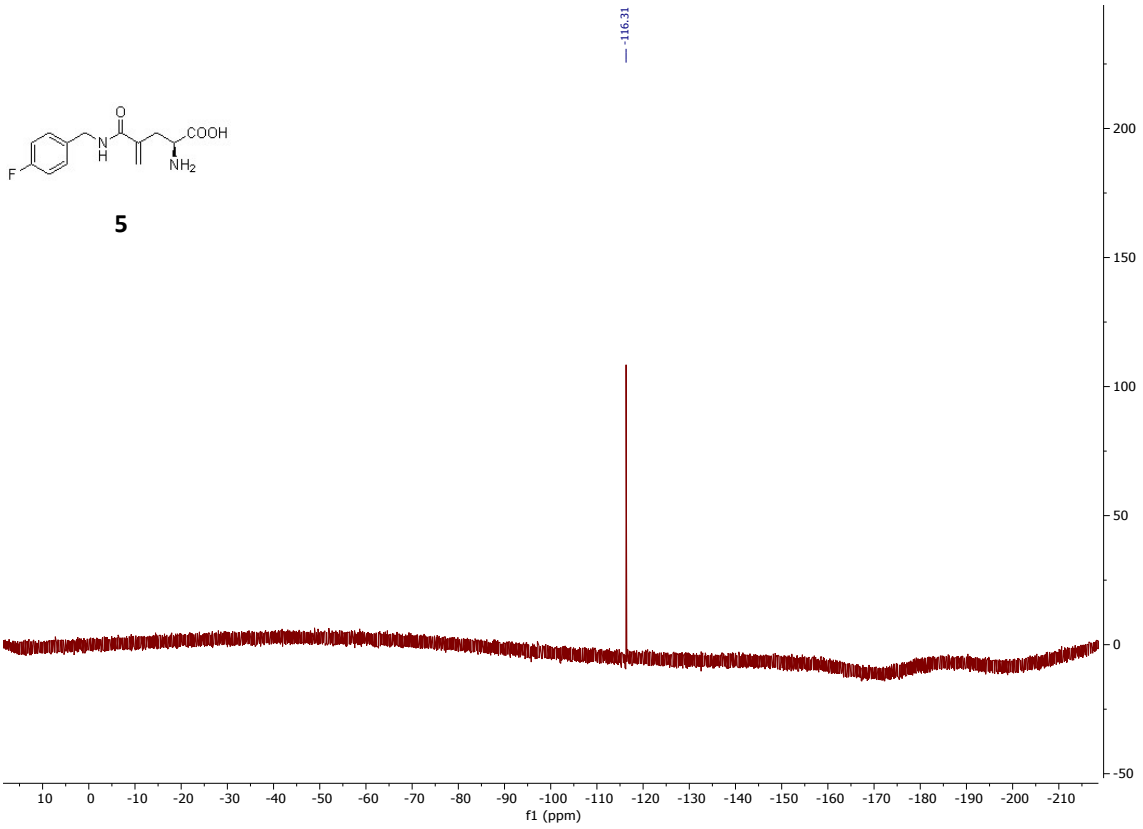
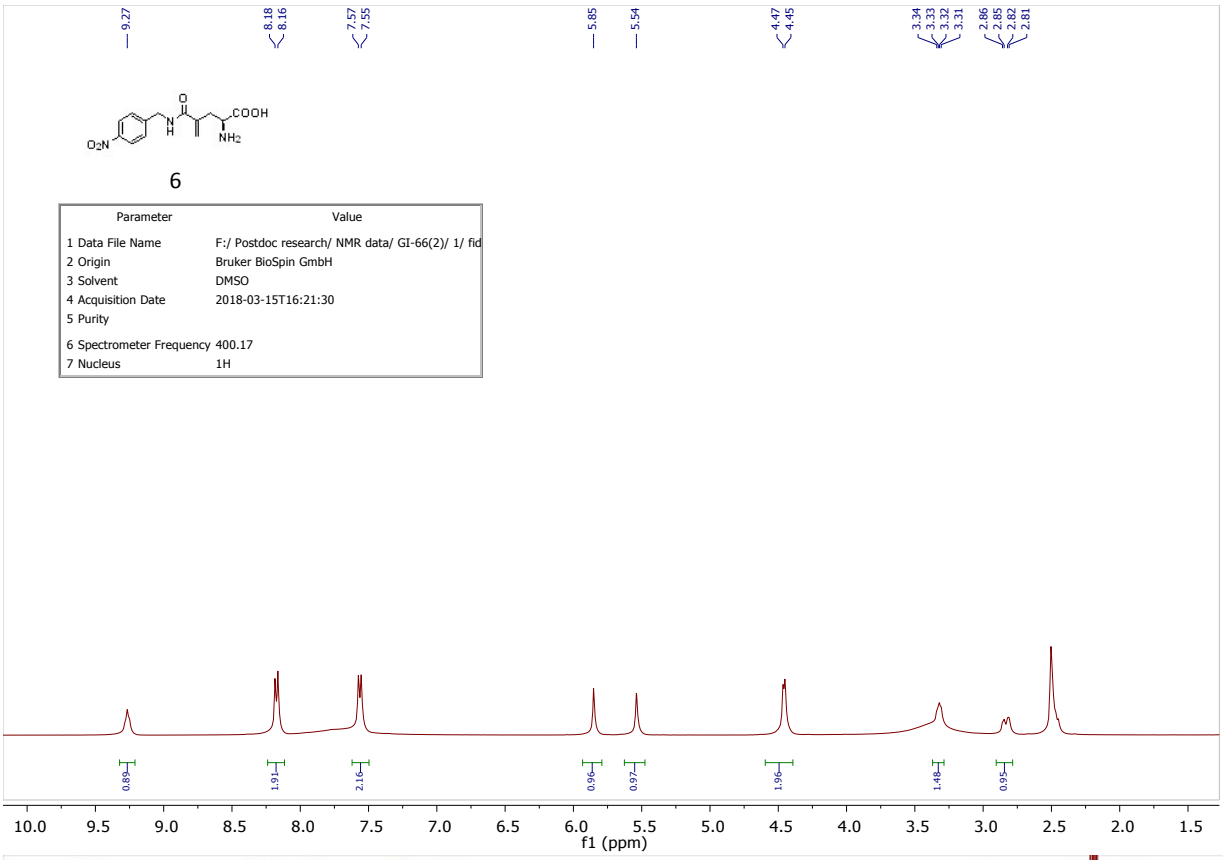



**Figure S14.** $^{19}F$ NMR spectra of compound **5**



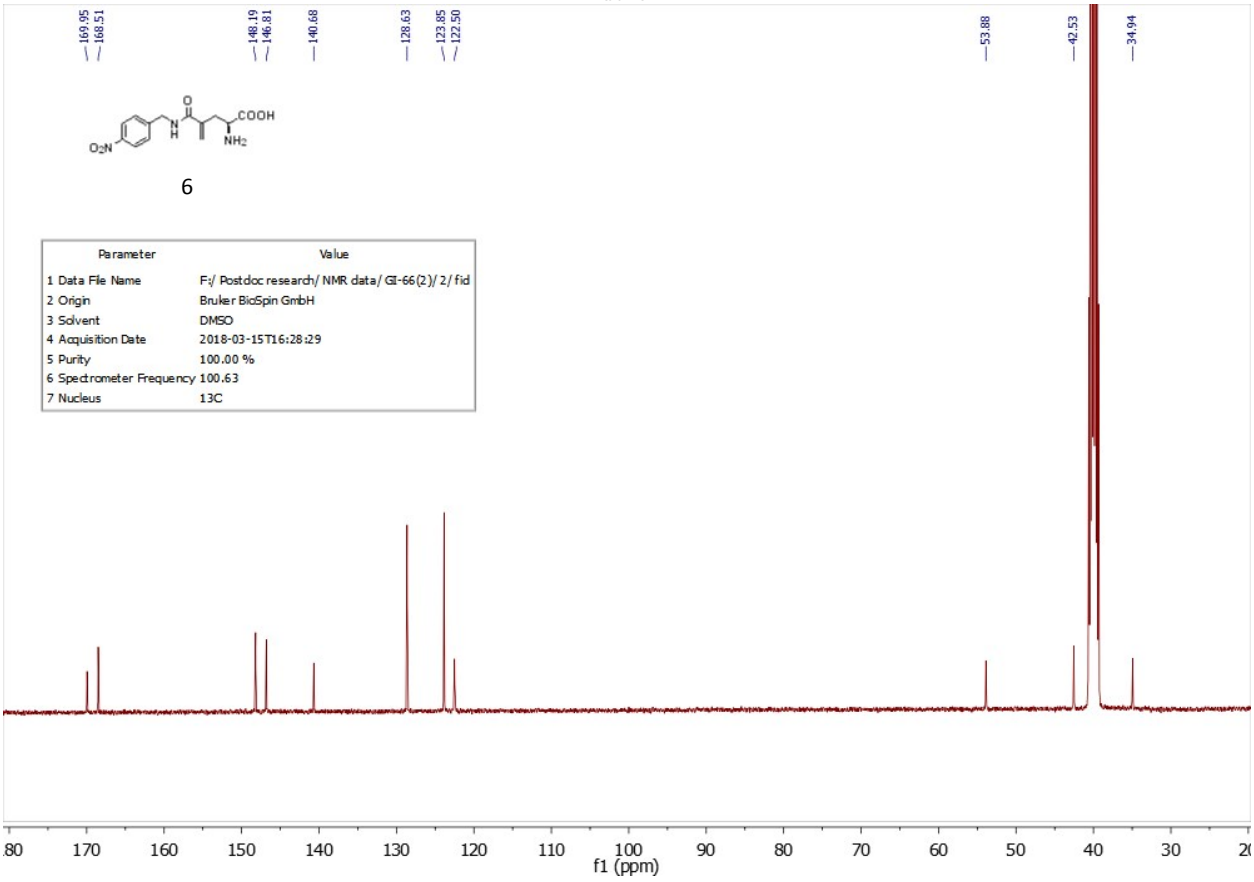
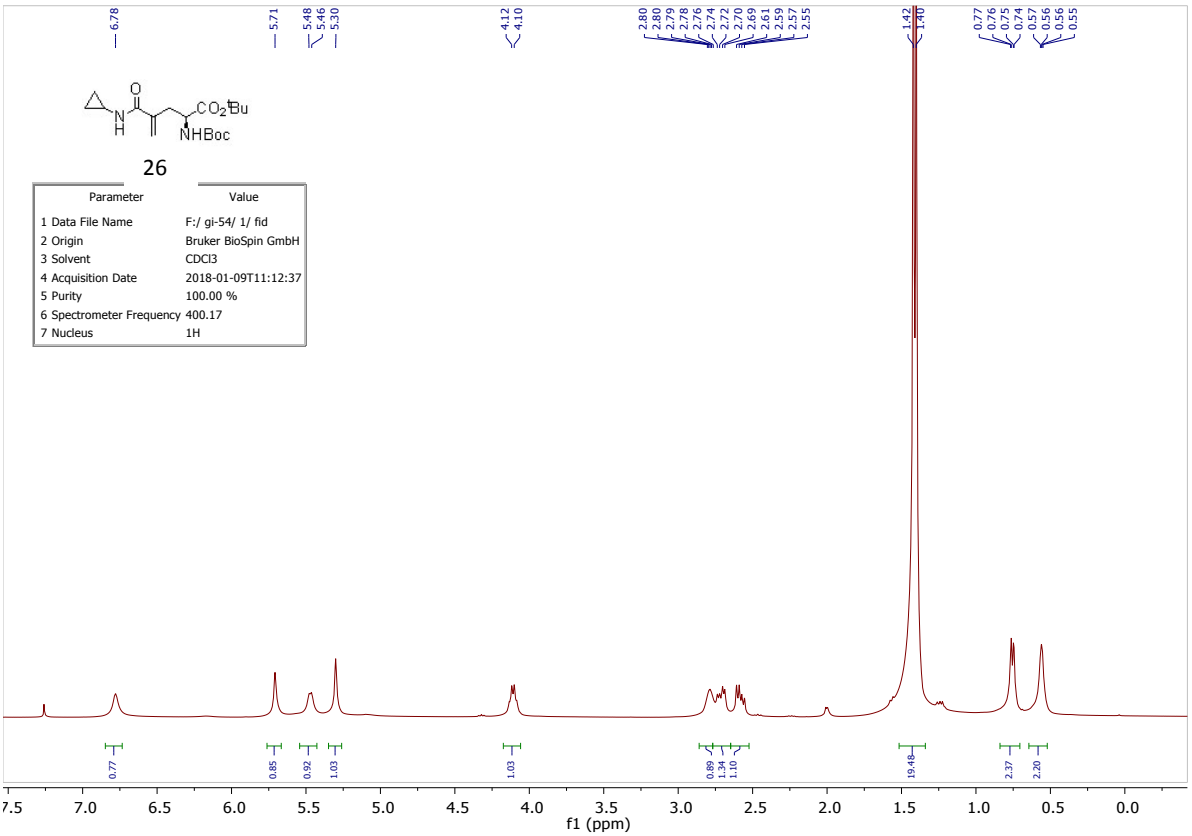




**Figure S15.** $^{1}H$ and $^{13}C$ NMR spectra of compound **6**



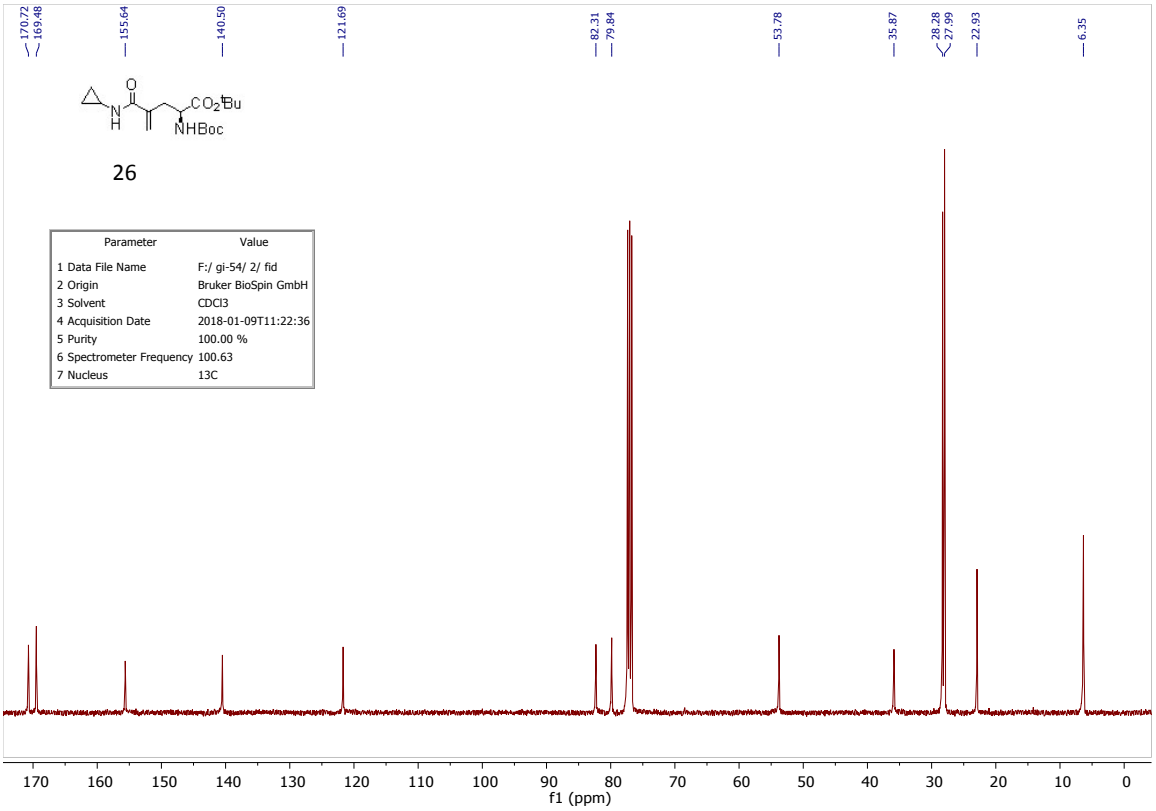
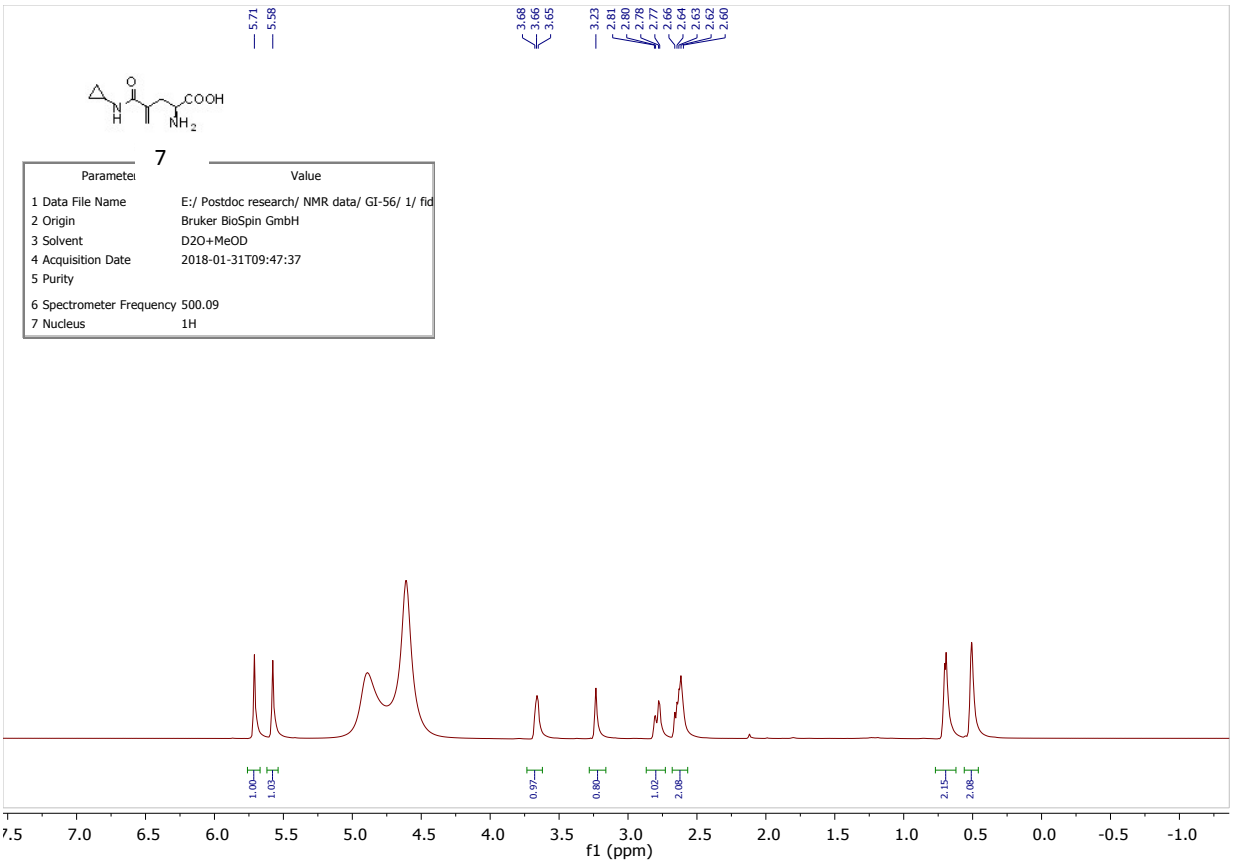




**Figure S16.** $^{1}H$ and $^{13}C$ NMR spectra of compound **26**



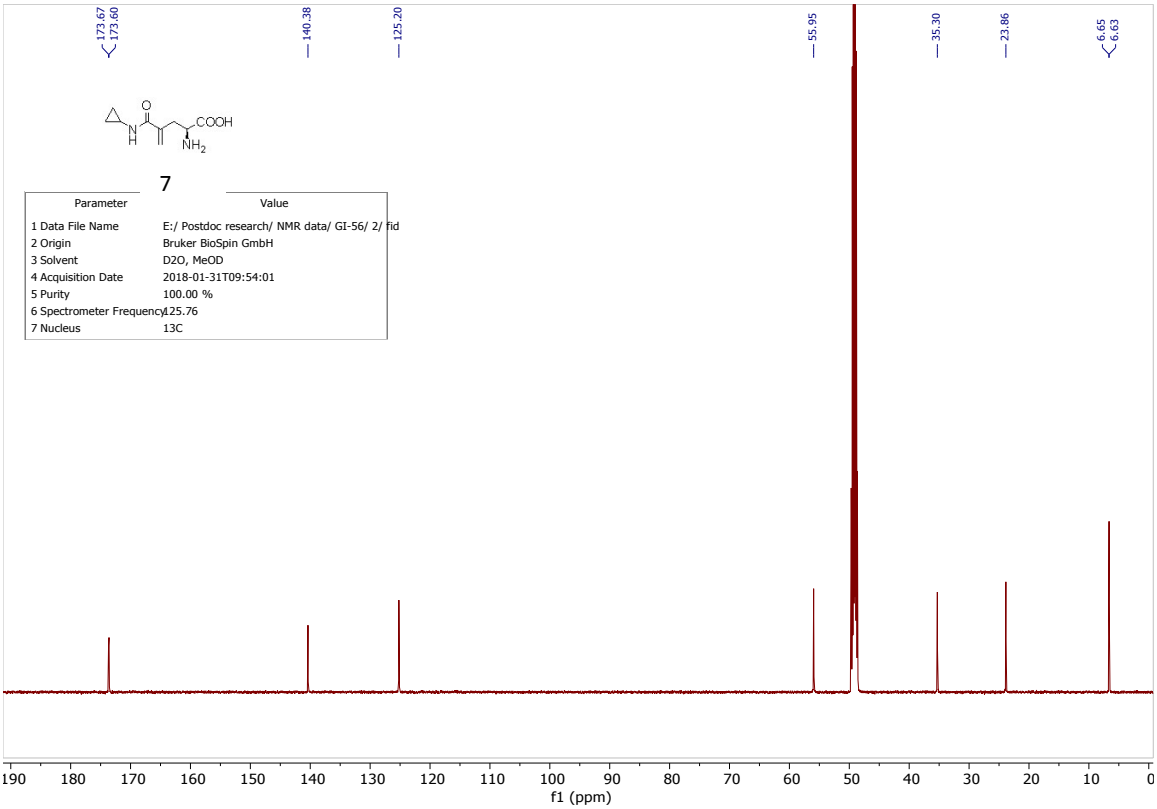
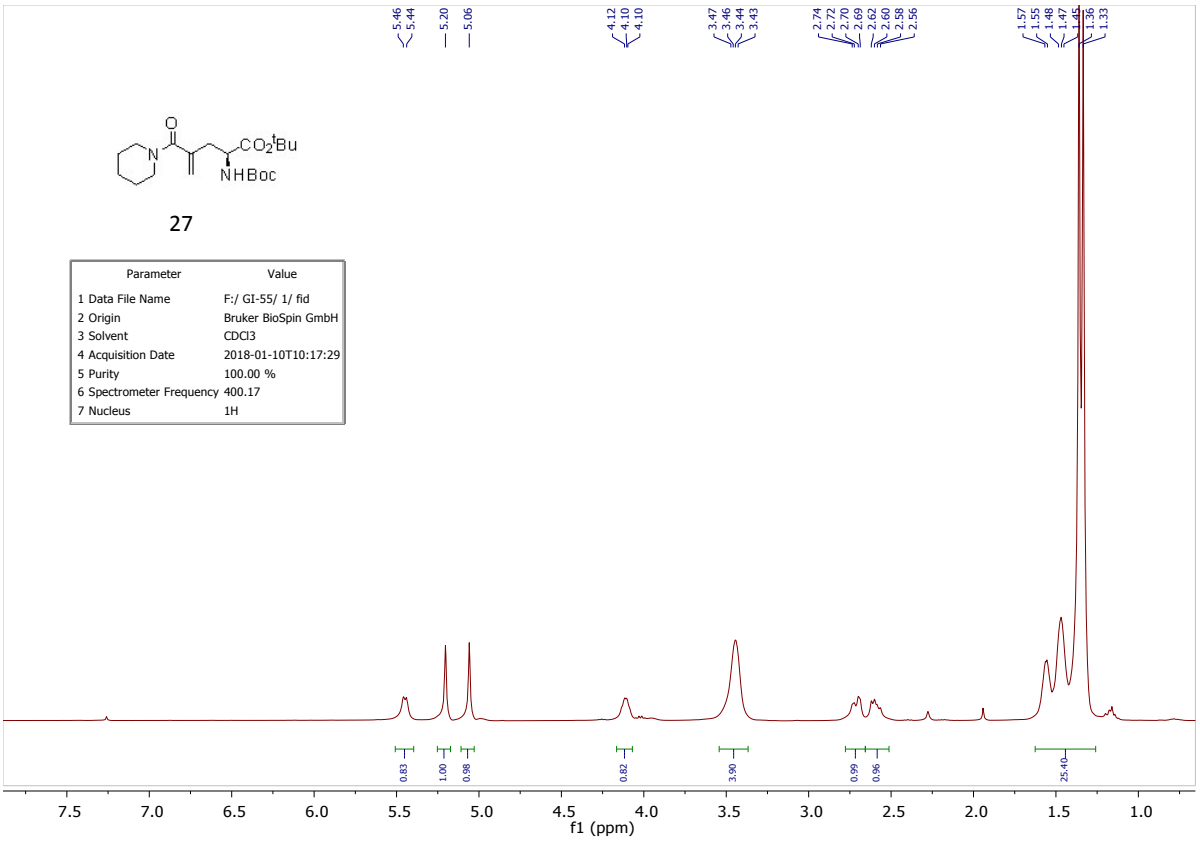




**Figure S17.** $^{1}H$ and $^{13}C$ NMR spectra of compound **7**



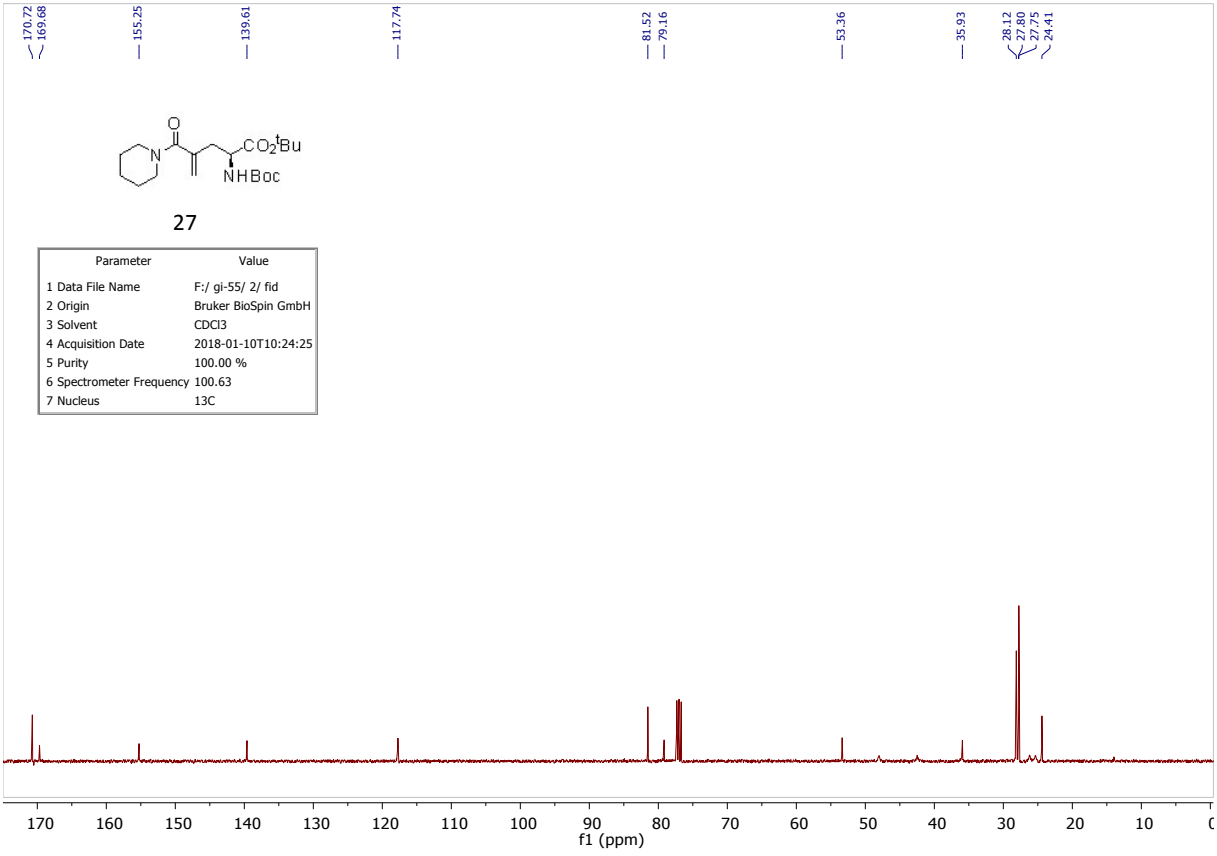
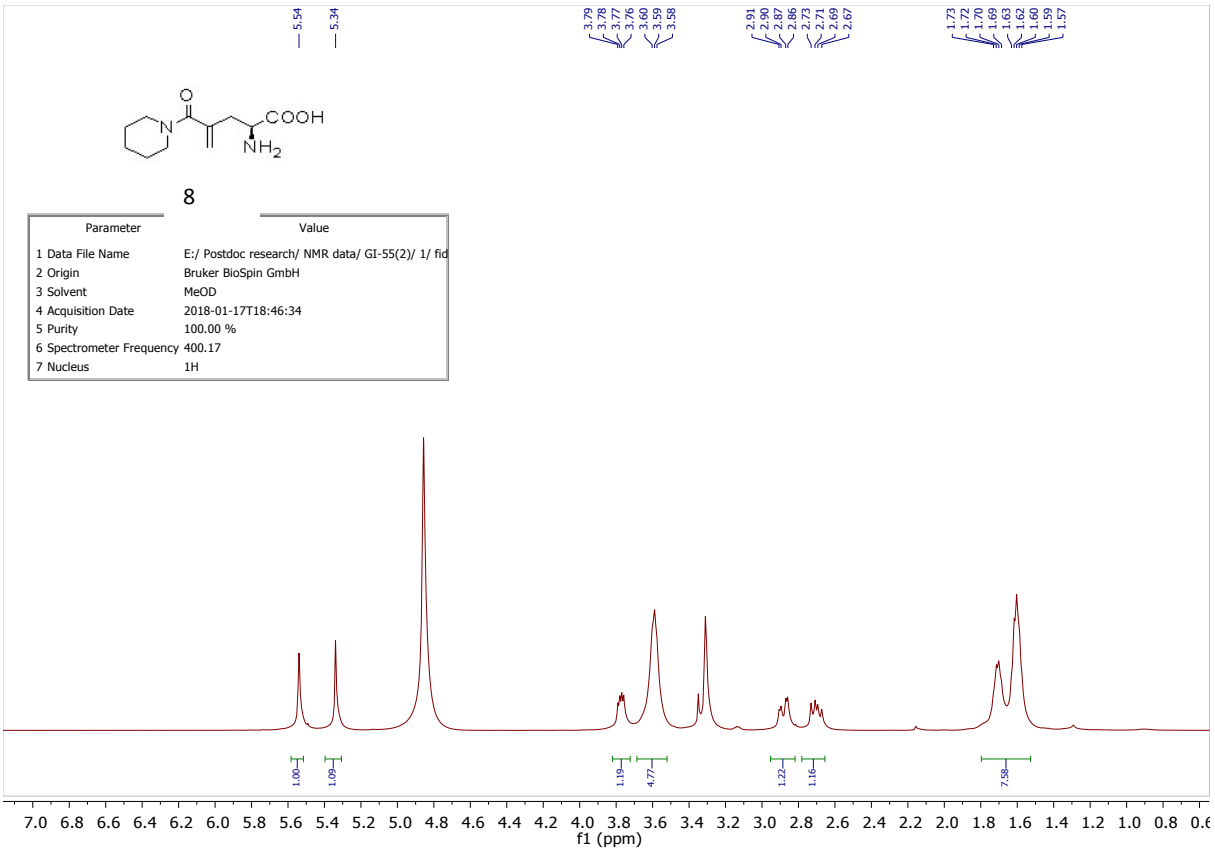




**Figure S18.** $^{1}H$ and $^{13}C$ NMR spectra of compound **27**



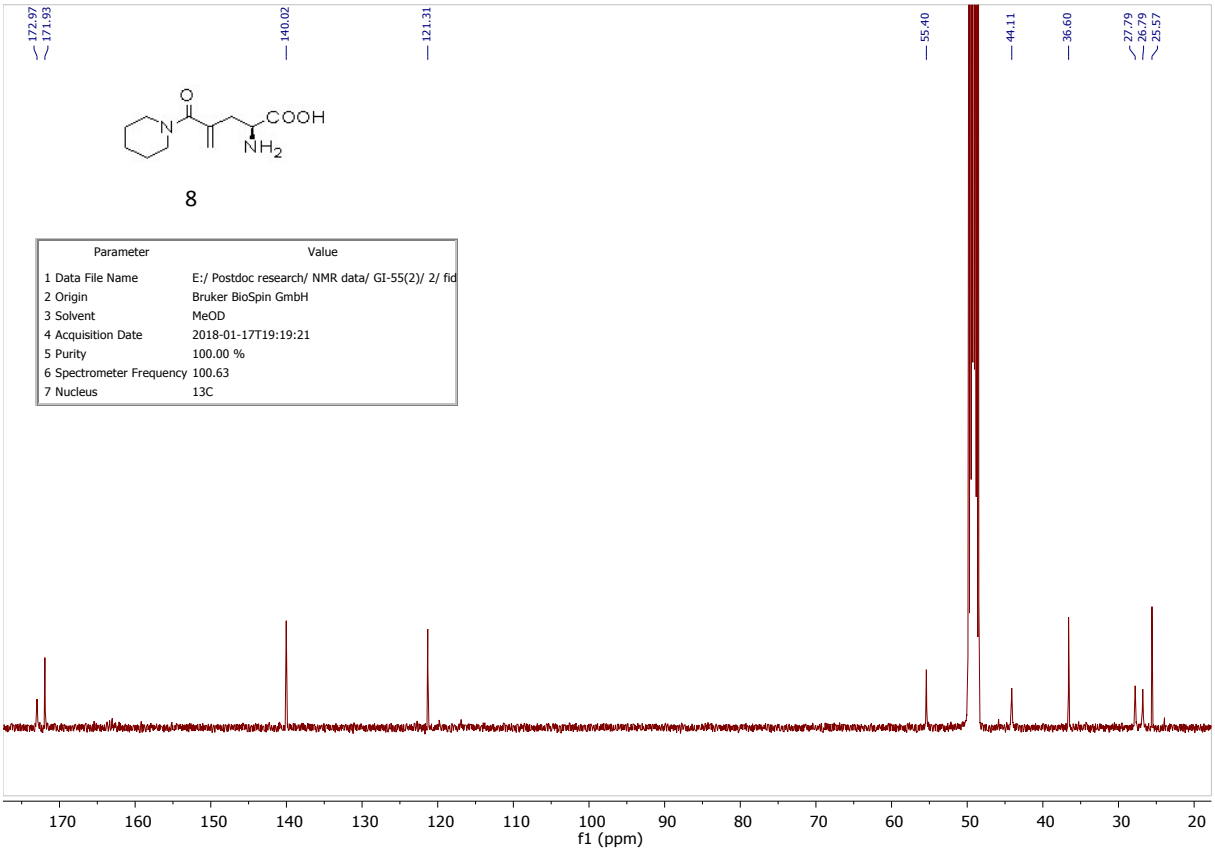




**Figure S19.** $^{1}H$ and $^{13}C$ NMR spectra of compound **8**

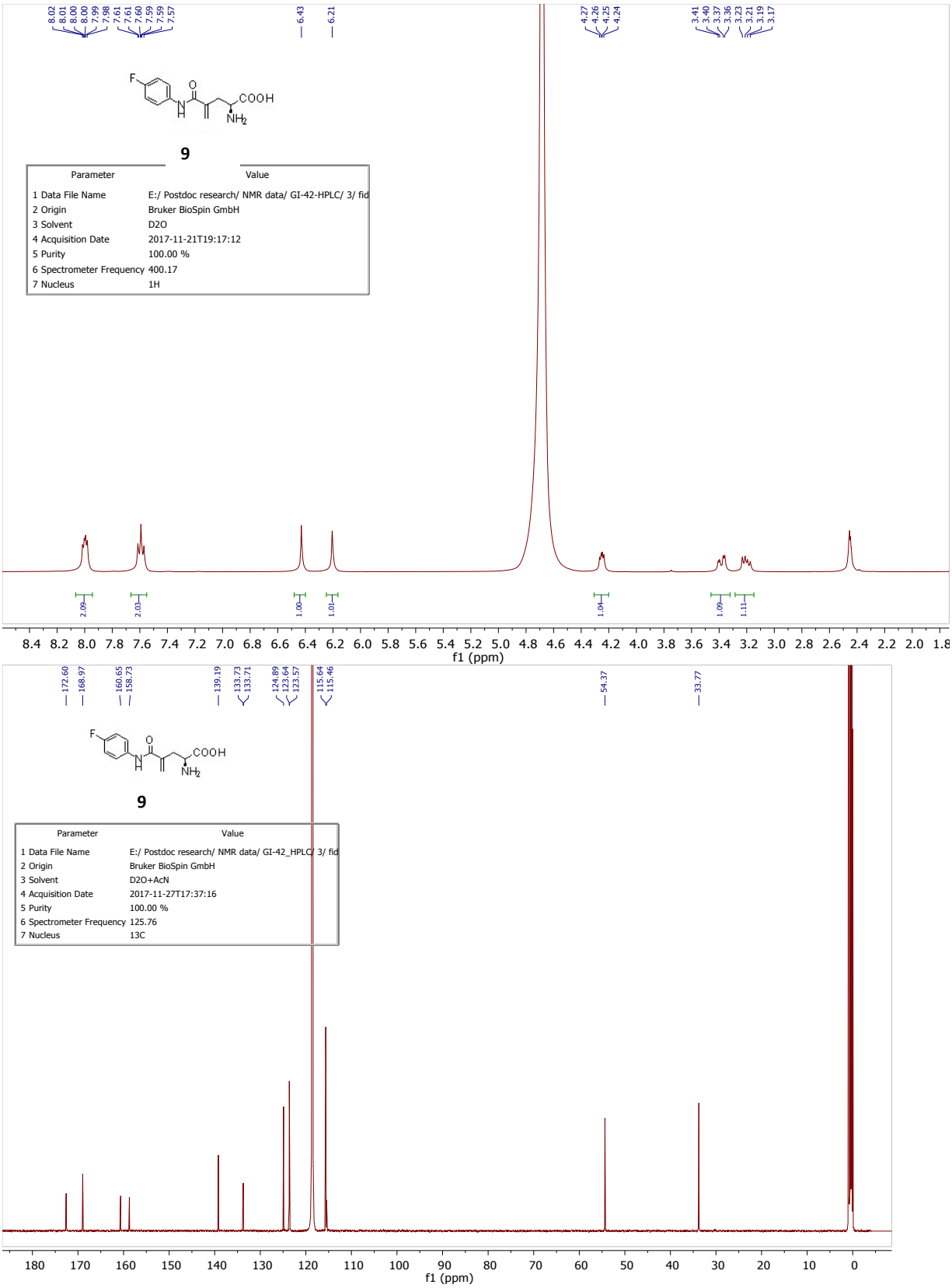



**Figure S20.** $^{1}H$ and $^{13}C$ NMR spectra of compound **9**

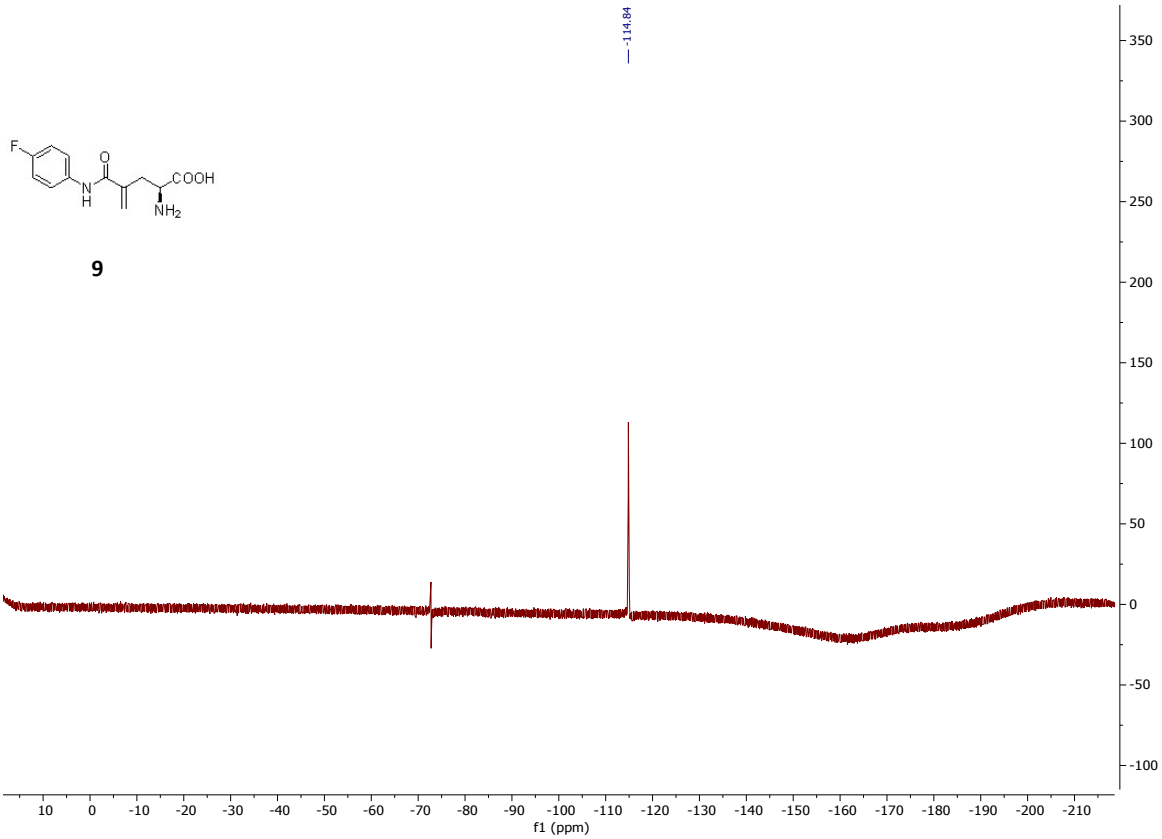
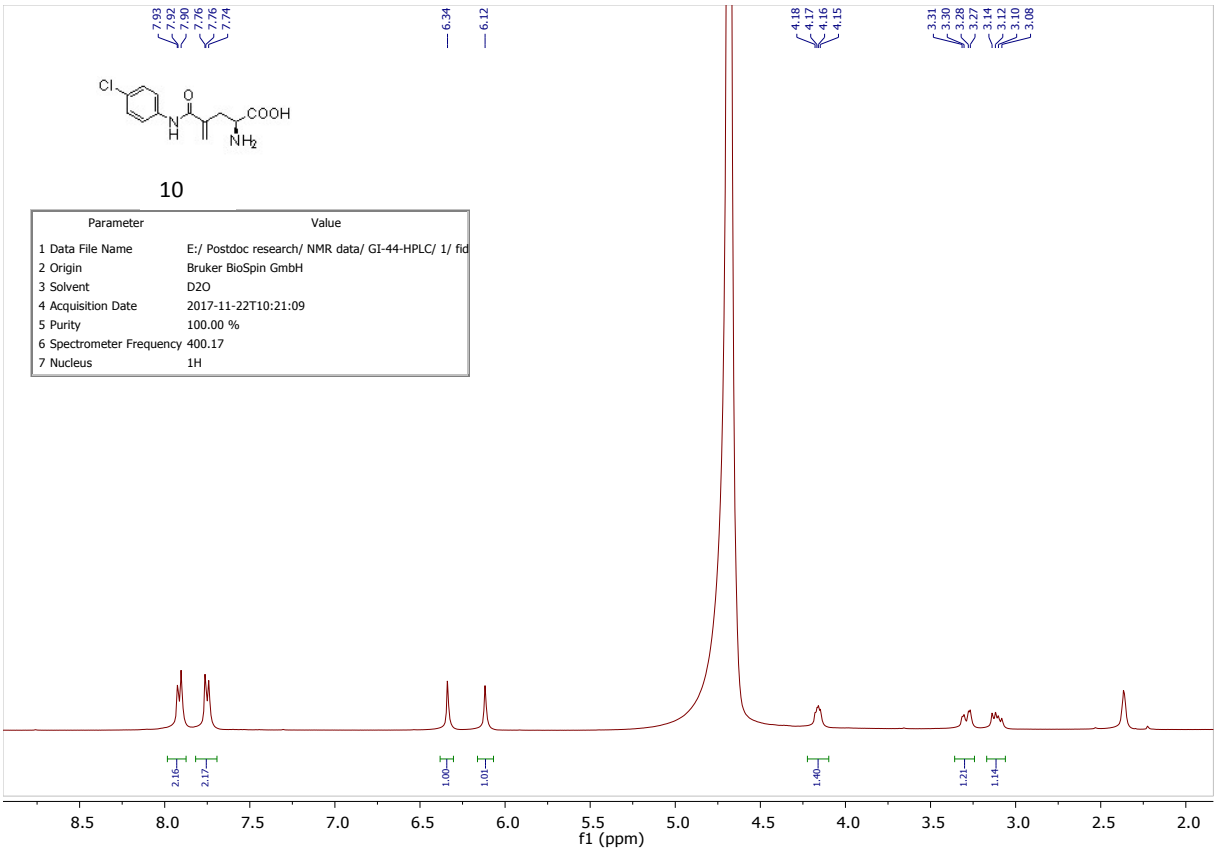



**Figure S21.** $^{19}F$ NMR spectra of compound **9**



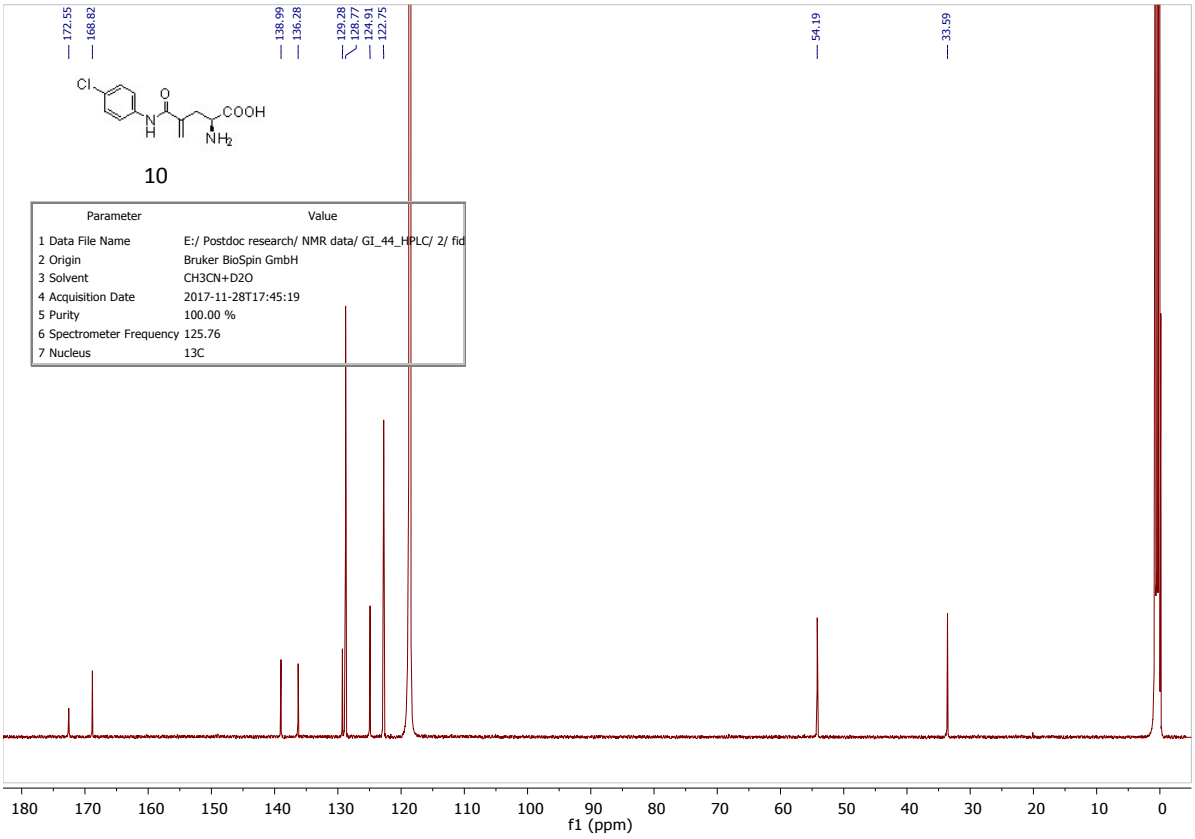




**Figure S22.** $^{1}H$ and $^{13}C$ NMR spectra of compound **10**

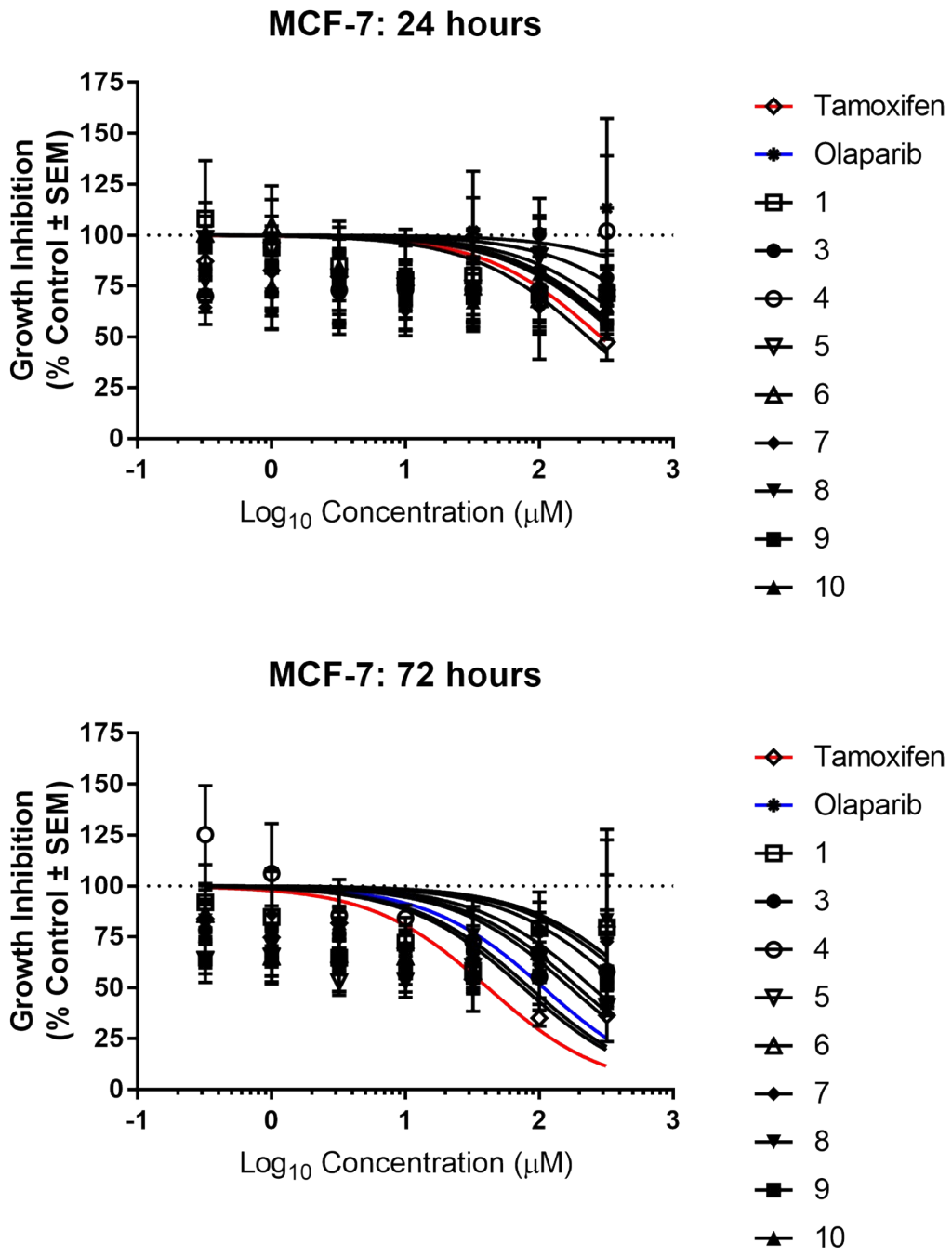



**Figure S23.** Dose-response (0.32 - 320 μM) of tamoxifen, olaparib, and compounds **1** and **3–10** on the inhibition of growth of MCF-7 breast cancer cells at 24 h (top) and 72 h (bottom) from treatment

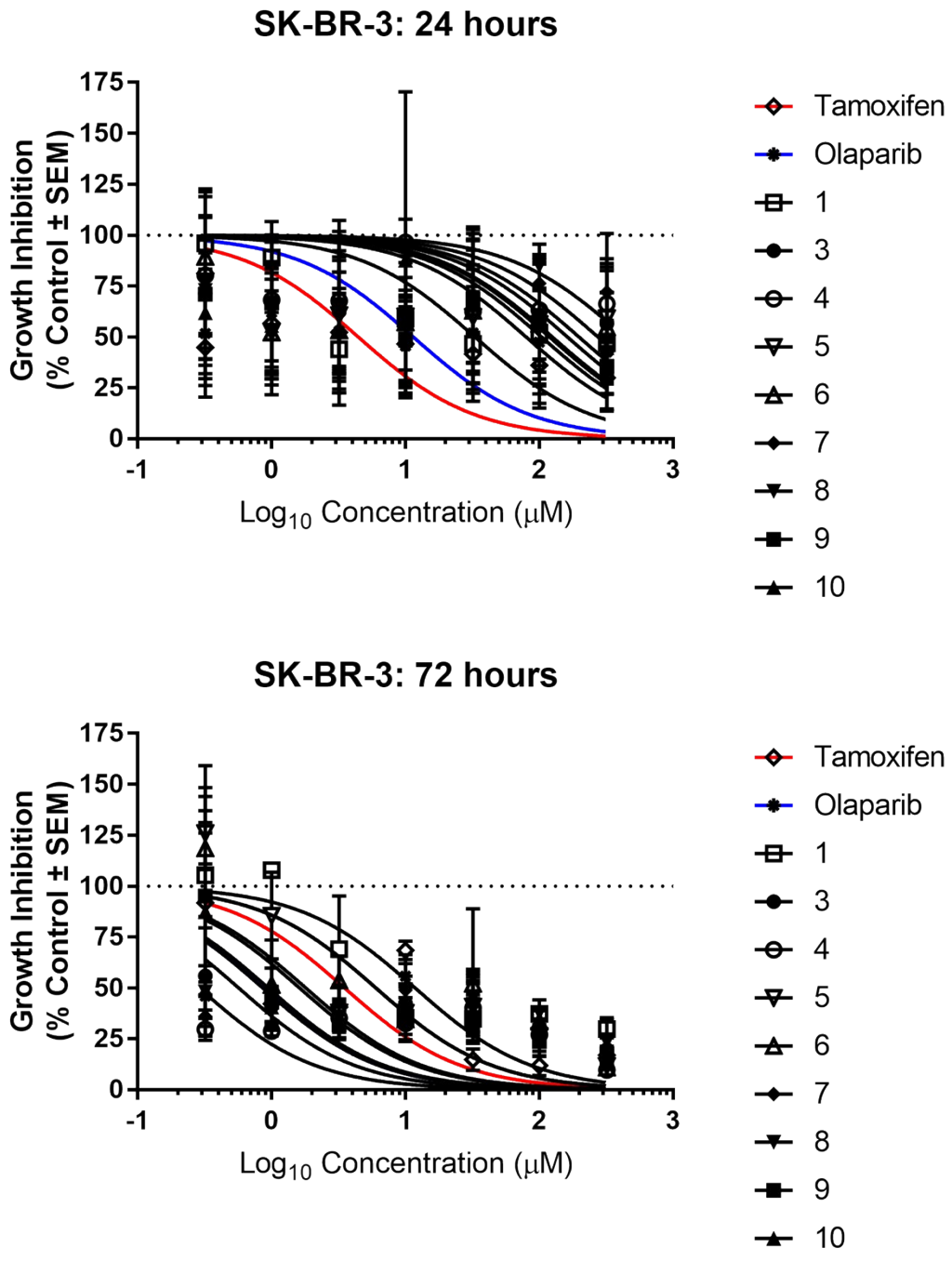



**Figure S24.** Dose-response (0.32 - 320 μM) of tamoxifen, olaparib, and compounds **1** and **3–10** on the inhibition of growth of SK-BR-3 breast cancer cells at 24 h (top) and 72 h (bottom) from treatment

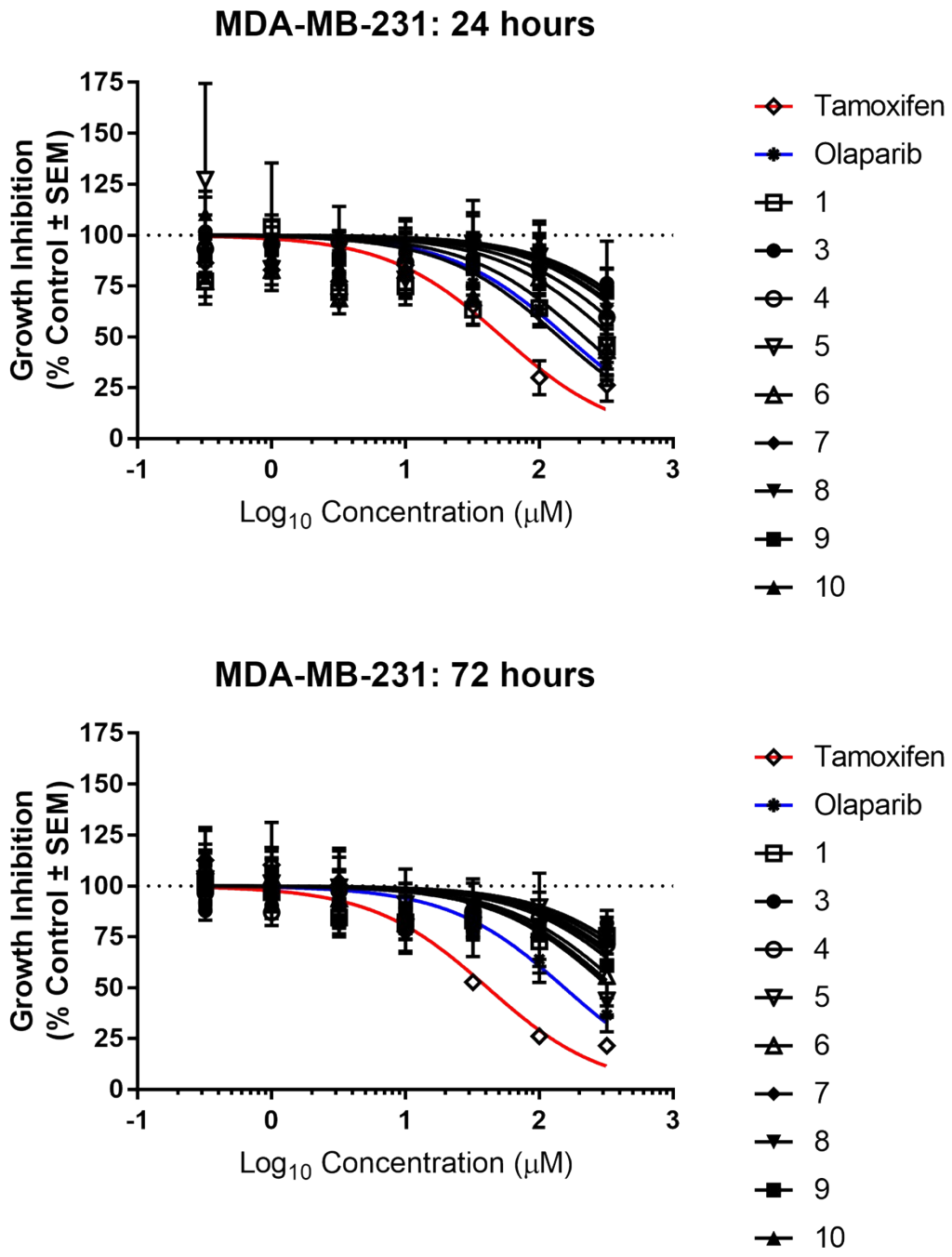



**Figure S25.** Dose-response (0.32 - 320 μM) of tamoxifen, olaparib, and compounds **1** and **3–10** on the inhibition of growth of triple-negative MDA-MB-231 breast cancer cells at 24 h (top) and 72 h (bottom) from treatment

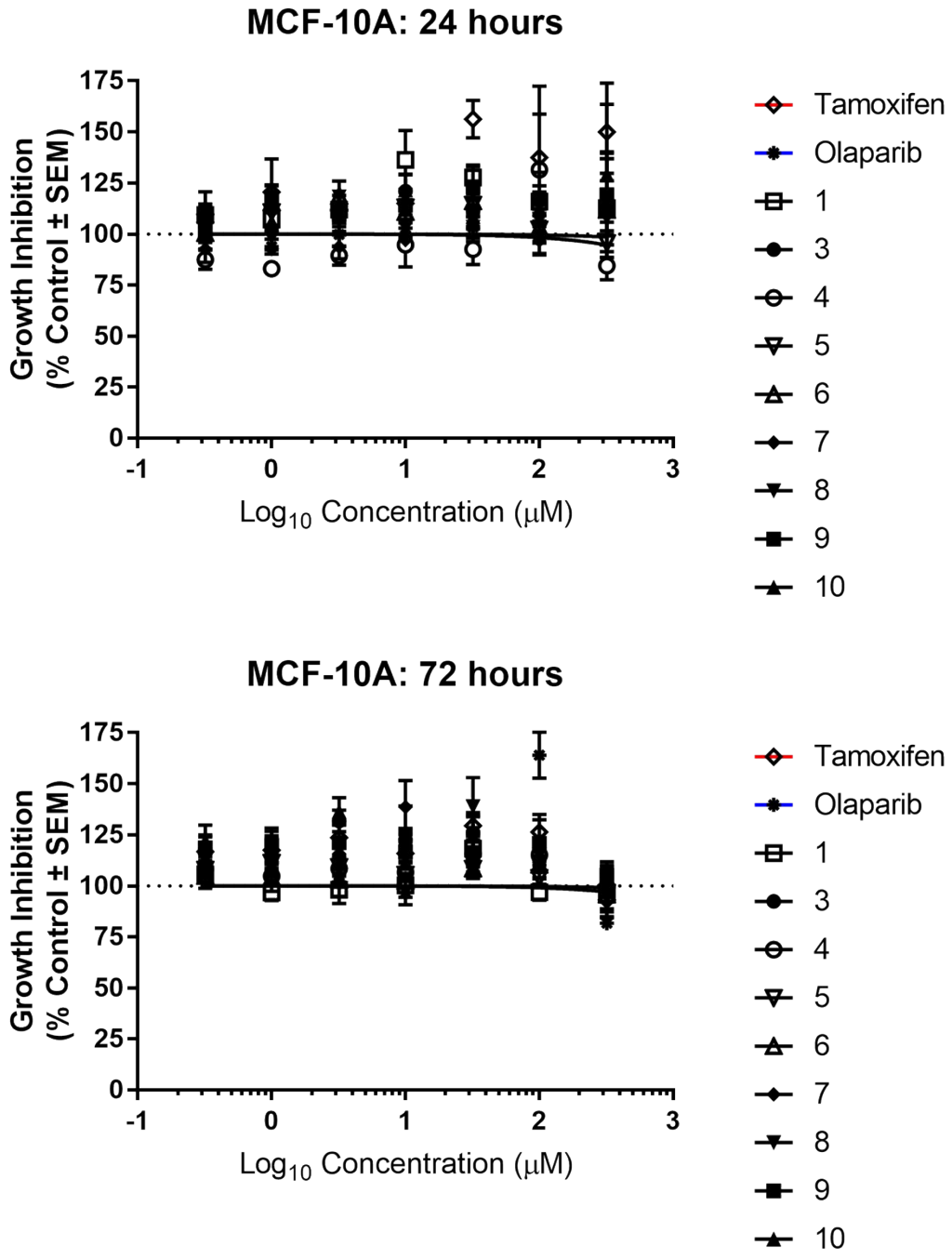



**Figure S26.** Dose-response (0.32 - 320 μM) of tamoxifen, olaparib, and compounds **1** and **3–10** on the inhibition of growth of noncancerous MCF-10A breast cells at 24 h (top) and 72 h (bottom) from treatment

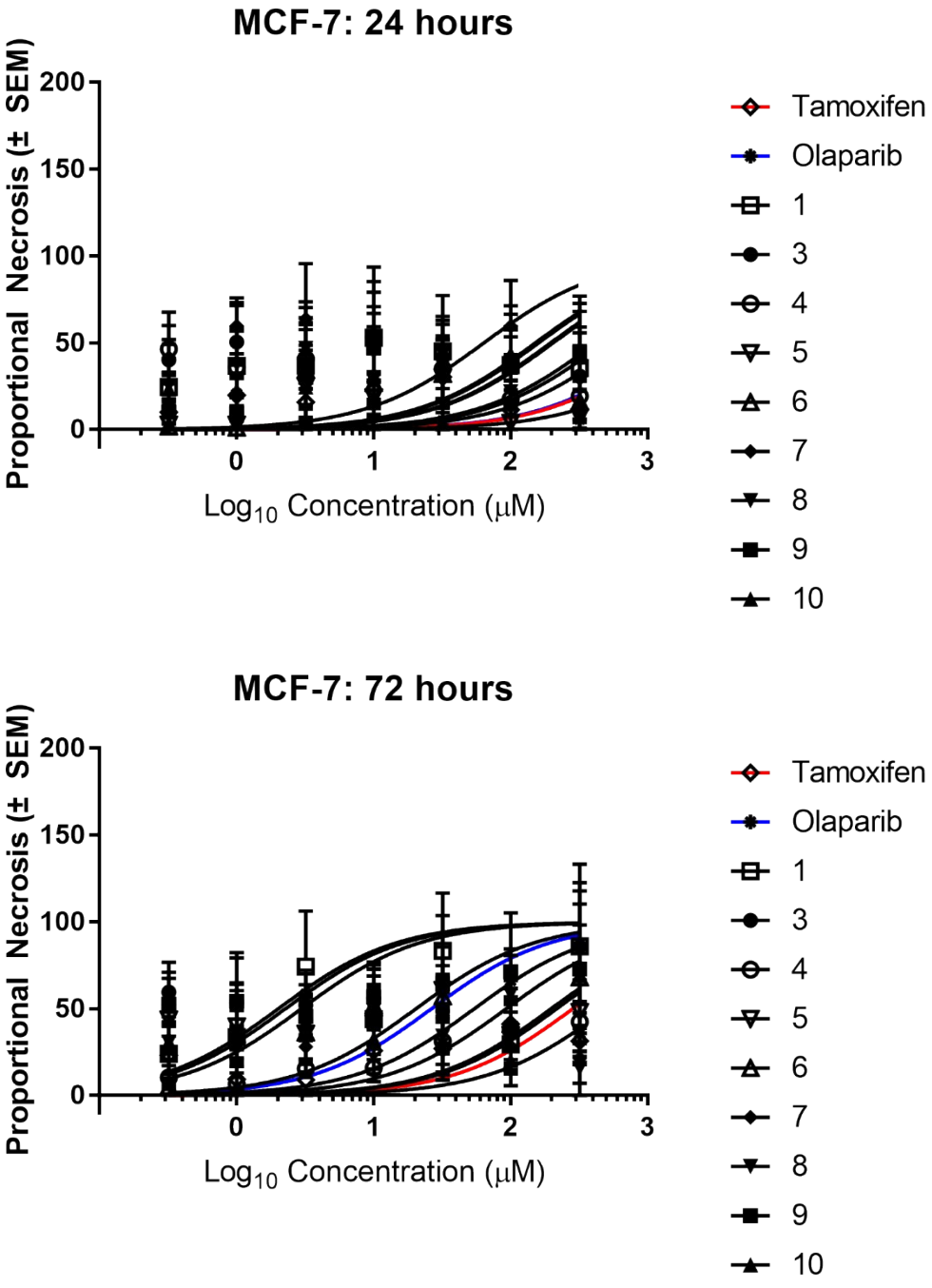



**Figure S27.** Dose-response (0.32 - 320 μM) of tamoxifen, olaparib, and compounds **1** and **3–10** on the cell death of MCF-7 breast cancer cells at 24 h (top) and 72 h (bottom) from treatment

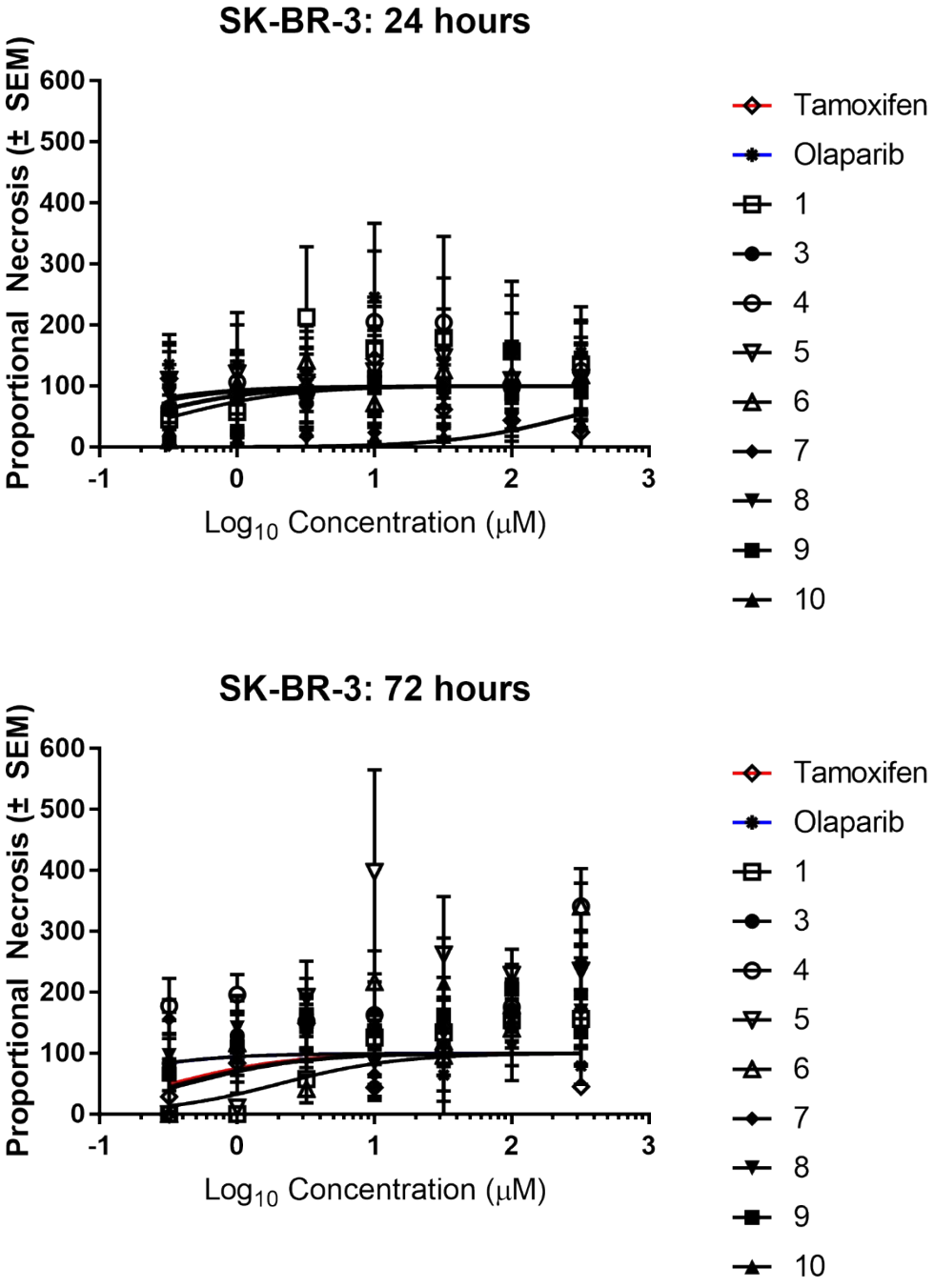



**Figure S28.** Dose-response (0.32 - 320 μM) of tamoxifen, olaparib, and compounds **1** and **3–10** on the cell death of SK-BR-3 breast cancer cells at 24 h (top) and 72 h (bottom) from treatment

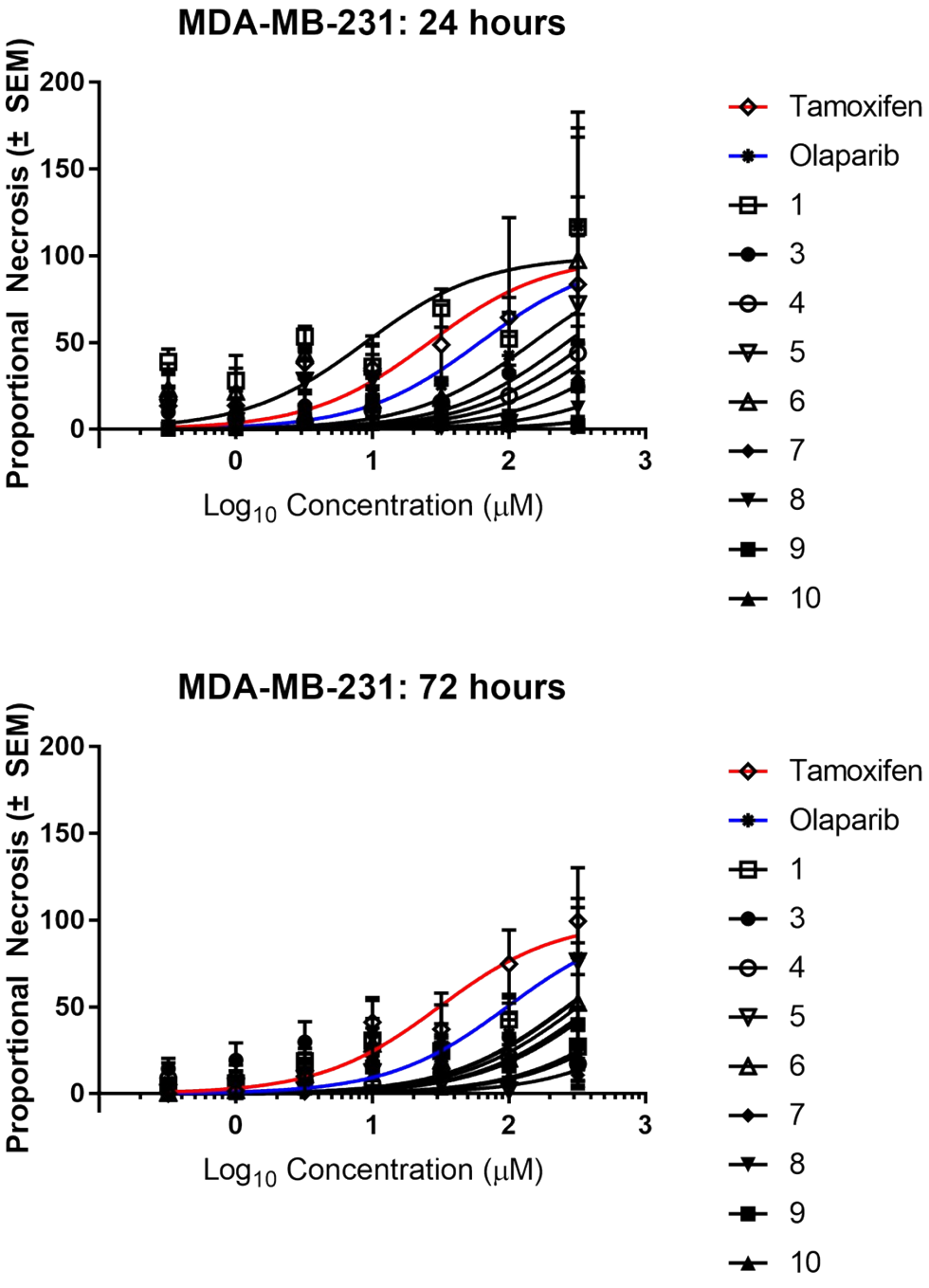



**Figure S29.** Dose-response (0.32 - 320 μM) of tamoxifen, olaparib, and compounds **1** and **3–10** on the cell death of triple-negative MDA-MB-231 breast cancer cells at 24 h (top) and 72 h (bottom) from treatment

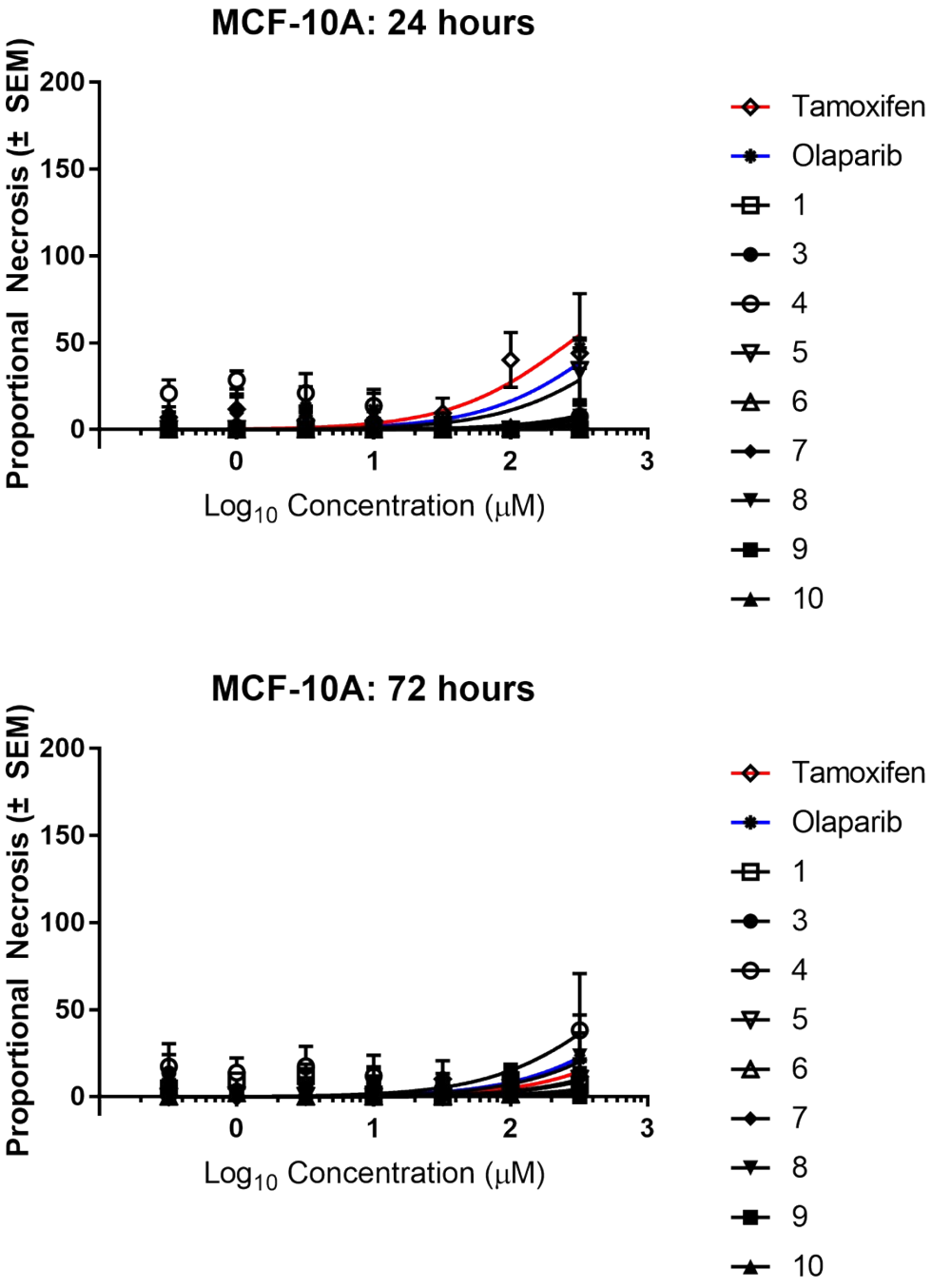



**Figure S30.** Dose-response (0.32 - 320 μM) of tamoxifen, olaparib, and compounds **1** and **3–10** on the cell death of noncancerous MCF-10A breast cells at 24 h (top) and 72 h (bottom) from treatment