

Synthesis of α -CF₃-substituted γ,δ -didehydro lysine derivatives

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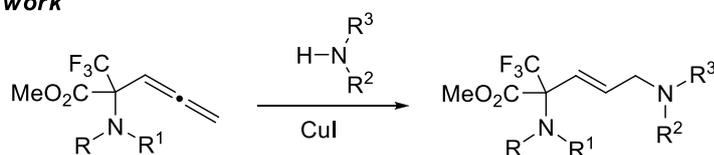
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General information

All solvents used in the reactions were freshly distilled from appropriate drying agents before use. All other reagents were distilled as necessary. Analytical TLC was performed with Merck silica gel 60 F₂₅₄ plates; visualization was accomplished with UV light, iodine vapors or by spraying with Ce(SO₄)₂ solution in 5% H₂SO₄. Chromatography was carried out using Merck silica gel (Kieselgel 60, 0.063–0.200 mm) and petroleum ether/ethyl acetate, ethyl acetate, ethyl acetate/methanol as eluents. NMR spectra were obtained with Inova 400, Bruker AV-400, AV-500 and AV-600 spectrometers operating at 400, 500 and 600 MHz, respectively, for ¹H (TMS reference), at 101, 126 and 151 MHz for ¹³C, and at 376 MHz for ¹⁹F (CCl₃F reference) and at 161 MHz for ³¹P (H₃PO₄ reference). High-resolution mass spectra (HRMS) were measured using AB Sciex TripleTOF 5600+ equipped with Nanospray III source. The starting propargylic α -amino acid derivatives were synthesized as previously described [G. T. Shchetnikov *et al.*, *Synlett*, 2007, 136; D. V. Vorobyeva *et al.*, *J. Fluorine Chem.*, 2010, **131**, 378].

Previous work



This work

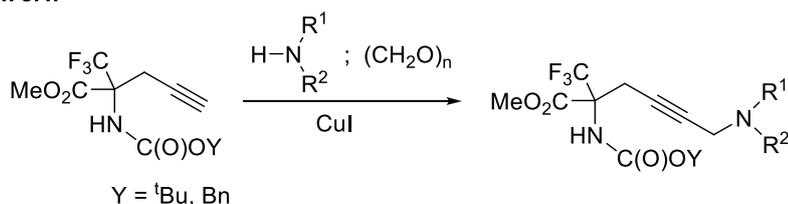
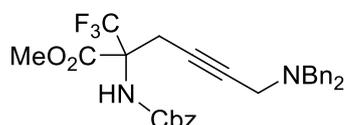


Figure S1

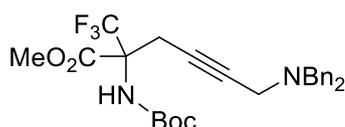
General procedure for Mannich reaction. An oven-dried 10 ml Schlenk tube equipped with a magnetic stirrer was thrice evacuated and then back-filled with argon. Under a stream of argon, the CF₃-containing acetylene (0.34 mmol) was added, followed by paraformaldehyde (25.5 mg, 0.85 mmol), the corresponding amine (0.61 mmol), 1,4-dioxane (2 ml) and copper iodide (19.0 mg, 0.10 mmol). The reaction mixture was stirred at 90 °C for 16 h, then it was cooled to room temperature and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, ethyl acetate or ethyl acetate/methanol) to obtain the desired product.

Methyl 2-benzyloxycarbonylamino-6-dibenzylamino-2-(trifluoromethyl)hex-4-ynoate (3a)



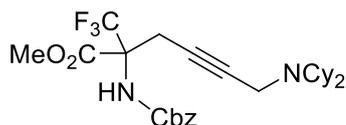
Yield: 78% as a thick light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 7.35 – 7.32 (m, 13H), 7.28 – 7.23 (m, 2H), 5.07 (s, 2H), 3.77 (s, 3H), 3.56 (s, 4H), 3.13 – 3.00 (m, 4H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.4, 154.5, 138.6, 136.2, 128.7, 128.4, 128.3, 128.1, 127.9, 127.1, 124.1 (q, *J* = 287.2 Hz), 78.4, 77.6, 66.3, 63.6, (q, *J* = 26.4 Hz) 56.5, 53.1, 40.7, 23.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -72.44. Found: C, 66.99; H, 5.48; N, 5.39. Calcd for C₃₀H₂₉F₃N₂O₄: C, 66.90; H, 5.43; N, 5.20%.

Methyl 2-*tert*-butoxycarbonylamino-6-dibenzylamino-2-(trifluoromethyl)hex-4-ynoate (3'a)



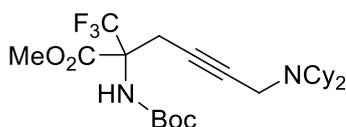
Yield: 99% as a thick light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 7.34 (d, *J* = 4.4 Hz, 8H), 7.28 – 7.24 (m, 2H), 3.77 (s, 3H), 3.57 (s, 4H), 3.09 – 2.93 (m, 4H), 1.38 (s, 9H). ¹³C NMR (151 MHz, CDCl₃) δ 166.8, 153.3, 139.0, 129.2, 128.4, 127.3, 123.7 (q, *J* = 288.4 Hz), 81.1, 78.7, 65.0 (q, *J* = 28.8 Hz), 57.6, 54.3, 41.4, 28.3. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -72.43. Found: C, 64.29; H, 6.29; N, 5.58. Calcd for C₂₇H₃₁F₃N₂O₄: C, 64.27; H, 6.19; N, 5.55 %.

Methyl 2-benzyloxycarbonylamino-6-dicyclohexylamino-2-(trifluoromethyl)hex-4-ynoate (3b)



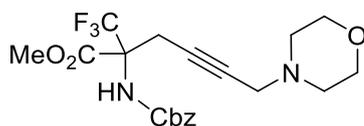
Yield: 72% as a thick light yellow oil. ^1H NMR (300 MHz, CDCl_3) δ 7.37 – 7.33 (m, 5H), 6.01 (s, 1H), 5.12 (s, 2H), 3.87 (s, 3H), 3.75 (d, $J = 16.6$ Hz, 1H), 3.39 (s, 2H), 3.07 (d, $J = 16.6$ Hz, 1H), 2.73 – 2.64 (m, 2H), 1.79 – 1.72 (m, 8H), 1.57 (d, $J = 11.7$ Hz, 2H), 1.25 – 1.18 (m, 8H), 1.14 – 1.01 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 166.4, 153.9, 135.9, 128.6, 128.4, 128.2, 123.5 (q, $J = 288.2$ Hz), 83.9, 74.5, 67.3, 65.0 (q, $J = 28.7$ Hz), 57.1, 54.3, 34.8, 31.1 (d, $J = 10.0$ Hz), 26.3, 26.1. ^{13}C NMR (151 MHz, CDCl_3) δ 166.4, 153.9, 135.9, 123.5 (q, $J = 288.2$ Hz), 83.9, 74.5, 67.3, 65.0 (q, $J = 28.7$ Hz), 57.1, 54.3, 34.8, 31.2, 31.1, 26.3. ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -72.56. HRMS (nESI) calcd for $\text{C}_{28}\text{H}_{38}\text{F}_3\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 523.2778, found: 523.2777.

Methyl 2-*tert*-butoxycarbonylamino-6-dicyclohexylamino-2-(trifluoromethyl)hex-4-ynoate (3'b)



Yield: 65% as a thick light yellow oil. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 7.99 (s, 1H), 3.70 (s, 3H), 2.94 – 2.80 (m, 2H), 2.64 (s, 2H), 1.68 (d, $J = 5.8$ Hz, 8H), 1.54 (d, $J = 11.6$ Hz, 2H), 1.37 (s, 11H), 1.22 – 1.18 (m, 8H), 1.08 – 1.04 (m, 2H). ^{13}C NMR (101 MHz, $\text{DMSO-}d_6$) δ 165.4, 153.6, 124.1 (q, $J = 286.9$ Hz), 83.5, 79.6, 74.2, 63.0 (q, $J = 25.8$ Hz), 56.4, 52.6, 34.5, 30.7, 27.8, 25.8, 25.5, 23.9. ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -72.56. Found: C, 60.27; H, 8.09; N, 5.05. Calcd for $\text{C}_{25}\text{H}_{39}\text{F}_3\text{N}_2\text{O}_4$: C, 61.46; H, 8.05; N, 5.73%.

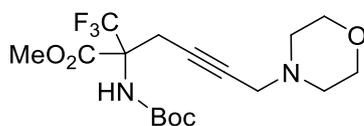
Methyl 2-benzyloxycarbonylamino-6-morpholino-2-(trifluoromethyl)hex-4-ynoate (3c)



Yield: 81% as a thick light yellow oil. ^1H NMR (400 MHz, C_6D_6) δ 7.14 (s, 1H), 7.09 – 7.01 (m, 4H), 6.26 (s, 1H), 5.05 (d, $J = 12.3$ Hz, 1H), 4.97 (d, $J = 12.2$ Hz, 1H), 4.06 (d, $J = 15.9$ Hz, 1H), 3.55 – 3.52 (m, 4H), 3.27 (s, 3H), 3.11 (d, $J = 16.7$ Hz, 1H), 2.94 (s, 2H), 2.24 – 2.21 (m, 4H). ^{13}C NMR (101 MHz, C_6D_6) δ 166.6, 154.1, 136.5, 128.7, 128.6, 124.3 (q, $J = 288.2$ Hz),

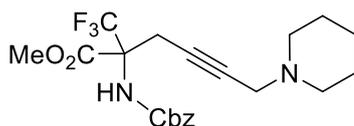
79.5, 77.7, 67.4, 66.9, 65.6 (q, $J = 28.7$ Hz), 53.9, 52.1, 47.4, 30.2. ^{19}F NMR (282 MHz, CDCl_3) δ -74.19. HRMS (nESI) calcd for $\text{C}_{20}\text{H}_{24}\text{F}_3\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 429.1632, found: 429.1637.

Methyl 2-*tert*-butoxycarbonylamino-6-morpholino-2-(trifluoromethyl)hex-4-ynoate (3'c)



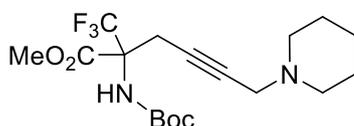
Yield: 90% as a thick light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.68 (s, 1H), 3.87 (s, 3H), 3.72 – 3.70 (m, 4H), 3.66 (s, 1H), 3.25 (s, 2H), 3.09 (d, $J = 16.9$ Hz, 1H), 2.51 – 2.48 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.6, 153.3, 123.5 (q, $J = 288.1$ Hz), 81.0, 78.4, 77.9, 66.8, 64.7 (q, $J = 28.4$ Hz), 54.3, 52.1, 47.5, 28.3. ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -72.52. Found: C, 51.59; H, 6.74; N, 6.87. Calcd for $\text{C}_{17}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_5$: C, 51.77; H, 6.39; N, 7.10%.

Methyl 2-benzyloxycarbonylamino-6-piperidino-2-(trifluoromethyl)hex-4-ynoate (3d)



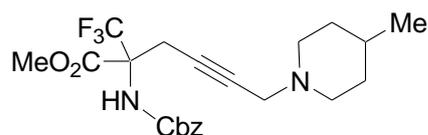
Yield: 67% as a thick light yellow oil. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.60 (s, 1H), 7.40 – 7.31 (m, 5H), 5.05 (s, 2H), 3.72 (s, 3H), 3.17 (s, 2H), 3.03 – 2.90 (m, 2H), 2.34 (s, 4H), 1.50 – 1.44 (m, 4H), 1.36-1.30 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.4, 154.0, 135.9, 128.7, 128.5, 128.3, 123.4 (q, $J = 287.8$ Hz), 67.4, 67.0 (q, $J = 22.9$ Hz), 54.5, 52.6, 47.4, 29.8, 25.4, 23.6, 21.3. ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -72.53. HRMS (nESI) calcd for $\text{C}_{21}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 427.1839, found : 427.1840.

Methyl 2-*tert*-butoxycarbonylamino-6-piperidino-2-(trifluoromethyl)hex-4-ynoate (3'd)



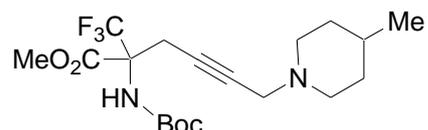
Yield: 69% as a thick light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.70 (s, 1H), 3.86 (s, 3H), 3.69 – 3.65 (m, 1H), 3.24 (s, 2H), 3.07 (d, $J = 16.7$ Hz, 1H), 2.44 (s, 4H), 1.61 – 1.56 (m, 4H), 1.43 (s, 11H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.7, 153.3, 123.6 (q, $J = 287.9$ Hz), 80.9, 79.3, 64.8 (q, $J = 28.8$ Hz), 60.5, 54.2, 53.0, 47.8, 28.3, 25.9, 23.9. ^{19}F NMR (376 MHz, CDCl_3) δ -74.27. Found: C, 54.67; H, 7.23; N, 6.73. Calcd for $\text{C}_{18}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_4$: C, 55.09; H, 6.94; N, 7.14%.

Methyl 2-benzyloxycarbonylamino-6-(4-methylpiperidin-1-yl)-2-(trifluoromethyl)-hex-4-ynoate (3e)



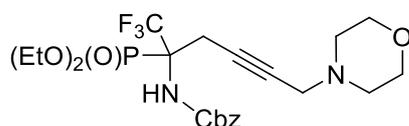
Yield: 70% as a thick light yellow oil. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.58 (s, 1H), 7.40 – 7.31 (m, 5H), 5.05 (s, 2H), 3.71 (s, 3H), 3.19 (s, 2H), 2.97 (q, $J = 17.7$ Hz, 2H), 2.66 (d, $J = 10.3$ Hz, 2H), 2.05 (t, $J = 11.0$ Hz, 2H), 1.55 (d, $J = 11.9$ Hz, 2H), 1.23 (s, 1H), 1.13 – 1.03 (m, 2H), 0.86 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 166.6, 154.1, 136.5, 128.7, 128.6, 128.5, 124.4 (q, $J = 287.9$ Hz), 80.2, 77.2, 67.4, 65.6 (q, $J = 29.4$ Hz), 53.8, 52.5, 47.5, 34.5, 30.6, 30.2, 22.0. ^{19}F NMR (282 MHz, C_6D_6) δ -73.61. HRMS (nESI) calcd for $\text{C}_{22}\text{H}_{28}\text{F}_3\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 441.1996, found : 441.1997.

Methyl 2-*tert*-butoxycarbonylamino-6-(4-methylpiperidin-1-yl)-2-(trifluoromethyl)-hex-4-ynoate (3'e)



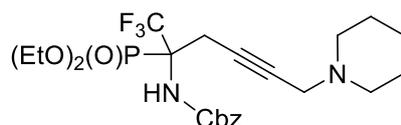
Yield: 75% as a thick light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 5.68 (s, 1H), 3.88 (s, 3H), 3.69 (s, 1H), 3.32 (s, 2H), 3.10 (d, $J = 16.6$ Hz, 1H), 2.81 (s, 2H), 2.22 (s, 2H), 1.66 (d, $J = 11.8$ Hz, 2H), 1.45 (s, 9H), 1.35 (s, 3H), 0.93 (d, $J = 5.1$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.7, 153.3, 123.6 (q, $J = 287.9$ Hz), 80.9, 79.4, 64.8 (q, $J = 28.5$ Hz), 54.2, 52.5, 47.5, 34.4, 30.4, 29.8, 28.3, 21.9, 21.5. ^{19}F NMR (376 MHz, CDCl_3) δ -74.06. Found: C, 56.04; H, 7.65; N, 6.65. Calcd for $\text{C}_{19}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_4$: C, 56.15; H, 7.19; N, 6.89%.

Benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(morpholino)hex-4-yn-2-yl]carbamate (5a)



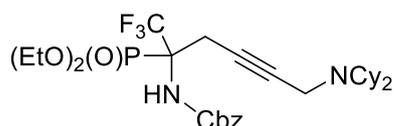
Yield: 83% as a thick light yellow oil. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.03 (d, $J = 6.7$ Hz, 1H), 7.40 – 7.30 (m, 5H), 5.06 (s, 2H), 4.19 – 4.04 (m, 4H), 3.57 – 3.51 (m, 4H), 3.28 – 3.24 (m, 1H), 3.21 (s, 2H), 3.06 (t, $J = 15.8$ Hz, 1H), 2.43 – 2.41 (m, 4H), 1.23 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 154.5 (d, $J = 10.1$ Hz), 136.6, 128.7, 128.6, 125.5 (qd, $J = 287.5$, 4.0 Hz), 79.5, 78.7 – 78.4 (m), 67.4, 67.0, 64.5 (d, $J = 6.9$ Hz), 64.2 (d, $J = 6.8$ Hz), 61.5 (dq, $J = 153.3$, 29.0 Hz), 52.4, 47.7, 30.2, 16.3. ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) δ -68.45. ^{31}P NMR (162 MHz, $\text{DMSO-}d_6$) δ 14.99. HRMS (nESI) calcd for $\text{C}_{22}\text{H}_{31}\text{F}_3\text{N}_2\text{O}_6\text{P}$ $[\text{M}+\text{H}]^+$: 507.1866, found: 507.1872.

Benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(piperidin-1-yl)hex-4-yn-2-yl]carbamate (5b)



Yield: 76% as a thick light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.34 (s, 5H), 5.66 (d, $J = 9.8$ Hz, 1H), 5.09 (s, 2H), 4.30 – 4.15 (m, 4H), 3.41 – 3.25 (m, 4H), 2.51 (s, 4H), 1.62 – 1.57 (m, 4H), 1.39 (s, 2H), 1.33 (t, $J = 7.0$ Hz, 6H). ^{13}C NMR (101 MHz, C_6D_6) δ 154.4, 136.6, 128.7, 128.6, 128.5, 125.5 (qd, $J = 288.9, 4.3$ Hz), 80.4, 78.0 (d, $J = 5.9$ Hz), 67.4, 64.5 (d, $J = 6.9$ Hz), 64.1 (d, $J = 6.9$ Hz), 61.9 (dq, $J = 150.6, 23.4$ Hz), 53.3, 48.2, 30.2, 26.2, 24.3, 16.3. ^{19}F NMR (376 MHz, CDCl_3) δ -70.69. ^{31}P NMR (162 MHz, CDCl_3) δ 15.48. HRMS (nESI) calcd for $\text{C}_{23}\text{H}_{33}\text{F}_3\text{N}_2\text{O}_5\text{P}$ $[\text{M}+\text{H}]^+$: 505.2074, found: 505.2076.

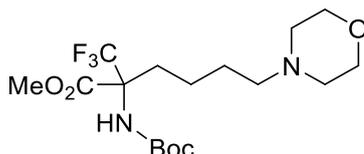
Benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(dicyclohexylamino)hex-4-yn-2-yl]carbamate (5c)



Yield: 67% as a thick light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.26 (s, 5H), 5.57 (d, $J = 8.0$ Hz, 1H), 5.02 (s, 2H), 4.21-4.09 (m, 4H), 3.36 (s, 2H), 3.17 (dd, $J = 12.9, 3.9$ Hz, 2H), 2.64 (t, $J = 8.7$ Hz, 2H), 1.71 (d, $J = 9.2$ Hz, 4H), 1.63 (d, $J = 9.7$ Hz, 4H), 1.48 (d, $J = 12.0$ Hz, 2H), 1.25 (t, $J = 6.8$ Hz, 6H), 1.17 – 1.09 (m, 8H), 1.02 – 0.96 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 154.0 (d, $J = 7.7$ Hz), 135.9, 128.5, 128.3, 128.2, 125.2 (qd, $J = 288.8, 6.1$ Hz), 83.7, 75.2, 67.3, 64.6 (d, $J = 6.9$ Hz), 64.1 (d, $J = 7.3$ Hz), (dq, $J = 154.9, 28.5$ Hz), 57.1, 35.0, 31.1 (d, $J = 7.3$ Hz), 26.3, 26.1, 21.9, 16.4 (d, $J = 5.8$ Hz). ^{19}F NMR (376 MHz, CDCl_3) δ -70.59. ^{31}P NMR (162 MHz, $\text{DMSO}-d_6$) δ 15.18. HRMS (nESI) calcd for $\text{C}_{30}\text{H}_{45}\text{F}_3\text{N}_2\text{O}_5\text{P}$ $[\text{M}+\text{H}]^+$: 601.3013, found: 601.3007.

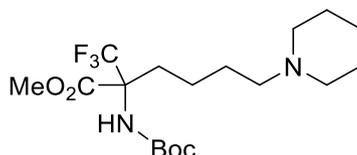
Typical procedure for hydrogenation. To a solution of the corresponding unsaturated amine **3'c,d** (0.46 mmol) in methanol (10 ml), 10% Pd/C (2.7 mg, 0.228 μmol) was added, and a slow stream of hydrogen was bubbled through the mixture at room temperature. When TLC and ^{19}F NMR indicated no starting material (~ 24 h), the mixture was filtered and the solvent was evaporated to dryness leading to the product which was pure enough.

Methyl 2-*tert*-butoxycarbonylamino-6-morpholino-2-(trifluoromethyl)hexanoate (6a)



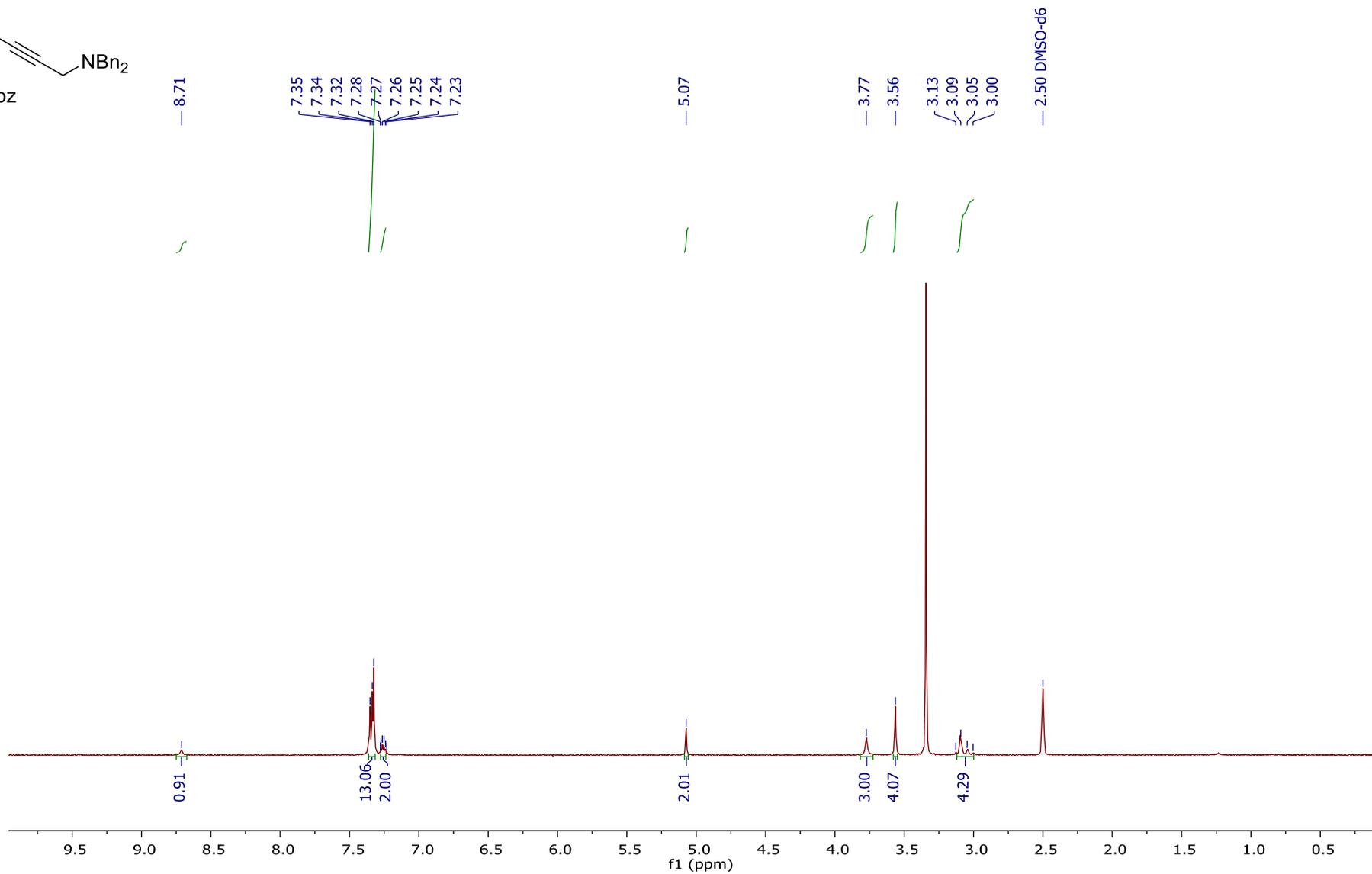
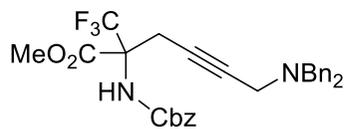
Yield: 75% as a thick colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.64 (s, 1H), 3.85 (s, 3H), 3.78 (s, 4H), 3.48 (s, 1H), 2.68 (s, 1H), 2.53 (s, 3H), 2.42 (s, 2H), 2.11 – 2.03 (m, 1H), 1.59 (s, 2H), 1.44 (s, 9H), 1.40 – 1.32 (m, 1H), 1.20 – 1.11 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 167.7, 153.3, 124.2 (q, $J = 287.4$ Hz), 80.6, 66.8, 65.9 (q, $J = 28.1$ Hz), 58.3, 53.9, 53.7, 28.7, 28.3, 25.8, 21.2. ^{19}F NMR (376 MHz, CDCl_3) δ -74.57. HRMS (nESI) calcd for $\text{C}_{17}\text{H}_{30}\text{F}_3\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 399.2101, found: 399.2104.

Methyl 2-*tert*-butoxycarbonylamino-6-piperidino-2-(trifluoromethyl)hexanoate (6b)

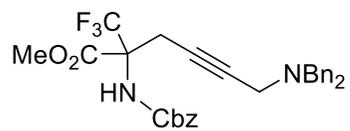


Yield: 71% as a thick colorless oil. ^1H NMR (300 MHz, C_6D_6) δ 5.59 (s, 1H), 3.75 (s, 3H), 3.38 (s, 2H), 2.54 – 2.40 (m, 4H), 2.37 – 2.32 (m, 2H), 2.01 – 1.91 (m, 1H), 1.61 (s, 4H), 1.38 (s, 2H), 1.34 (s, 9H), 1.28 – 1.17 (m, 2H), 1.09 – 1.03 (m, 1H). ^{19}F NMR (282 MHz, C_6D_6) δ -74.45. ^{13}C NMR (101 MHz, CDCl_3) δ 167.6, 153.4, 128.5, 125.6 (q, $J = 288.1$ Hz), 122.8, 119.9, 80.5, 65.7 (q, $J = 28.4$ Hz), 58.4, 54.4, 53.7, 28.2, 25.8, 25.4, 24.2, 21.3. HRMS (nESI) calcd for $\text{C}_{18}\text{H}_{32}\text{F}_3\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 397.2309, found: 397.2311.

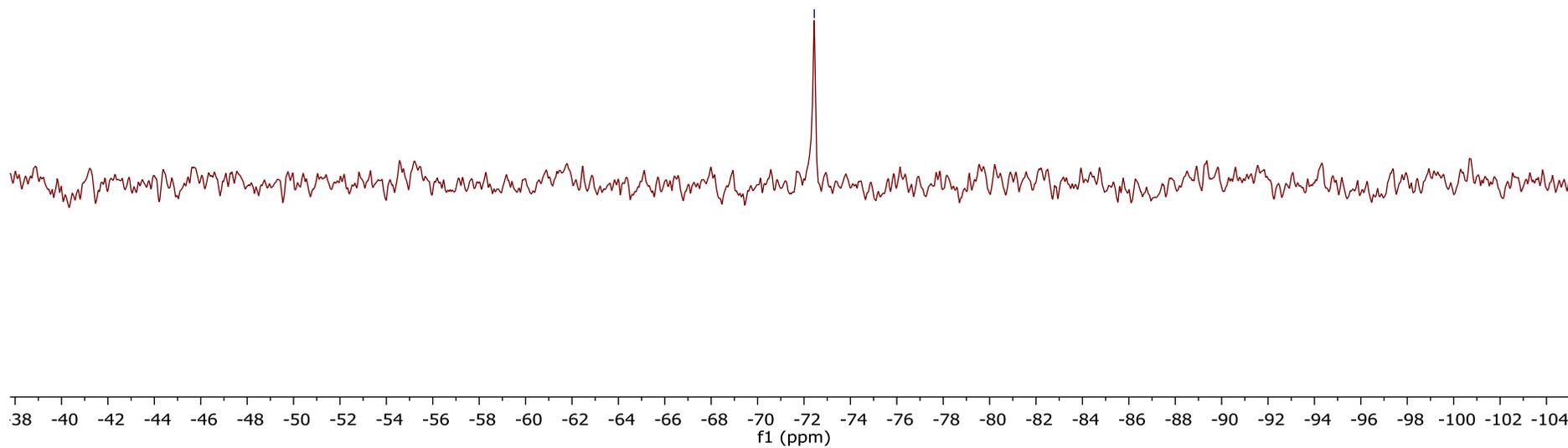
NMR spectra



¹H NMR (400 MHz, DMSO-d₆) of methyl 2-benzyloxycarbonylamino-6-dibenzylamino-2-(trifluoromethyl)hex-4-ynoate (3a)

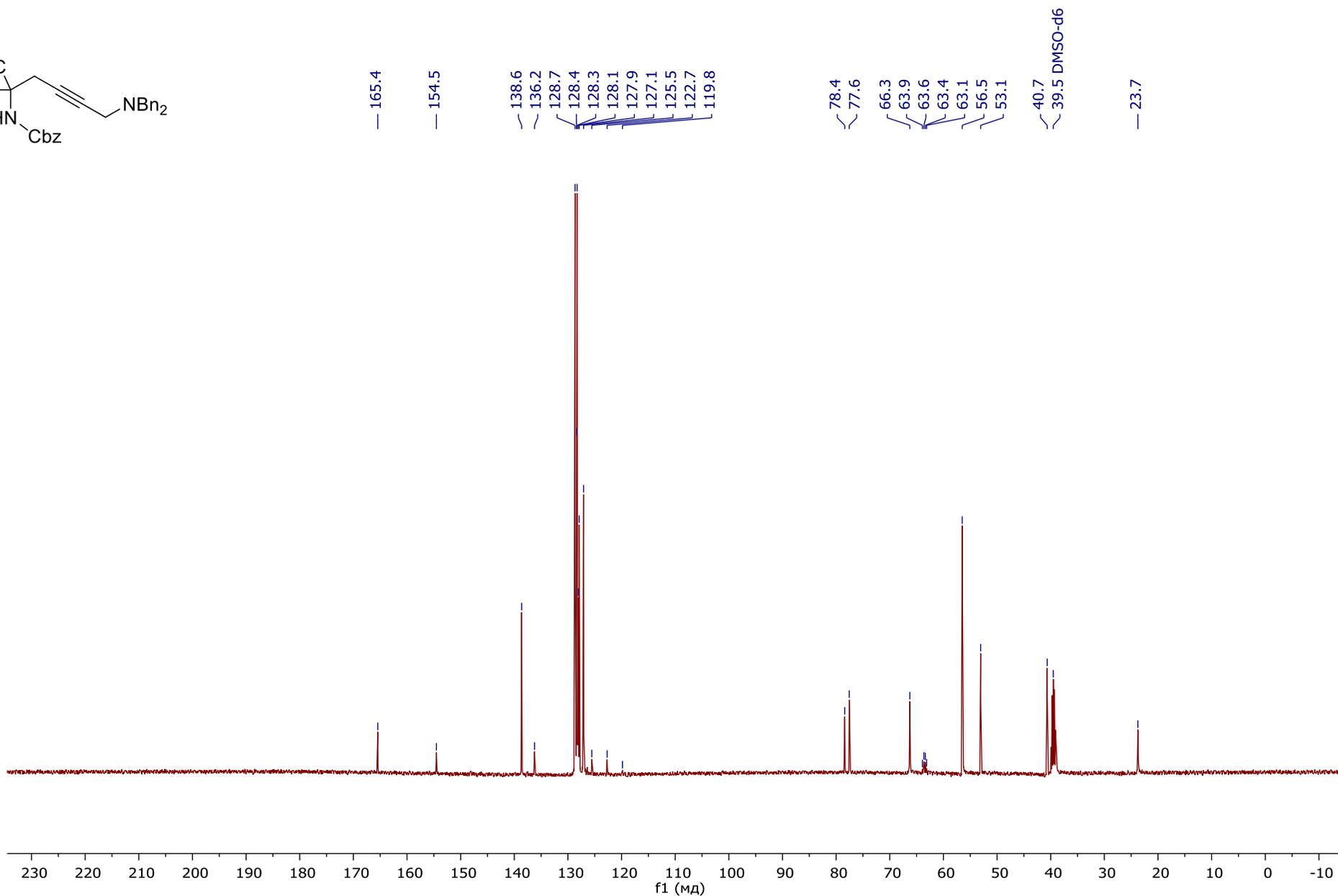
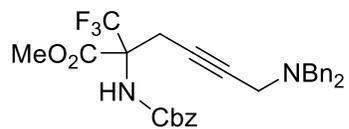


-72.44

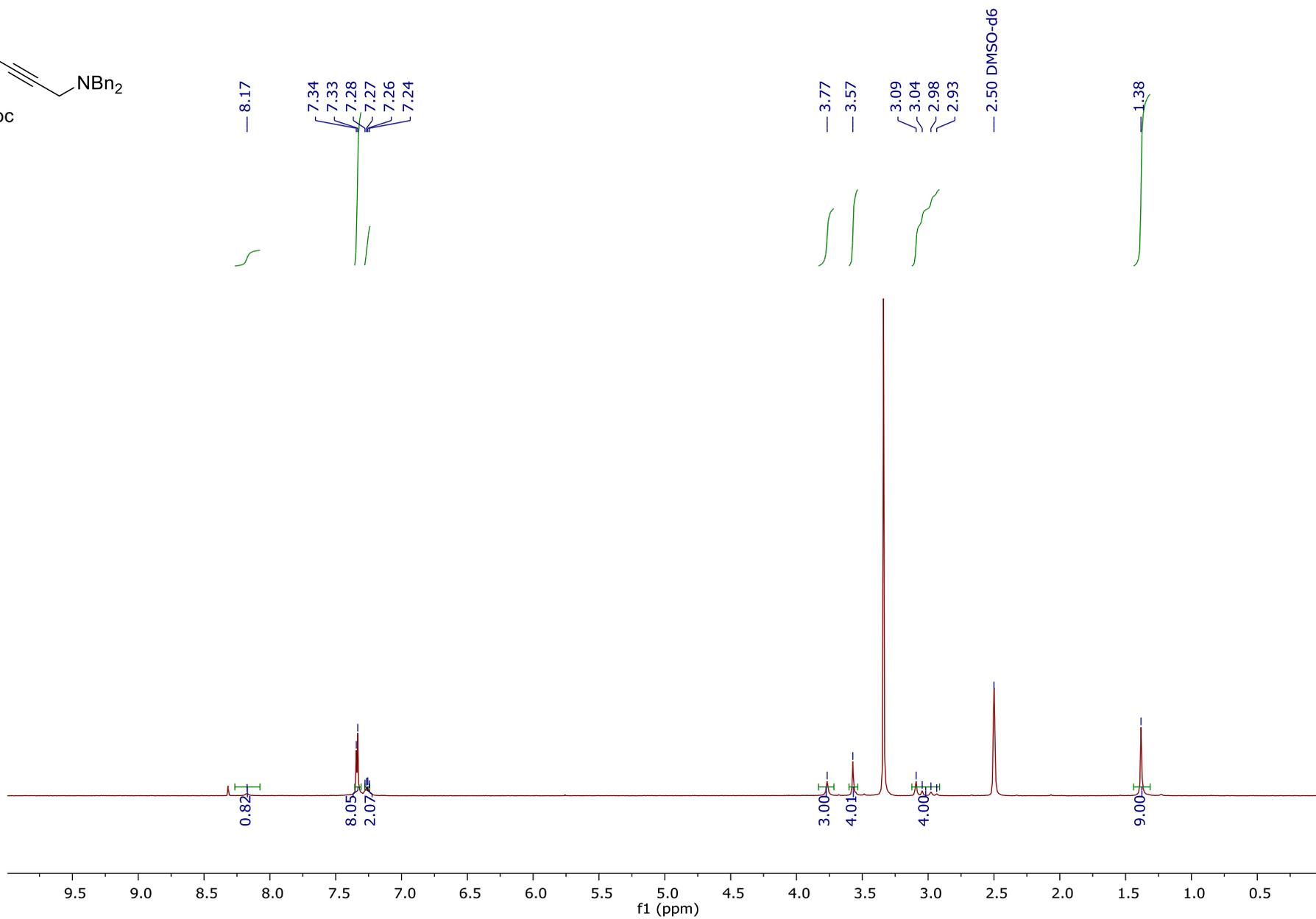
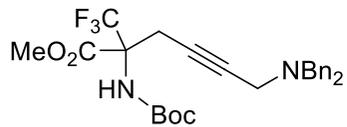


¹⁹F NMR (376 MHz, DMSO-*d*₆) of methyl 2-benzyloxycarbonylamino-6-dibenzylamino-2-(trifluoromethyl)hex-4-ynoate (3a)

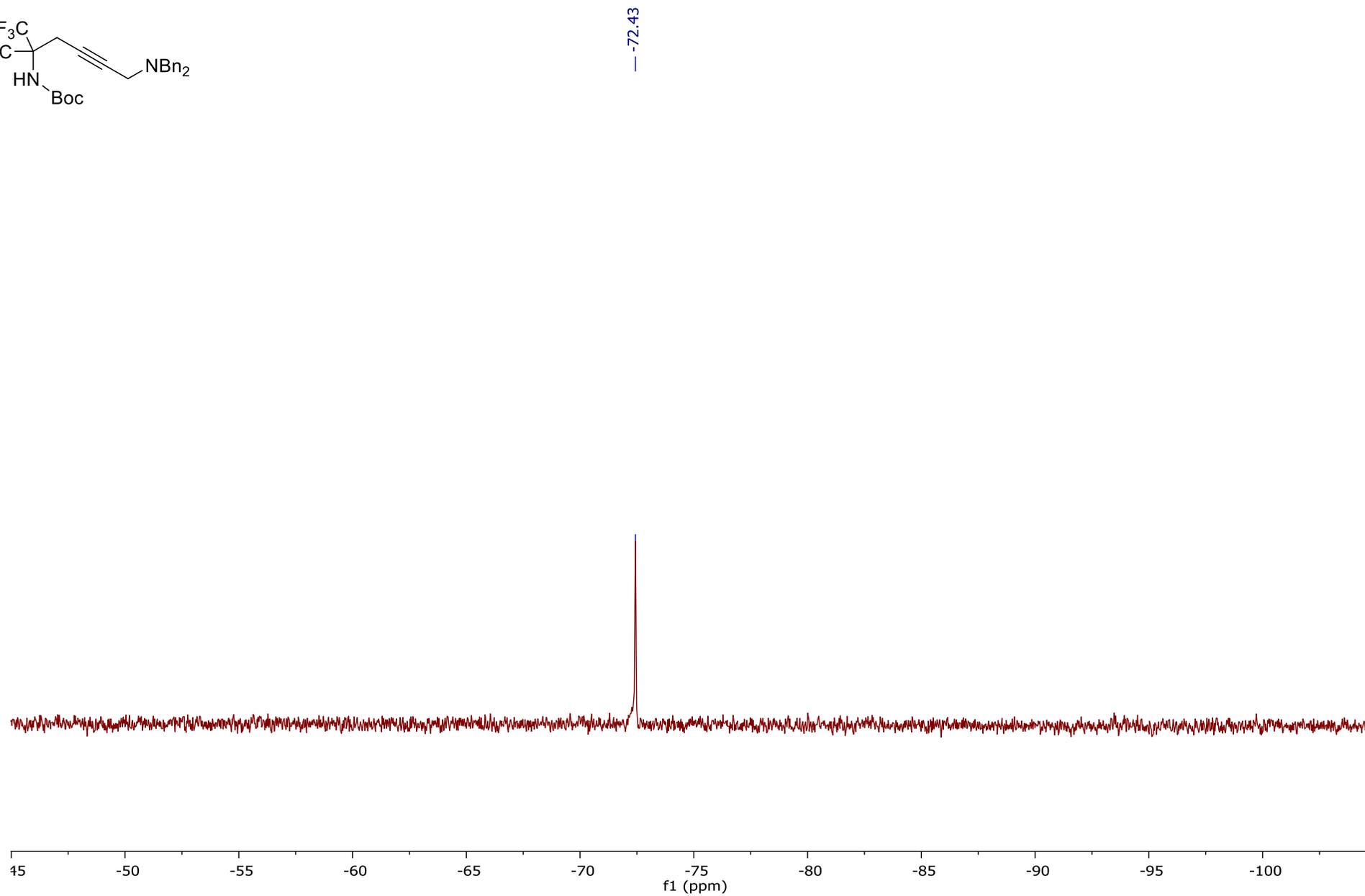
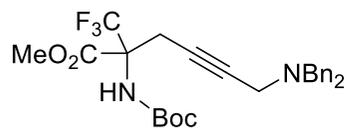
S9



¹³C NMR (101 MHz, DMSO-*d*₆) of methyl 2-benzyloxycarbonylamino-6-dibenzylamino-2-(trifluoromethyl)hex-4-ynoate (3a)

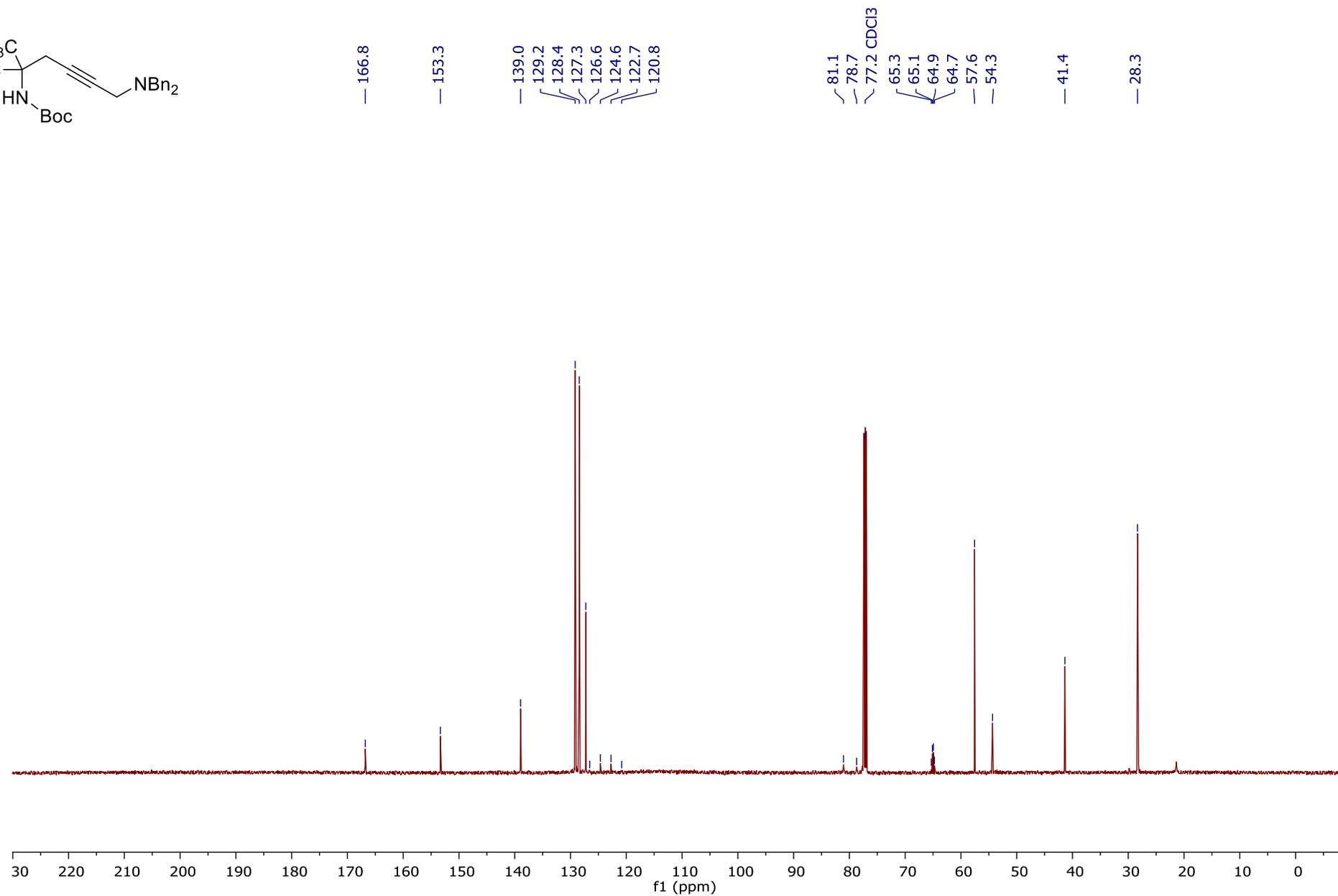
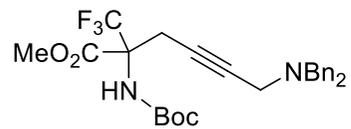


¹H NMR (400 MHz, DMSO-*d*₆) of methyl 2-*tert*-butoxycarbonylamino-6-dibenzylamino-2-(trifluoromethyl)hex-4-ynoate (3'a)

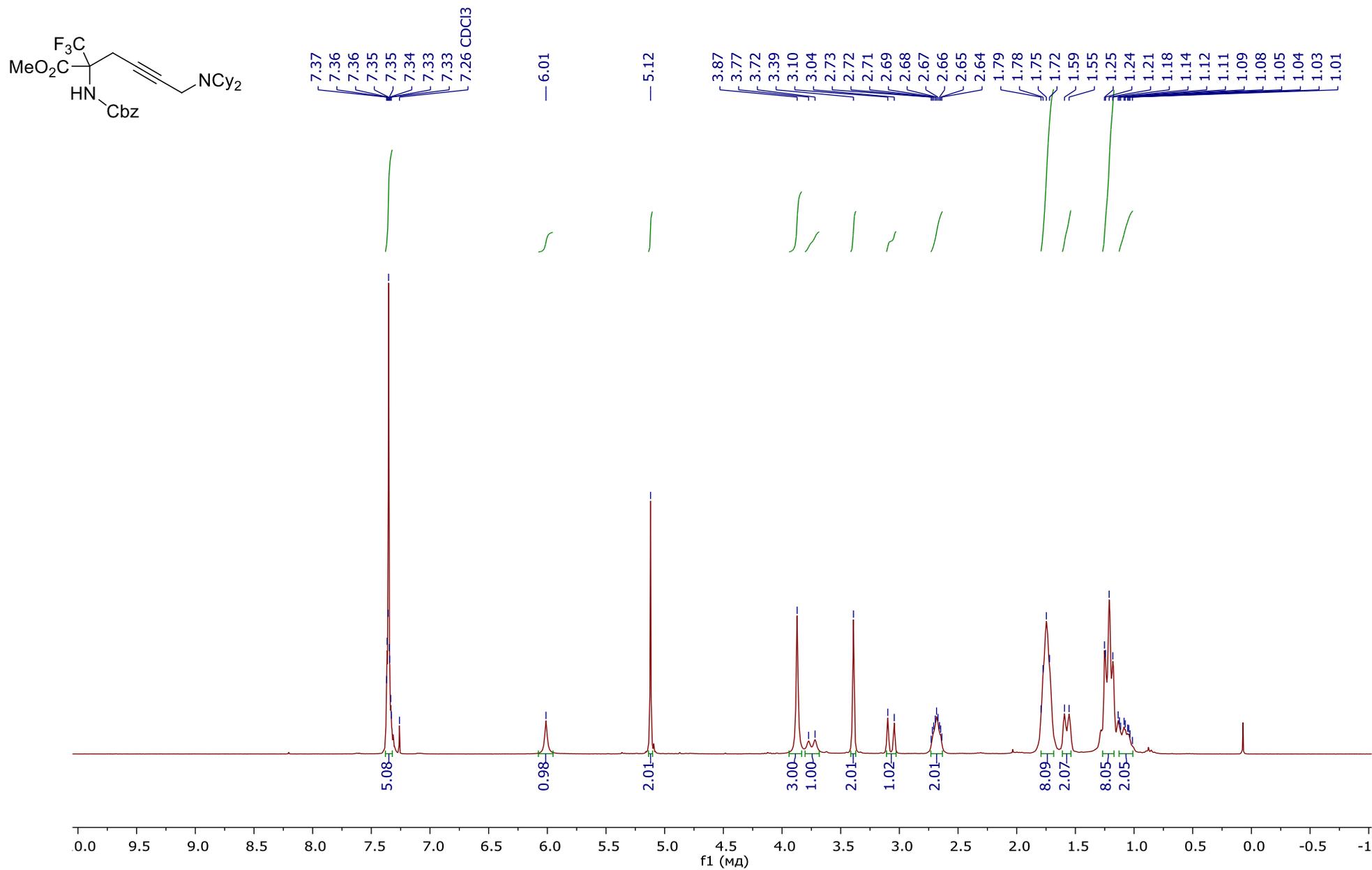


¹⁹F NMR (376 MHz, DMSO-*d*₆) of methyl 2-*tert*-butoxycarbonylamino-6-dibenzylamino-2-(trifluoromethyl)hex-4-ynoate (3'a)

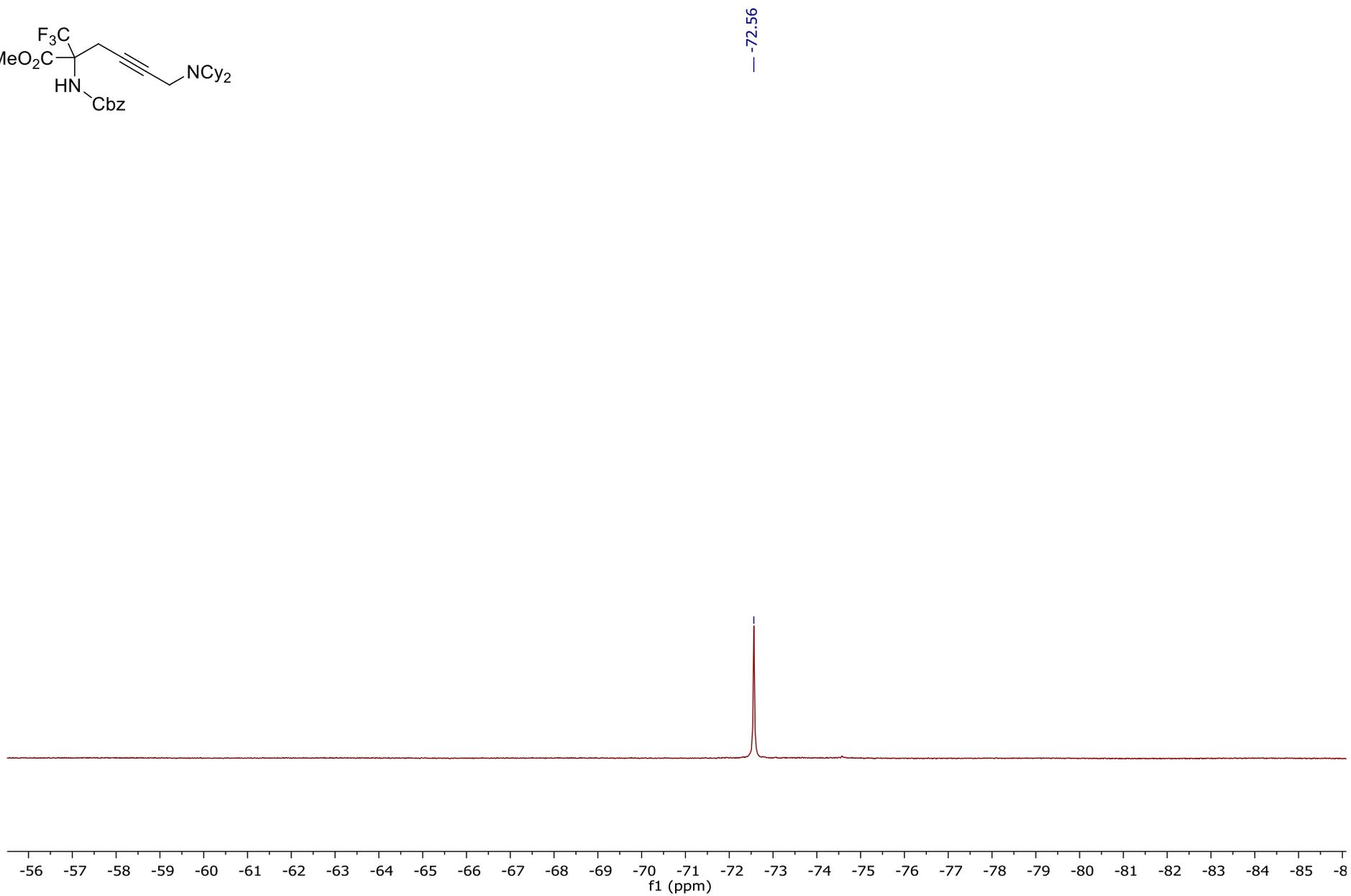
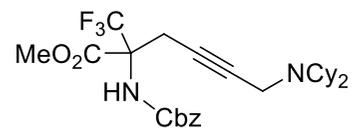
S12



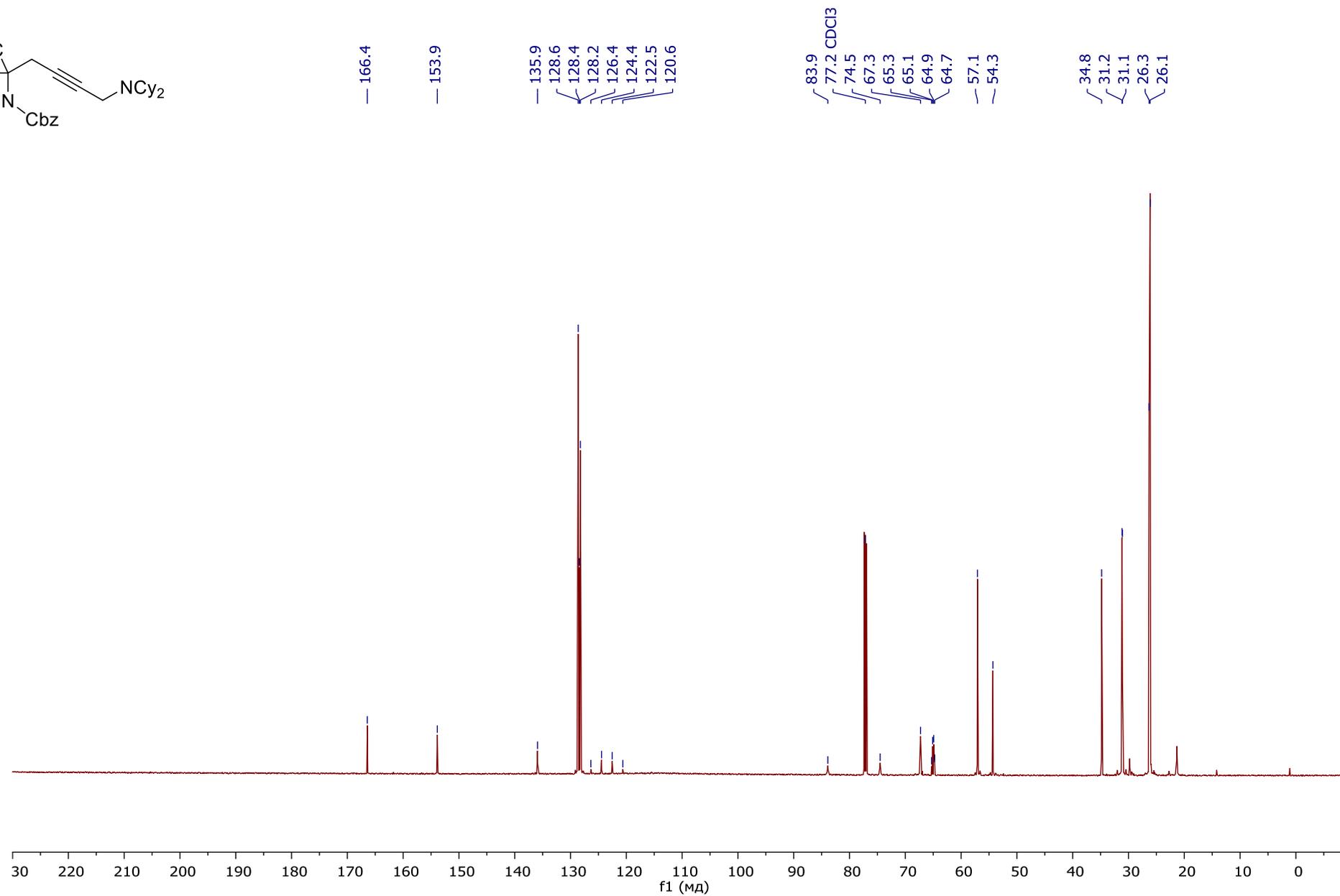
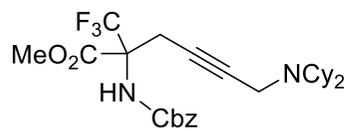
^{13}C NMR (151 MHz, CDCl_3) of methyl 2-*tert*-butoxycarbonylamino-6-dibenzylamino-2-(trifluoromethyl)hex-4-ynoate (3'a)



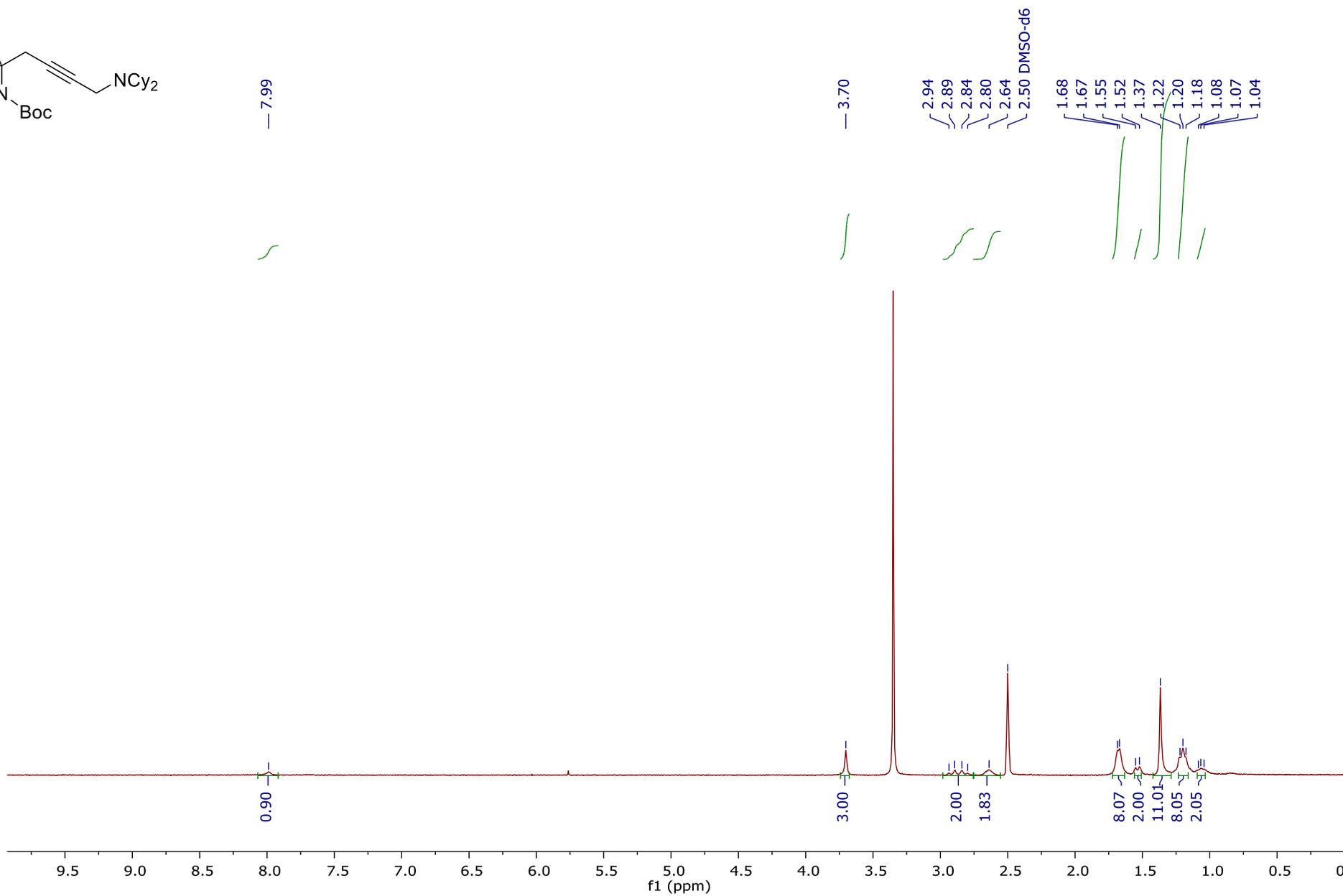
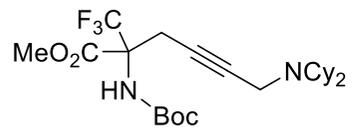
¹H NMR (300 MHz, CDCl₃) of methyl 2-benzyloxycarbonylamino-6-dicyclohexylamino-2-(trifluoromethyl)hex-4-ynoate (3b)



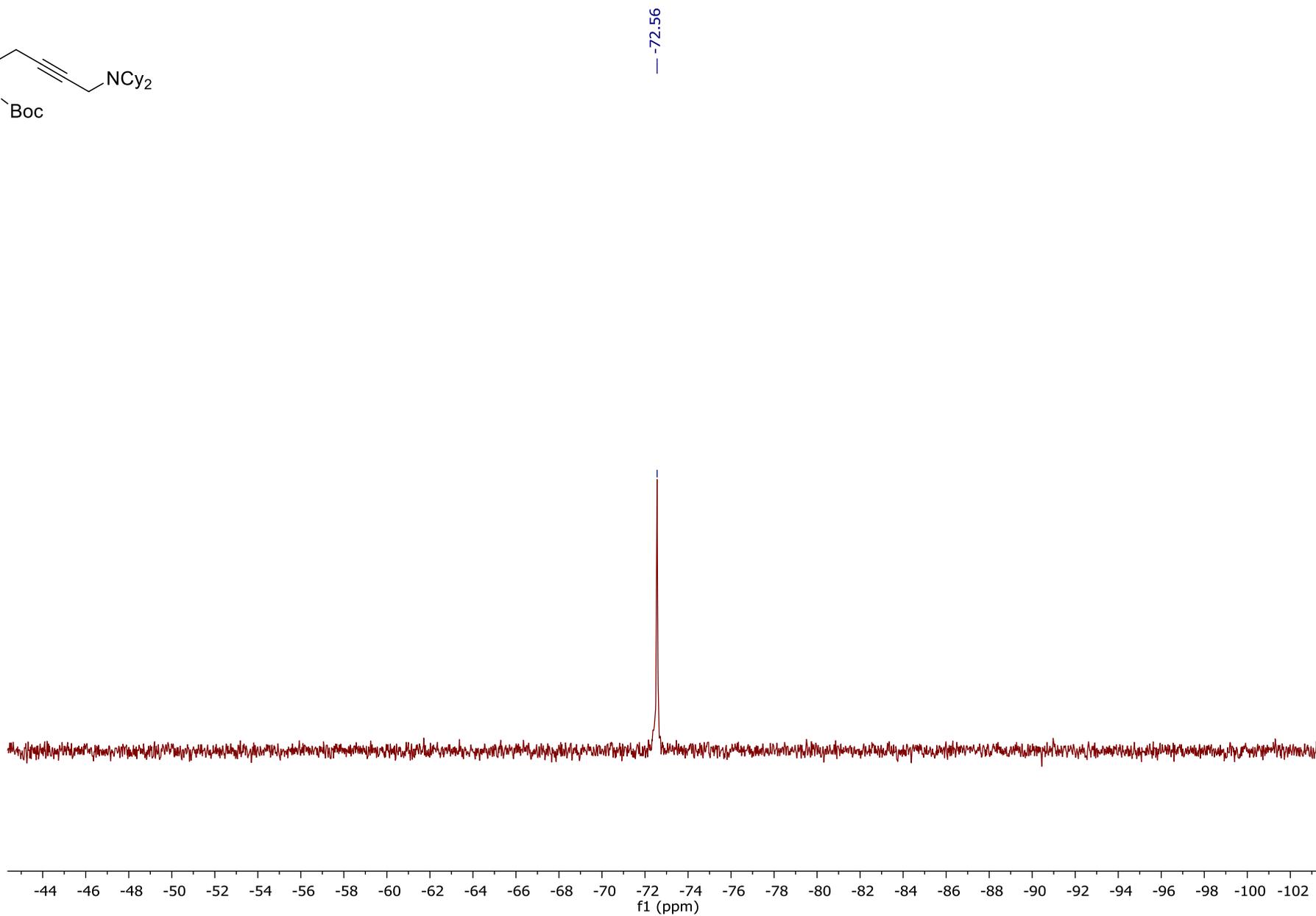
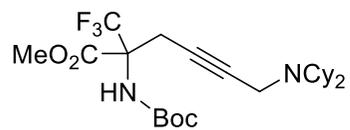
¹⁹F NMR (376 MHz, DMSO-*d*₆) of methyl 2-benzoyloxycarbonylamino-6-dicyclohexylamino-2-(trifluoromethyl)hex-4-ynoate (3b)



¹³C NMR (151 MHz, CDCl₃) of methyl 2-benzyloxycarbonylamino-6-dicyclohexylamino-2-(trifluoromethyl)hex-4-ynoate (3b)

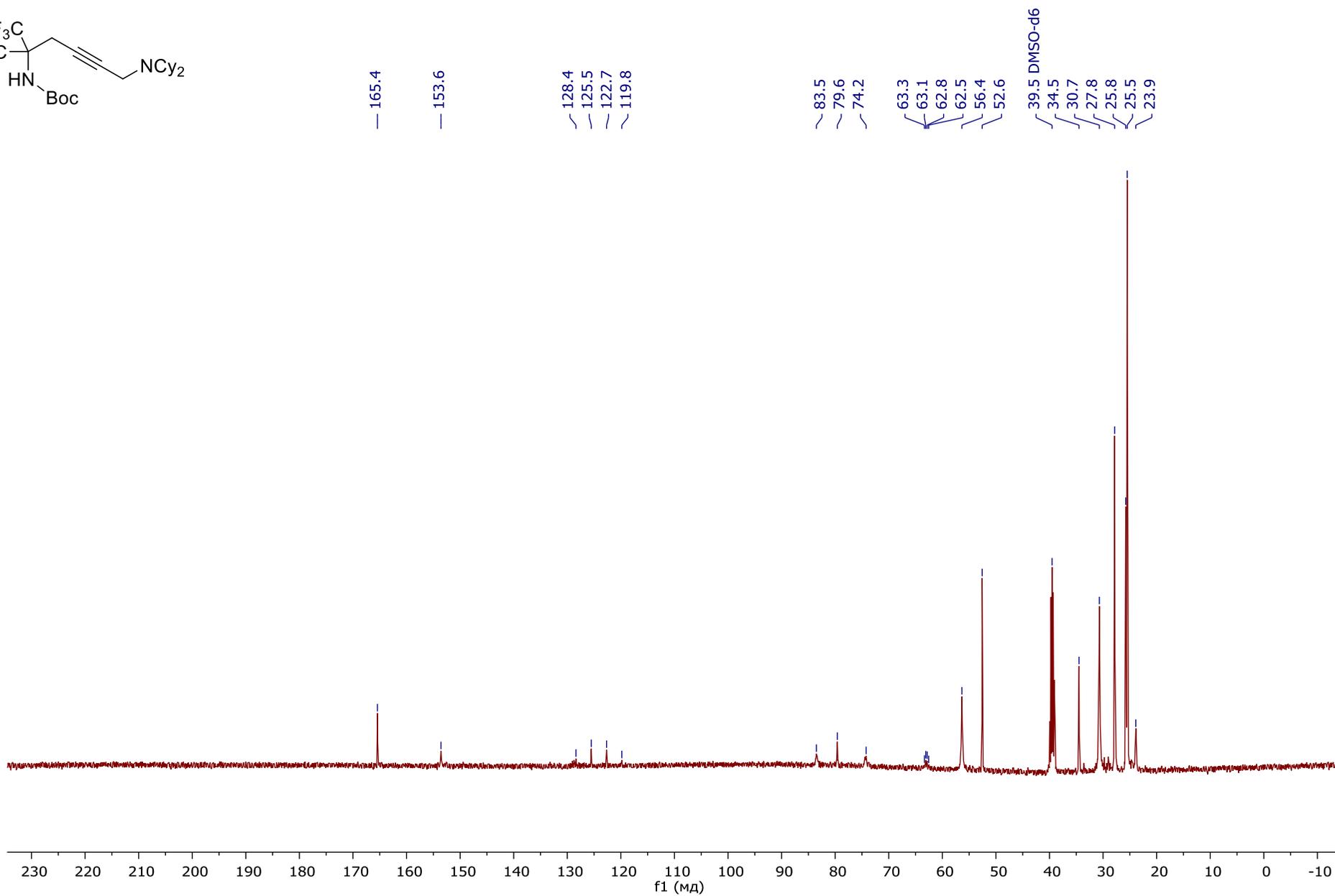
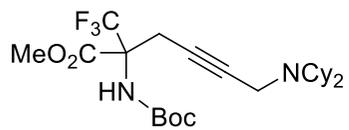


¹H NMR (400 MHz, DMSO-*d*₆) of methyl 2-*tert*-butoxycarbonylamino-6-dicyclohexylamino-2-(trifluoromethyl)hex-4-ynoate (3'b)

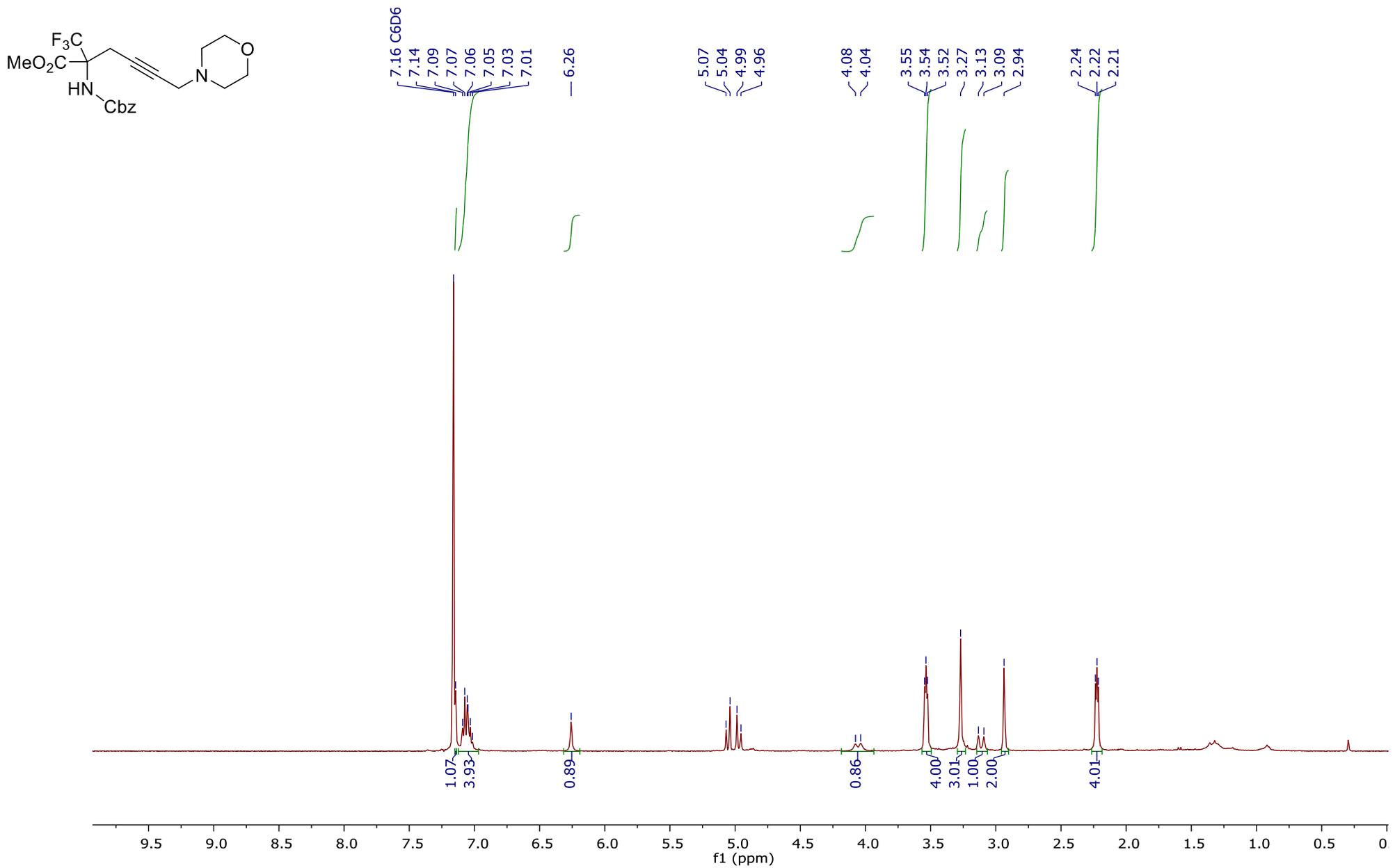


¹⁹F NMR (376 MHz, DMSO-*d*₆) of methyl 2-*tert*-butoxycarbonylamino-6-dicyclohexylamino-2-(trifluoromethyl)hex-4-ynoate (3'b)

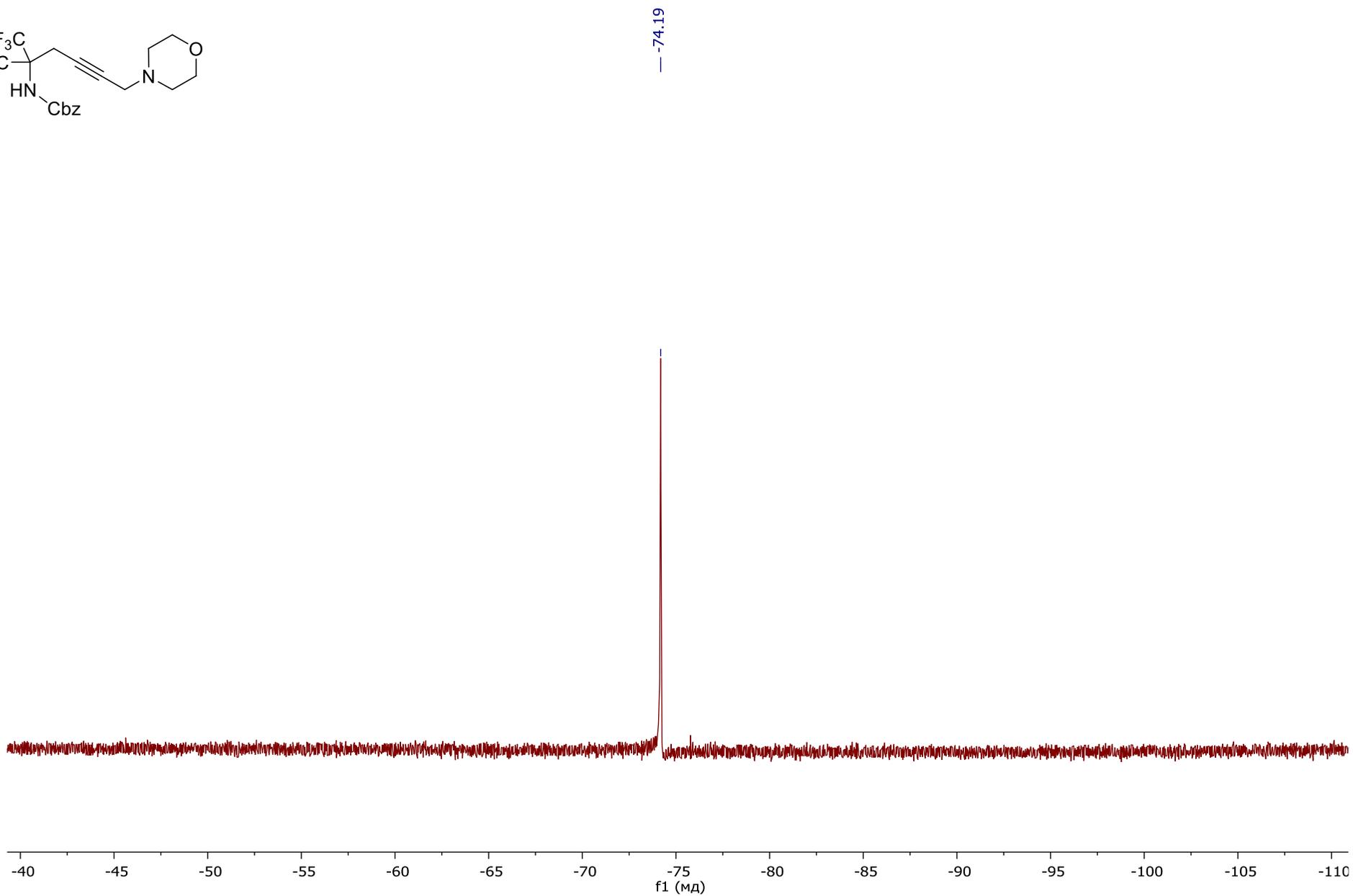
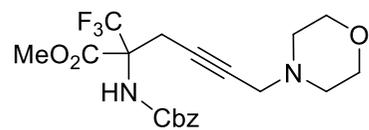
S18



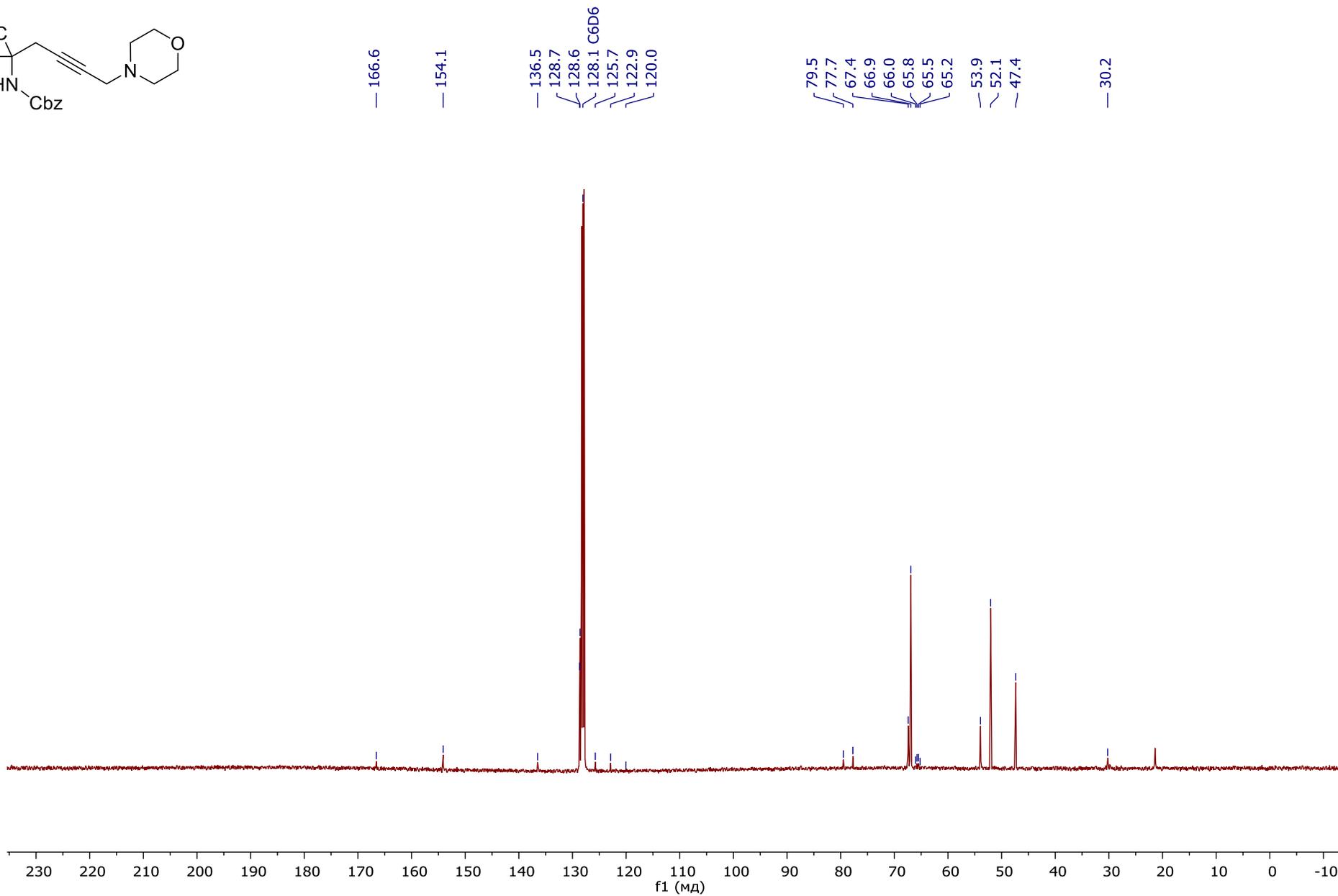
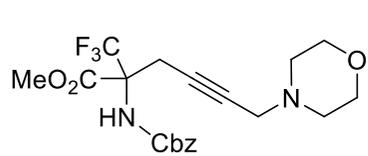
¹³C NMR (101 MHz, DMSO-*d*₆) of methyl 2-*tert*-butoxycarbonylamino-6-dicyclohexylamino-2-(trifluoromethyl)hex-4-ynoate (3'b)



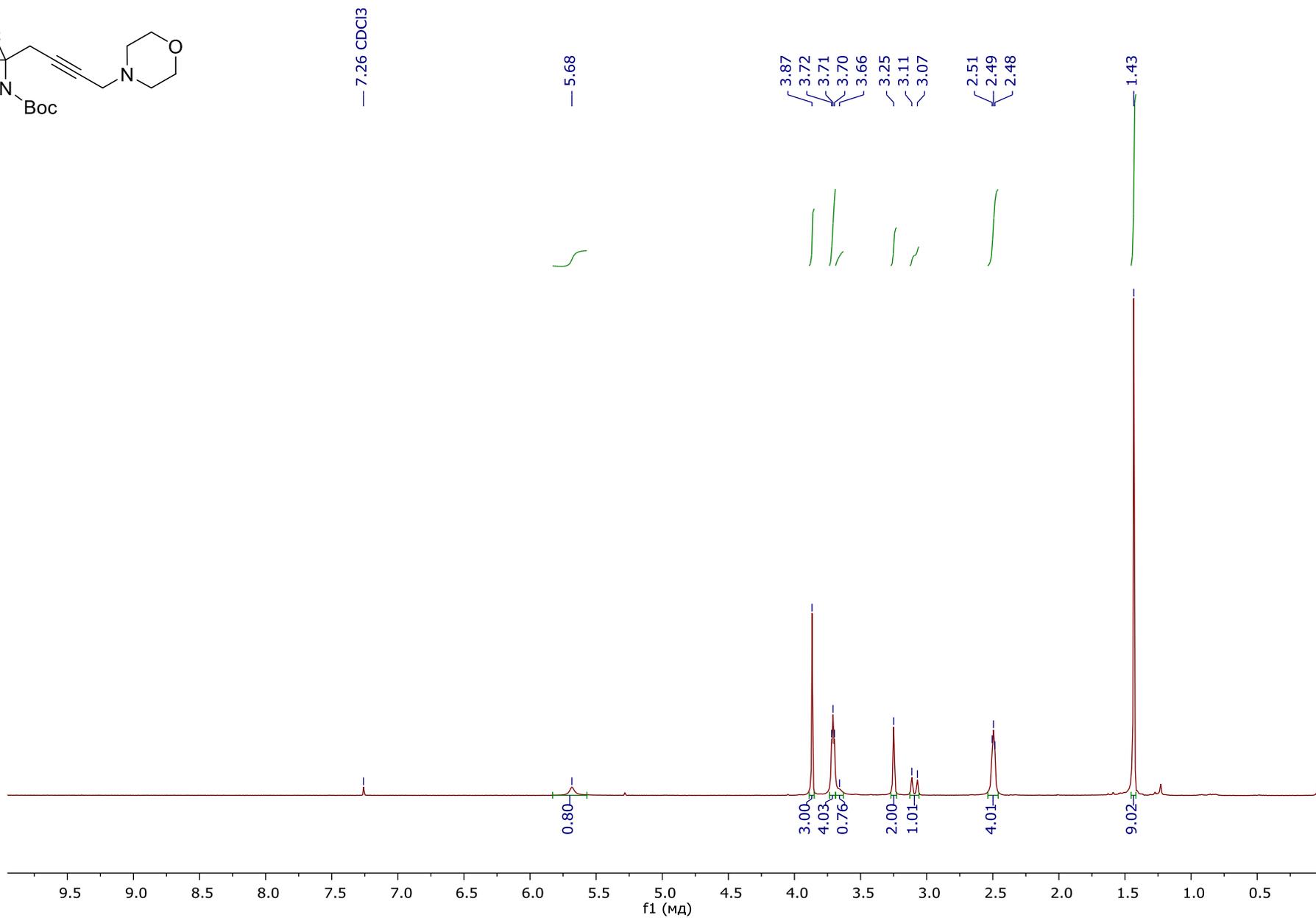
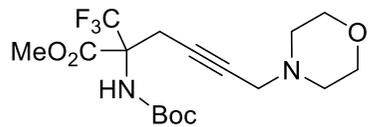
¹H NMR (400 MHz, C₆D₆) of methyl 2-benzyloxycarbonylamino-6-morpholino-2-(trifluoromethyl)hex-4-ynoate (3c)



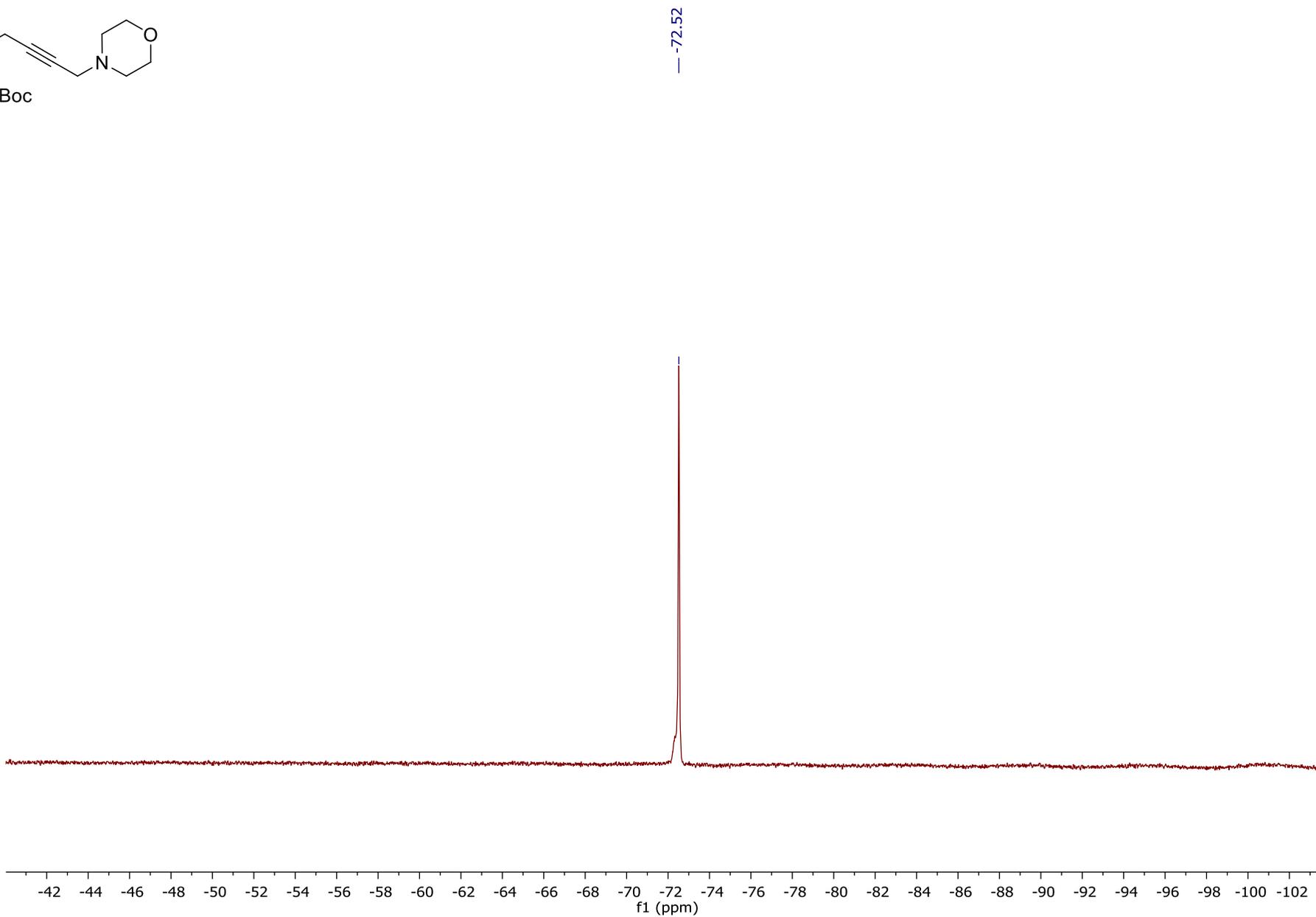
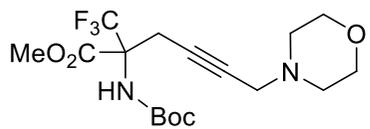
¹⁹F NMR (282 MHz, Chloroform-*d*) of methyl 2-benzyloxycarbonylamino-6-morpholino-2-(trifluoromethyl)hex-4-ynoate (3c)



¹³C NMR (101 MHz, C₆D₆) of methyl 2-benzyloxycarbonylamino-6-morpholino-2-(trifluoromethyl)hex-4-ynoate (3c)

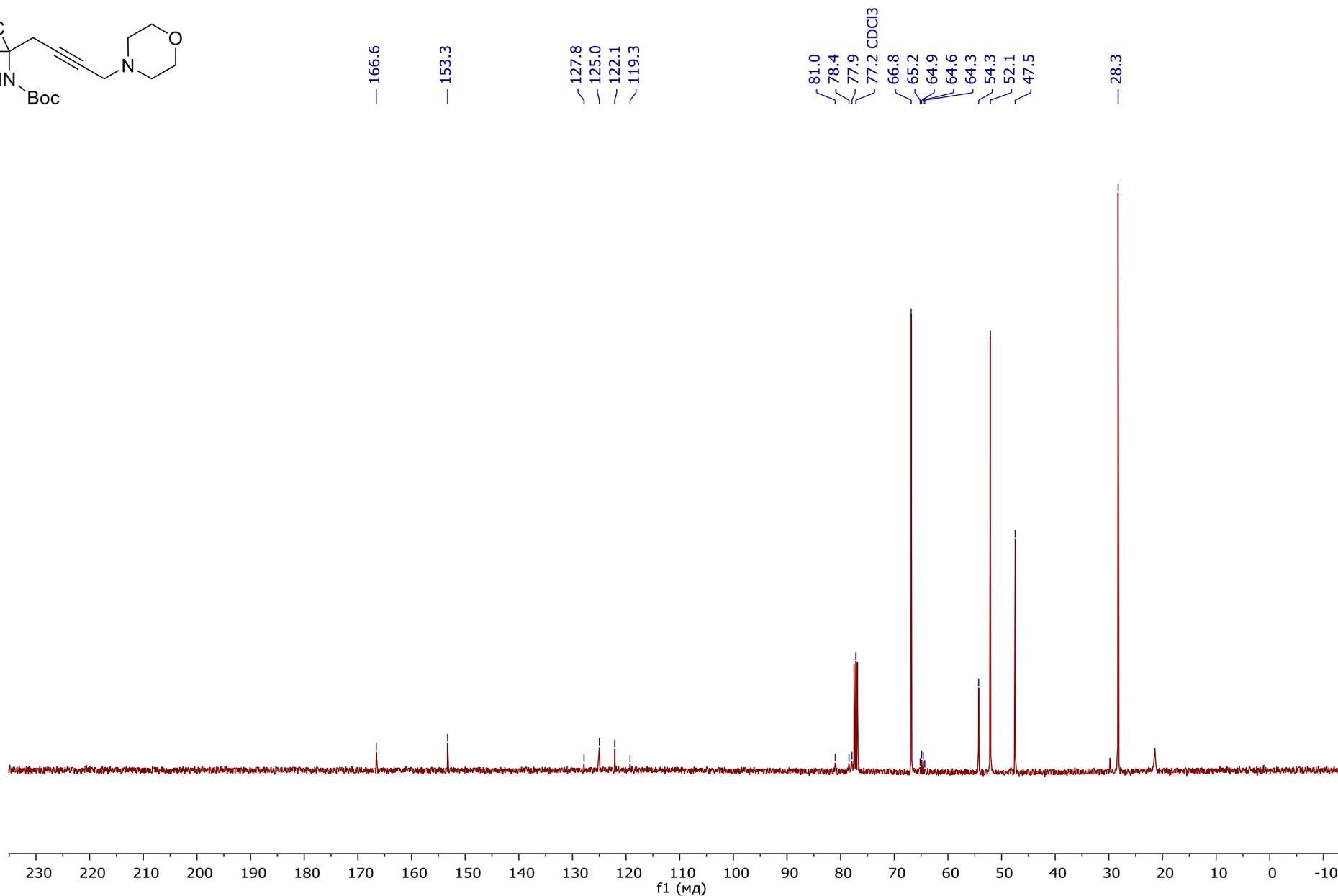
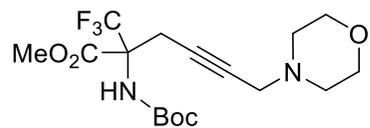


¹H NMR (400 MHz, CDCl₃) of methyl 2-*tert*-butoxycarbonylamino-6-morpholino-2-(trifluoromethyl)hex-4-ynoate (3'*c*)

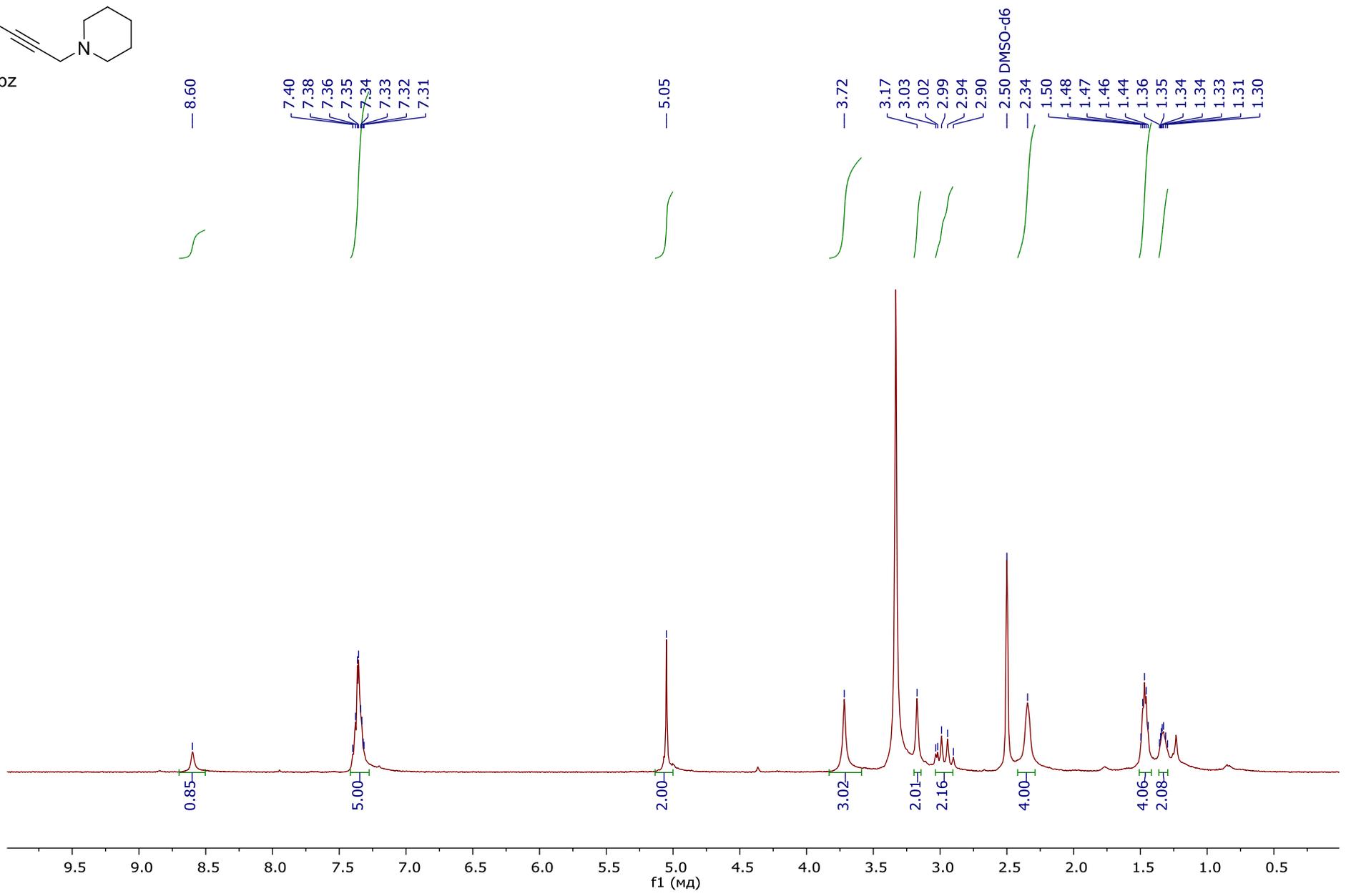
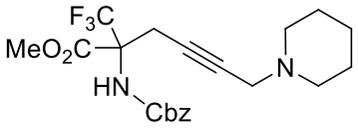


¹⁹F NMR (376 MHz, DMSO-*d*₆) of methyl 2-tert-butoxycarbonylamino-6-morpholino-2-(trifluoromethyl)hex-4-ynoate (3'c)

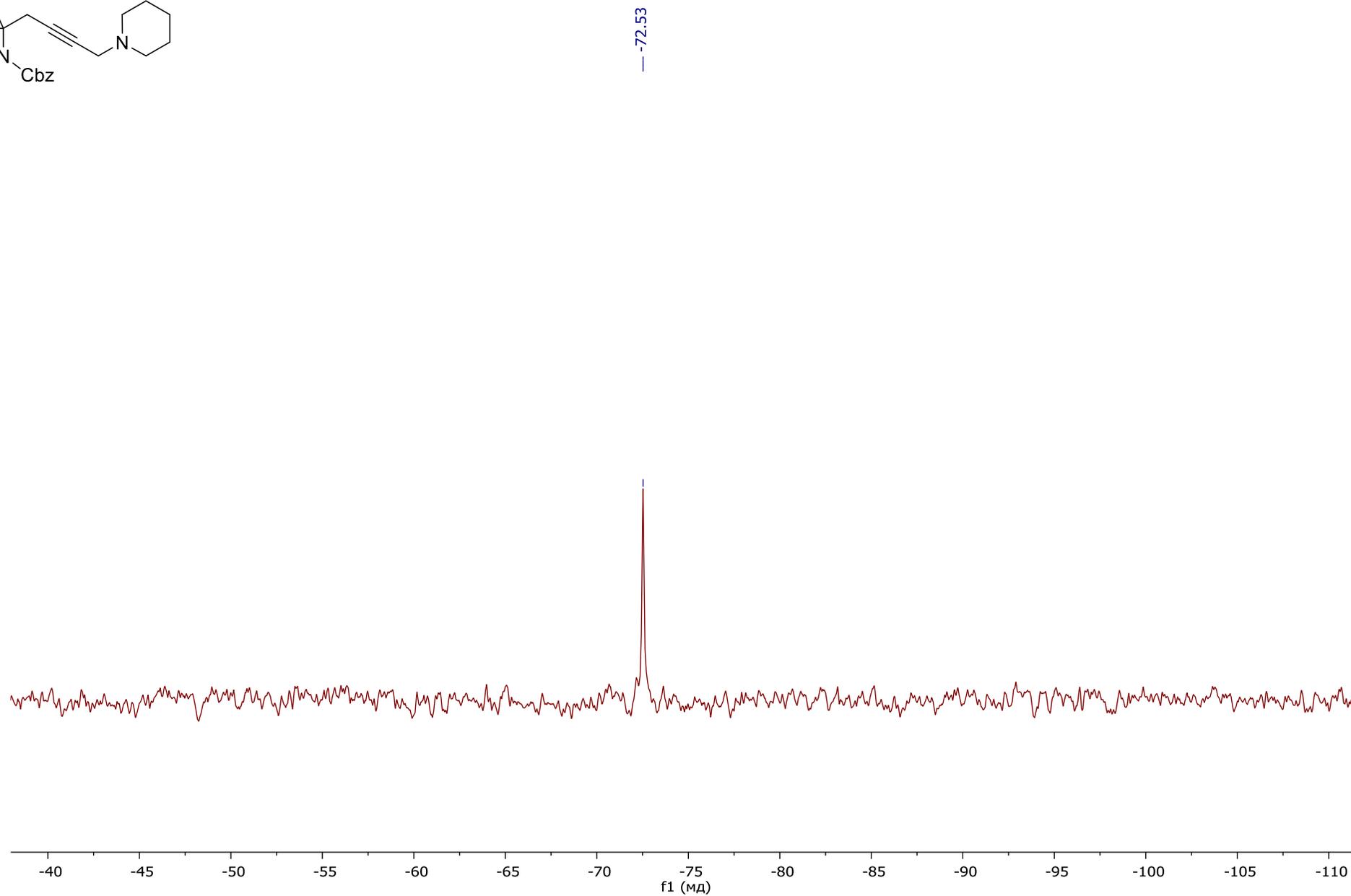
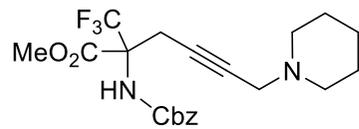
S24



^{13}C NMR (101 MHz, CDCl_3) of methyl 2-*tert*-butoxycarbonylamino-6-morpholino-2-(trifluoromethyl)hex-4-ynoate (3'*c*)

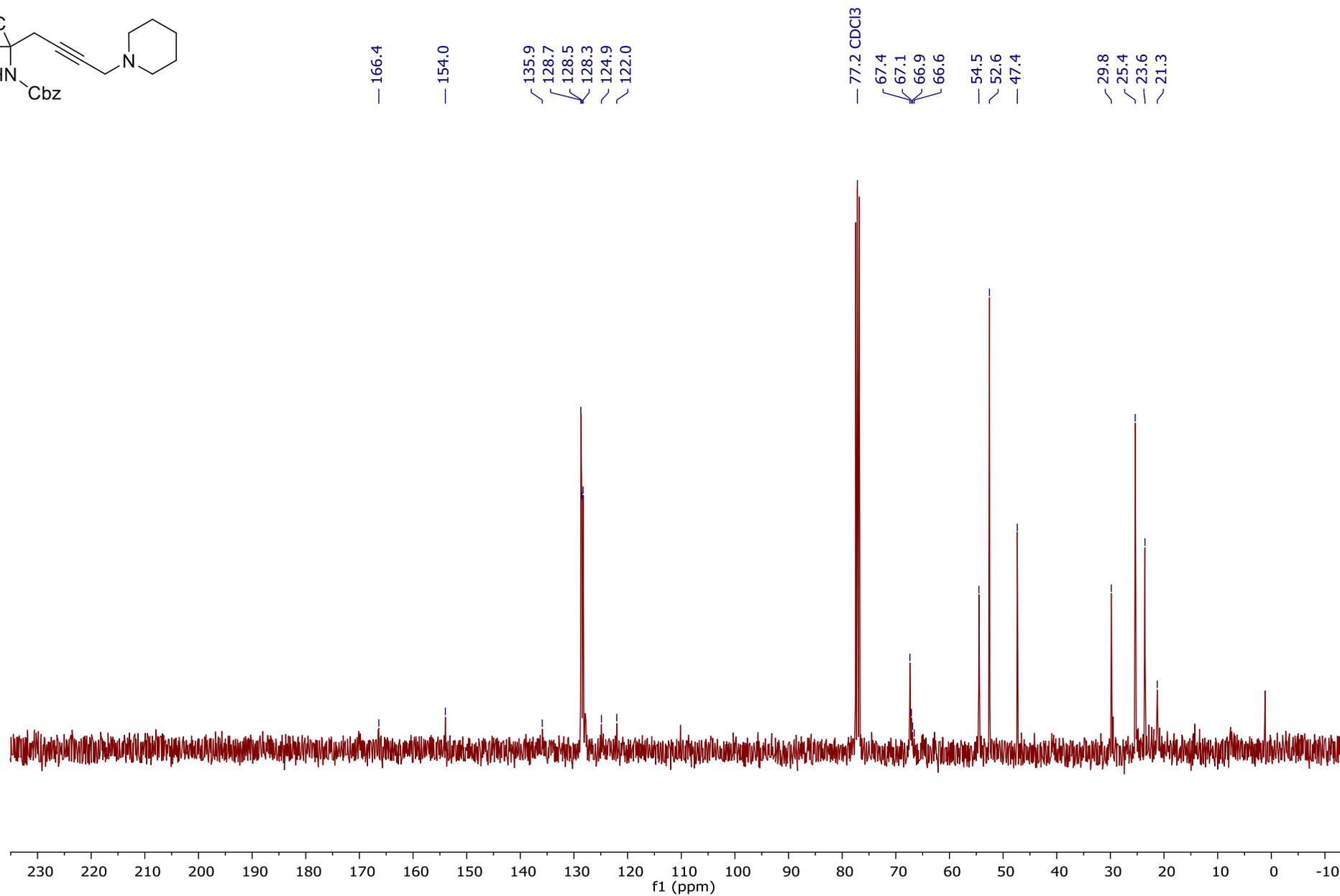
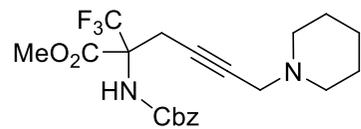


¹H NMR (400 MHz, DMSO-*d*₆) of methyl 2-benzyloxycarbonylamino-6-piperidino-2-(trifluoromethyl)hex-4-ynoate (3d)

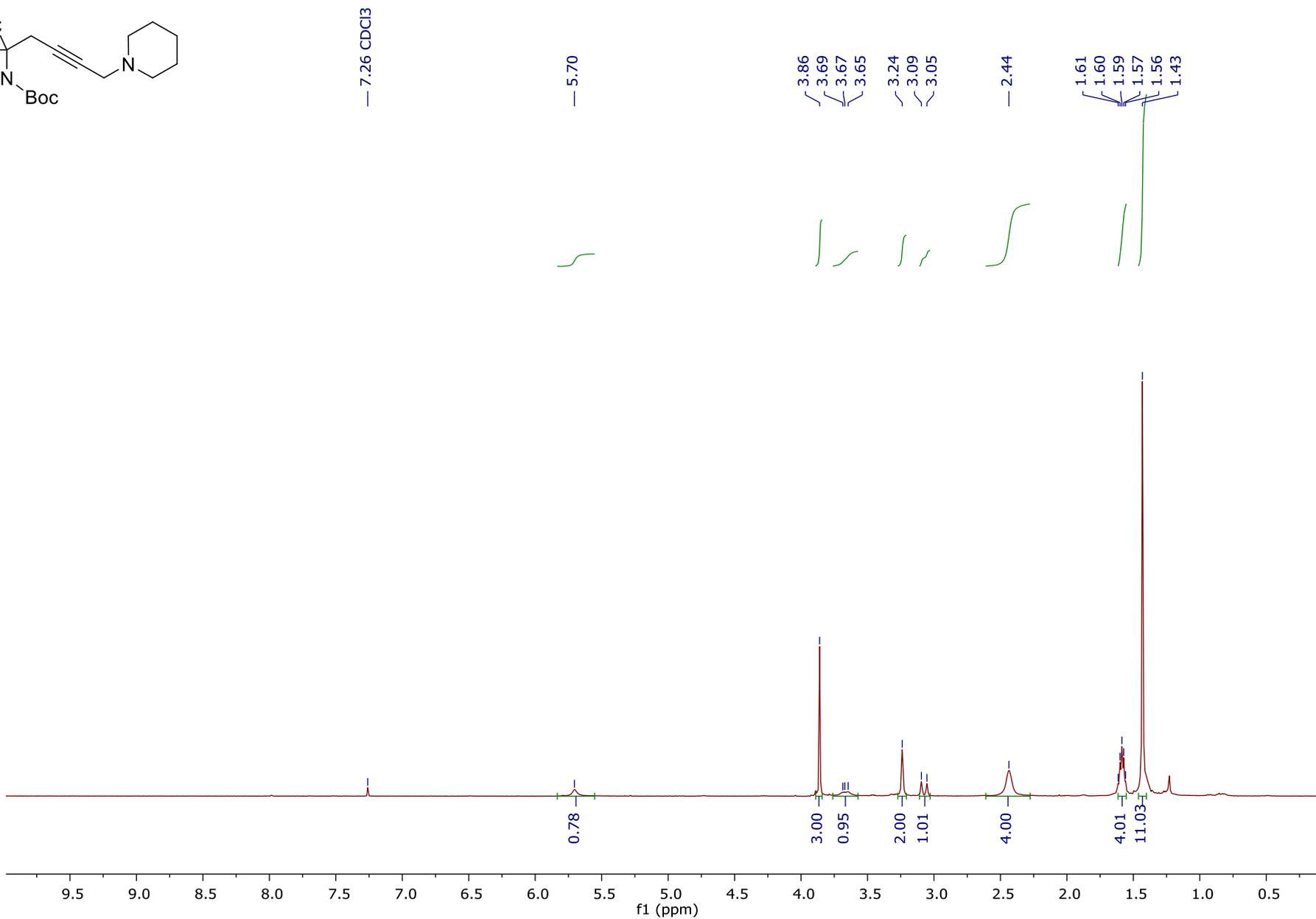
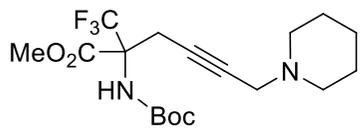


¹⁹F NMR (376 MHz, DMSO-*d*₆) of methyl 2-benzyloxycarbonylamino-6-piperidino-2-(trifluoromethyl)hex-4-ynoate (3d)

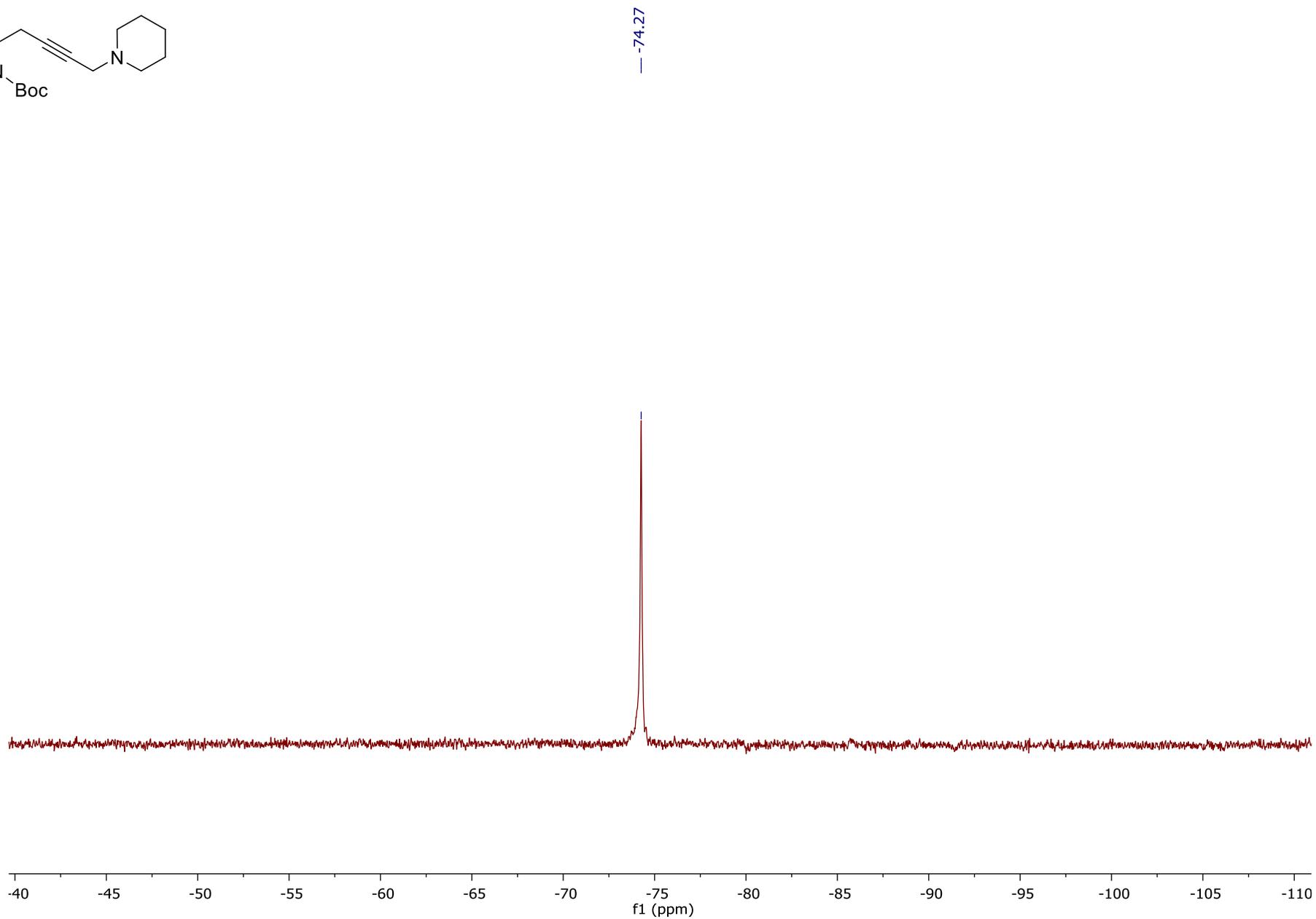
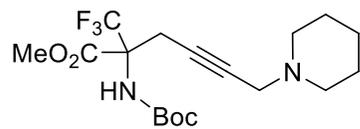
S27



¹³C NMR (101 MHz, CDCl₃) of methyl 2-benzyloxycarbonylamino-6-piperidino-2-(trifluoromethyl)hex-4-ynoate (3d)

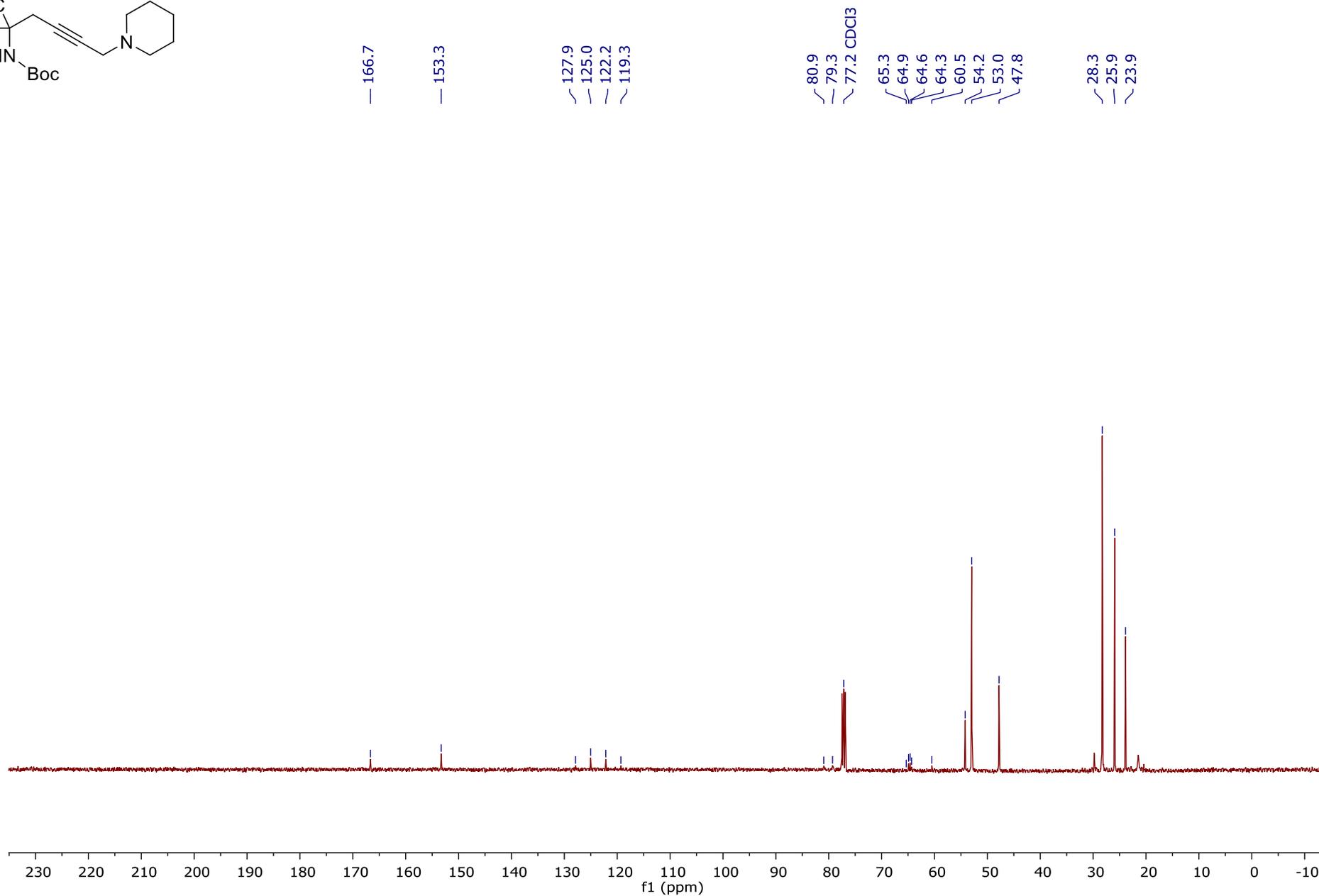
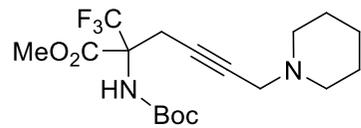


¹H NMR (400 MHz, CDCl₃) of methyl 2-*tert*-butoxycarbonylamino-6-piperidino-2-(trifluoromethyl)hex-4-ynoate (3'd)

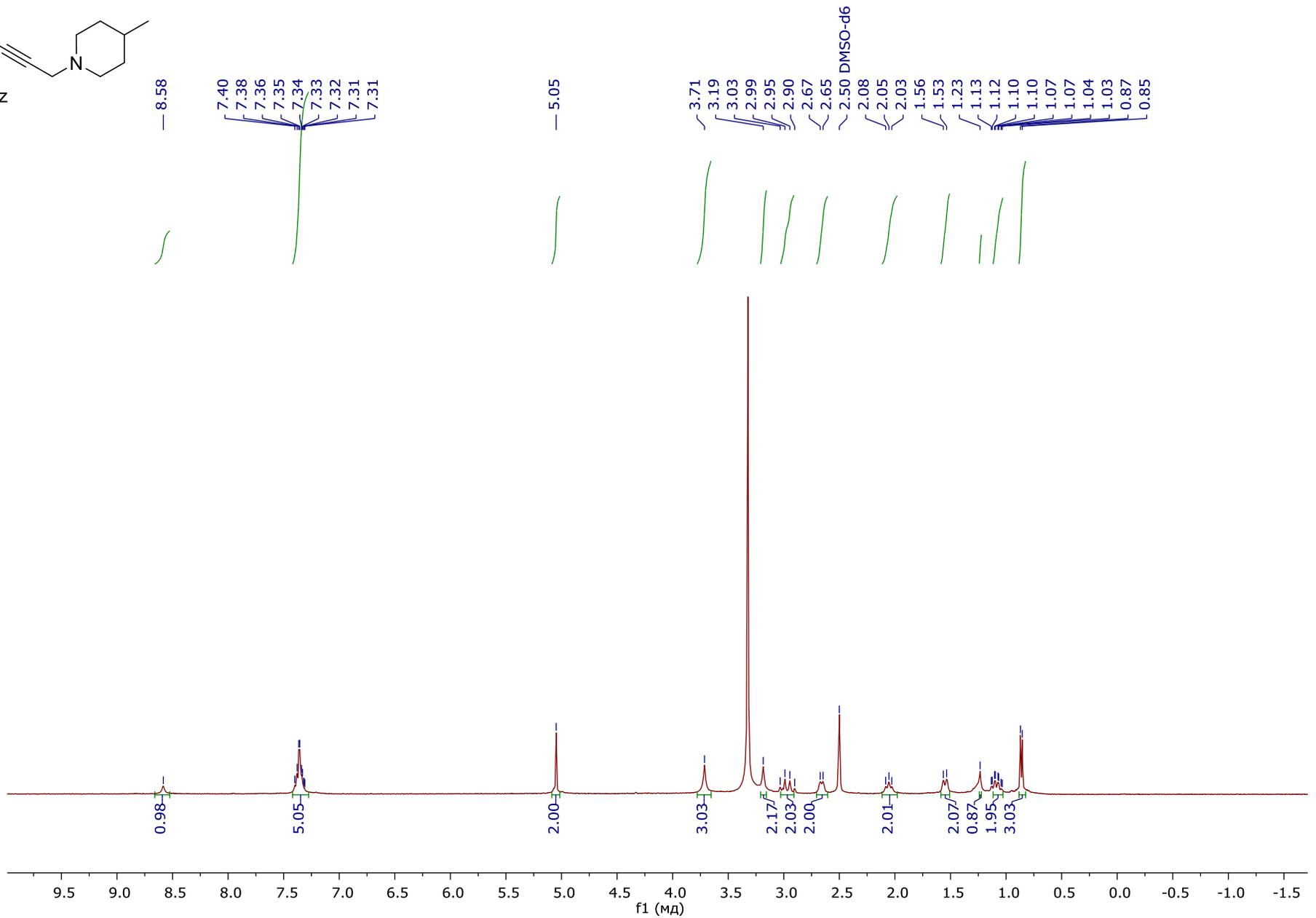
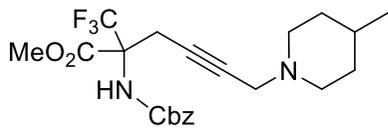


¹⁹F NMR (376 MHz, CDCl₃) of methyl 2-*tert*-butoxycarbonylamino-6-piperidino-2-(trifluoromethyl)hex-4-ynoate (3'd)

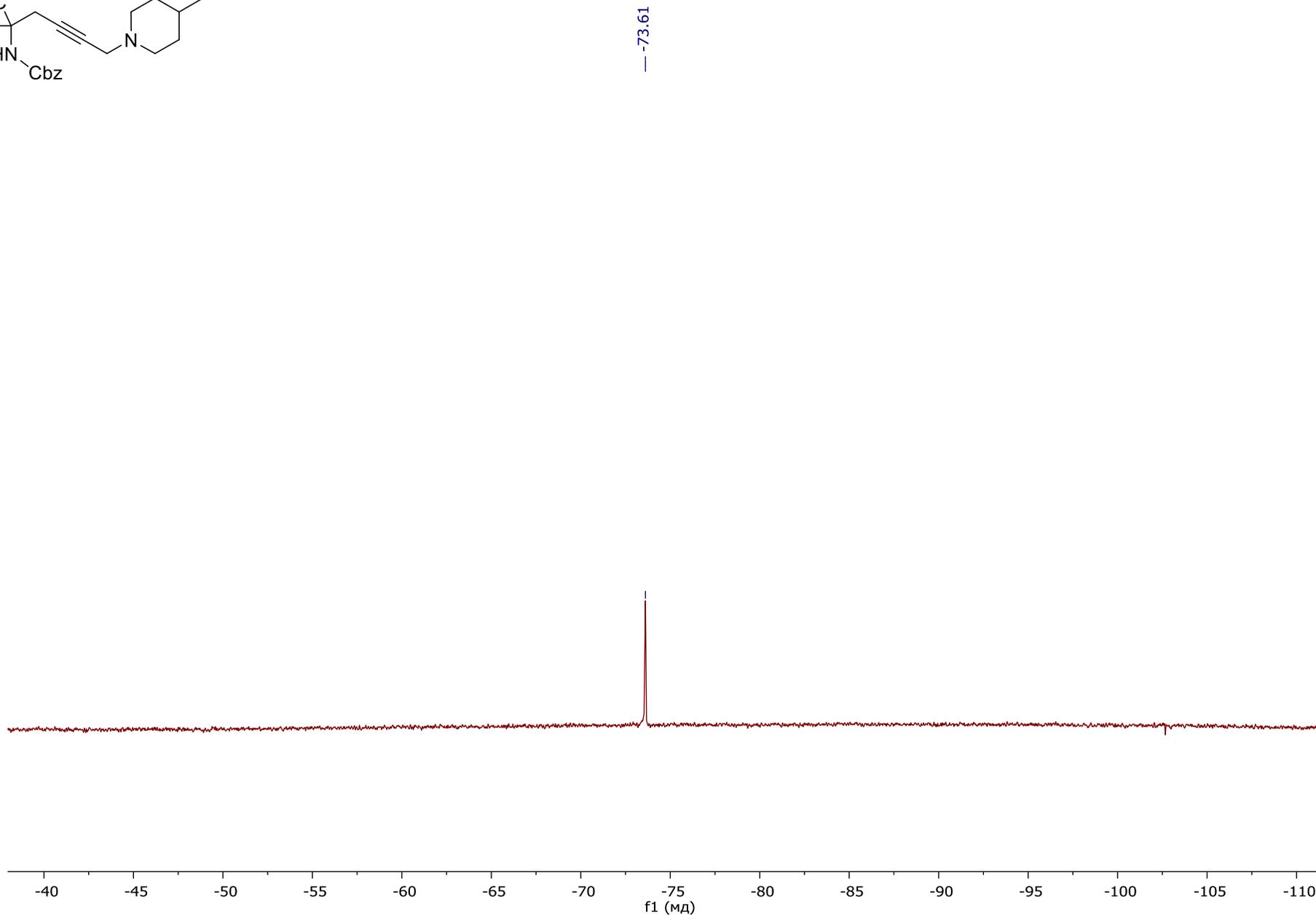
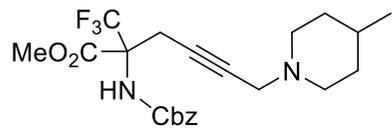
S30



¹³C NMR (101 MHz, CDCl₃) of methyl 2-*tert*-butoxycarbonylamino-6-piperidino-2-(trifluoromethyl)hex-4-ynoate (3'd)

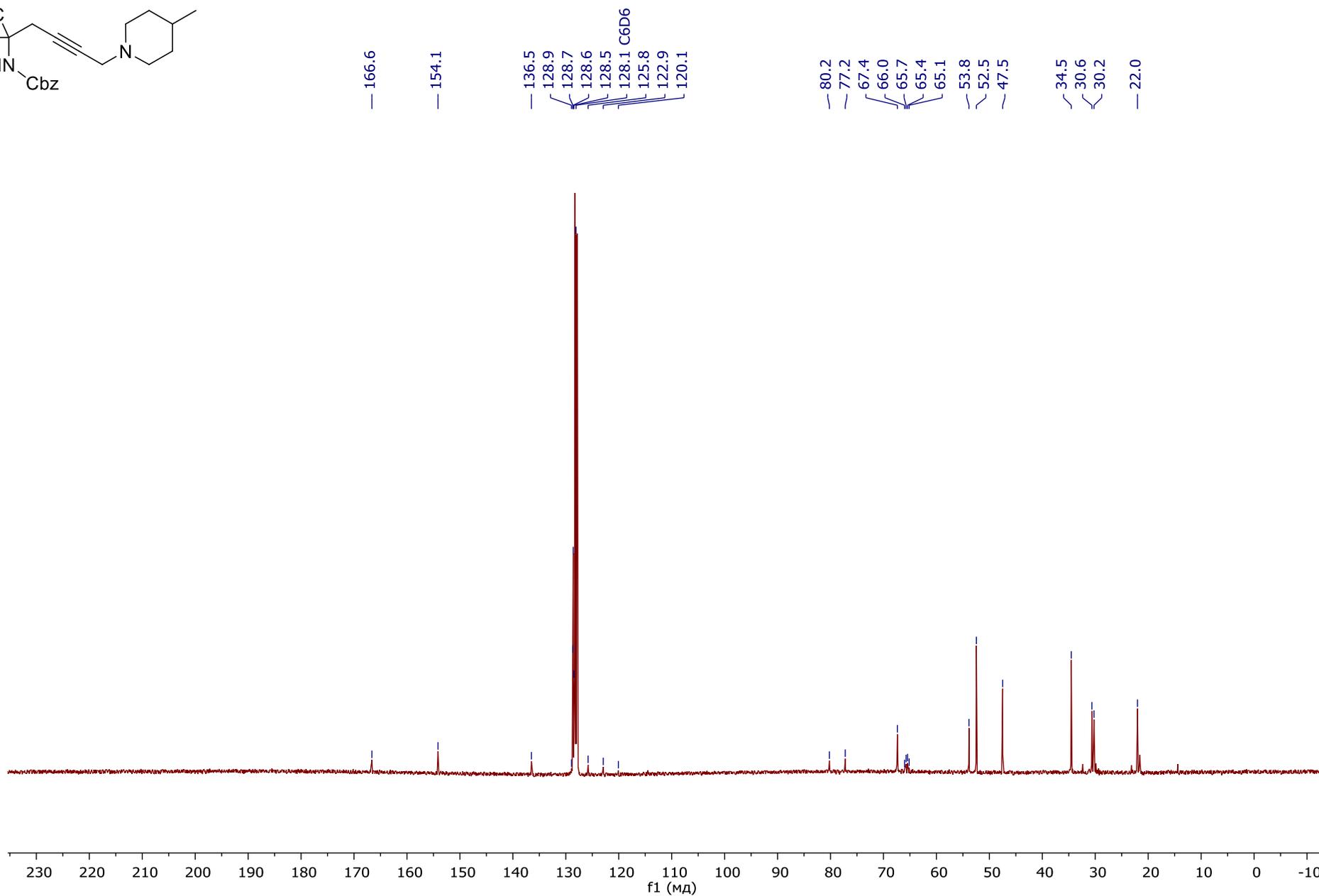
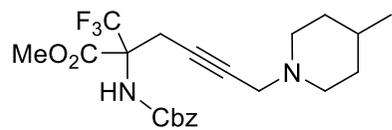


^1H NMR (400 MHz, DMSO- d_6) of methyl 2-benzoyloxycarbonylamino-6-(4-methylpiperidin-1-yl)-2-(trifluoromethyl)hex-4-ynoate (3e)

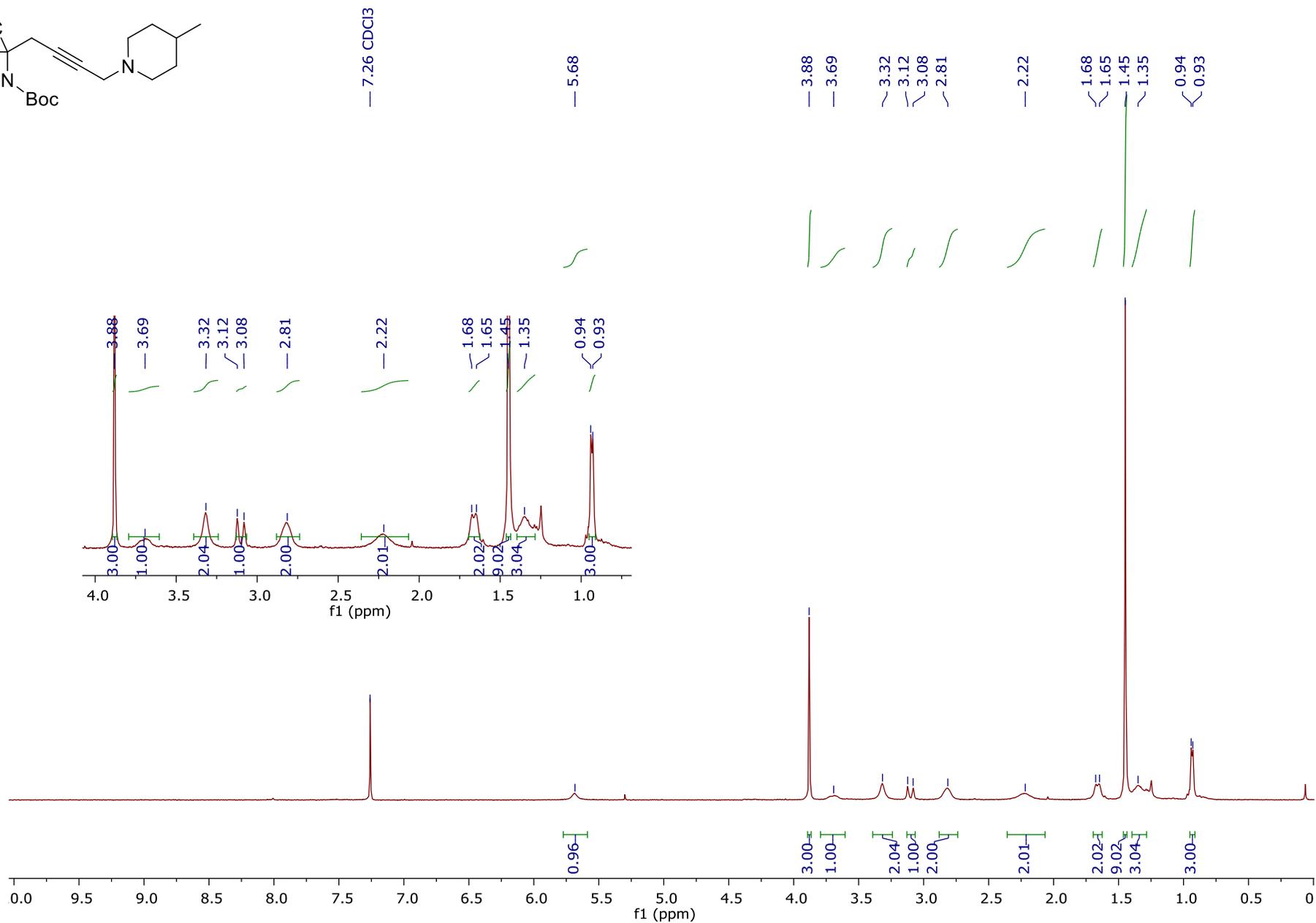
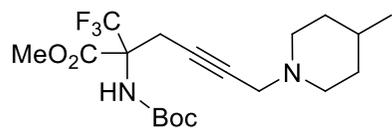


¹⁹F NMR (282 MHz, C₆D₆) of methyl 2-benzyloxycarbonylamino-6-(4-methylpiperidin-1-yl)-2-(trifluoromethyl)hex-4-ynoate (3e)

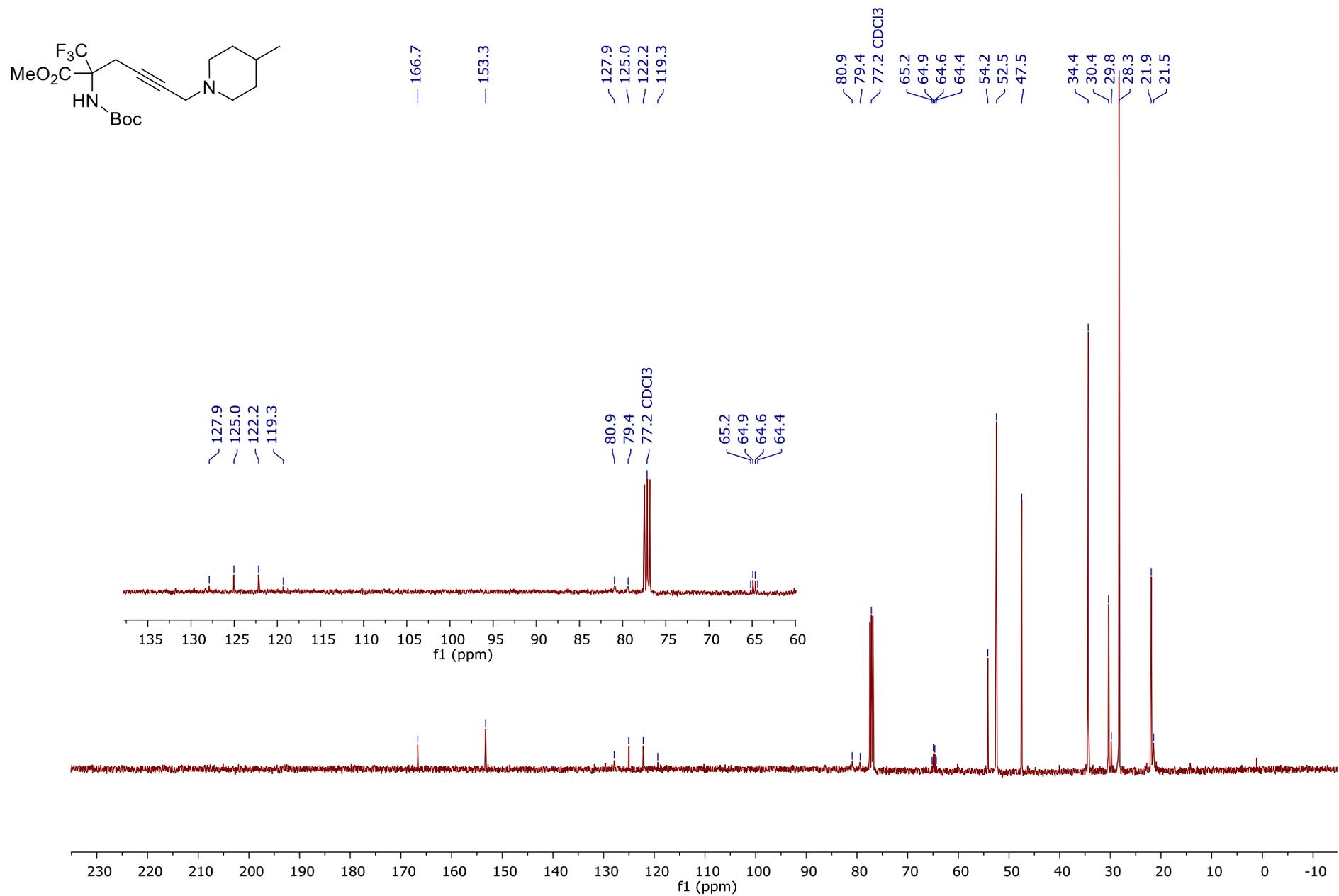
S33



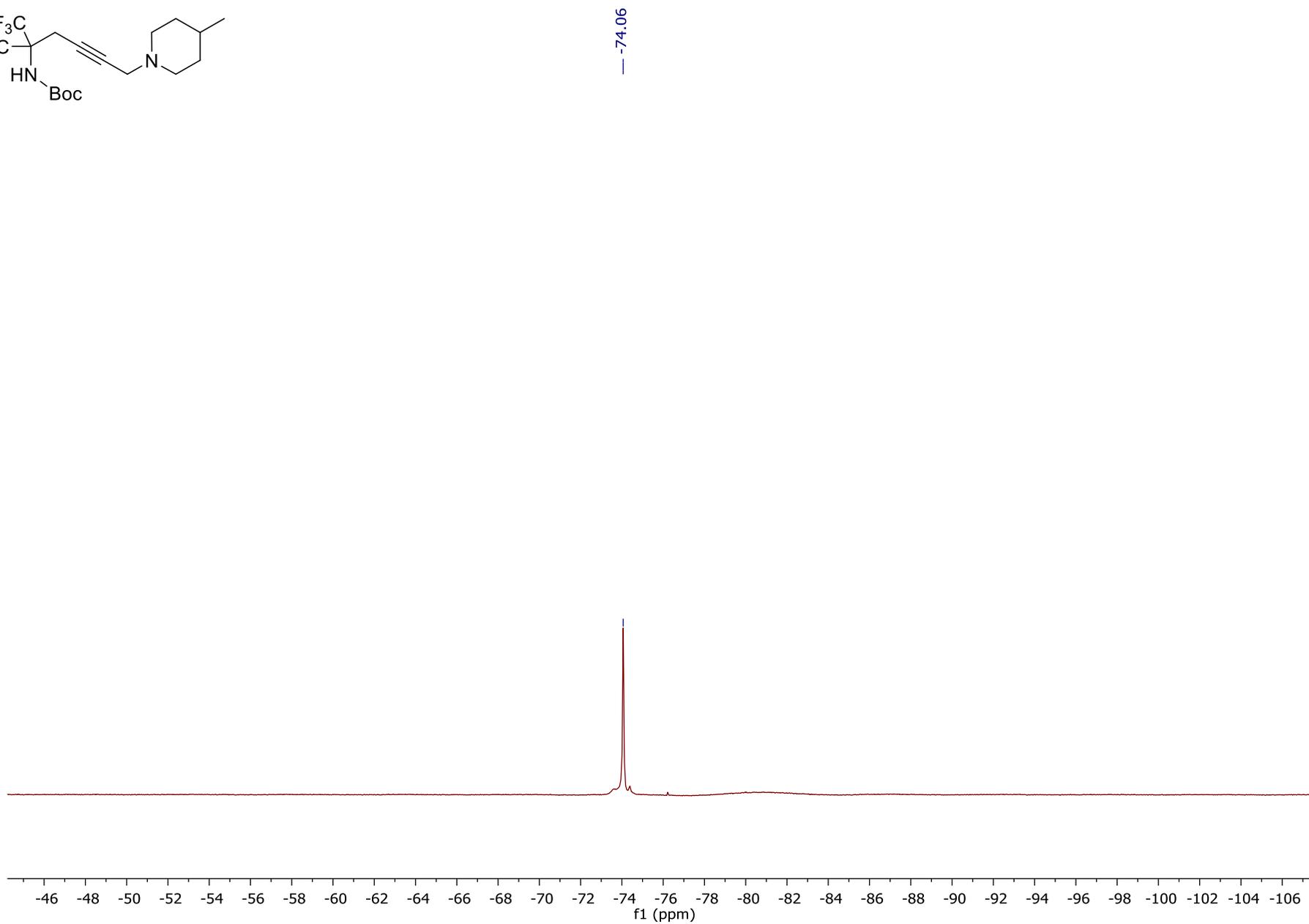
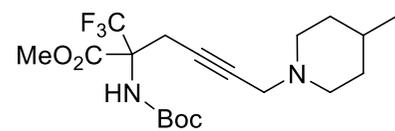
¹³C NMR (101 MHz, C₆D₆) of methyl 2-benzyloxycarbonylamino-6-(4-methylpiperidin-1-yl)-2-(trifluoromethyl)hex-4-ynoate (3e)



¹H NMR (400 MHz, CDCl₃) of methyl 2-*tert*-butoxycarbonylamino-6-(4-methylpiperidin-1-yl)-2-(trifluoromethyl)hex-4-ynoate (3'e)

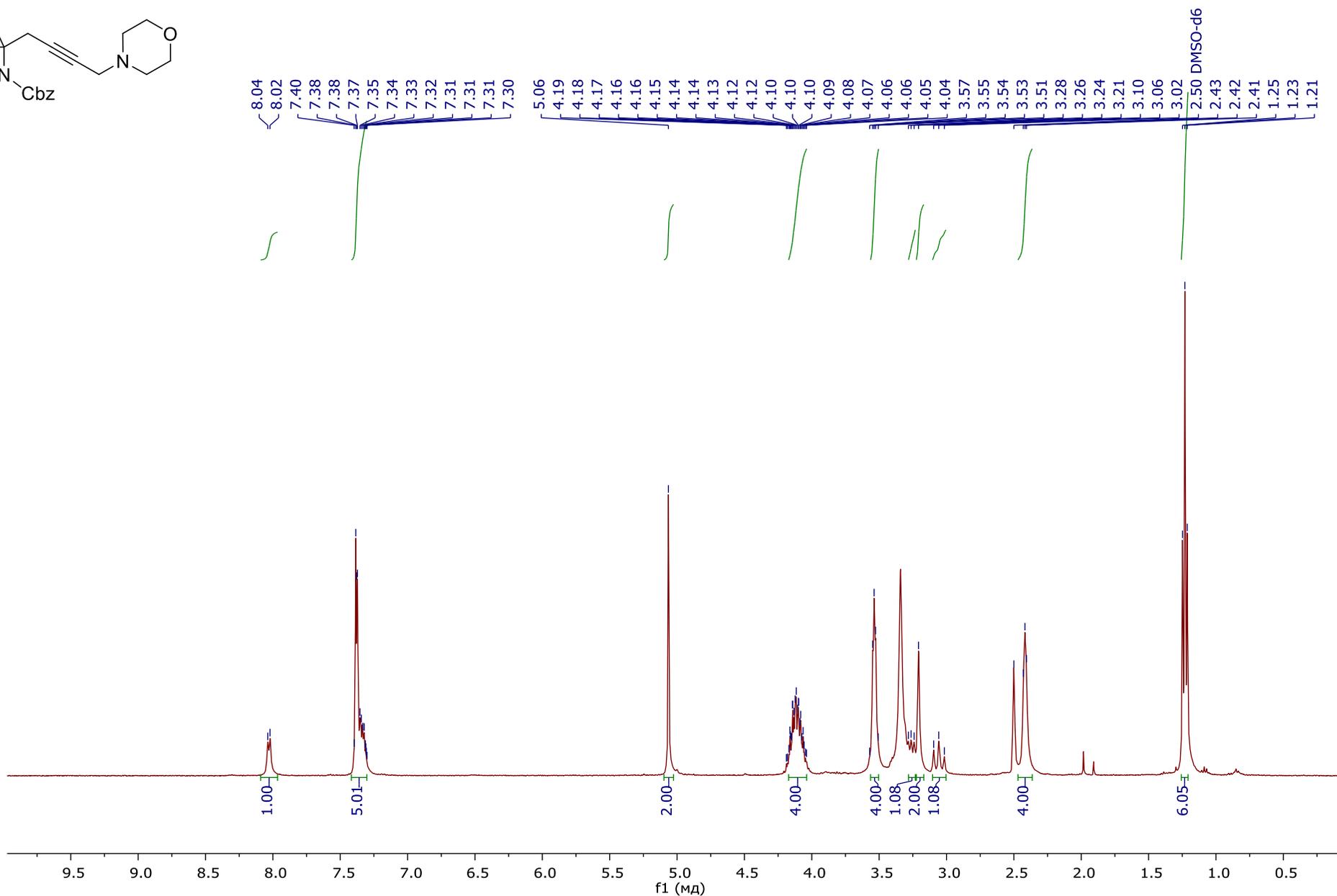
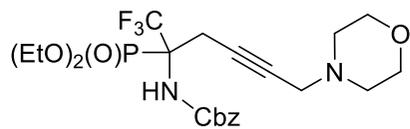


^{13}C NMR (101 MHz, CDCl_3) of methyl 2-*tert*-butoxycarbonylamino-6-(4-methylpiperidin-1-yl)-2-(trifluoromethyl)hex-4-ynoate (3'e)

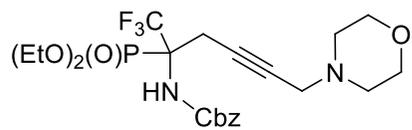


¹⁹F NMR (376 MHz, CDCl₃) of methyl 2-tert-butoxycarbonylamino-6-(4-methylpiperidin-1-yl)-2-(trifluoromethyl)hex-4-ynoate (3'e)

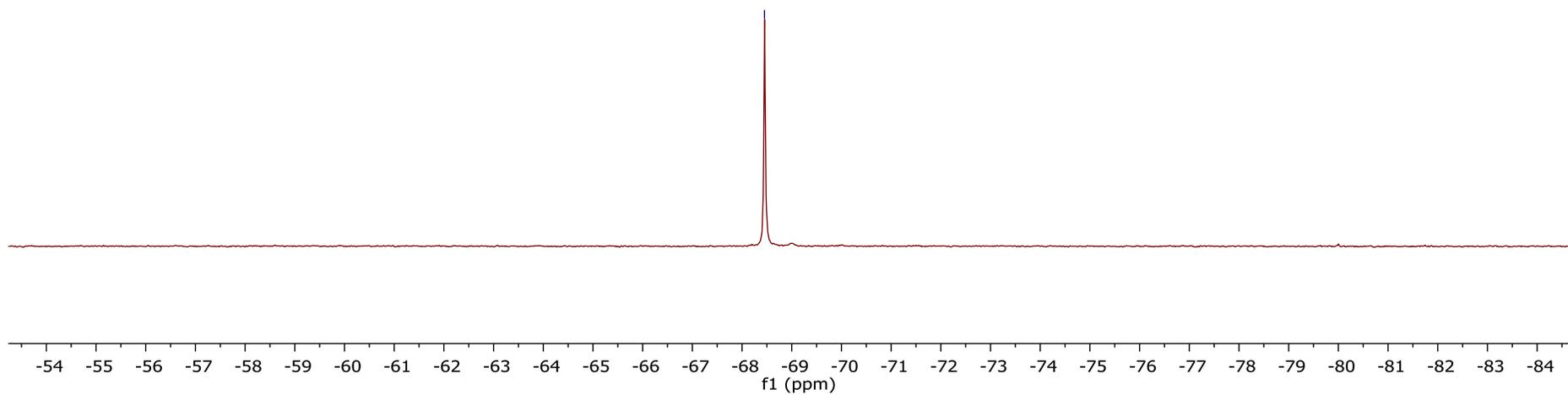
S37



¹H NMR (400 MHz, DMSO-*d*₆) of benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(morpholino)hex-4-yn-2-yl]carbamate (5a)

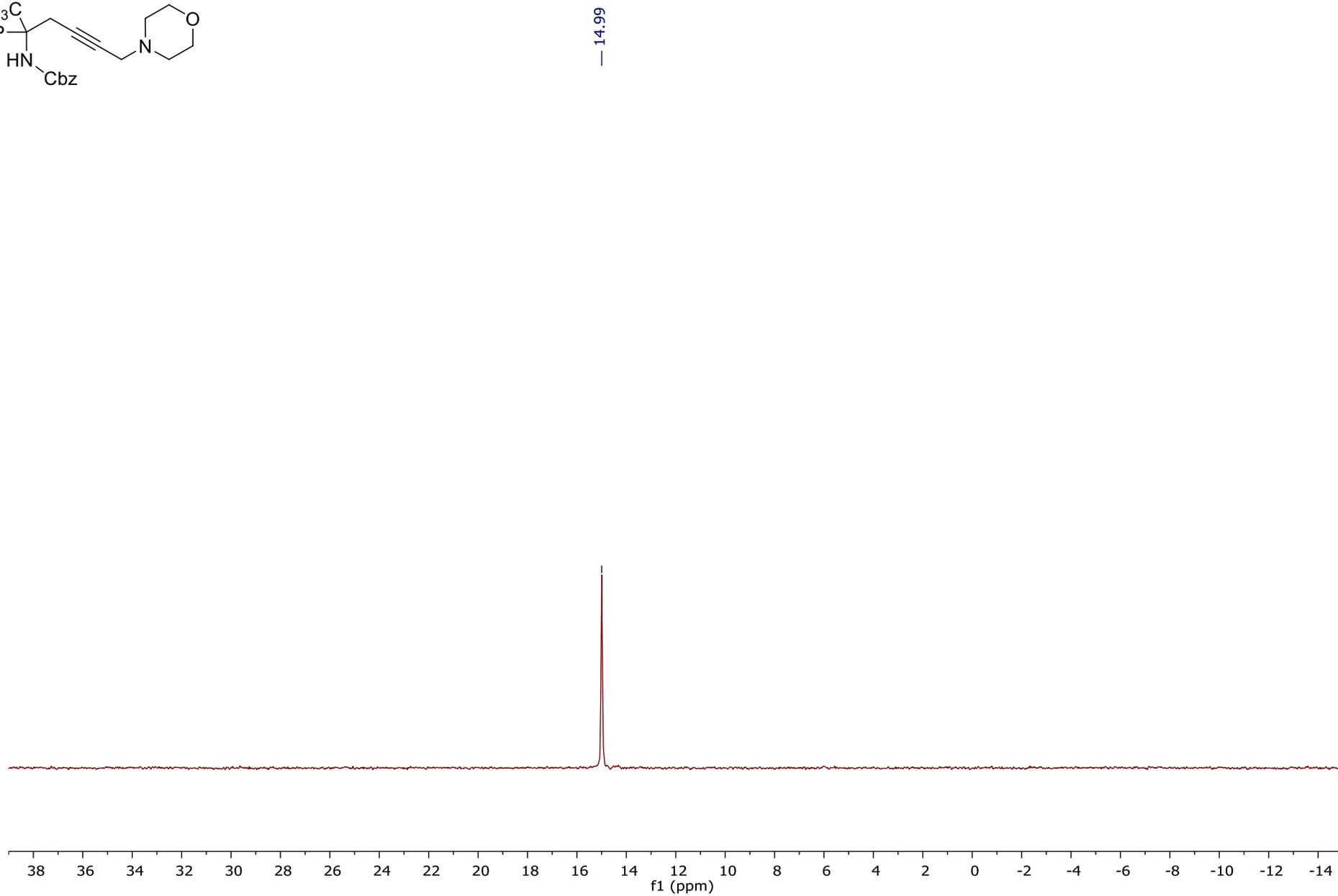
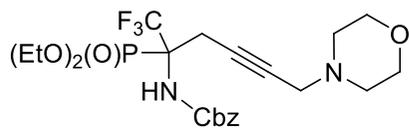


— -68.45



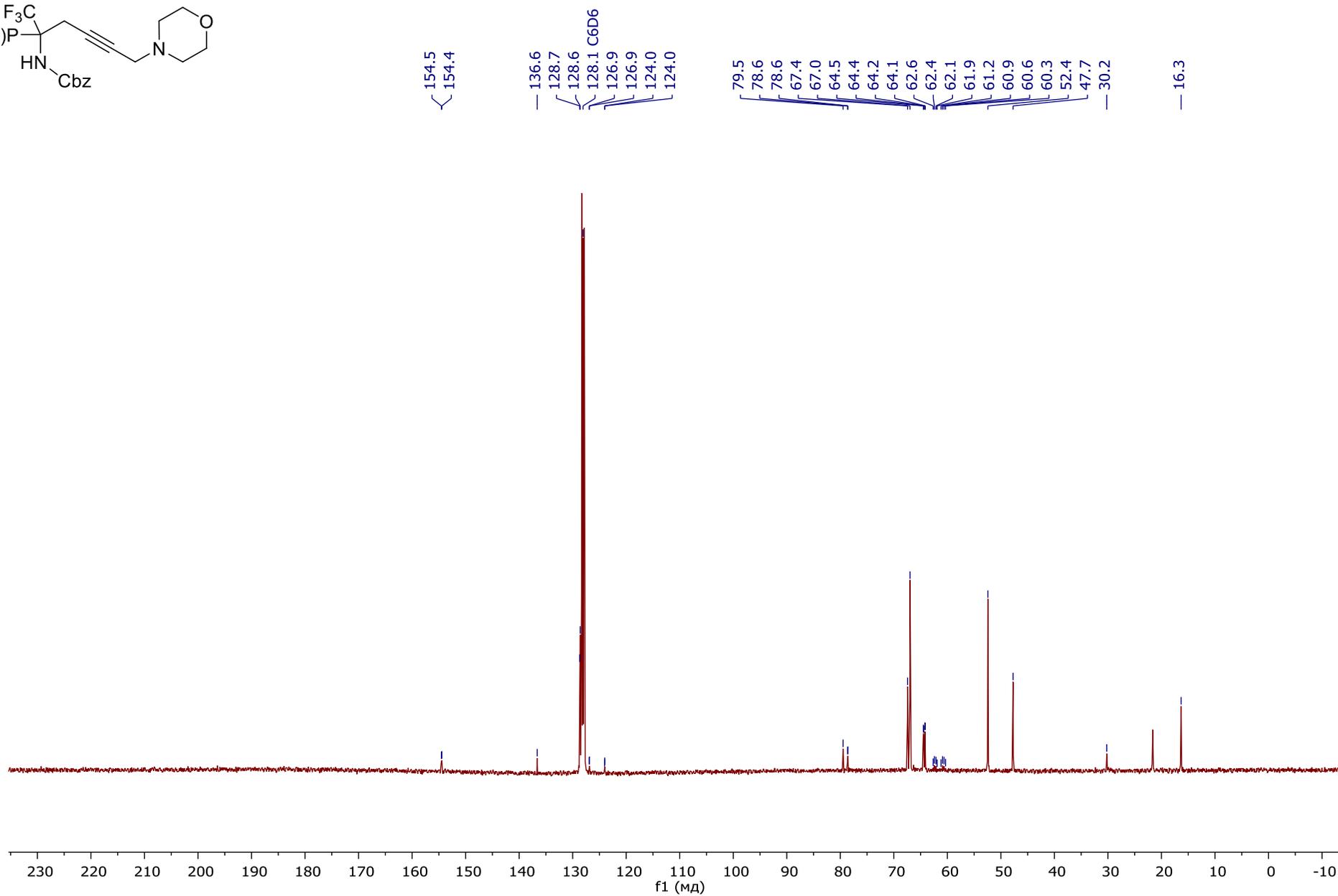
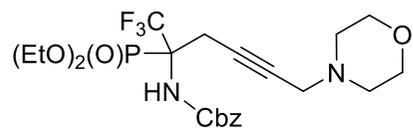
¹⁹F NMR (376 MHz, DMSO-*d*₆) of benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(morpholino)hex-4-yn-2-yl]carbamate (5a)

S39

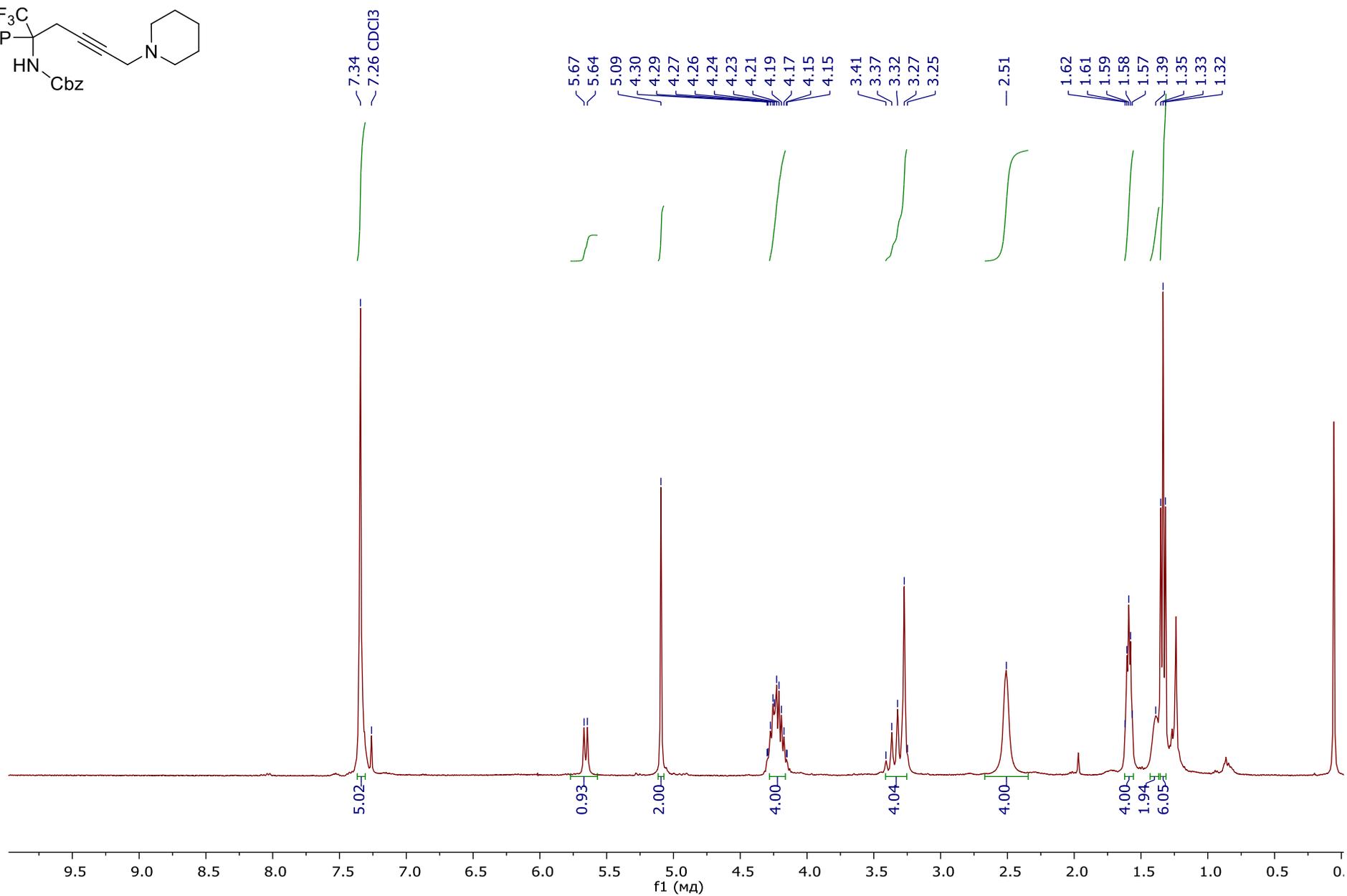
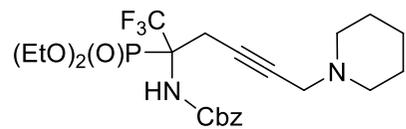


³¹P NMR (162 MHz, DMSO-*d*₆) of benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(morpholino)hex-4-yn-2-yl]carbamate (5a)

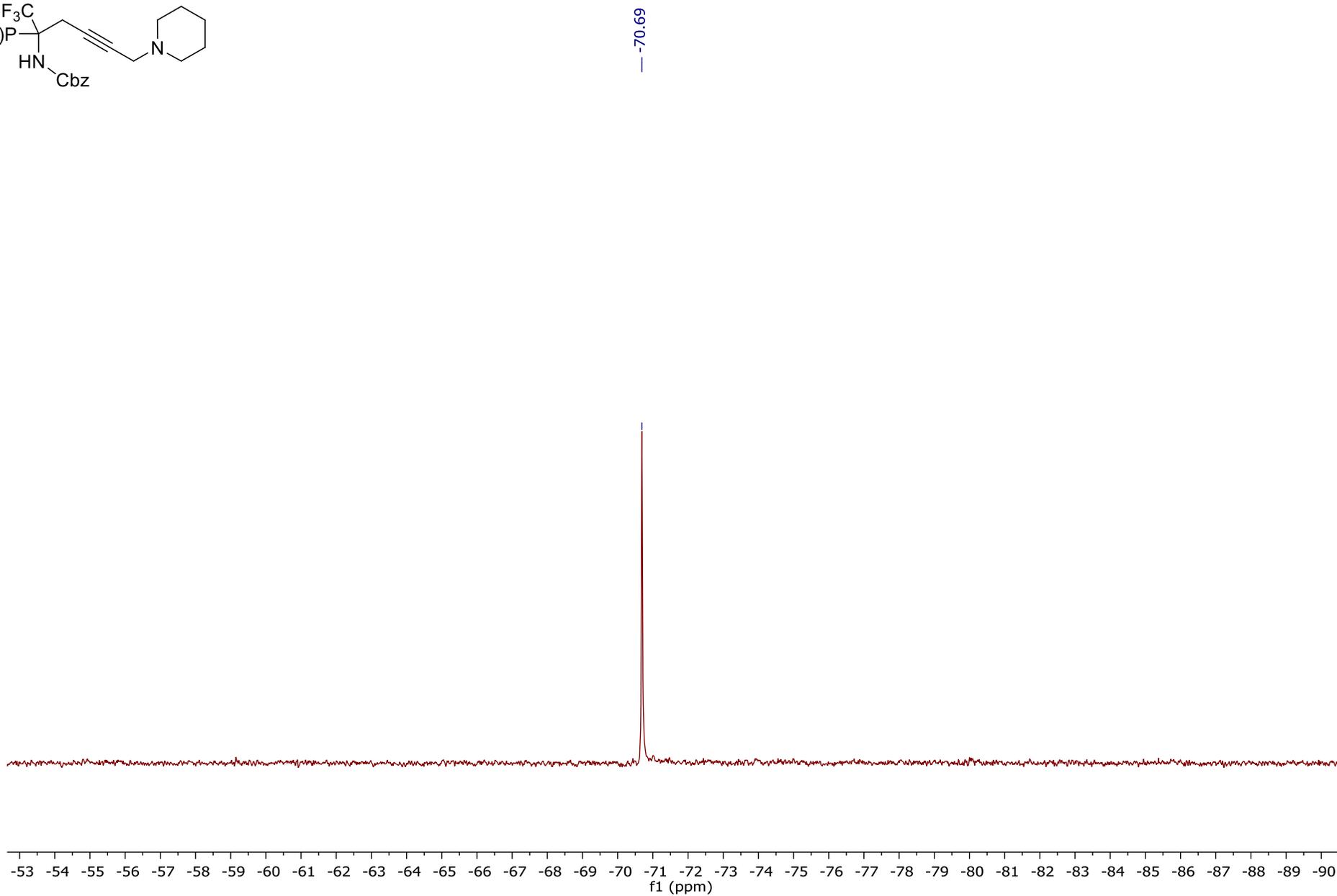
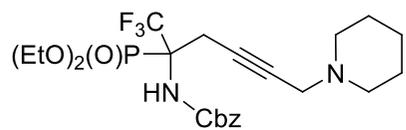
S40



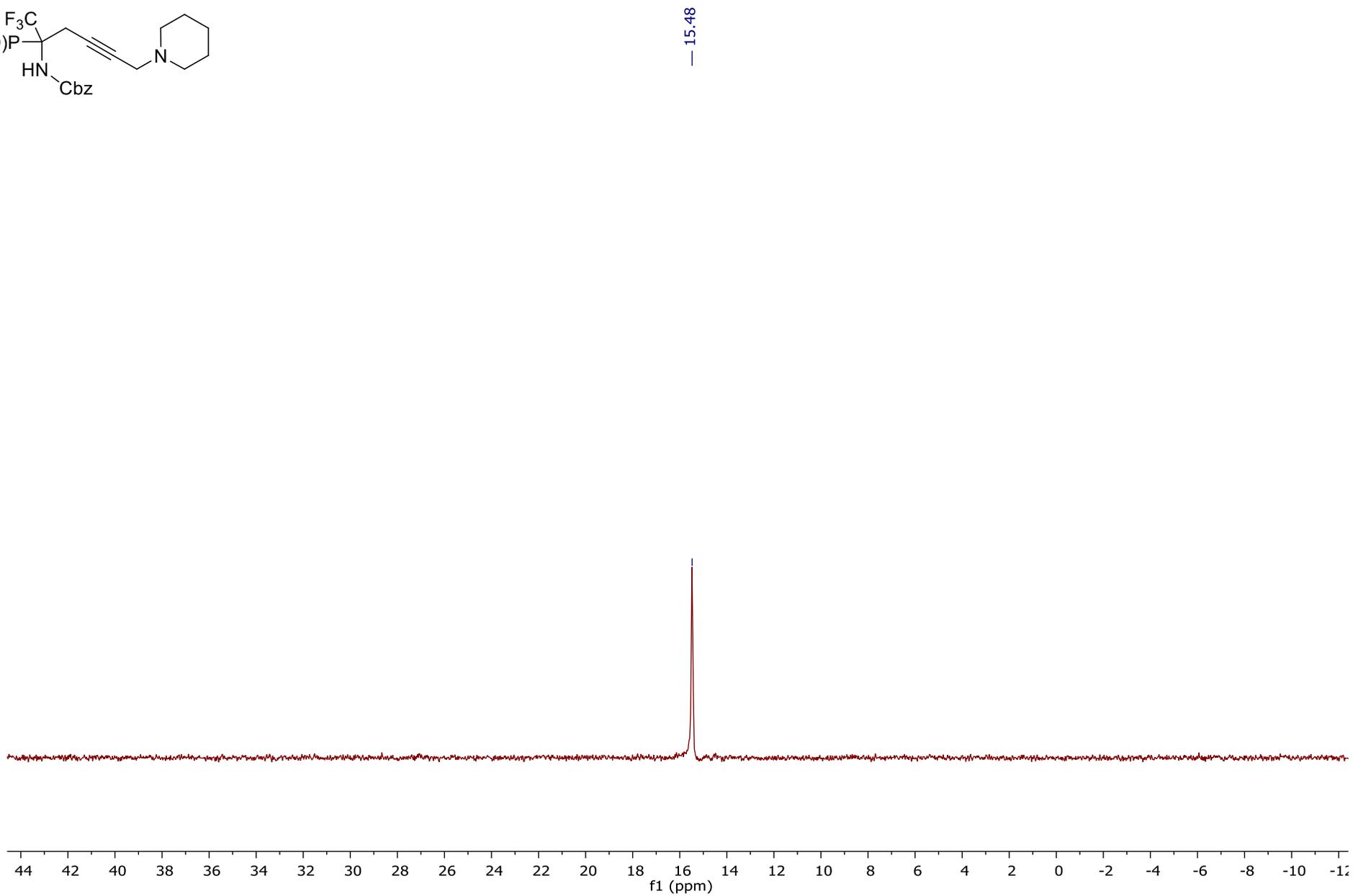
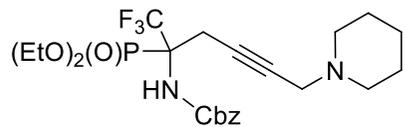
¹³C NMR (101 MHz, C₆D₆) of benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(morpholino)hex-4-yn-2-yl]carbamate (5a)



^1H NMR (400 MHz, CDCl_3) of benzyl N-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(piperidin-1-yl)hex-4-yn-2-yl]carbamate (5b)

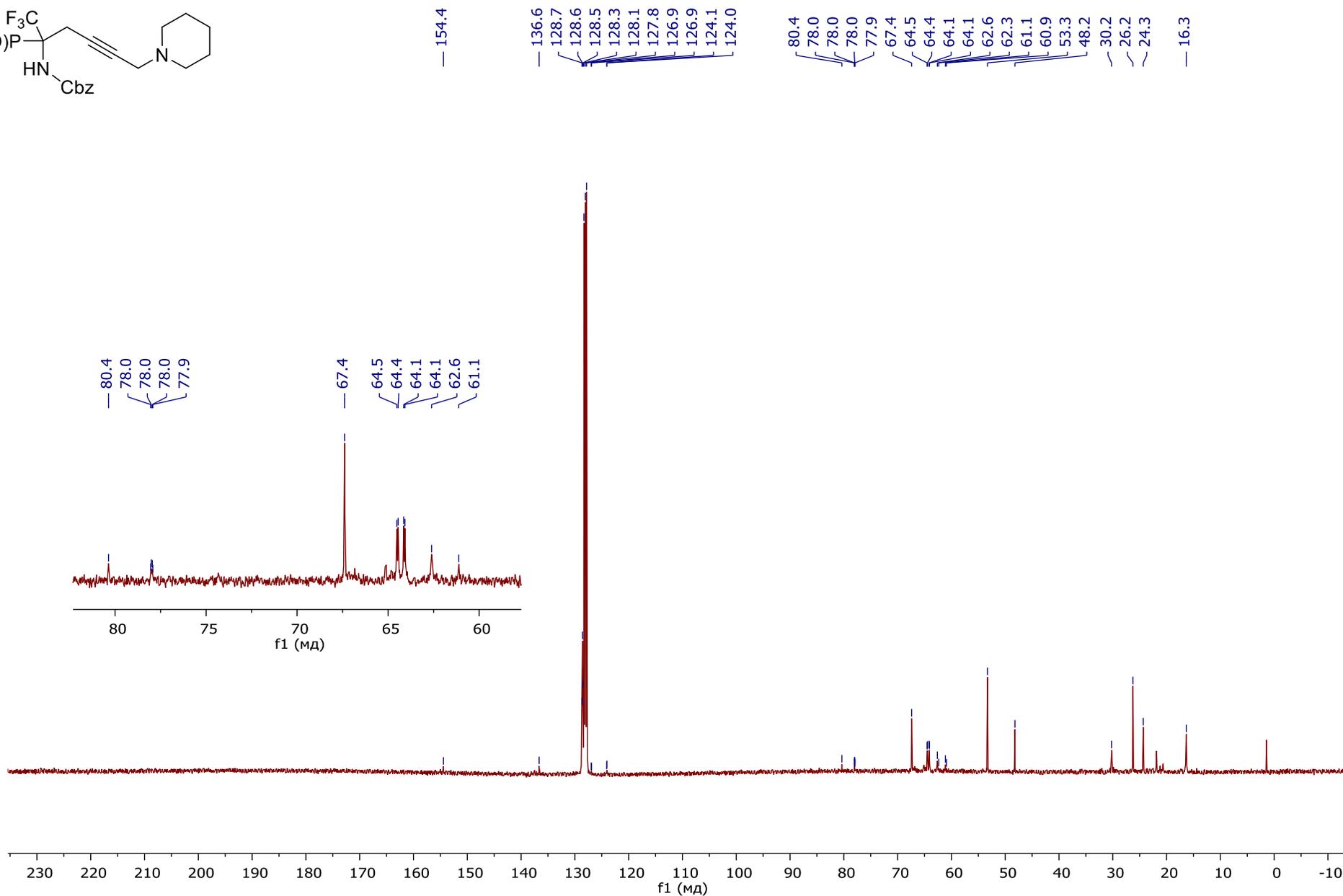
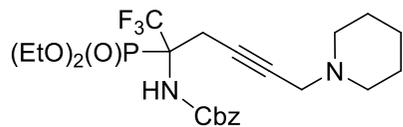


^{19}F NMR (376 MHz, CDCl_3) of benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(piperidin-1-yl)hex-4-yn-2-yl]carbamate (**5b**)

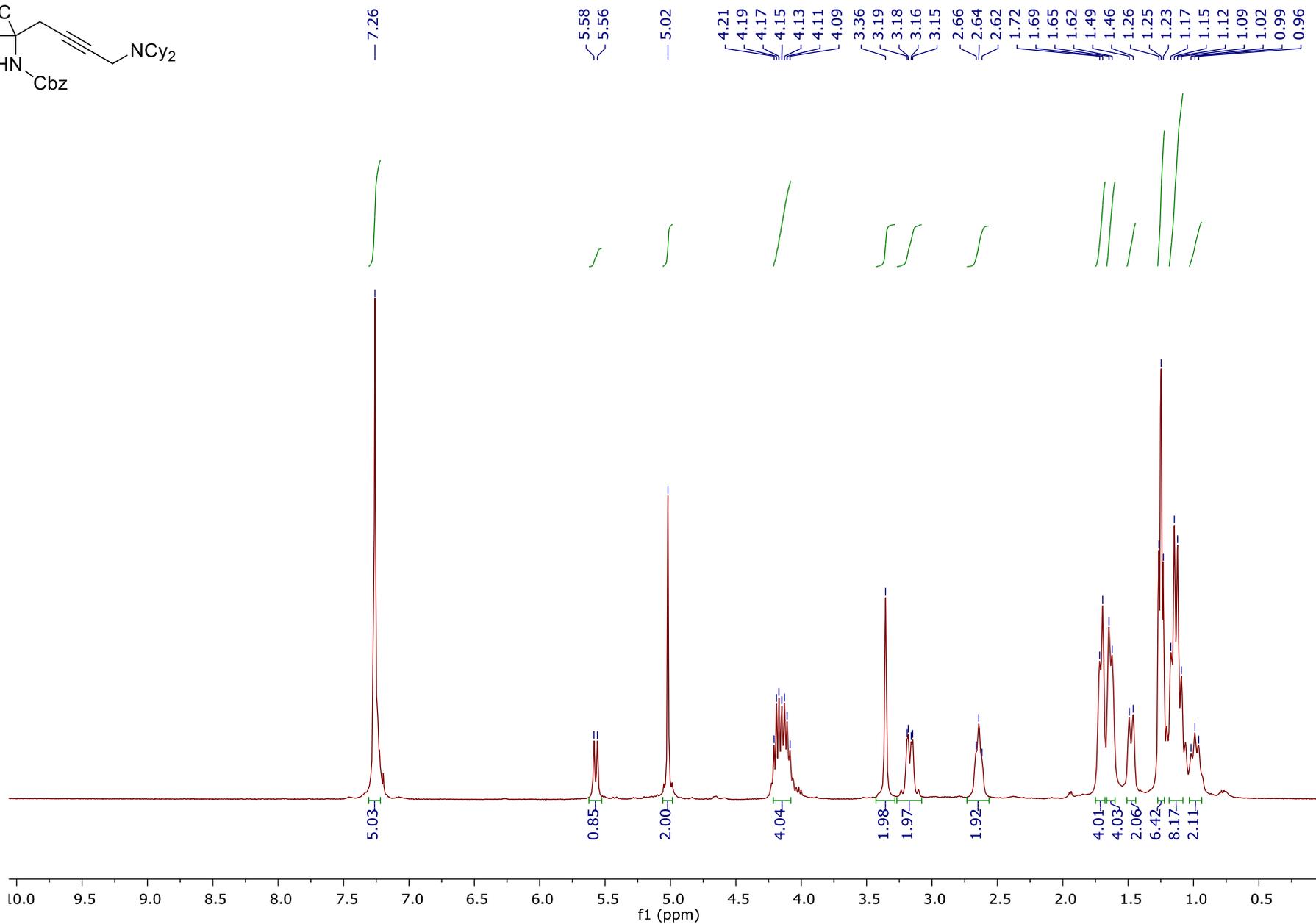
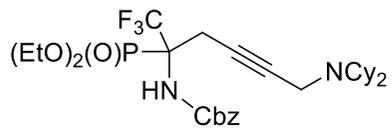


³¹P NMR (162 MHz, CDCl₃) of Benzyl N-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(piperidin-1-yl)hex-4-yn-2-yl]carbamate (5b)

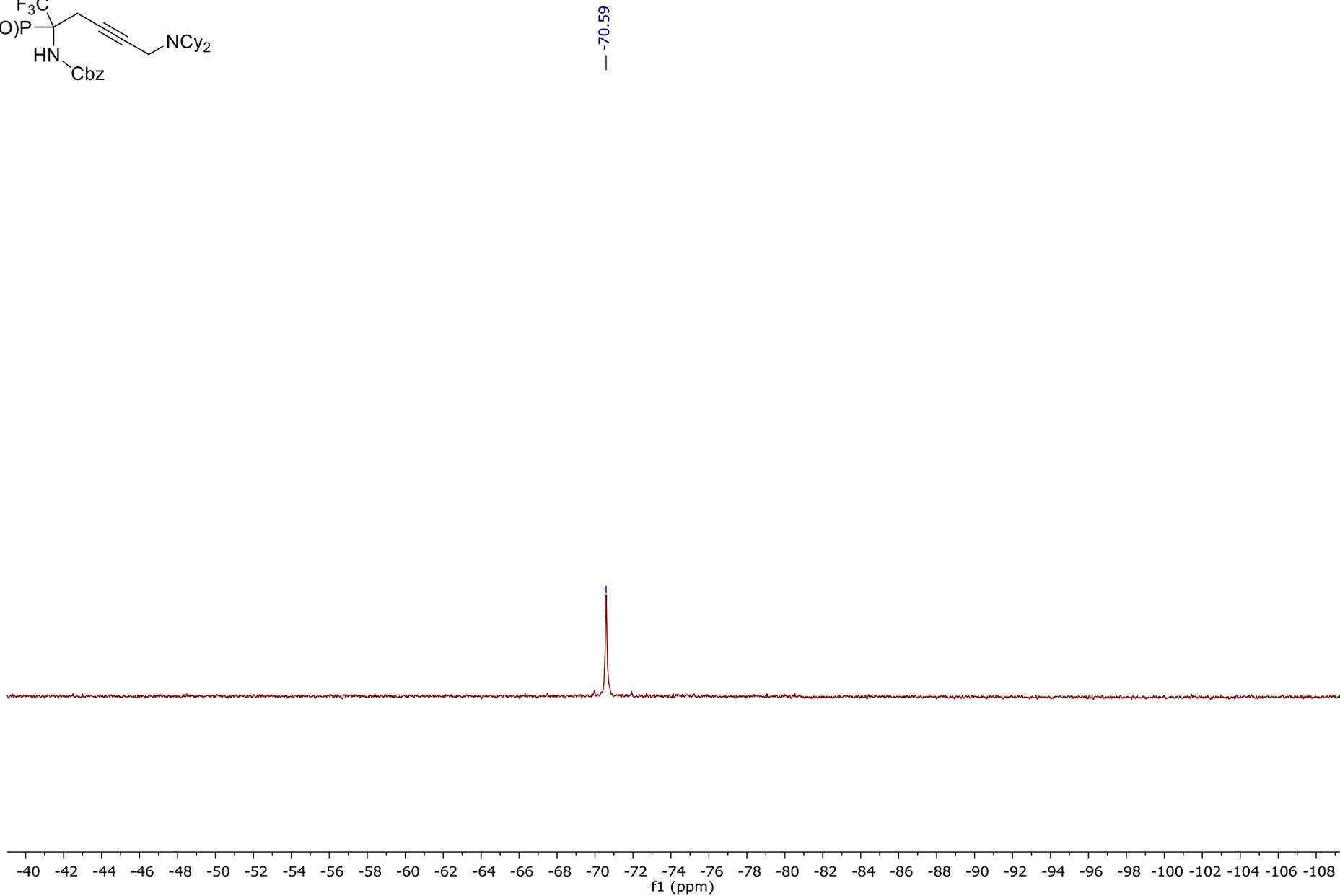
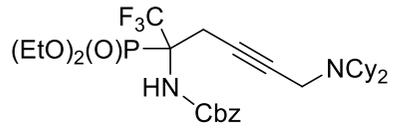
S44



¹³C NMR (101 MHz, C₆D₆) of Benzyl N-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(piperidin-1-yl)hex-4-yn-2-yl]carbamate (5b)

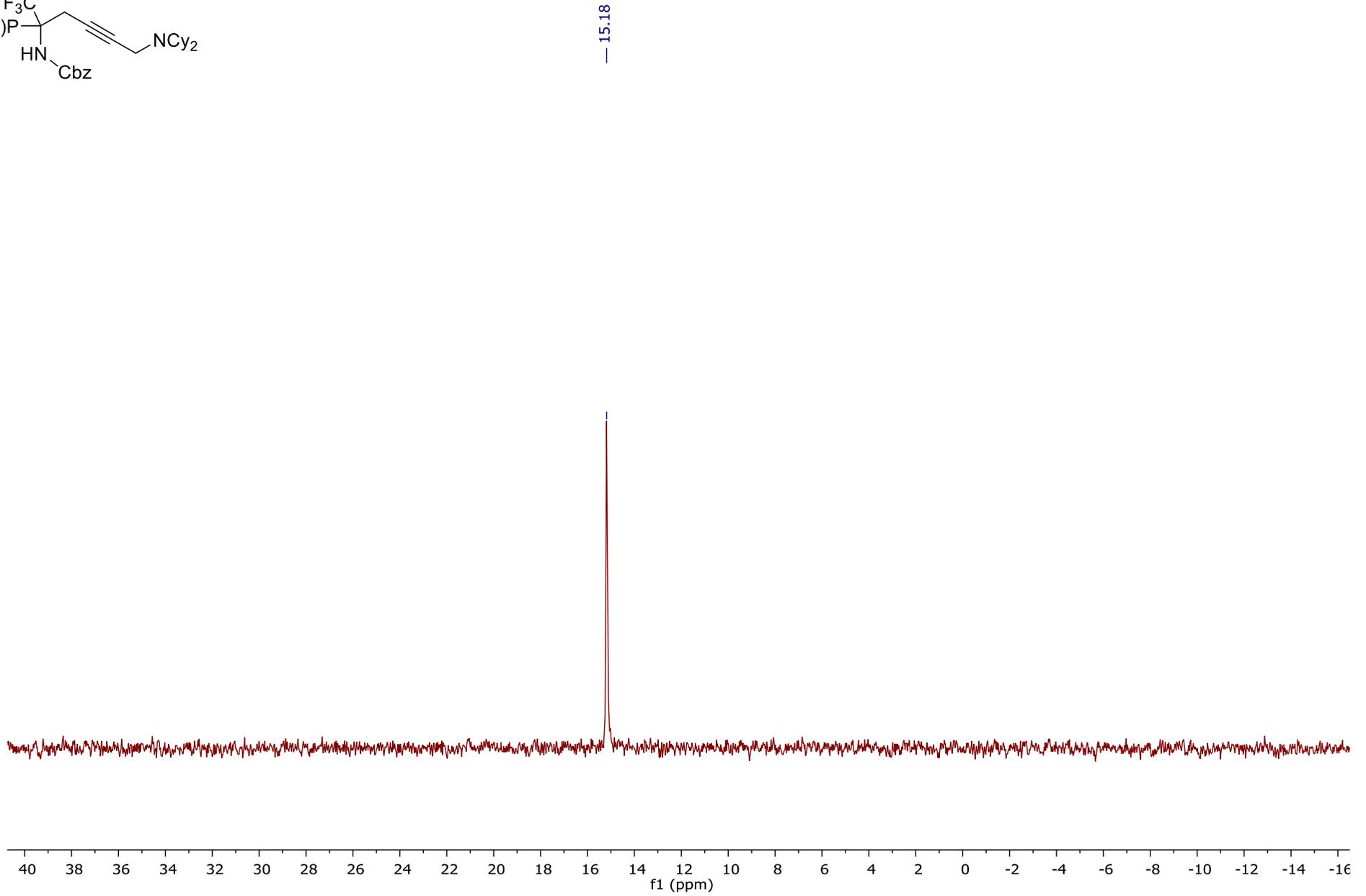
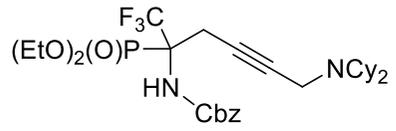


¹H NMR (400 MHz, CDCl₃) of benzyl N-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(dicyclohexylamino)hex-4-yn-2-yl]carbamate (5c)



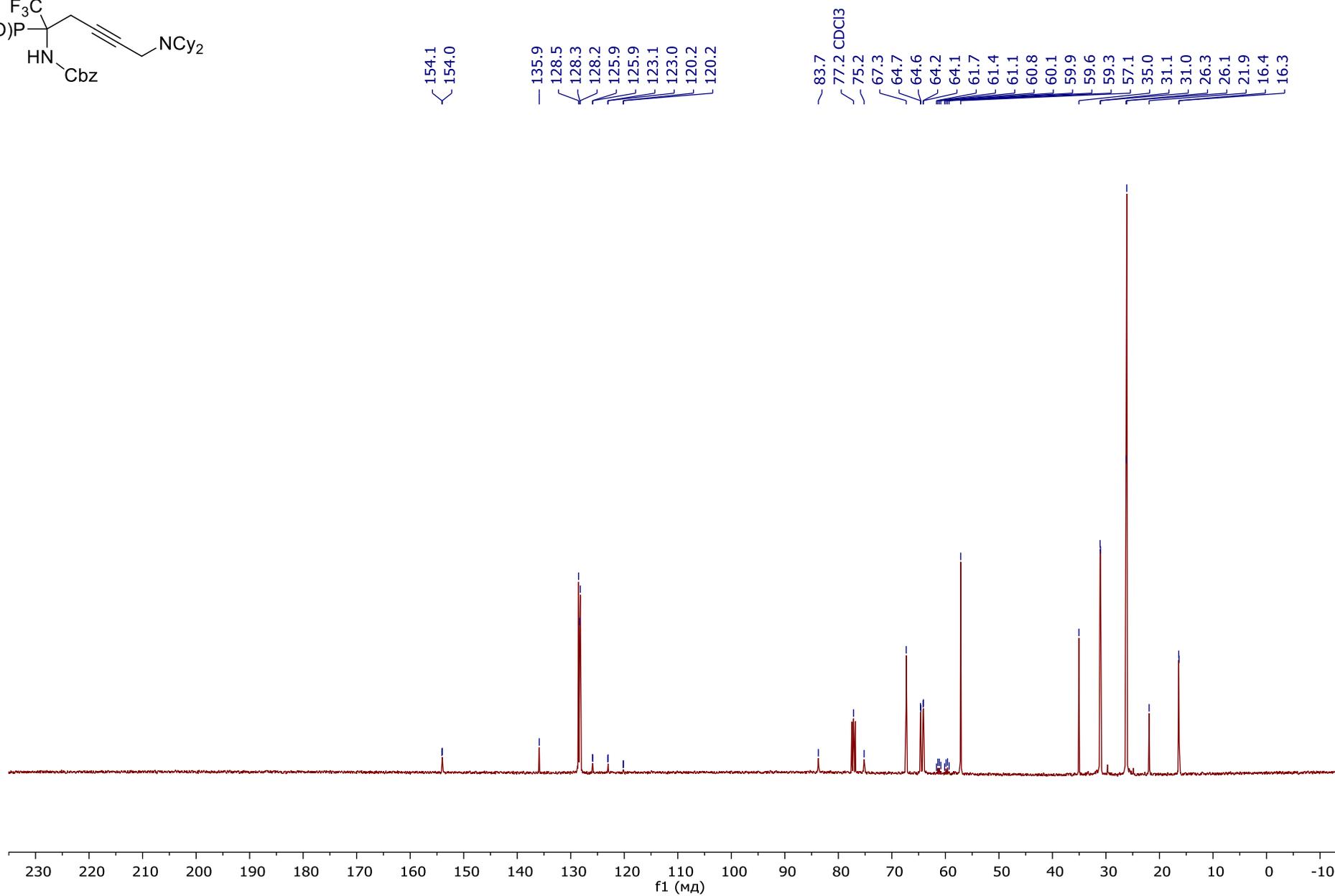
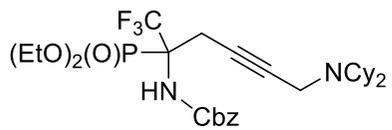
¹⁹F NMR (376 MHz, CDCl₃) of benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(dicyclohexylamino)hex-4-yn-2-yl]carbamate (5c)

S47

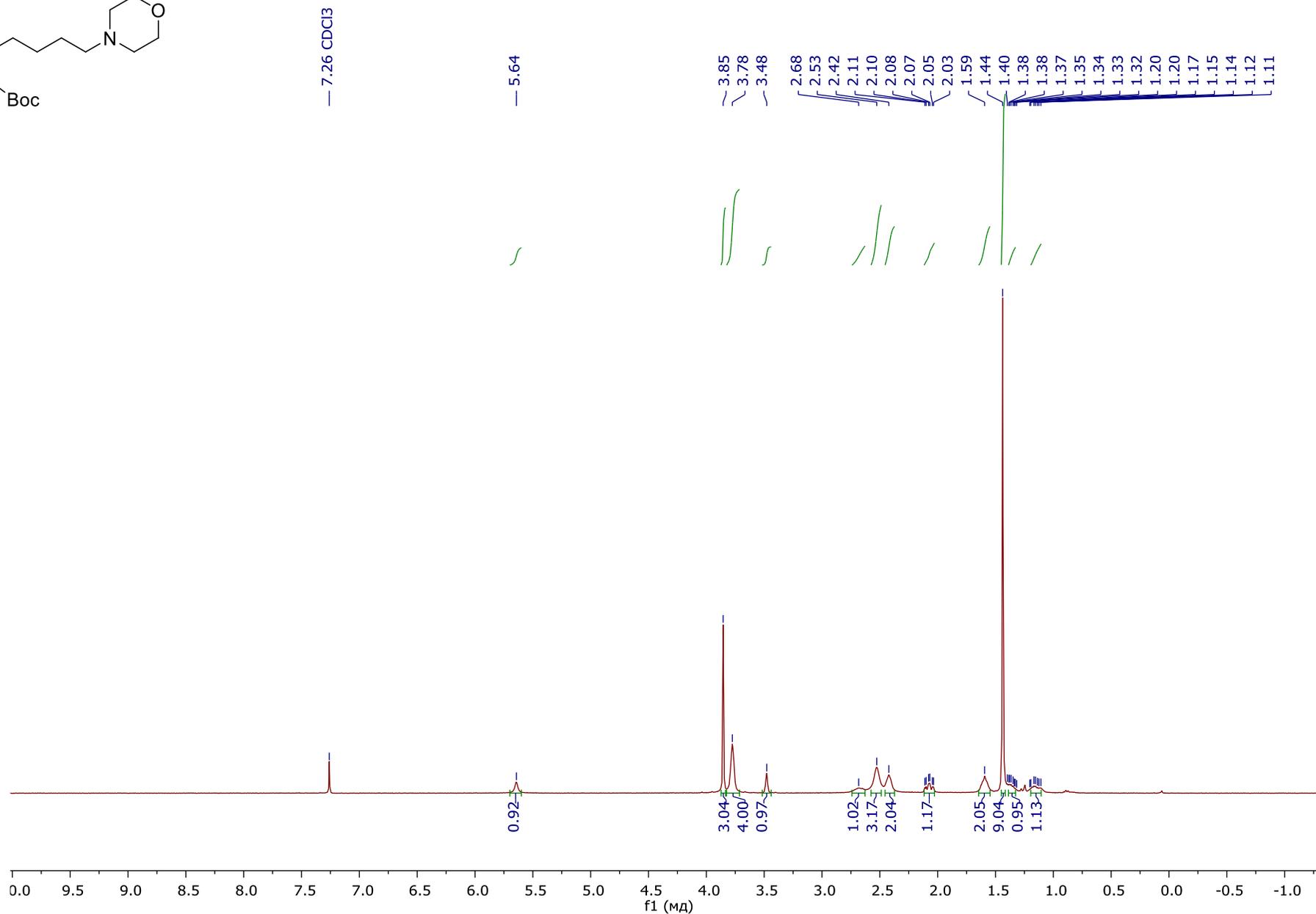
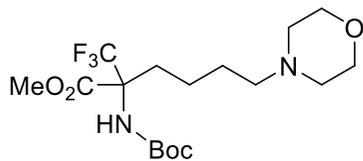


³¹P NMR (162 MHz, DMSO-*d*₆) of benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(dicyclohexylamino)hex-4-yn-2-yl]carbamate (5c)

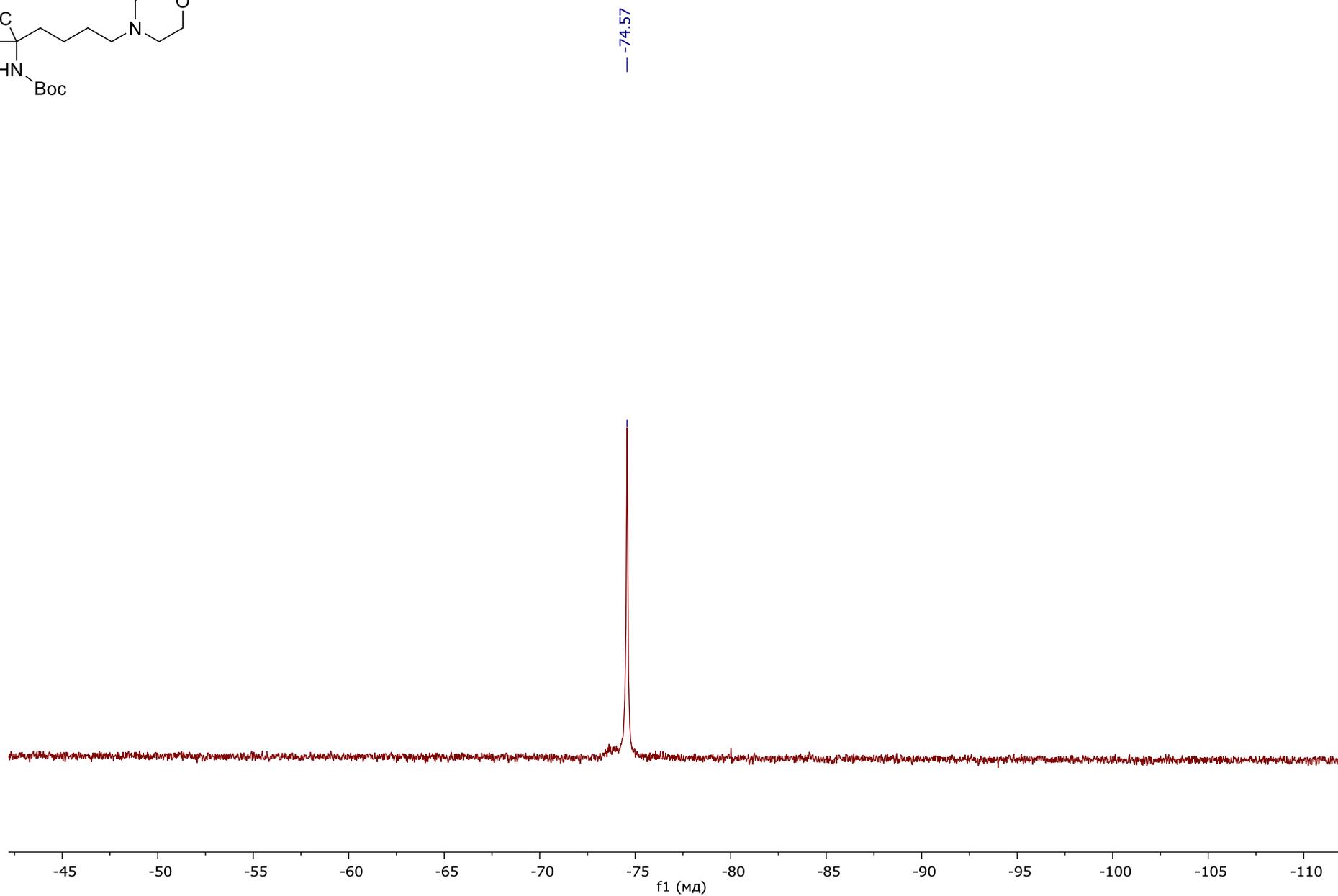
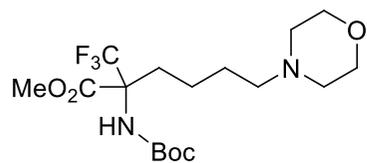
S48



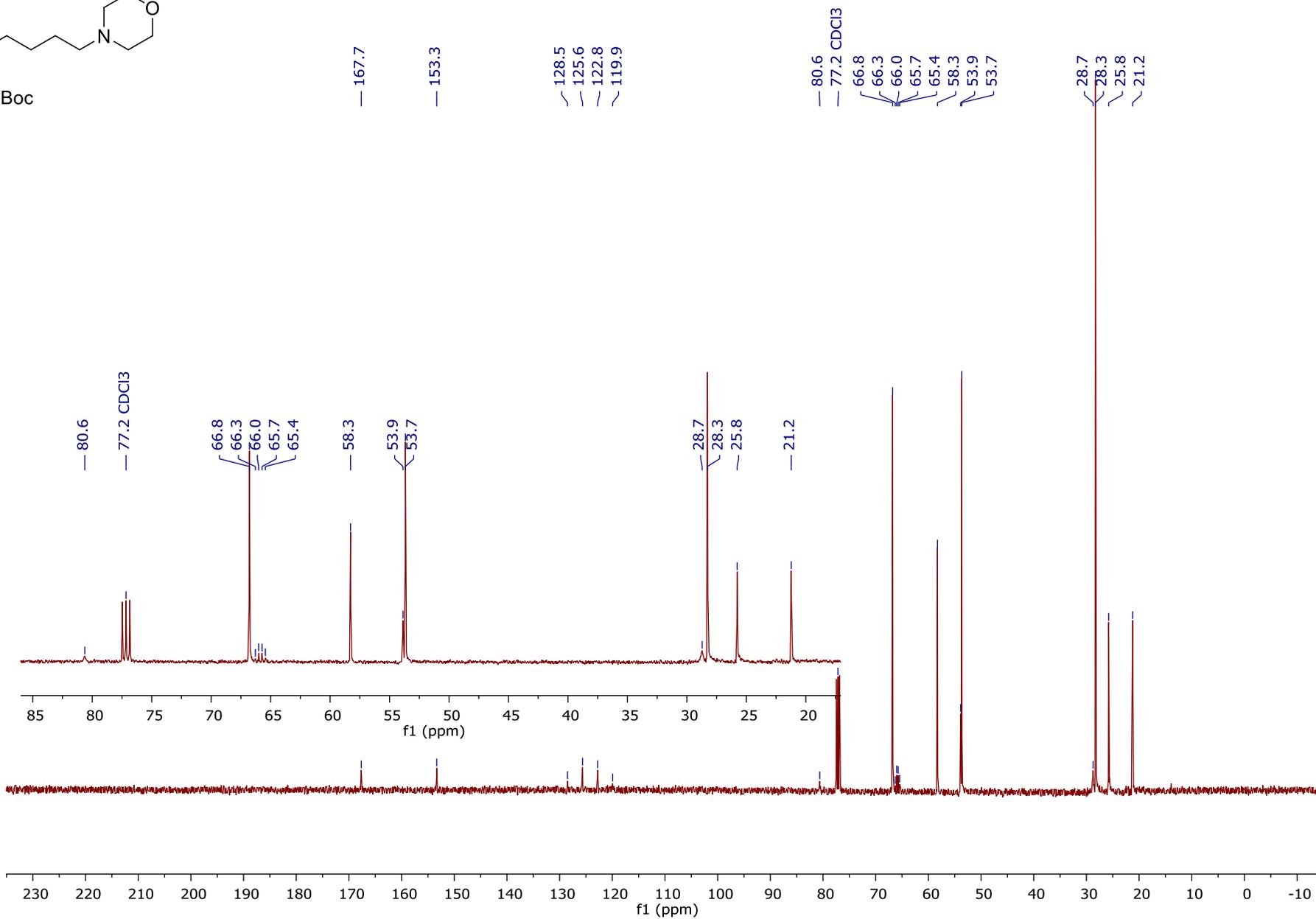
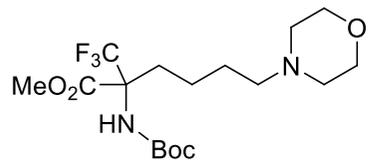
^{13}C NMR (101 MHz, CDCl_3) of benzyl *N*-[2-diethoxyphosphoryl-1,1,1-trifluoro-6-(dicyclohexylamino)hex-4-yn-2-yl]carbamate (5c)



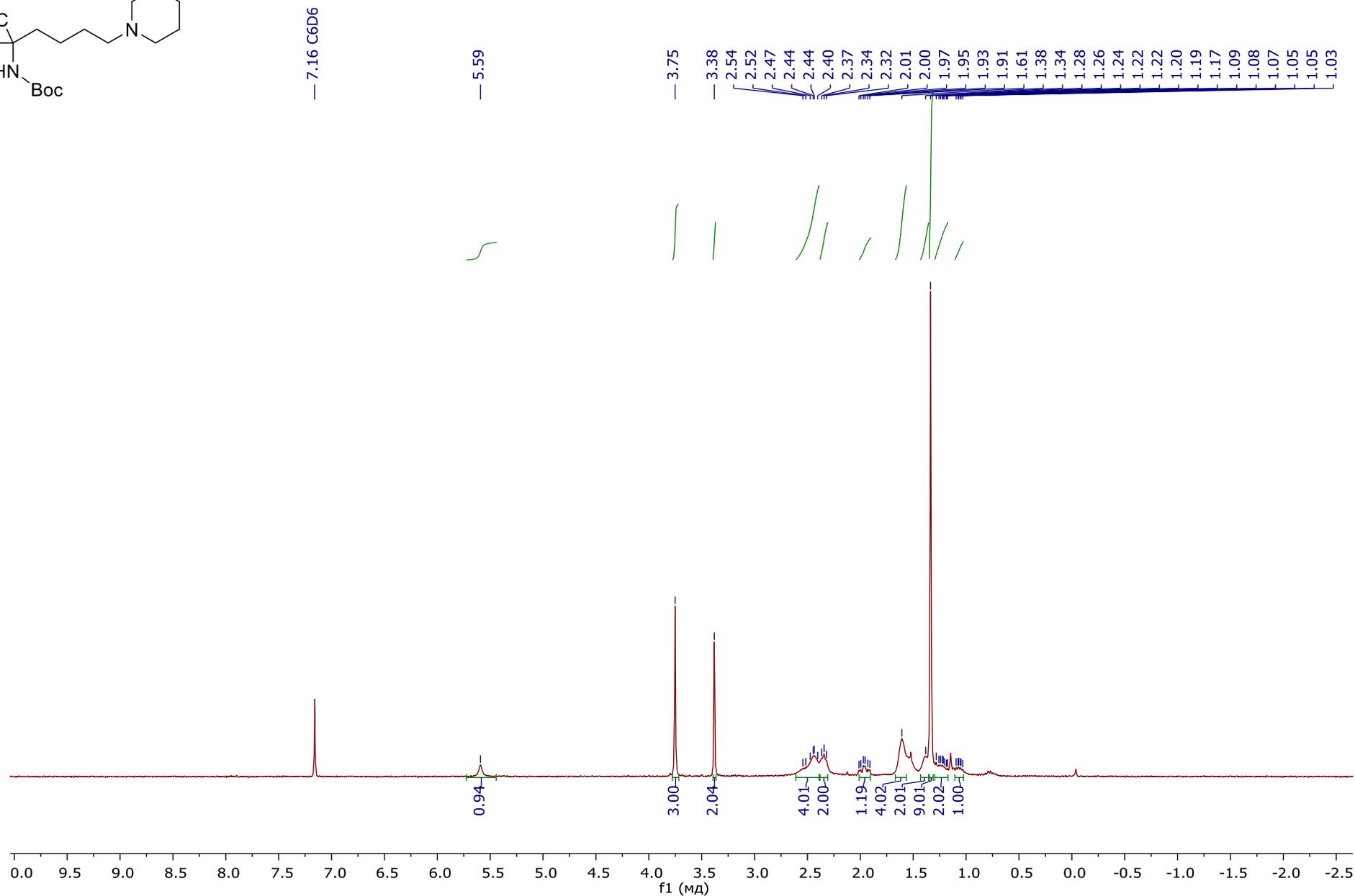
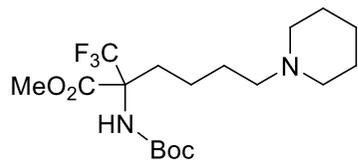
¹H NMR (400 MHz, CDCl₃) of methyl 2-*tert*-butoxycarbonylamino-6-morpholino-2-(trifluoromethyl)hexanoate (6a)



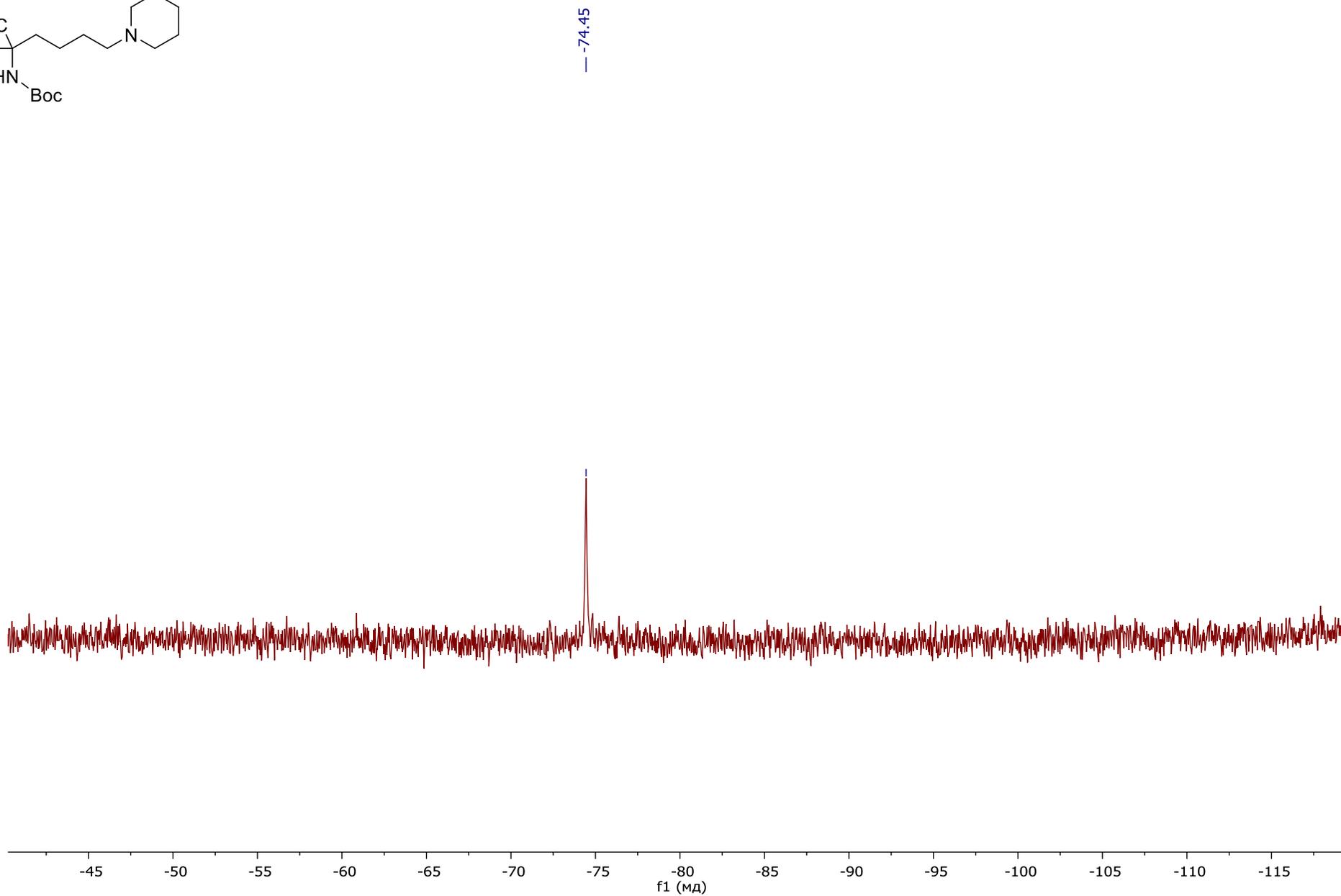
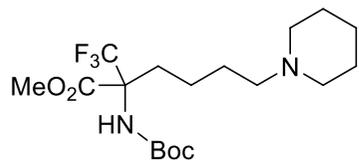
¹⁹F NMR (376 MHz, CDCl₃) of methyl 2-*tert*-butoxycarbonylamino-6-morpholino-2-(trifluoromethyl)hexanoate (6a)



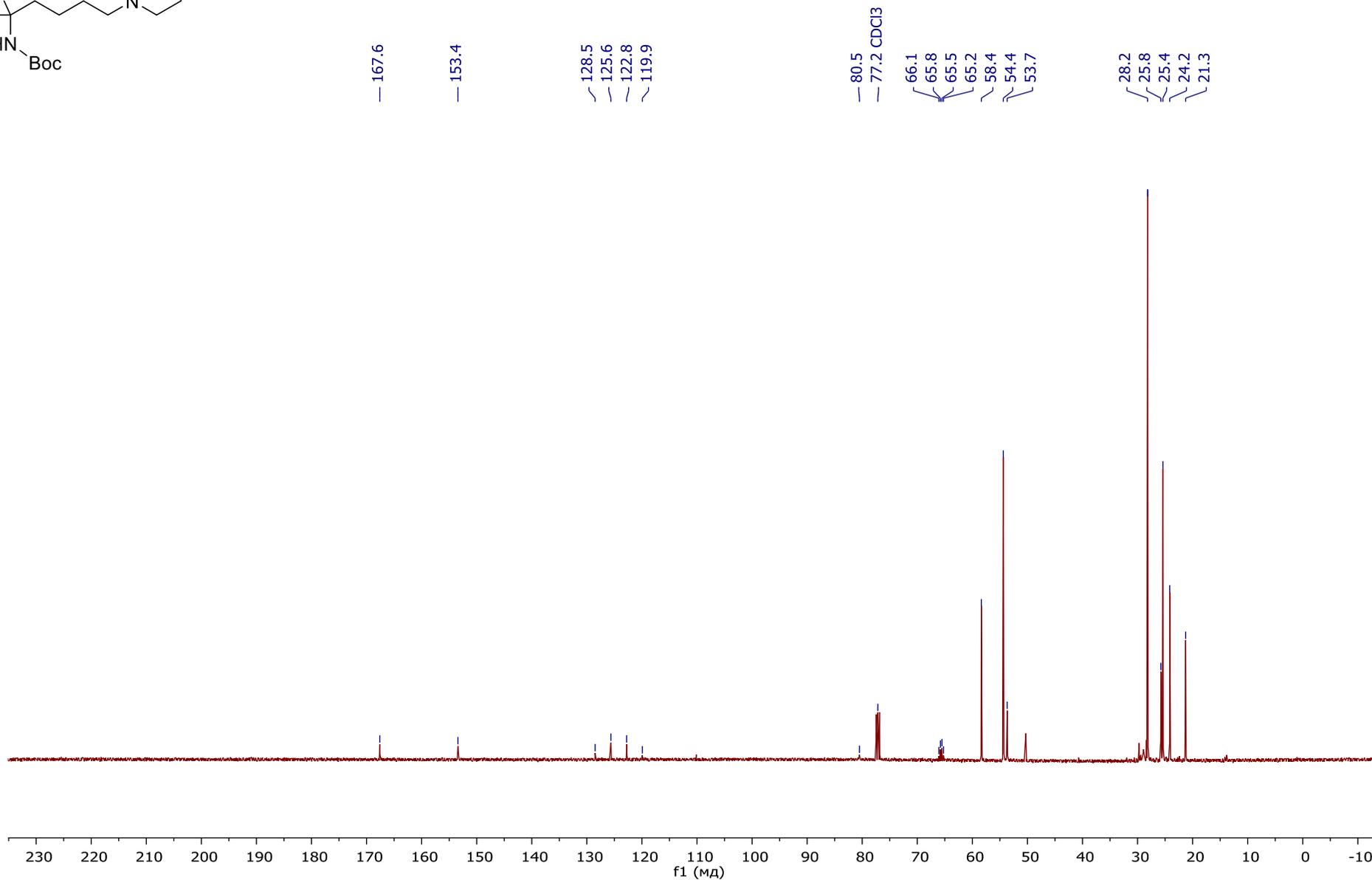
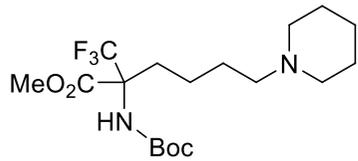
¹³C NMR (400 MHz, CDCl₃) of methyl 2-*tert*-butoxycarbonylamino-6-morpholino-2-(trifluoromethyl)hexanoate (6a)



¹H NMR (300 MHz, C₆D₆) of methyl 2-*tert*-butoxycarbonylamino-6-piperidino-2-(trifluoromethyl)hexanoate (6b)



¹⁹F NMR (282 MHz, C₆D₆) of methyl 2-tert-butoxycarbonylamino-6-piperidino-2-(trifluoromethyl)hexanoate (6b)



¹³C NMR (101 MHz, CDCl₃) of methyl 2-tert-butoxycarbonylamino-6-piperidino-2-(trifluoromethyl)hexanoate (6b)