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General details

The solvents were purified according to the standard procedures.[1] All reagents were obtained from Enamine stock. Melting points were measured on the MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C{^{1}H} NMR), on Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for ^{13}C{^{1}H} NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C{^{1}H} NMR and 376 MHz for ^{19}F{^{1}H} NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, coupling constants (Hz), integration. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Lipophilicity measurements were performed on Agilent 1260 HPLC instrument equipped with diode-array detector (G1365A) and Agilent 6120B Quadrupole LC–MS with ESI ionization. Preparative HPLC purification was performed using XBridge C18 OBD column (30×100 mm, 5 μm). CCDC contains the supplementary

crystallographic data for this paper (CCDC 2497465–2497472). This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The structures were solved by the direct method using the SHELXTL package.[2] The structure overlay was performed using Olex2 package.[3] Structure data for *N*-Boc-isonipecotic acid,[4] *trans*-4-*t*-butyl-1-cyclohexanecarboxylic acid[5] and *N*-benzoylnipecotic acid[6] were found in literature and retrieved from CCDC free of charge.

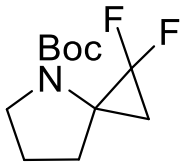
General procedure for the preparation of the alkenes 3a–e:

A solution of corresponding lactam or lactone **1a**–**e** (1.00 mol) in toluene (2 L) and freshly prepared Petasis reagent Me_2TiCp_2[7] (ca. 40 % w/w solution in toluene, 673 g, 1.30 mol for compound **1a** or 778 g, 1.50 mol for other substrates) were mixed in a round-bottomed flask equipped with a condenser and wrapped with aluminum foil. The reaction mixture was carefully warmed to 85 °C in an oil bath and stirred at the same temperature for 16 h. After the reaction completion (according to a ^{1}H NMR spectrum of a small aliquot of the reaction mixture), reaction mixture was cooled to rt and concentrated under reduced pressure at 40 °C (CAUTION! The evaporation step should be performed in the dark). The residue was triturated with hexanes (3.5 L), filtered, and the filtrate was concentrated under reduced pressure to give alkene **3a**–**e** with ca. 80% purity by ^{1}H NMR in ca. 40-70% yield. The product was used in the next step without further purification.

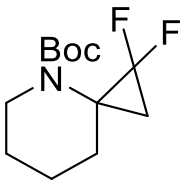
General procedure for the preparation of the difluorocyclopropanes 4a–e:

To a stirred solution of alkene **3a**–**e** (1.00 mol) in THF (3.8 L), solid NaI (30.2 g, 0.200 mol), toluene solution of Me_2TiCp_2 (29.7 g, 35% w/w, 50.0 mmol), and $TMSCF_3$ (148 mL, 1.00 mol) were added, the resulting solution was heated to reflux in the dark, following by the slow dropwise addition of another portion of $TMSCF_3$ (518 mL, 3.50 mol) (Caution! After an induction period of ca. 2 h, vigorous gas evolution was observed). After stirring at reflux for 3 h, the solvent was evaporated under reduced pressure. The residue was dissolved in *t*-BuOMe (0.5 L), filtered, and concentrated under reduced pressure to afford crude product **4a**–**e**, which was purified by flash column chromatography.

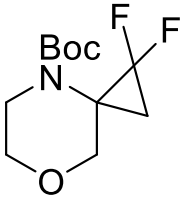
General note: close proximity of the spirocyclic fragment to the N-Boc group increased barrier of rotation about the C–N bond, leading to rotamer interconversion that is slow on the NMR timescale and therefore to significant broadening of the signals, especially in ^{13}C NMR.



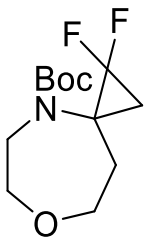
***tert*-Butyl 1,1-difluoro-4-azaspiro[2.4]heptane-4-carboxylate (4a).** The crude material was purified by flash column chromatography on silica gel (hexanes – EtOAc, 10:1 v/v, R_f = 0.4). Yield 50.0 g, 0.214 mol, 49% (from 80.0 g of **3a**). Yellow crystals, mp = 28 – 30 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 – 3.43 (m, 2H), 2.99 (s, 1H), 2.05 – 1.92 (m, 2H), 1.92 – 1.82 (m, 1H), 1.81 – 1.70 (m, 1H), 1.39 (s, 9H), 1.37 – 1.27 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.8, 111.4 (dd, *J* = 299.6, 293.3 Hz), 79.5, 48.0, 47.3 (dd, *J* = 10.5, 8.5 Hz), 29.9, 27.8, 21.8, 17.0. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –138.2 (br s), –142.0 (d, *J* = 153.5 Hz). HRMS (ESI/QTOF) m/z: $[M - C_4H_8 + H]^+$ Calcd for $C_7H_{10}F_2NO_2^+$: 178.0674; Found: 178.0671.



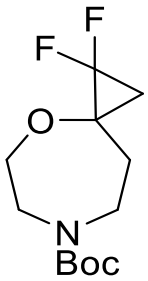
***tert*-Butyl 1,1-difluoro-4-azaspiro[2.5]octane-4-carboxylate (4b).** The crude material was purified by flash column chromatography on silica gel (hexanes – EtOAc, 8:1 v/v, R_f = 0.43). Yield 70.0 g, 0.283 mol, 47% (from 110 g of **3b**). Orange oil. The compound existed as a mixture of rotamers, ca. 1:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (br s, 1H), 2.83 (br s, 1H), 1.85 – 1.62 (m, 3H), 1.58 – 1.45 (m, 3H), 1.44 (s, 9H), 1.37 – 1.07 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.4, 113.7 (t, *J* = 288.7 Hz), 80.2, 77.2, 47.7, 45.1, 28.2, 27.00, 24.7, 22.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –134.3 (d, *J* = 186.0 Hz), –138.9 (d, *J* = 165.0 Hz), –141.8, –144.6 (mixture of rotamers). HRMS (ESI/QTOF) m/z: $[M - C_4H_8 + H]^+$ Calcd for $C_8H_{12}F_2NO_2^+$: 192.0831; Found: 192.0826.



***tert*-Butyl 1,1-difluoro-7-oxa-4-azaspiro[2.5]octane-4-carboxylate (4c).** The crude material was purified by flash column chromatography on silica gel (hexanes – EtOAc, 6:1 v/v, R_f = 0.41). Yield 80.0 g, 0.321 mol, 49% (from 130 g of **3c**). Orange crystals, mp = 80 – 82 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 – 3.47 (m, 5H), 3.40 (s, 1H), 1.85 (br s, 1H), 1.56 (q, *J* = 9.5 Hz, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.9, 112.2 (t, *J* = 288.0 Hz), 81.1, 66.9, 66.3, 47.2, 44.1, 28.1, 21.6. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –140.3 (br s) and –144.7 (br s). HRMS (ESI/QTOF) m/z: $[M - C_4H_8 + H]^+$ Calcd for $C_7H_{10}F_2NO_3^+$: 194.0620; Found: 194.0617.



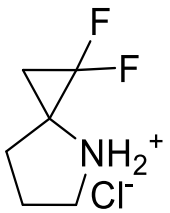
***tert*-Butyl 1,1-difluoro-7-oxa-4-azaspiro[2.6]nonane-4-carboxylate (4d).** The crude material was purified by flash column chromatography on silica gel (hexanes – EtOAc, 3:1 v/v, R_f = 0.4). Yield 95.0 g, 0.361 mol, 64% (from 120 g of **3d**). Orange crystals, mp = 70 – 72 °C. The compound existed as a mixture of rotamers, ca. 80:20. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.81 – 3.57 (m, 5H), 3.03 (br s, 0.2×1H), 2.92 (dt, *J* = 14.3, 5.6 Hz, 0.8×1H), 2.22 (dt, *J* = 14.0, 6.3 Hz, 0.8×1H), 1.79 (br s, 0.2×1H), 1.75 – 1.63 (m, 2H), 1.54 – 1.45 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.0, 113.9 (t, *J* = 132.1, 131.1 Hz), 79.7, 69.8, 69.4, 45.7, 43.7, 32.5, 28.1, 22.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ –136.20 (d, *J* = 157.6 Hz), –137.67 (d, *J* = 157.5 Hz). HRMS (ESI/QTOF) m/z: $[M – C_4H_8 + H]^+$ Calcd for $C_8H_{12}F_2NO_3^+$: 208.0777; Found: 208.0775.



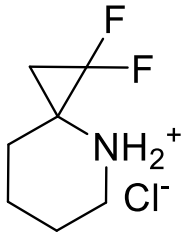
***tert*-Butyl 1,1-difluoro-4-oxa-7-azaspiro[2.6]nonane-7-carboxylate (4e).** The crude material was purified by flash column chromatography on silica gel (hexanes – EtOAc, 6:1 v/v, R_f = 0.33). Yield 62.0 g, 0.235 mol, 40% (from 124 g of **3e**). Orange oil. The compound existed as a mixture of rotamers, ca. 50:50. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 – 3.77 (m, 1H), 3.77 – 3.55 (m, 3H), 3.49 – 3.36 (m, 2H), 2.14 – 2.03 (m, 1H), 2.03 – 1.87 (m, 1H), 1.52 – 1.46 (m, 1H), 1.44 (s, 9H), 1.30 – 1.13 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.9, 113.1 (t, *J* = 292.5 Hz), 79.9, 68.4 and 67.9, 63.2 (dd, *J* = 12.0, 8.5 Hz), 48.5 and 47.9, 44.0 and 43.2, 31.5 and 31.1, 28.4, 22.6 (t, *J* = 9.0 Hz) and 22.2 (t, *J* = 9.7 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ –135.1 (d, *J* = 103.0 Hz) and –135.6 (d, *J* = 103.2 Hz), –144.2 (d, *J* = 69.5 Hz) and –144.6 (d, *J* = 69.6 Hz). HRMS (ESI/QTOF) m/z: $[M – C_4H_8 + H]^+$ Calcd for $C_8H_{12}F_2NO_3^+$: 208.0777; Found: 208.0774.

General procedure for the preparation of the hydrochlorides 5a–e:

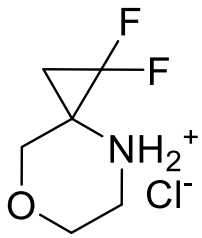
tert-Butyl carbamate **4a-e** (0.100 mol) was dissolved in methanolic HCl (2 M in methanol, 200 mL). After stirring for 30 min at rt, the reaction mixture was concentrated under reduced pressure. The residue was triturated with Et_2O to afford corresponding amine **5a–e** as a hydrochloride.



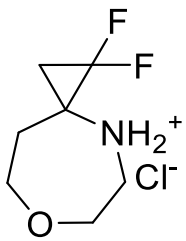
1,1-Difluoro-4-azaspiro[2.4]heptane hydrochloride (5a). Yield 1.00 g, 5.90 mmol, 91% (from 1.50 g of **4a**). Colourless crystals, mp = 130 – 132 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 3.62 – 3.46 (m, 2H), 2.42 – 2.20 (m, 3H), 2.20 – 2.10 (m, 2H), 2.03 – 1.91 (m, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, CD_3OD) δ 109.0 (dd, *J* = 292.6, 286.8 Hz), 47.1, 46.0 (dd, *J* = 9.2, 8.7 Hz), 26.5, 23.3, 19.2 (t, *J* = 10.7 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_3OD) δ –139.0 (d, *J* = 166.5 Hz), –140.3 (d, *J* = 166.4 Hz). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_6H_{10}F_2N^+$: 134.0776; Found: 134.0774.



1,1-Difluoro-4-azaspiro[2.5]octane hydrochloride (5b). Yield 29.0 g, 0.158 mol, 78% (from 50.0 g of **4b**). Brown crystals, mp = 89 – 91 °C. ^{1}H NMR (400 MHz, D_2O) δ 3.22 (t, *J* = 5.7 Hz, 2H), 1.93 – 1.74 (m, 6H), 1.73 – 1.64 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, D_2O) δ 110.6 (dd, *J* = 291.2, 288.5 Hz), 45.2, 42.3 (t, *J* = 10.8 Hz), 24.6, 21.8, 20.6, 20.4 (t, *J* = 10.6 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, D_2O) δ –141.7 (d, *J* = 167.5 Hz), –142.2 (d, *J* = 169.8 Hz). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{12}F_2N^+$: 148.0932; Found: 148.0929.

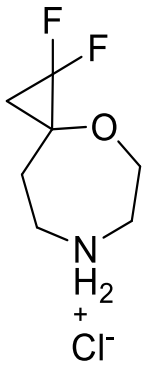


1,1-Difluoro-7-oxa-4-azaspiro[2.5]octane hydrochloride (5c). Yield 52.4 g, 0.282 mol, 88% (from 80.0 g of **4c**). Gray crystals, mp = 103 – 106 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 4.19 – 3.75 (m, 4H), 3.64 – 3.24 (m, 2H), 2.36 – 1.94 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, CD_3OD) δ 109.3 (dd, *J* = 287.7, 287.0 Hz). 63.9, 63.00, 44.0, 40.4 (dd, *J* = 9.5, 9.0 Hz), 18.6 (t, *J* = 11.0 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_3OD) δ –141.9 (d, *J* = 172.6 Hz), –143.5 (d, *J* = 172.5 Hz). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_6H_{10}F_2NO^+$: 150.0725; Found: 150.0723.



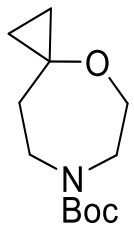
1,1-Difluoro-7-oxa-4-azaspiro[2.6]nonane hydrochloride (5d). Yield 61.9 g, 0.310 mol, 86% (from 95.0 g of **4d**). Gray crystals, mp = 89 – 92 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 3.98 (t, *J* = 4.9 Hz, 2H), 3.84 (t, *J* = 5.8 Hz, 2H), 3.54 – 3.35 (m, 2H), 2.33 – 2.26 (m, 2H), 2.25 – 2.15 (m, 1H), 2.05 (td, *J* = 10.5, 9.0 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (126 MHz, CD_3OD) δ 110.2 (dd, *J* = 289.0, 288.1 Hz), 65.9, 64.2, 42.6 (t,

J = 11.1 Hz), 29.2, 19.8 (t, J = 10.8 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_3OD) δ –140.2 (d, J = 167.9 Hz), –141.1 (d, J = 167.3 Hz). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{12}F_2NO^+$: 164.0881; Found: 164.0882.



1,1-Difluoro-4-oxa-7-azaspiro[2.6]nonane hydrochloride (5e). Yield 44.6 g, 0.223 mol, 95% (from 62.0 g of **4e**). Gray crystals, mp = 139 – 141 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 9.76 (s, 1H), 3.98 – 3.87 (m, 2H), 3.34 – 3.18 (m, 4H), 2.43 – 2.27 (m, 1H), 2.20 – 2.07 (m, 1H), 1.70 – 1.56 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 113.8 (t, J = 292.8 Hz), 65.0, 63.6 (dd, J = 11.7, 8.5 Hz), 47.0, 43.0, 27.7, 22.8 (t, J = 9.1 Hz). $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ –135.3 (d, J = 155.9 Hz), –142.8 (d, J = 155.6 Hz). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{12}F_2NO^+$: 164.0881; Found: 164.0882.

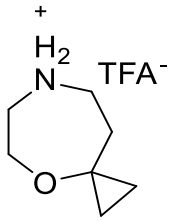
***tert*-Butyl 4-oxa-7-azaspiro[2.6]nonane-7-carboxylate (6e).** Et_2Zn (742.5 mL, 1 M in *n*-hexane) was dissolved in DCM (1.9 L) in a three-neck round-bottomed flask under argon atmosphere. The mixture was cooled to 0 °C and alkene **3e** (132 g, ca. 0.620 mol) was added. After additional stirring at the same temperature for 20 min, CH_2I_2 (74.6 mL, 0.930 mol) was slowly added in a dropwise manner. The mixture was warmed to rt and stirred 4 h. After reaction completion, the reaction mixture was washed with saturated aq NH_4Cl (1.2 L), the organic layer was dried over with Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to give crude product, which was purified by flash chromatography (hexanes – EtOAc 5:1 v/v, R_f = 0.34) to give pure product **6e**.



Yield 39.4 g, 0.173 mol, 28% (from 132 g of **3e**). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.60 – 3.55 (m, 2H), 3.52 – 3.44 (m, 3H), 3.43 – 3.39 (m, 1H), 1.80 (q, J = 5.4, 5.0 Hz, 2H), 1.39 (s, 9H), 0.78 – 0.69 (m, 2H), 0.46 – 0.37 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 155.2, 79.4, 77.3, 67.1 and 66.7, 60.6, 49.0 and 48.4, 44.8 and 44.0, 36.8 and 36.5, 28.4, 13.3 and 12.9. HRMS (ESI/QTOF) m/z: $[M - t\text{Bu} + H]^+$ Calcd for $C_8H_{14}NO_3^+$: 172.0965; Found: 172.0963.

4-Oxa-7-azaspiro[2.6]nonane trifluoroacetate (7e). *tert*-Butyl carbamate **6e** (39.4 g, 0.173 mol) was dissolved in a DCM/TFA mixture (310 mL, 1:1 v/v). After stirring for 30

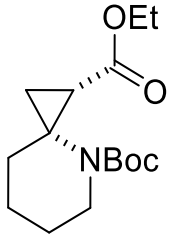
min at rt, the reaction mixture was concentrated under reduced pressure to give corresponding amine as trifluoroacetate **7e**.



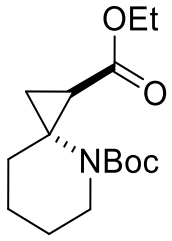
Yield 32.2 g, 0.133 mol, 77% (from 39.4 g of **6e**). Greenish crystals, mp = 78 – 80 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (s, 2H), 3.81 – 3.73 (m, 2H), 3.31 – 3.17 (m, 4H), 2.02 – 1.92 (m, 2H), 0.76 – 0.72 (m, 2H), 0.56 – 0.49 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 158.9 (q, J = 31.9 Hz), 117.0 (q, J = 298.5 Hz), 63.5, 60.8, 46.9, 43.5, 33.2, 12.8. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_7H_{14}NO^+$: 128.1070; Found: 128.1069.

General procedure for the preparation of the esters *trans*-8b,c and *cis*-8b,c:

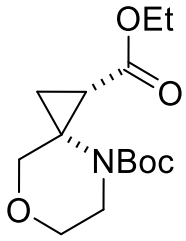
To the solution of crude alkene **3b,c** (ca. 1.00 mol) in DCM (2.3 L) the catalyst Cu(OTf)·benzene (25.1 g, 50.0 mmol) was added in one portion. The vigorously stirred solution was purged with argon and then the solution of ethyl diazoacetate (171 g, 1.50 mol) in DCM (1.5 L) was added in a dropwise manner over 1 h, keeping the internal temperature below 25 °C. After stirring for 3 h at rt, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude material was purified by flash column chromatography to give *N*-Boc-protected amino ester as separate diastereomers.



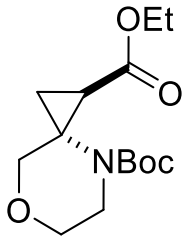
4-*tert*-Butyl 1-ethyl-(1*S*,3*R*)-4-azaspiro[2.5]octane-1,4-dicarboxylate (*cis*-8b). The crude material was purified by flash column chromatography (hexanes – EtOAc, 8:1 v/v, R_f = 0.25). Yield 80.0 g, 0.282 mol, 47% (from 118 g of **3b**). Yellow oil. The compound existed as a mixture of rotamers, ca. 70:30. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 – 3.93 (m, 3H), 2.81 (s, 0.3×1H), 2.34 (s, 0.7×1H), 2.16 – 1.83 (m, 2H), 1.83 – 1.44 (m, 3H), 1.47 (s, 1H), 1.38 (s, 9H), 1.29 – 1.20 (m, 1H), 1.20 (s, 3H), 0.86 (s, 0.3×1H), 0.76, (s, 0.7×1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.4, 154.9, 79.4, 60.3, 46.9, 34.5, 28.3, 26.8, 24.8, 24.0, 14.2 (significant broadening of the piperidine C was observed). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{26}NO_4^+$: 284.1856; Found: 284.1848.



4-*tert*-Butyl 1-ethyl-(1*R*,3*R*)-4-azaspiro[2.5]octane-1,4-dicarboxylate (*trans*-8b). The crude material was purified by flash column chromatography (hexanes – EtOAc, 8:1 v/v, R_f = 0.42). Yield 40.0 g, 0.141 mol, 24% (from 120 g of **3b**). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 – 4.07 (m, 2H), 3.58 (s, 1H), 3.25 (s, 1H), 1.87 (s, 1H), 1.77 (d, *J* = 11.2 Hz, 1H), 1.73 – 1.63 (m, 2H), 1.58 – 1.47 (m, 3H), 1.44 (s, 9H), 1.43 – 1.33 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.7, 155.4, 79.9, 60.5, 46.9, 28.4, 26.6, 25.1, 24.2, 22.5, 14.3. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{26}NO_4^+$: 284.1856; Found: 284.1848.



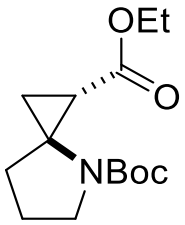
4-*tert*-Butyl 1-ethyl-(1*R*,3*S*)-7-oxa-4-azaspiro[2.5]octane-1,4-dicarboxylate (*cis*-8c). The crude material was purified by flash column chromatography (hexanes – EtOAc, 5:1 v/v, R_f = 0.21). Yield 48.0 g, 0.168 mol, 24% (from 140 g of **3c**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 – 3.99 (m, 2H), 4.00 – 3.60 (m, 3H), 3.60 – 3.44 (m, 1H), 3.22 – 2.71 (m, 2H), 2.33 – 2.03 (m, 1H), 1.92 (t, *J* = 7.4 Hz, 1H), 1.42 (s, 9H), 1.33 – 1.25 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.1, 154.0, 79.8, 72.2, 66.0, 60.00, 47.0, 45.3, 27.8, 25.7, 18.8, 13.7. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_5^+$: 286.1649; Found: 286.1644.



4-*tert*-Butyl 1-ethyl-(1*R*,3*R*)-7-oxa-4-azaspiro[2.5]octane-1,4-dicarboxylate (*trans*-8c). The crude material was purified by flash column chromatography (hexanes – EtOAc, 5:1 v/v, R_f = 0.32). Yield 52.0 g, 0.182 mol, 26% (from 140 g of **3c**). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18 – 4.02 (m, 2H), 3.74 (s, 2H), 3.71 – 3.60 (m, 2H), 3.59 – 3.49 (m, 1H), 3.43 – 3.34 (m, 1H), 1.91 (t, *J* = 8.1 Hz, 1H), 1.62 (s, 1H), 1.48 (t, *J* = 6.5 Hz, 1H), 1.41 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.1, 154.9, 80.6, 67.1, 66.3, 60.8, 47.3, 46.2, 28.3, 27.4, 20.8, 14.1. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_5^+$: 286.1649; Found: 286.1640.

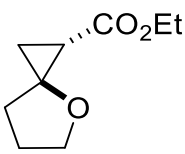
4-*tert*-Butyl 1-ethyl (1*S*,3*S*)-4-azaspiro[2.4]heptane-1,4-dicarboxylate (*trans*-8a). To a solution of crude alkene **3a** (130 g, ca. 0.709 mol) in DCM (1.3 L) the catalyst $Cu(acac)_2$ (9.29 g, 35.5 mmol) was added in one portion. The vigorously stirred solution was purged

with argon and then the solution of ethyldiazoacetate (121 g, 1.06 mol) in DCM (1 L, ca. 1 M) was added in a dropwise manner over 1 h keeping the internal temperature below 25 °C. After stirring for 3 h at rt, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (hexanes – EtOAc 10:1 v/v, R_f = 0.4) to afford pure ester *trans*-**8a**.



Yield 80.0 g, 0.297 mol, 42% (from 130 g of **3a**). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 (q, *J* = 7.1 Hz, 2H), 3.49 – 3.38 (m, 2H), 2.07 – 1.93 (m, 2H), 1.78 (dt, *J* = 12.5, 6.1 Hz, 1H), 1.74 – 1.62 (m, 1H), 1.37 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 5.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.5, 152.8, 79.6, 60.3, 50.2, 48.5, 31.1, 28.4, 23.0, 22.5, 15.4, 14.3. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NO_4^+$: 270.1700; Found: 270.1692.

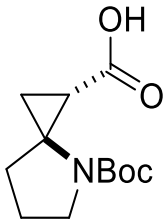
Ethyl 4-oxaspiro[2.4]heptane-1-carboxylate (8f). After completion of the olefination step, the reaction mixture containing alkene **3f** (ca. 90.0 g, 1.07 mol) was diluted with an equal volume of DCM (1.8 L) relative to the amount of toluene used in the previous step, following by the addition of the catalyst $[CuOTf]_2$·benzene (15.6 g, 53.5 mmol) and the resulting mixture was purged with argon. A solution of ethyl diazoacetate (183 g, 1.61 mol) in DCM was added in a dropwise manner over 1 h while maintaining the internal temperature below 25 °C. After stirring for 3 h at rt, the reaction mixture was concentrated under reduced pressure at 40 °C (Caution! In the dark!). The residue was treated with *t*-BuOMe (3 L), filtered, the filtrate was concentrated under reduced pressure to afford crude ester **8f**. The crude material was purified by distillation under reduced pressure (bp = 59 – 61 °C (1 mmHg)) and flash column chromatography on silica gel (hexanes – EtOAc, 10:1 v/v, R_f = 0.37) to give pure ester **8f**.



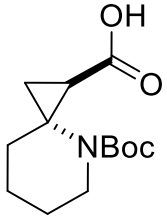
Yield 38.3 g, 0.225 mol, 21% (over 2 steps, from 92.0 g of **3f**). Colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 – 4.07 (m, 2H), 3.94 – 3.87 (m, 1H), 3.85 – 3.78 (m, 1H), 2.15 – 1.93 (m, 4H), 1.86 (dd, *J* = 9.6, 6.7 Hz, 1H), 1.43 (dd, *J* = 9.6, 5.9 Hz, 1H), 1.30 (t, *J* = 6.4 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.0, 70.7, 68.3, 60.3, 27.3, 25.9, 25.6, 17.4, 14.3. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_9H_{15}O_3^+$: 171.1016; Found: 171.1006.

General procedure for the preparation of the acids *trans*-9a and *trans*-9b:

To a solution of ester *trans*-**8a** or *trans*-**8b** (0.100 mol) in MeOH/H_2O mixture (250 mL, 1:1 v/v) in a round-bottomed flask, KOH (28.1 g, 0.500 mol) was added. The obtained mixture was stirred at 45 °C for 1 h. After the reaction completion, methanol was evaporated under reduced pressure, and the residue was acidified with 10% aq $NaHSO_4$ to pH = 2 and extracted with *t*-BuOMe (2 × 150 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by crystallization from hexanes or hexanes – *t*-BuOMe mixture to give *N*-Boc protected amino acid.



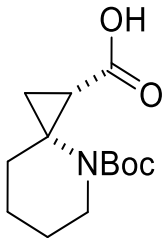
(1*S*,3*S*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.4]heptane-1-carboxylic acid (*trans*-9a). The crude material was purified by crystallization from hexanes – *t*-BuOMe mixture (2:1 v/v). Yield 20.0 g, 82.9 mmol, 56% (from 40.0 g of *trans*-**8a**). Colourless crystals, mp = 70 – 72 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 3.48 (s, 2H), 2.55 (s, 1H), 2.36 – 1.98 (m, 3H), 1.94 – 1.70 (m, 2H), 1.42 (s, 9H), 1.11 (s, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3OD) δ 173.8, 152.6, 79.3, 49.4, 47.8, 30.5, 26.9, 22.0, 21.5, 14.2. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{20}NO_4^+$: 242.1387; Found: 242.1382.



(1*R*,3*R*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.5]octane-1-carboxylic acid (*trans*-9b). The crude material was purified by crystallization from minimum amounts of hexanes. Yield 14.0 g, 54.8 mmol, 40% (from 40.0 g of *trans*-**8b**). Colourless crystals, mp = 105 – 107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.46 (br s, 1H), 3.58 (s, 1H), 3.23 (s, 1H), 1.86 (t, *J* = 7.8 Hz, 1H), 1.82 – 1.61 (m, 3H), 1.61 – 1.47 (m, 4H), 1.43 (s, 9H), 1.40 – 1.36 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 176.8, 154.8, 79.7, 47.2, 46.5, 26.2, 24.5, 23.6, 22.5. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{22}NO_4^+$: 256.1543; Found: 256.1536.

(1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.5]octane-1-carboxylic acid (*cis*-9b). To a solution of ester *cis*-**8b** (0.100 mol) in MeOH/H_2O mixture (250 mL, 1:1 v/v) in a round-bottomed flask KOH (28.1 g, 0.500 mol) was added. The obtained mixture was stirred at 45 °C for 16 h. After the reaction completion, methanol was evaporated under reduced pressure, the residue was acidified with 10% aq $NaHSO_4$ to pH = 2 and extracted with *t*-BuOMe (2×150 mL). The organic layer was dried over Na_2SO_4, filtered and

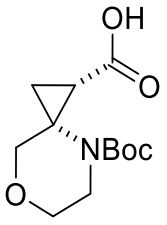
concentrated under reduced pressure. The crude material was purified by crystallization from *n*-hexane to give *N*-Boc protected amino acid *cis*-**9b**.



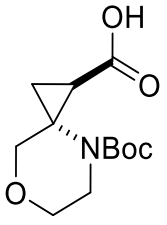
Yield 21.0 g, 82.3 mmol, 80% (from 30.0 g of *cis*-**8b**). Yellow crystals, mp = 126 – 129 °C. Compound existed as a ca. 3:7 mixture of rotamers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.20 (br s, 1H), 4.17 – 3.88 (m, 1H), 2.92 – 2.79 (m, 0.3×1H), 2.51 (q, *J* = 14.2, 13.4 Hz, 0.7×1H), 2.14 (s, 1H), 2.00 (s, 1H), 1.83 – 1.42 (m, 6H), 1.40 (s, 9H), 1.00 (s, 0.3×1H), 0.84 (s, 0.7×1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.0, 154.4, 79.3, 47.5, 45.7, 33.9, 27.8, 25.8, 24.4, 23.8, 23.5. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{22}NO_4^+$: 256.1543; Found: 256.1539.

General procedure for the preparation of the acids *trans*-9c and *cis*-9c:

To a solution of corresponding ester *trans*-**8c** or *cis*-**8c** (0.100 mol) in MeOH/H_2O mixture (280 mL, 1:1 v/v) in a round-bottomed flask KOH (28.1 g, 0.500 mol) was added. The obtained mixture was stirred at 50 °C for 1 h. After the reaction completion, methanol was evaporated under reduced pressure, the residue was acidified with 10% aq $NaHSO_4$ to pH = 2 and extracted with *t*-BuOMe (2 × 200 mL). The organic layer was dried over Na_2SO_4, filtered and and concentrated under reduced pressure. The crude material was purified by crystallization from hexanes – *t*-BuOMe mixture (2:1 v/v) to afford corresponding *N*-Boc protected amino acids.



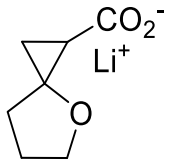
(1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-7-oxa-4-azaspiro[2.5]octane-1-carboxylic acid (*cis*-9c). Yield 34.0 g, 0.132 mol, 79% (from 48.0 g of *cis*-**8c**). Yellow crystals, mp = 127 – 129 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.53 (br s, 1H), 4.06 – 3.43 (m, 4H), 2.98 (s, 2H), 2.34 (s, 1H), 1.96 (t, *J* = 7.4 Hz, 1H), 1.43 (s, 9H), 1.41 – 1.30 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.1, 153.9, 80.2, 72.3, 66.0, 46.3, 45.8, 27.8, 25.4, 19.6. HRMS (ESI/QTOF) m/z: $[M - t\text{Bu} + H]^+$ Calcd for $C_8H_{12}NO_5^+$: 202.0707; Found: 202.0704.



(1*R*,3*R*)-4-[(*tert*-butoxy)carbonyl]-7-oxa-4-azaspiro[2.5]octane-1-carboxylic acid (*trans*-9c). Yield 22.0 g, 85.5 mmol, 47% (from 52.0 g of *trans*-**8c**). Brown crystals, mp = 114 – 116 °C. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 10.77 (br s, 1H), 3.90 – 3.69 (m, 4H), 3.68 – 3.52 (m, 1H), 3.50 – 3.35 (m, 1H), 1.92 (t, *J* = 7.6 Hz, 1H), 1.78 (s, 1H), 1.56 (t, *J* = 6.5 Hz, 1H), 1.44 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 175.6, 154.3, 80.5, 66.5, 65.8, 46.8, 46.5, 27.8, 26.6, 20.9. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{20}NO_5^+$: 258.1336; Found: 258.1329.

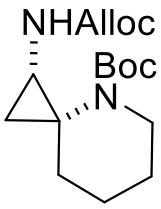
Lithium 4-oxaspiro[2.4]heptane-1-carboxylate (9f). To a solution of ester **8f** (38.3 g, 0.225 mol) in a MeOH/H_2O mixture (350 mL, 9:1 v/v) in one neck round-bottomed flask $LiOH·H_2O$ (9.44 g, 0.225 mol) was added. After stirring for 16 h at rt, the reaction mixture was concentrated under reduced pressure to give the target carboxylic acid in the form of lithium salt **9f**.



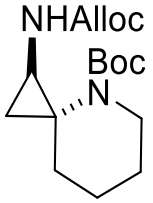
Yield 32.0 g, 0.216 mol, 96% (from 38.3 g of **8f**). Colourless powder, mp = 200 – 202 °C. ^1H NMR (600 MHz, D_2O) δ 3.84 – 3.76 (m, 1H), 3.73 (q, *J* = 7.0, 6.4 Hz, 1H), 2.01 – 1.82 (m, 3H), 1.66 (t, *J* = 8.1 Hz, 1H), 1.14 (d, *J* = 7.3 Hz, 1H), 1.03 (t, *J* = 6.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, D_2O) δ 179.8, 69.1, 68.00, 28.4, 27.1, 25.2, 15.4. HRMS (ESI/QTOF) m/z: $[M - H]^-$ Calcd for $C_7H_9O_3^-$: 141.0557; Found: 141.0556.

General procedure for the preparation of allyl carbamates *trans*-10b,c and *cis*-10b,c

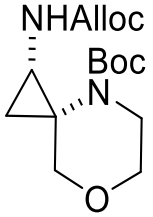
To a pre-cooled to −15 °C solution of carboxylic acid *trans*-**9b,c** or *cis*-**9b,c** (1.00 mmol) and Et_3N (0.209 mL, 1.50 mmol) in THF (5 mL), ethyl chloroformate (0.0912 mL, 1.20 mmol) was added in a dropwise manner under argon atmosphere. The resulting mixture was stirred at 0 °C for 1 h, following by the addition of the 20% aq NaN_3 (1.63 g, 5.00 mmol) at −10 °C. After stirring for 1 h at rt, the reaction mixture was diluted with water (75 mL) and extracted with toluene (75 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to half of the starting volume. The obtained solution was diluted with toluene (35 mL), followed by the addition of AllylOH (0.204 mL, 3.00 mmol). The reaction mixture was slowly heated to 100 °C in an oil bath and stirred for 16 h at this temperature. After the reaction completion, the reaction mixture was concentrated under reduced pressure give the corresponding crude allyl carbamate.



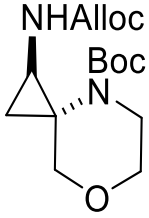
***tert*-Butyl (1*R*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate (*cis*-10b).** The crude material was purified by flash column chromatography (hexanes – EtOAc, 6:1 v/v, R_f = 0.22). Yield 600 mg, 1.93 mmol, 33% (from 1.50 g of *cis*-**9b**). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 – 5.86 (m, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.57 (s, 2H), 2.71 (d, *J* = 7.5 Hz, 1H), 1.85 – 1.67 (m, 3H), 1.59 (s, 1H), 1.57 – 1.52 (m, 3H), 1.49 (s, 9H), 1.47 (s, 1H), 1.07 (s, 1H), 0.90 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.4, 132.4, 116.9, 79.7, 64.9, 46.8, 34.4, 31.4, 27.8, 24.5, 22.9, 19.7 (significant broadening of the piperidine core signals was observed). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{27}N_2O_4^+$: 311.1965; Found: 311.1962.



***tert*-Butyl (1*S*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate (*trans*-10b).** The crude material was purified by flash column chromatography (hexanes – EtOAc, 3:1 v/v, R_f = 0.43). Yield 560 mg, 1.80 mmol, 70% (from 660 mg of *trans*-**9b**). Yellow powder, mp = 100 – 101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.85 (m, 1H), 5.32 (d, *J* = 17.5 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.87 (s, 1H), 4.59 (s, 2H), 3.48 (s, 2H), 2.83 (s, 1H), 1.75 – 1.49 (m, 6H), 1.47 (s, 9H), 1.43 – 1.36 (m, 1H), 0.76 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.3, 155.2, 132.2, 117.2, 79.00, 65.0, 45.6, 41.9, 35.9, 27.9, 26.7, 24.6, 23.0, 20.5. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{27}N_2O_4^+$: 311.1965; Found: 311.1959.



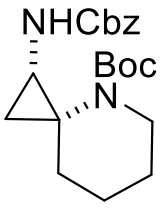
***tert*-Butyl (1*R*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate (*cis*-10c).** The crude material was purified by flash column chromatography (hexanes – EtOAc, 1:1 v/v, R_f = 0.49). Yield 730 mg, 2.34 mmol, 60% (from 1.00 g of *cis*-**9c**). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 – 5.86 (m, 1H), 5.32 (d, *J* = 17.5 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.59 (s, 2H), 3.84 – 3.57 (m, 3H), 3.46 (s, 3H), 2.94 – 2.84 (m, 1H), 1.50 (s, 9H), 1.32 – 1.16 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.2, 155.7, 132.3, 117.1, 80.5, 70.8, 65.7, 65.1, 47.1, 42.1, 33.0, 27.8, 18.3. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{25}N_2O_5^+$: 313.1758; Found: 313.1755.



***tert*-Butyl (1*S*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate (*trans*-10c).** The crude material was purified by flash column chromatography (hexanes – EtOAc, 1:1 v/v, R_f = 0.53). Yield 800 mg, 2.56 mmol, 66% (from 1.00 g of *trans*-**9c**). Colourless powder, mp = 85 – 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (s, 1H), 5.32 (d, *J* = 17.3 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.59 (s, 2H), 3.81 (q, *J* = 12.4, 11.6 Hz, 3H), 3.59 (t, *J* = 11.0 Hz, 1H), 3.47 (t, *J* = 11.3 Hz, 2H), 2.75 (t, *J* = 7.1 Hz, 1H), 1.78 (t, *J* = 6.9 Hz, 1H), 1.47 (s, 9H), 1.11 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.2, 154.7, 132.1, 117.2, 79.9, 67.6, 66.0, 65.1, 46.3, 42.2, 34.5, 27.8, 20.1. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{25}N_2O_5^+$: 313.1758; Found: 313.1749.

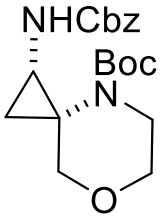
General procedure for the preparation of benzyl carbamates *cis*-11b,c and *trans*-11c:

To a pre-cooled to −15 °C mechanically stirred solution of carboxylic acid *cis*-**9b**,**c** or *trans*-**9c** (1.00 mmol) and Et_3N (0.209 mL, 1.50 mmol) in THF (5 mL) ethyl chloroformate (0.0912 mL, 1.20 mmol) was added in a dropwise manner under argon atmosphere. The resulting mixture was stirred at 0 °C for 1 h, following by the addition of 20% aq NaN_3 (1.63 g, 5.00 mmol) at −10 °C. After stirring for 1 h at rt, the reaction mixture was diluted with water (15 mL) and extracted with toluene (15 mL). The organic layer was dried over Na_2SO_4, filtered and and concentrated under reduced pressure to the half of the starting volume. The obtained solution was diluted with toluene (2.5 mL), following by the addition of BnOH (0.108 mL,1.05 mmol). The reaction mixture was slowly heated to 100 °C in an oil bath and stirred for 16 h at this temperature. After the reaction completion, the reaction mixture was concentrated under reduced pressure to give corresponding crude carbamate.

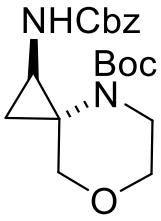


***tert*-Butyl (1*S*,3*R*)-1-{[(benzyloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate (*cis*-11b).** The crude material was purified by flash column chromatography (hexanes – EtOAc, 4:1 v/v, R_f = 0.33). Yield 650 mg, 1.80 mmol, 30% (from 1.50 g of *cis*-**9b**). Colourless powder, mp = 85 – 87 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 5.21 – 5.04 (m, 2H), 2.71 (s, 1H), 1.81 – 1.60 (m, 2H),

1.58 – 1.49 (m, 2H), 1.46 (s, 9H), 1.22 – 0.57 (m, 4H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 157.1, 136.7, 128.4, 128.0, 80.3, 66.5, 47.3, 42.9, 35.7, 32.0, 28.4, 25.1, 23.4, 20.3 (significant broadening of the piperidine core signals was observed). HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{29}N_2O_4^+$: 361.2122; Found: 361.2130.

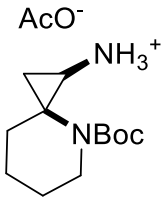


***tert*-Butyl (1*R*,3*S*)-1-{[(benzyloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate (*cis*-11c).** The crude material was purified by flash column chromatography (hexanes – EtOAc, 3:2 v/v, R_f = 0.34). Yield 44.5 g, 0.123 mol, 62% (from 51.0 g of *cis*-**9c**). Colourless powder, mp = 130 – 131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 5H), 5.26 – 4.98 (m, 2H), 3.80 – 3.55 (m, 3H), 3.56 – 3.14 (m, 3H), 2.90 (s, 1H), 1.46 (s, 9H), 1.29 – 1.14 (m, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 156.8, 156.3, 136.5, 128.5, 128.1, 81.1, 71.4, 66.8, 66.2, 47.7, 42.6, 33.6, 28.3, 18.9. HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_2O_5Na^+$: 385.1734; Found: 385.1732.



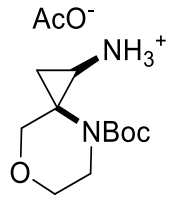
***tert*-Butyl (1*S*,3*S*)-1-{[(benzyloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate (*trans*-11c).** The crude material was purified by flash column chromatography (hexanes – EtOAc, 3:2 v/v, R_f = 0.34). Yield 39.0 g, 0.108 mol, 57% (from 48.5 g of *trans*-**9c**). Colourless powder, mp = 110 – 112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 5H), 5.29 (s, 1H), 5.10 (s, 3H), 3.90 – 3.65 (m, 3H), 3.55 (s, 1H), 3.45 (d, *J* = 11.8 Hz, 2H), 2.83 – 2.67 (m, 1H), 1.74 (s, 1H), 1.44 (s, 9H), 1.08 (s, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.8, 155.2, 136.2, 128.5, 128.2, 80.4, 68.2, 66.9, 66.5, 46.9, 42.7, 35.0, 28.3, 20.8. HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_2O_5Na^+$: 385.1734; Found: 385.1732.

***tert*-Butyl (1*R*,3*S*)-1-amino-4-azaspiro[2.5]octane-4-carboxylate acetate (*cis*-12b).** To a solution of benzyl carbamate *cis*-**11b** (0.65 g, 1.81 mmol) in 1,4-dioxane (10 mL) and Pd/C (10% w/w, 193 mg) and AcOH (0.103 mL, 0.101 mol) were added. The resulting mixture was stirred under H_2 (1 atm) for 16 h. After the reaction completion, the catalyst was filtered off, filtrate was concentrated under reduced pressure to afford corresponding amine as an acetate *cis*-**12b**.



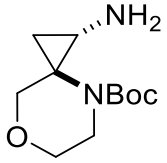
Yield 450 mg, 1.57 mmol, 87% (from 650 mg of *cis*-**11c**). Yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ 3.70 – 3.66 (m, 2H), 3.33 (dt, *J* = 4.2, 2.1 Hz, 1H), 2.56 (s, 1H), 1.95 (s, 1H), 1.83 – 1.72 (m, 2H), 1.64 – 1.54 (m, 2H), 1.52 (s, 9H), 1.48 – 1.42 (m, 2H), 1.18 – 1.06 (m, 2H), 1.06 – 0.91 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CD_3OD) δ 178.2, 157.1, 80.3, 66.7, 42.1, 33.5, 31.2, 27.2, 24.6, 23.1, 22.4, 18.5. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{23}N_2O_2^+$: 227.1754; Found: 227.1750.

***tert*-Butyl (1*R*,3*S*)-1-amino-7-oxa-4-azaspiro[2.5]octane-4-carboxylate acetate (*cis*-12c).** To a solution of benzyl carbamate *cis*-**11c** (36.5 g, 0.101 mol) in methanol (550 mL) Pd/C (10% w/w, 5.37 g) and AcOH (5.77 mL, 0.101 mol) were added. The resulting mixture was stirred under H_2 (1 atm) for 16 h. After the reaction completion, the catalyst was filtered off, filtrate was concentrated under reduced pressure to afford amine as an acetate *cis*-**9c**.



Yield 25.0 g, 86.7 mmol, 86% (from 36.5 g of *cis*-**11c**). Yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ 3.81 (br s, 1H), 3.71 (d, *J* = 11.4 Hz, 1H), 3.65 – 3.49 (m, 2H), 3.41 – 3.29 (m, 1H), 3.19 (br s, 1H), 2.63 (t, *J* = 6.7 Hz, 1H), 1.91 (s, 3H), 1.47 (s, 9H), 1.44 – 1.38 (m,1H), 1.28 – 1.17 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD) δ 176.3, 156.7, 81.0, 70.7, 65.7, 42.0, 32.5, 27.2, 21.1, 17.1. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{21}N_2O_3^+$: 229.1547; Found: 229.1542.

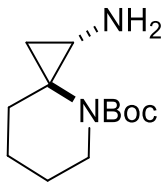
***tert*-Butyl (1*R*,3*R*)-1-amino-7-oxa-4-azaspiro[2.5]octane-4-carboxylate (*trans*-12c).** To a solution of benzyl carbamate *trans*-**11c** (39.0 g, 0.108 mol) in 1,4-dioxane (600 mL) Pd/C (10% w/w, 5.74 g) as added. The resulting mixture was stirred under H_2 (1 atm) for 16 h. After the reaction completion, the catalyst was filtered off, filtrate was concentrated under reduced pressure and purified by flash column chromatography (hexanes – EtOAc – Et_3N 2:1:1 v/v, R_f = 0.41) to afford amine *trans*-**12c**.



Yield 15.0 g, 65.7 mmol, 61% (from 39.0 g of *trans*-**11c**). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (d, *J* = 11.5 Hz, 1H), 3.69 (d, *J* = 11.8 Hz, 1H), 3.68 – 3.54 (m, 3H), 3.49 – 3.40 (m, 1H), 2.69 – 2.64 (m, 1H), 2.13 (s, 2H), 1.44 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 1H), 0.80 (t, *J* = 5.8 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.0, 79.5, 68.0, 66.1, 46.5, 42.8,

36.4, 27.9, 20.8. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{21}N_2O_3^+$: 229.1547; Found: 229.1538.

***tert*-Butyl (1*S*,3*S*)-1-amino-4-azaspiro[2.5]octane-4-carboxylate (*trans*-12b).** To a solution of *N*-Alloc-protected amine *trans*-**10b** (600 mg, 1.93 mmol) in DCM (15 ml) $Pd(PPh_3)_4$ (67.0 mg, 0.058 mmol) and Et_2NH (0.300 mL, 2.90 mmol) were added. The reaction mixture was stirred at rt for 1.5 h. After the reaction completion, the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (hexanes – EtOAc – Et_3N 5:1:1 v/v, R_f = 0.34) to afford target amine *trans*-**12b**.



Yield 300 mg, 1.32 mmol, 68% (from 600 mg of *trans*-**10b**). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53 (s, 1H), 3.11 (s, 1H), 2.62 (t, *J* = 6.6 Hz, 1H), 1.78 – 1.69 (m, 1H), 1.69 – 1.56 (m, 2H), 1.57 – 1.46 (m, 5H), 1.44 (s, 9H), 0.86 (t, *J* = 7.0 Hz, 1H), 0.41 – 0.33 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.4, 78.6, 45.6, 42.9, 37.8, 27.9, 26.4, 25.1, 23.7, 21.00. HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{23}N_2O_2^+$: 227.1754; Found: 227.1749.

Physicochemical experiments

Determination of Distribution Coefficient (LogP)

Benzamide derivatization was used because of specific features of the measurement method, i.e., facilitated quantitative analysis by the tandem mass spectrometry and the subsequent interpretation of the results, as well as shifting the Log*P* values into a more suitable range.

Method

Applied method corresponded to those reported previously.[8]

Incubations were carried out in Eppendorf-type polypropylene microtubes in triplicates. 2.5 µL aliquot of 20 mM DMSO stock of a test compound was added into the previously mutually saturated mixture containing 500 µL of H_2O and 500 µL of octanol. The solution was allowed to mix in a rotator for 1 hour at 30 rpm. Phase separation was assured by centrifugation for 2 min at 6000 rpm. The octanol phase was diluted 100-fold with 40% acetonitrile, and the aqueous phase was diluted 10-fold. The samples (both phases) were analyzed using an HPLC system coupled with a tandem mass spectrometer. Mebendazole was used as a reference compound.

Calculations of the partition ratios were carried out using the equation below.

$$P = \frac{p_o \cdot S_O}{p_p \cdot S_P}$$

where: S_O– peak area of the analyte in octanol phase

S_P– peak area of the analyte in water

p_o – dilution coefficient for octanol phase

p_p – dilution coefficient for aqueous phase

X-Ray data

X-Ray diffraction studies were performed on an automatic “Bruker APEX II” diffractometer (graphite monochromated MoKα radiation, CCD-detector, φ- and ω-scanning). The structures were solved using OLEX2[3] package with SHELXT and SHELXL modules [2]. Positions of the hydrogen atoms were located from electron density difference maps and refined by “riding” model with U_{iso} = nU_{eq} of the carrier atom (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms). The crystallographic data and experimental parameters are listed in Table S1. Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). The deposition numbers are given in Table S1.

Table S1. The crystallographic data and experimental parameters for compounds **4a**, **4c**, **4d**, *cis*-**9b**, *cis*-**9c**, *trans*-**9a**, *trans*-**9b** and *trans*-**9c**.

Parameter	**4a**	**4c**	**4d**	*cis*-**9b**	*cis*-**9c**	*trans*-**9a**	*trans*-**9b**	*trans*-**9c**
Unit cell a, Å	12.0887(13)	12.0124(12)	13.8252(8)	9.9152(8)	34.780(2)	7.4095(7)	9.3040(3)	9.0041(11)
b, Å	7.1133(7)	9.4611(8)	8.6262(5)	11.9315(8)	34.780(2)	9.9652(11)	9.3040(3)	20.947(3)
c, Å	14.3070(15)	10.8809(9)	12.0107(9)	24.1840(16)	6.0905(5)	10.3101(11)	16.1197(8)	7.5369(11)
α, deg	90.0	90.0	90.0	90.0	90.0	106.988(7)	90.0	90.0
β, deg	95.555(6)	92.868(7)	110.273(3)	90.0	90.0	102.226(7)	90.0	109.647(4)
γ, deg	90.0	90.0	90.0	90.0	120.0	106.171(7)	90.0	90.0
V, Å^3	1224.5(2)	1235.07(19)	1343.65(15)	2861.0(4)	6380.4(9)	662.68(13)	1395.39(11)	1338.8(3)
F(000)	496	528	560	1104	2484	260	552	552
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Trigonal	Triclinic	Tetragonal	Monoclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/c$	*P*bca	*R*-3	*P*-1	$P4_3$	$P2_1/c$

Z	4	4	4	8	18	2	4	4
T, K	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)
μ, mm^{-1}	0.106	0.116	0.110	0.087	0.094	0.090	0.089	0.099
D_{calc}, g/cm^3	1.265	1.340	1.301	1.185	1.205	1.209	1.215	1.276
$2\Theta_{max}$, grad	50	50	50	50	50	50	50	50
Measured reflections	15414	8321	9186	36270	30293	9336	20217	8400
Independent reflections	2156	2176	2375	2521	2502	2344	2474	2354
R_{int}	0.0390	0.0580	0.0476	0.0873	0.0952	0.0447	0.0359	0.0346
Reflections with F>4σ(F)	1568	1438	1751	1656	1847	1444	2280	1848
Parameters	149	157	166	167	167	158	168	167
R_1 [I>2σ(I)]	0.0433	0.0531	0.0567	0.0635	0.0714	0.0506	0.0365	0.0387
wR_2 [I>2σ(I)]	0.1174	0.1170	0.1166	0.1128	0.1572	0.1171	0.0714	0.0828
R_1 [all data]	0.0637	0.0901	0.0809	0.1113	0.0980	0.0951	0.0418	0.0539
wR_2 [all data]	0.1382	0.1391	0.1237	0.1291	0.1687	0.1384	0.0733	0.0924
S	1.039	1.034	1.124	1.085	1.150	1.025	1.062	1.029
CCDC number	2497468	2497469	2497466	2497471	2497470	2497467	2497465	2497472

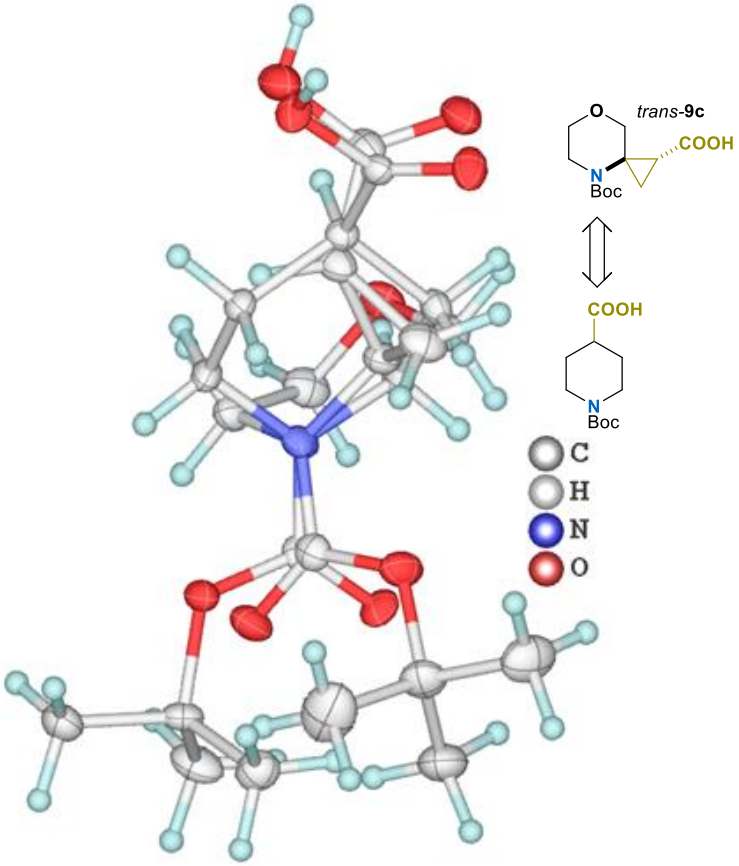


Figure S1. Overlay of compound *trans*-**9c** and *N*-Boc-isonipecotic acid.[4]

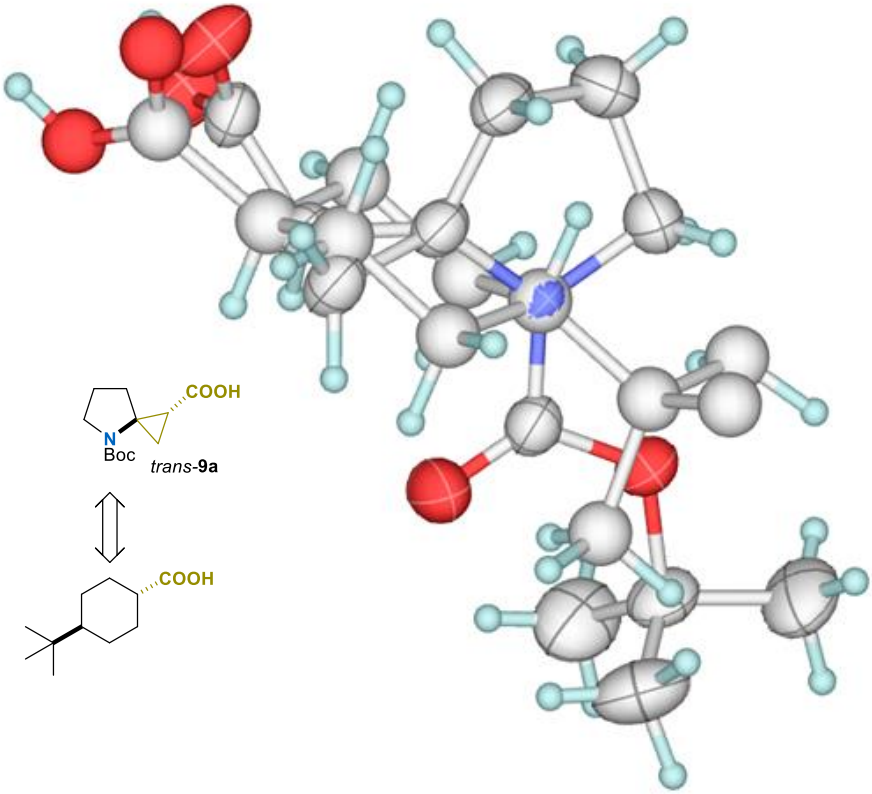


Figure S2. Overlay of compound *trans*-**9a** and *trans*-4-*t*-butyl-1-cyclohexanecarboxylic acid.[5]

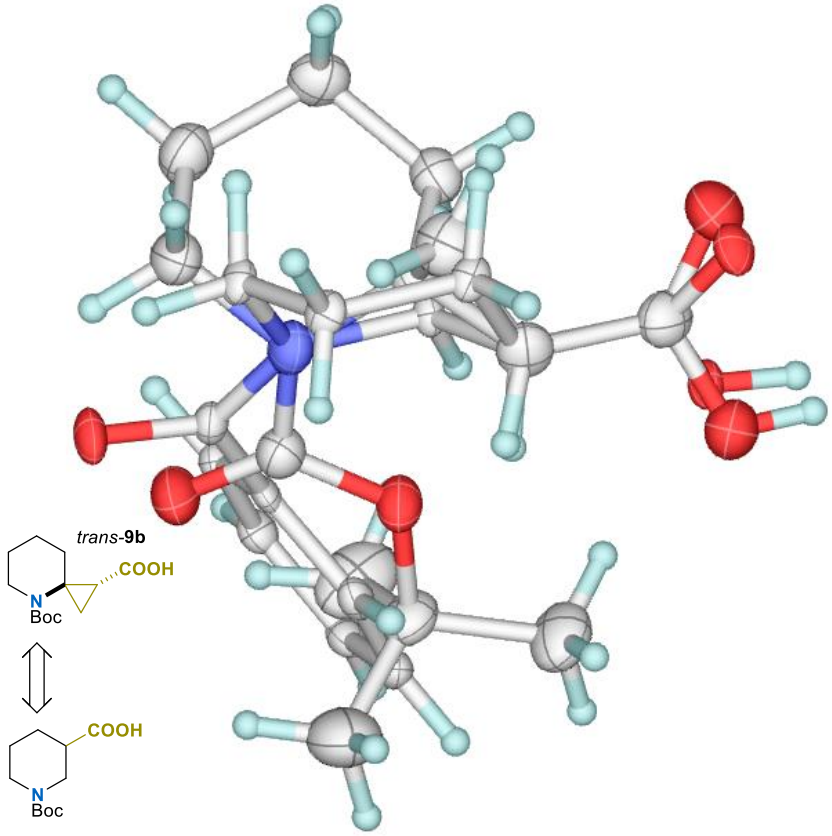
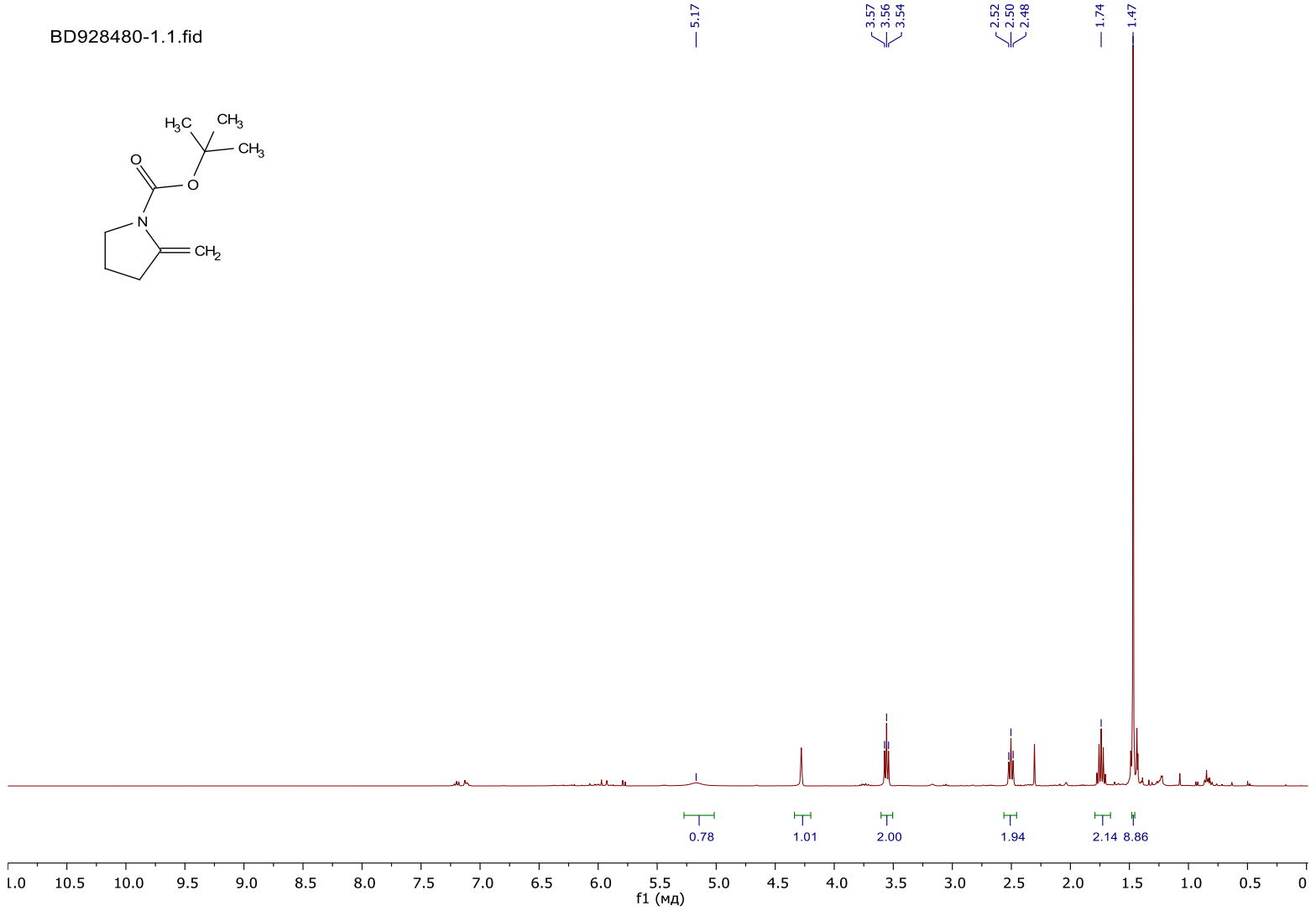


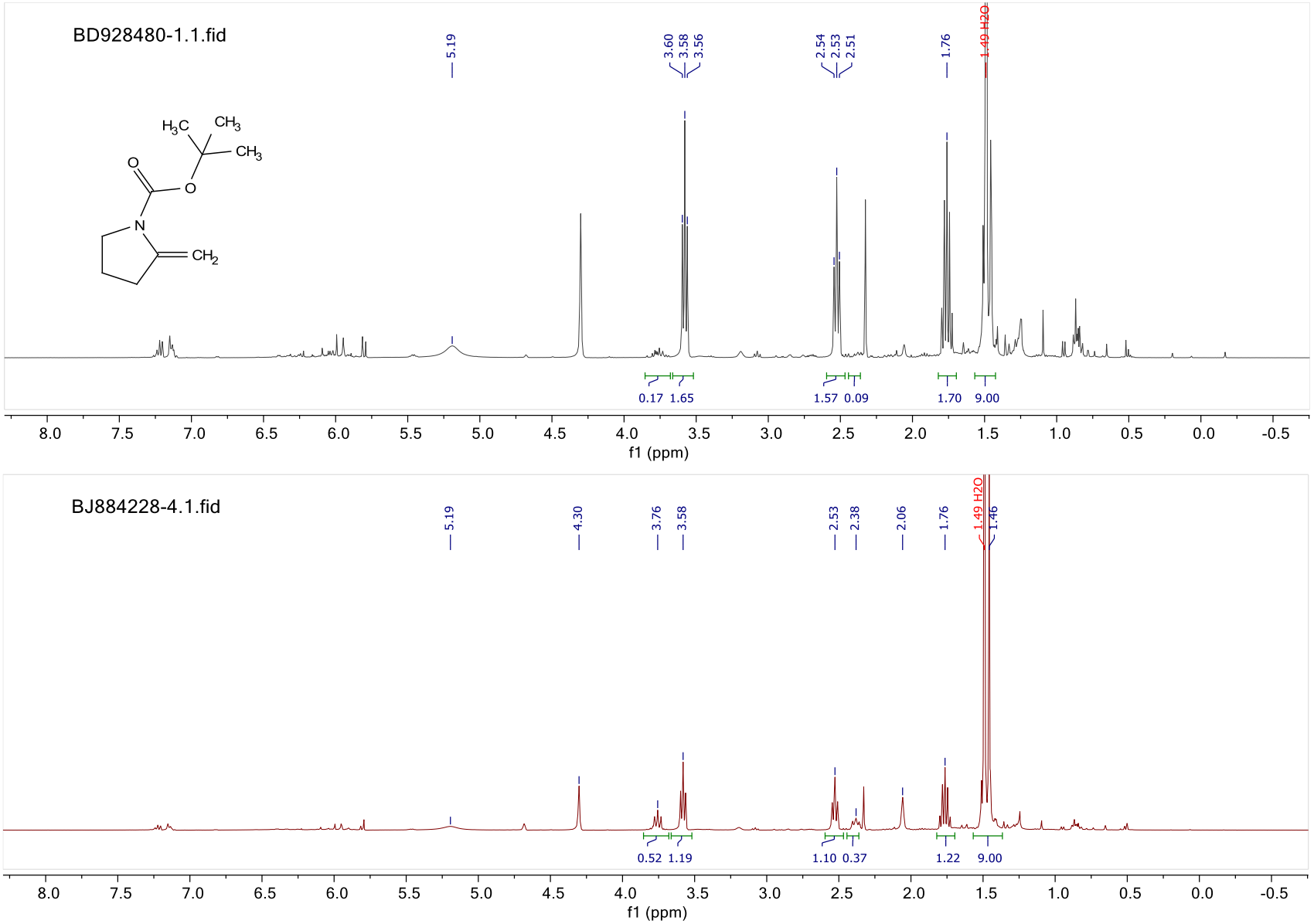
Figure S3. Overlay of compound *trans*-**9b** and *N*-benzoylnipecotic acid.[6]

Copies of NMR spectra

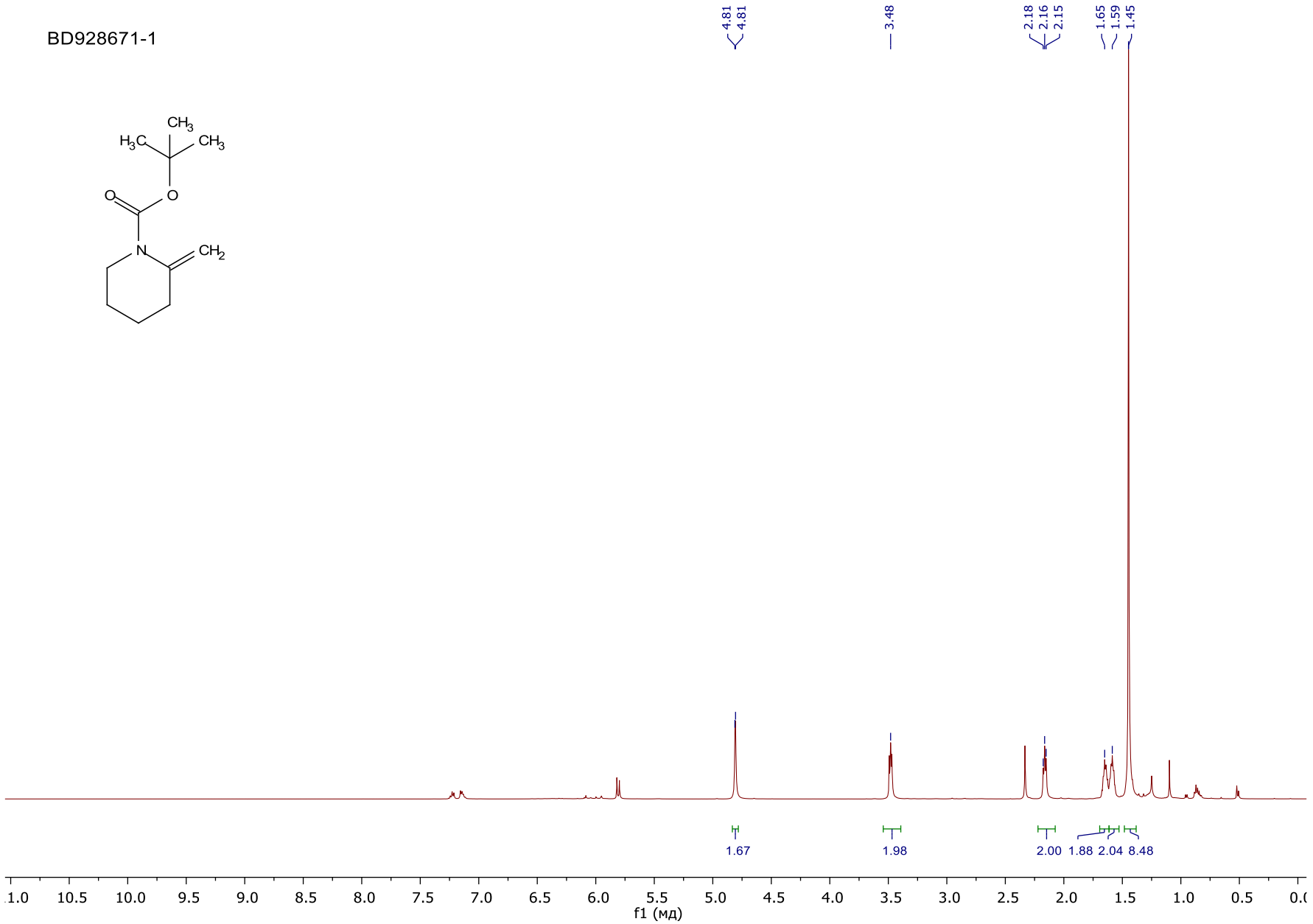
*Crude enamines **3a-e***



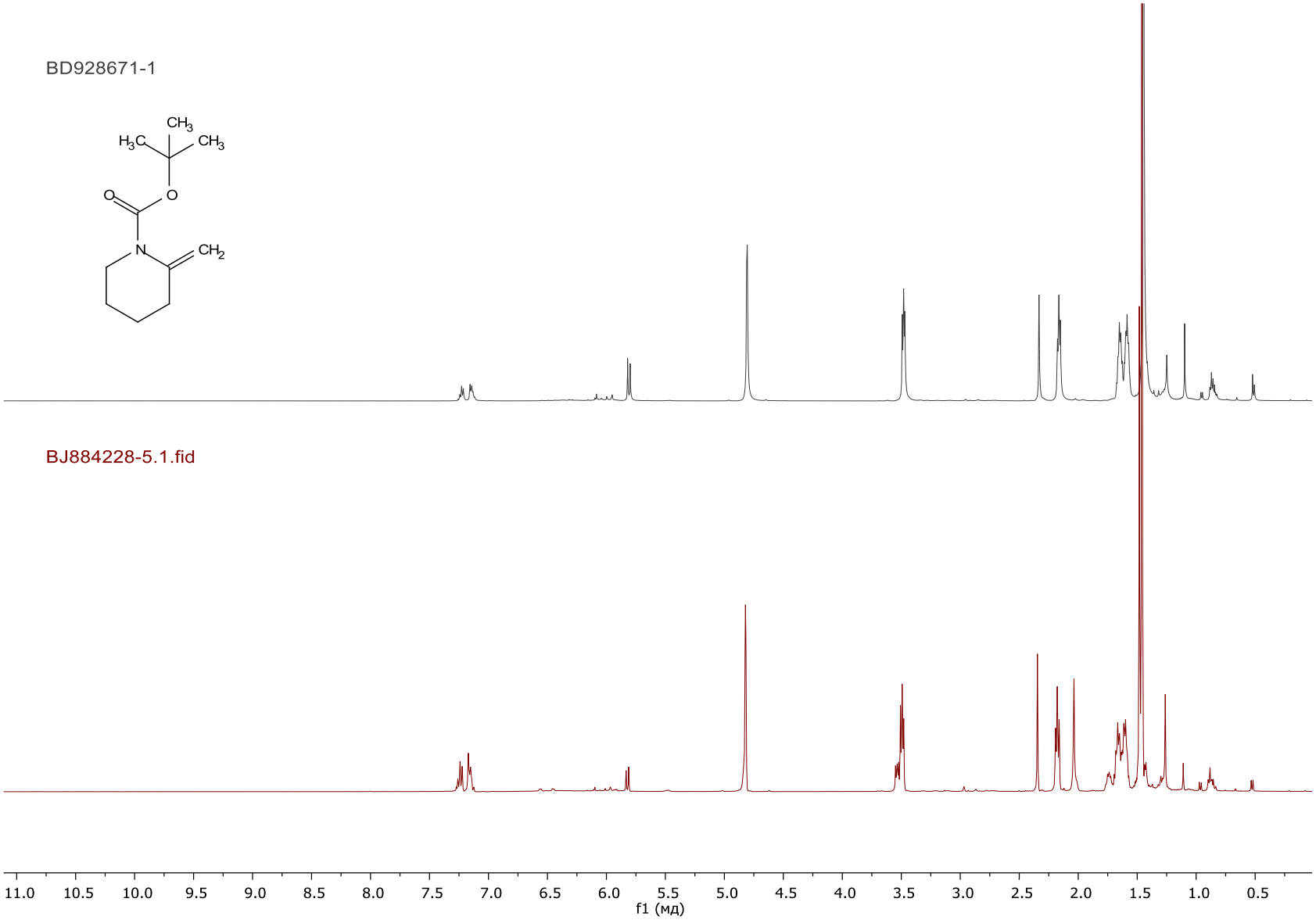
Spectrum 1. *tert*-Butyl 2-methylenepyrrolidine-1-carboxylate **3a** (freshly prepared), ^{1}H NMR (400 MHz, $CDCl_3$).



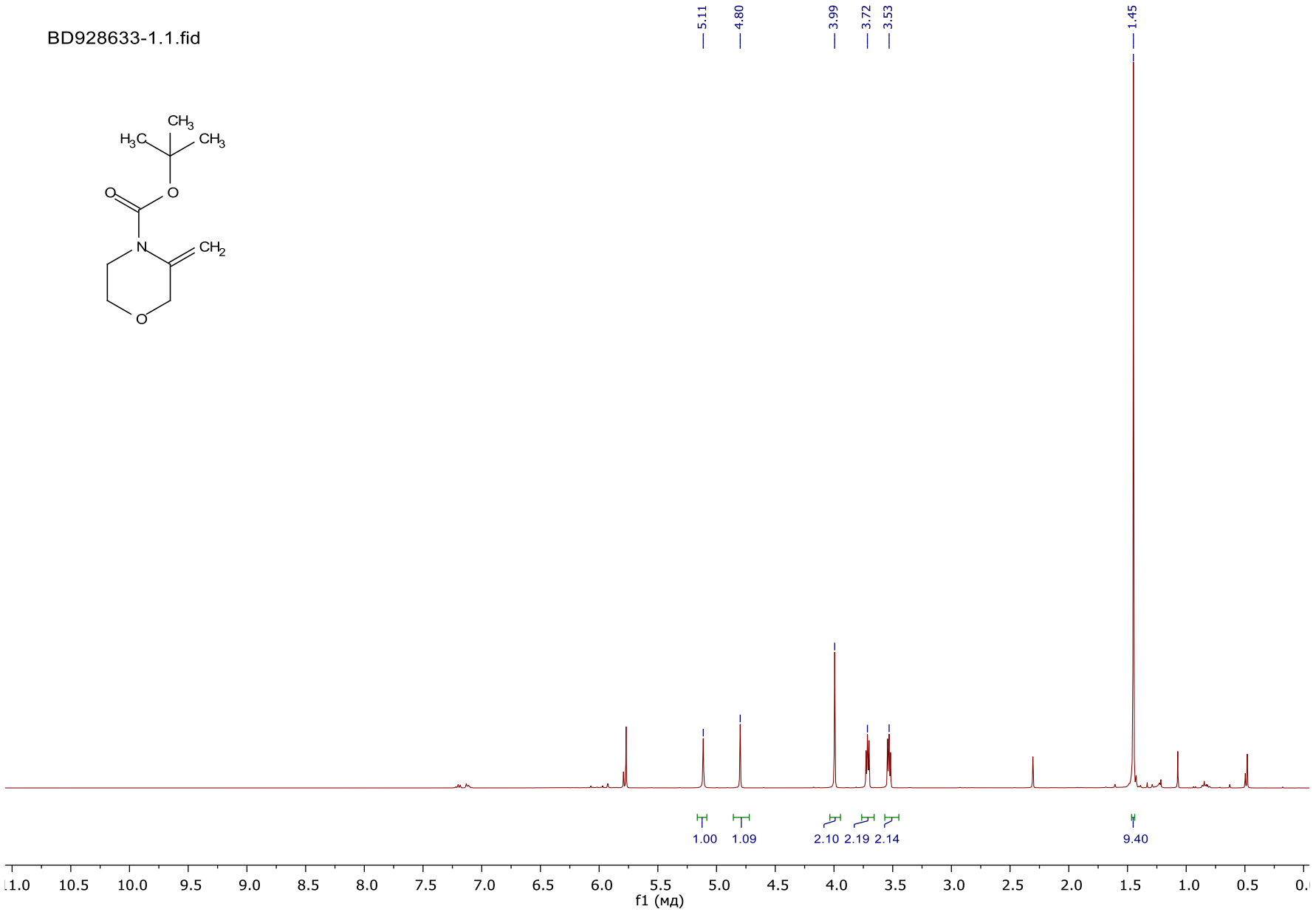
Spectrum 2. Comparison of ^{1}H NMR spectra of the product **3a**: freshly prepared (*top*) and after one year of storage at −10 °C (*bottom*).



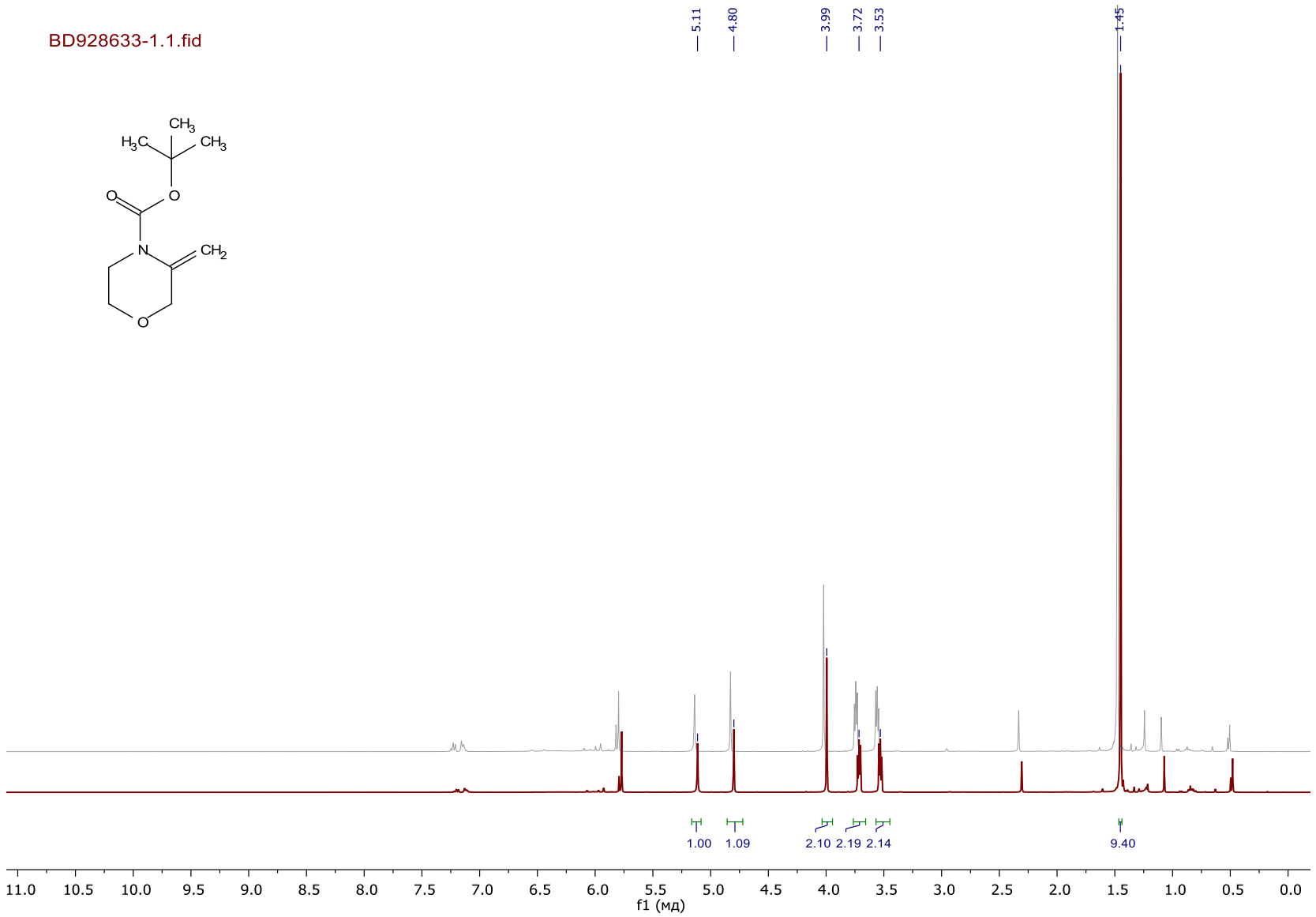
Spectrum 3. *tert*-Butyl 2-methylenepiperidine-1-carboxylate **3b** (freshly prepared), ^{1}H NMR (400 MHz, $CDCl_3$).



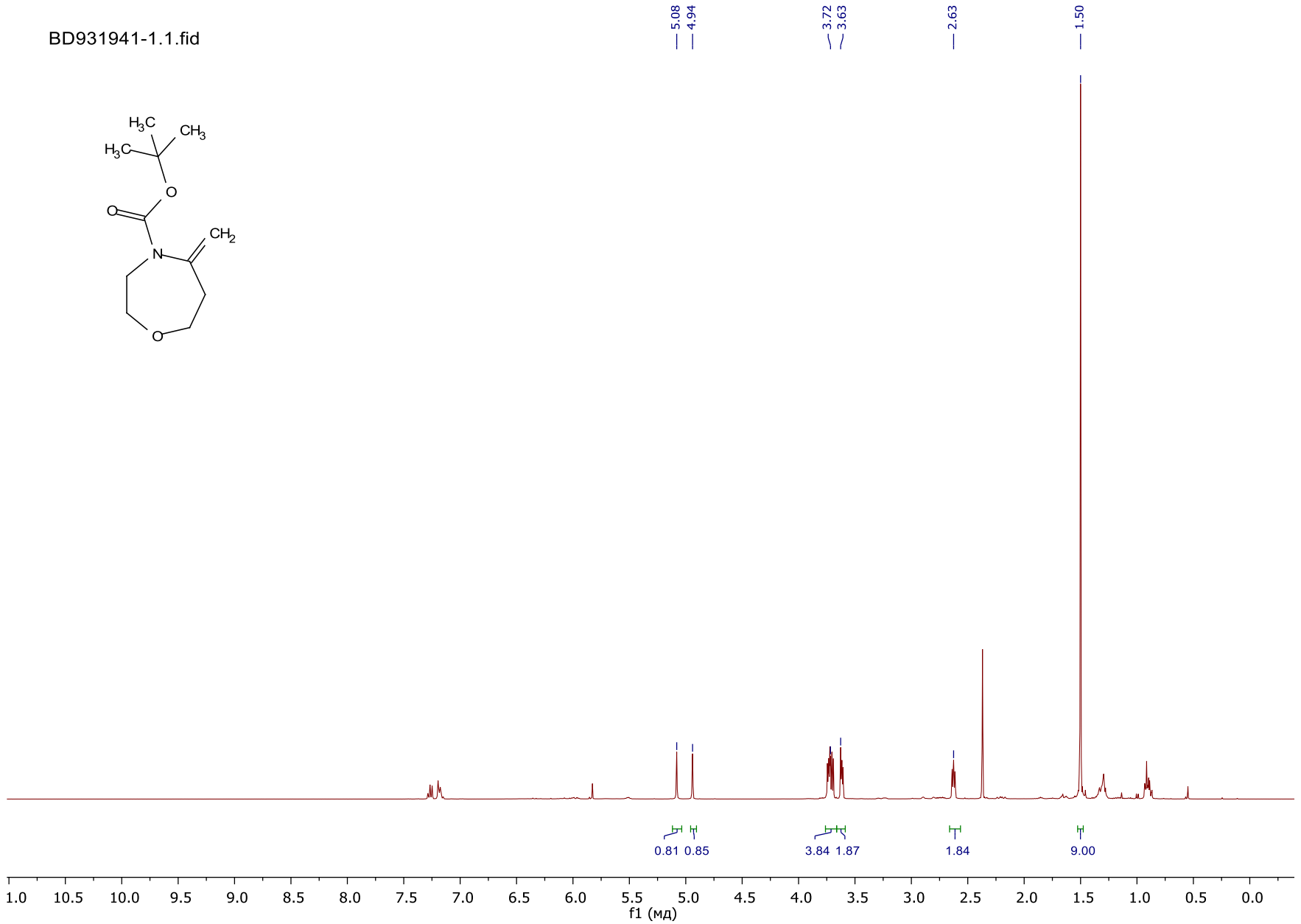
Spectrum 4. Comparison of ^{1}H NMR spectra of the product **3b**: freshly prepared *(top)* and after one year of the storage *(bottom)*.



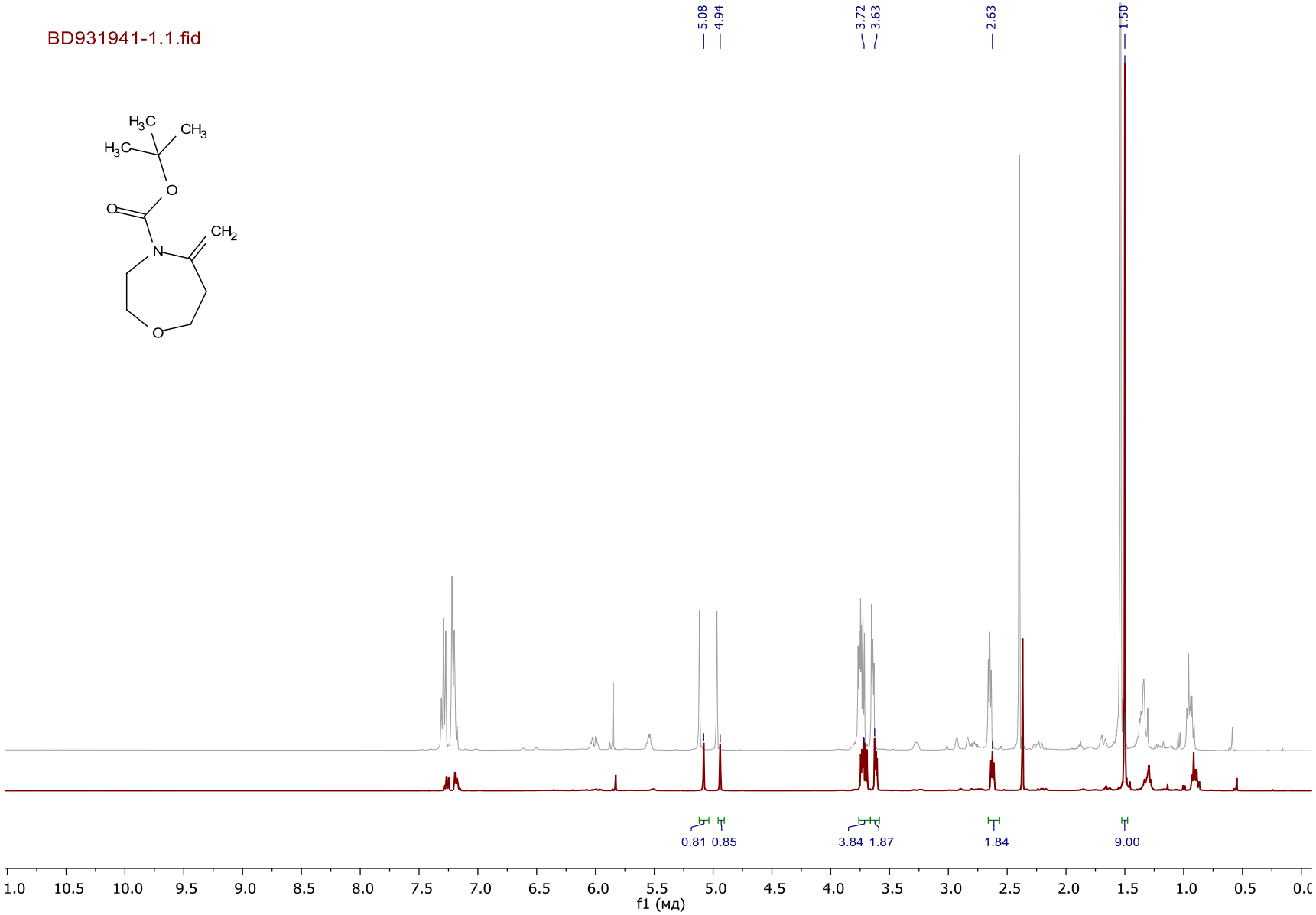
Spectrum 5. *tert*-Butyl 3-methylenemorpholine-4-carboxylate **3c** (freshly prepared), ^{1}H NMR (400 MHz, $CDCl_3$).



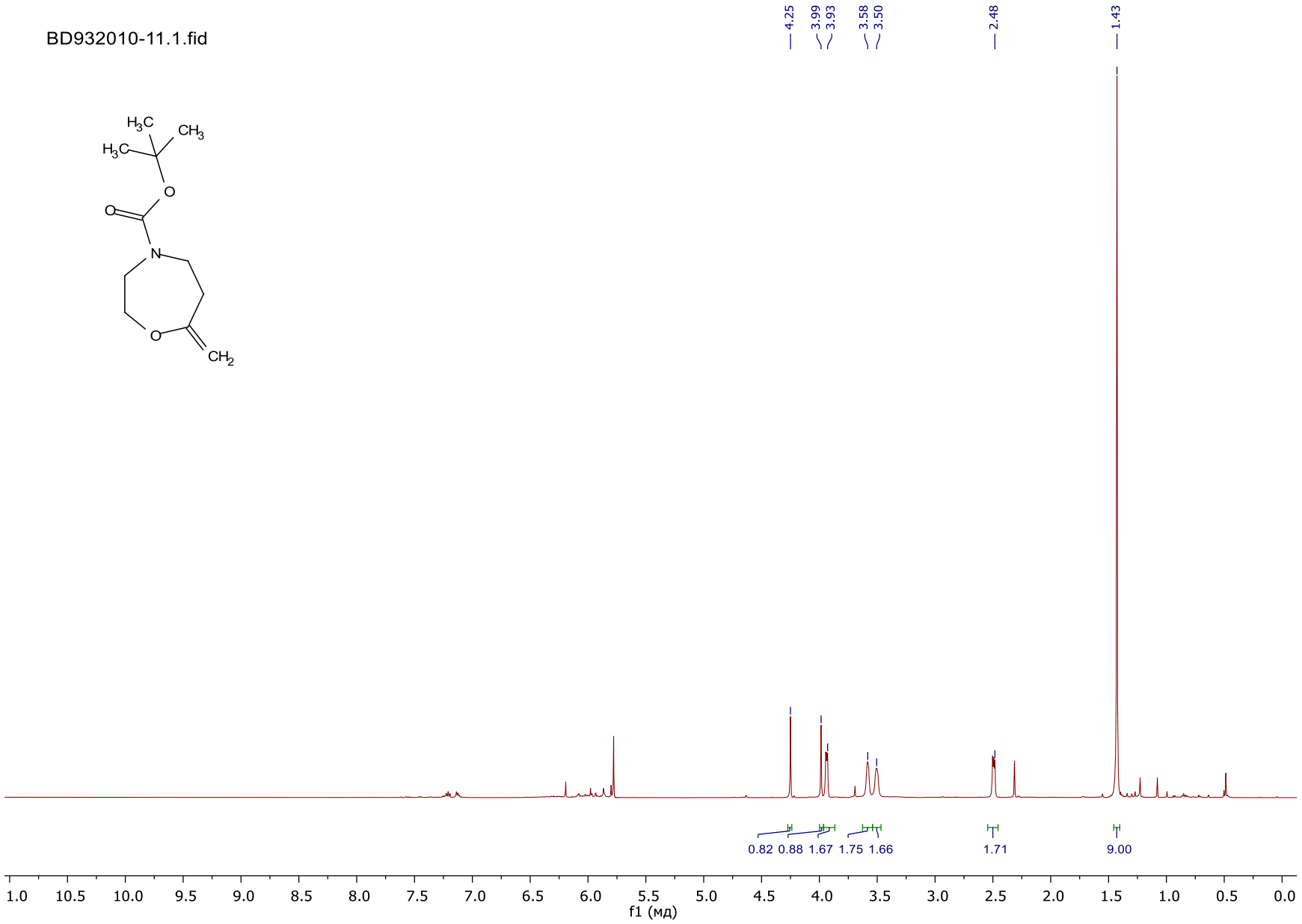
Spectrum 6. *Comparison of ^{1}H NMR spectra of the product **3c**: freshly prepared (top) and after one year of storage (bottom)*.



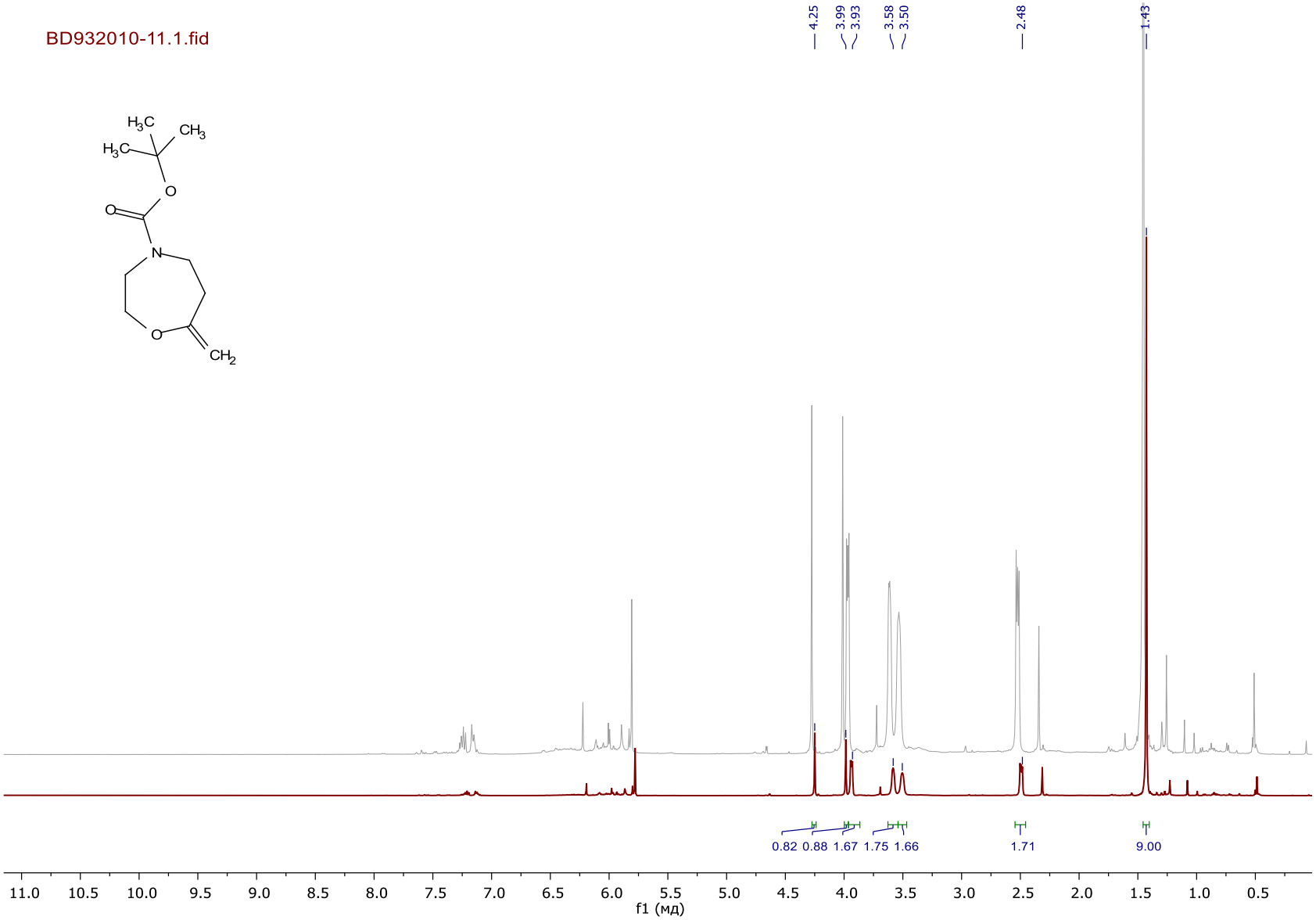
Spectrum 7. *tert*-Butyl 5-methylene-1,4-oxazepane-4-carboxylate **3d** (freshly prepared), ^{1}H NMR (400 MHz, $CDCl_3$).



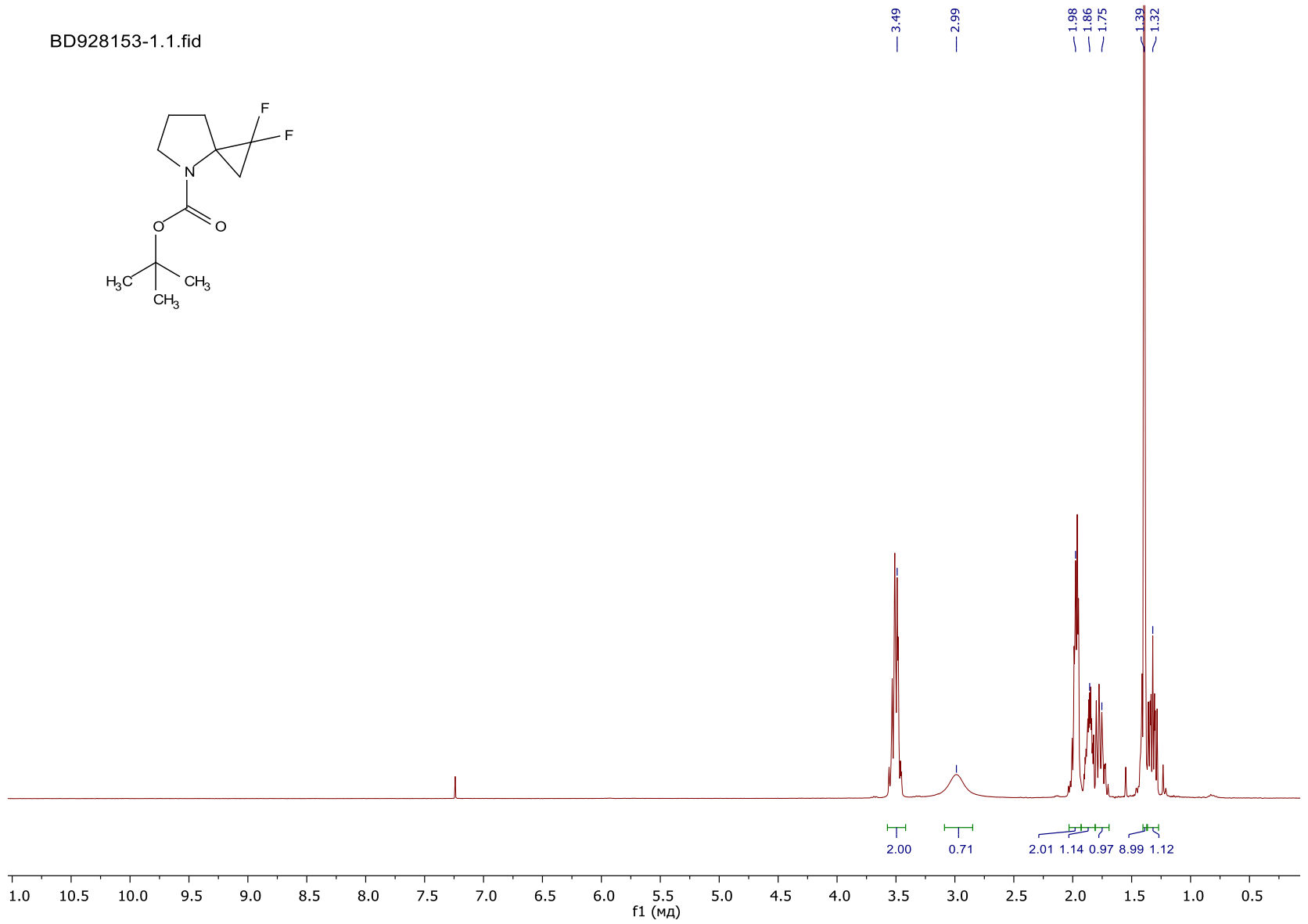
Spectrum 8. Comparison of ^{1}H NMR spectra of the product **3d**: freshly prepared (top) and after one year of storage (bottom).



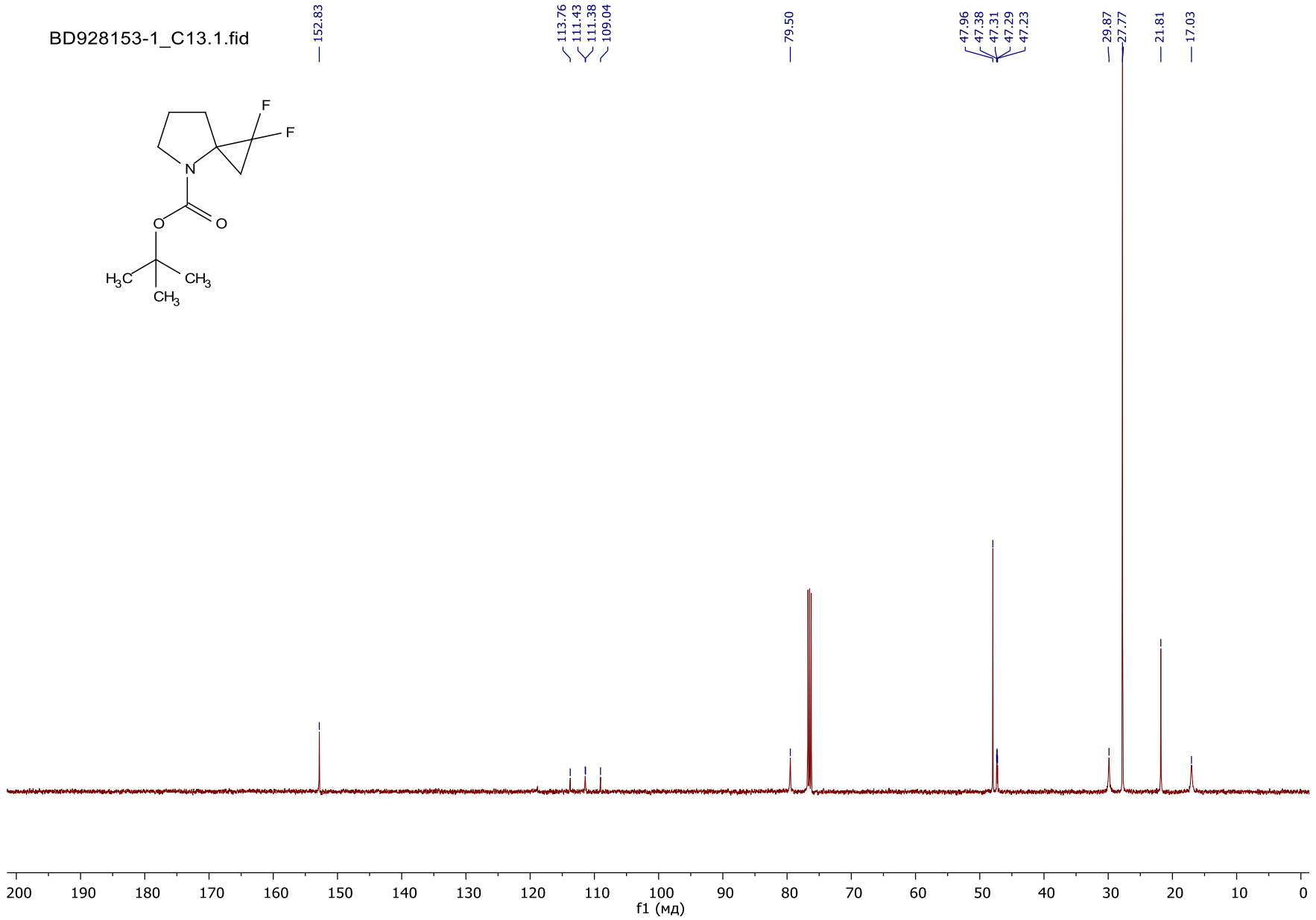
Spectrum 9. *tert*-Butyl 7-methylene-1,4-oxazepane-4-carboxylate **3e** (freshly prepared), ^{1}H NMR (400 MHz, $CDCl_3$).



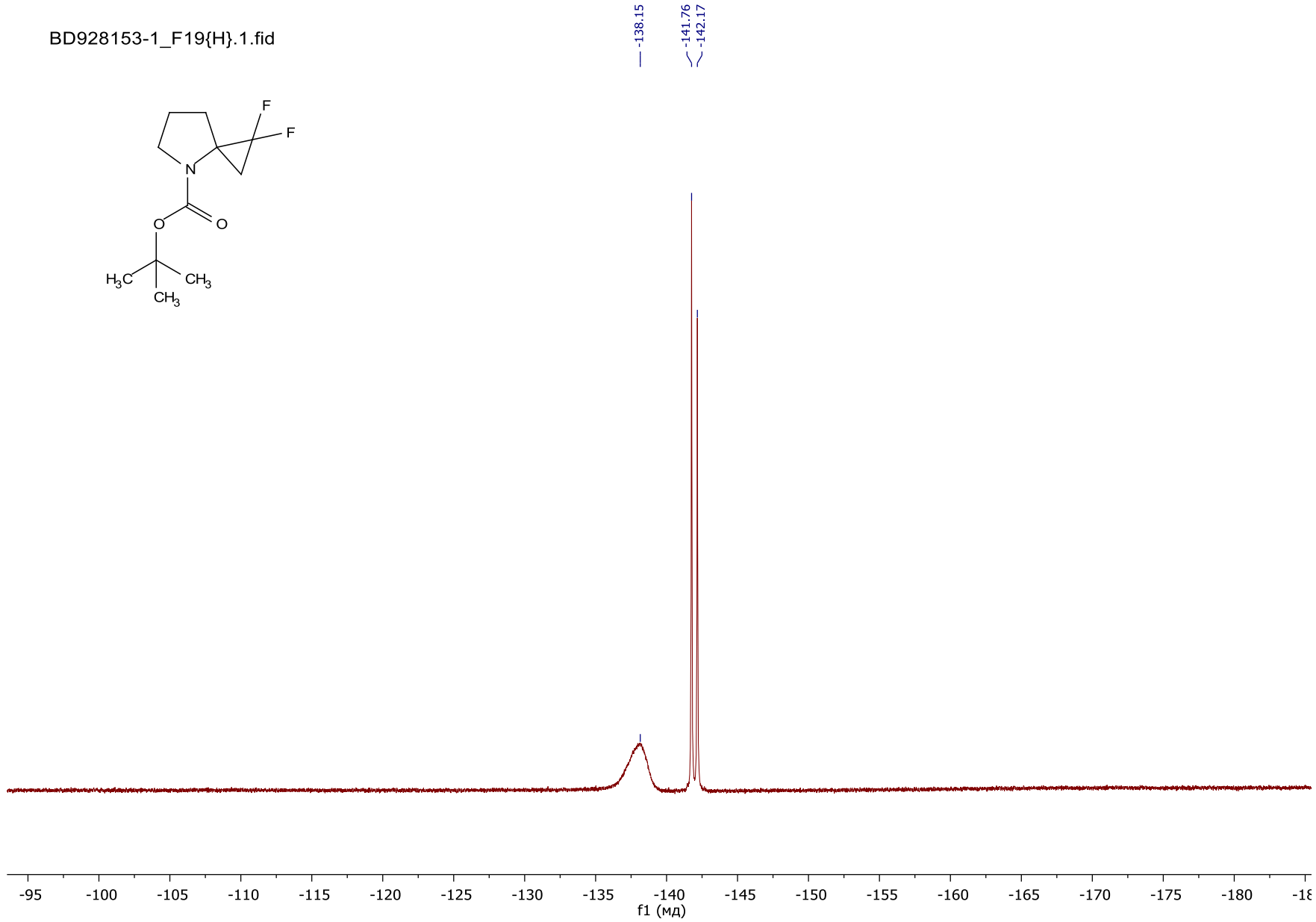
Spectrum 10. Comparison of ^{1}H NMR spectra of the product **3e**: freshly prepared (*top*) and after one year of storage (*bottom*).



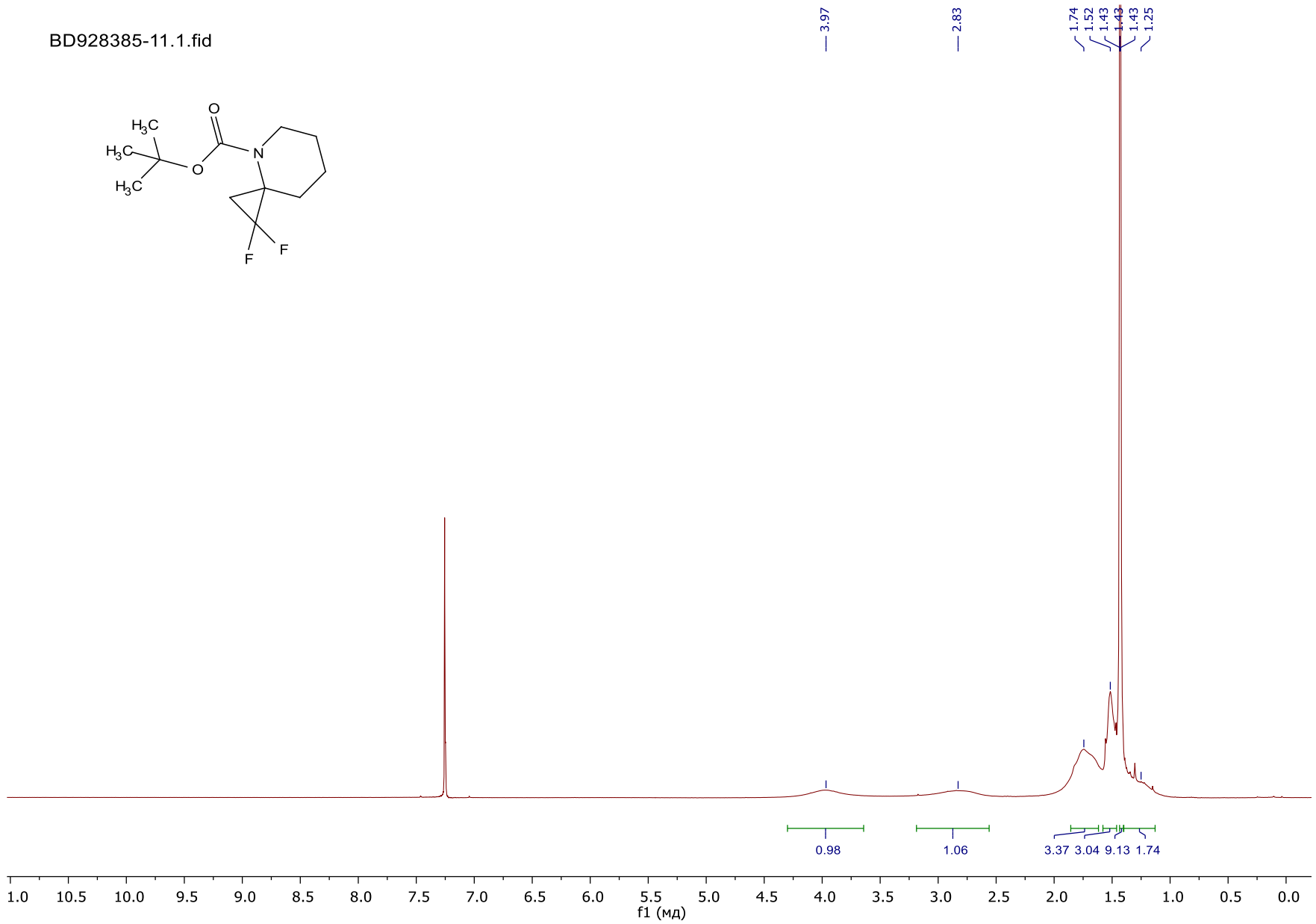
Spectrum 11. *tert*-Butyl 1,1-difluoro-4-azaspiro[2.4]heptane-4-carboxylate **4a**, ^{1}H NMR (400 MHz, $CDCl_3$).



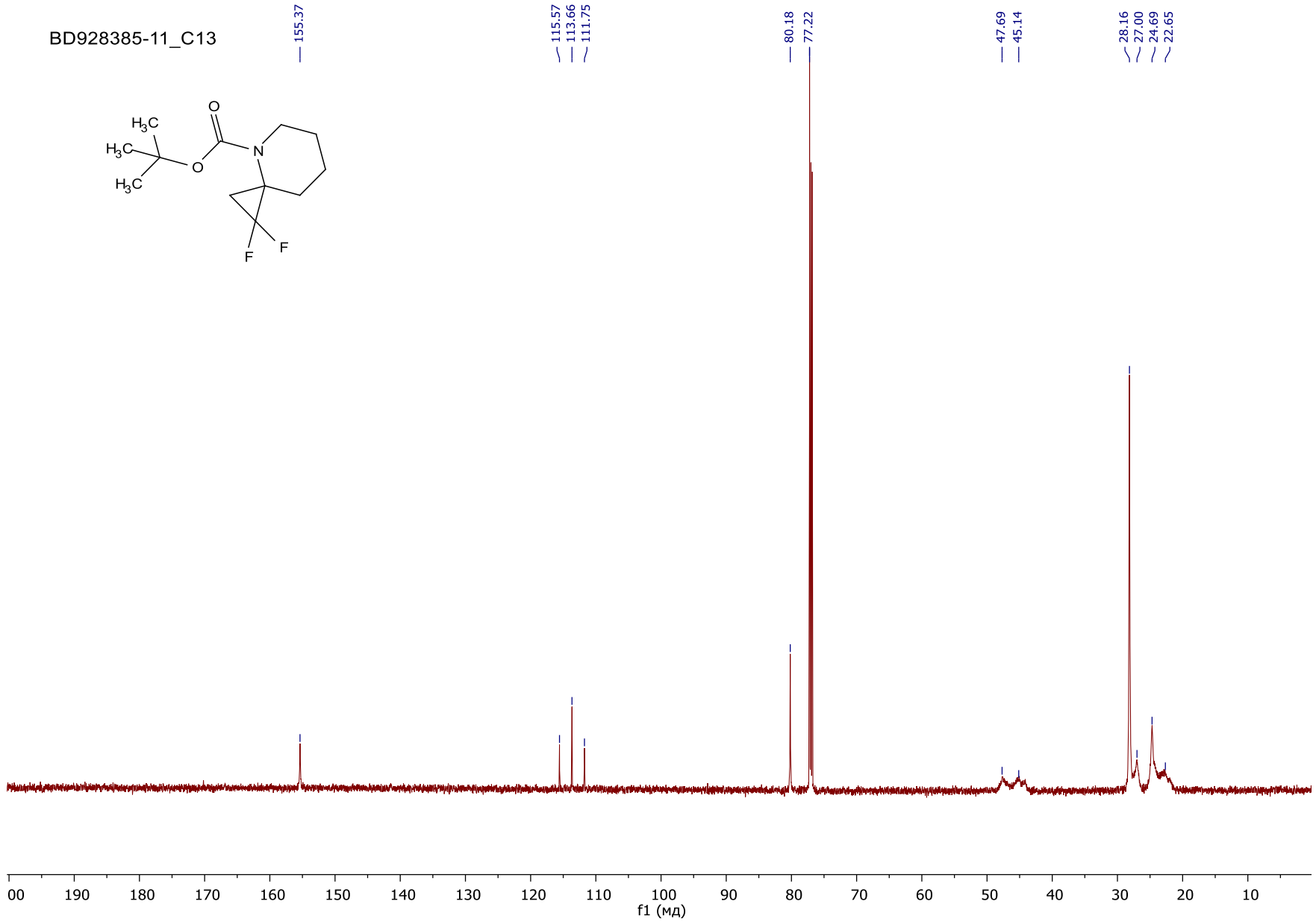
Spectrum 12. *tert*-Butyl 1,1-difluoro-4-azaspiro[2.4]heptane-4-carboxylate **4a**, ^{13}C NMR (126 MHz, $CDCl_3$).



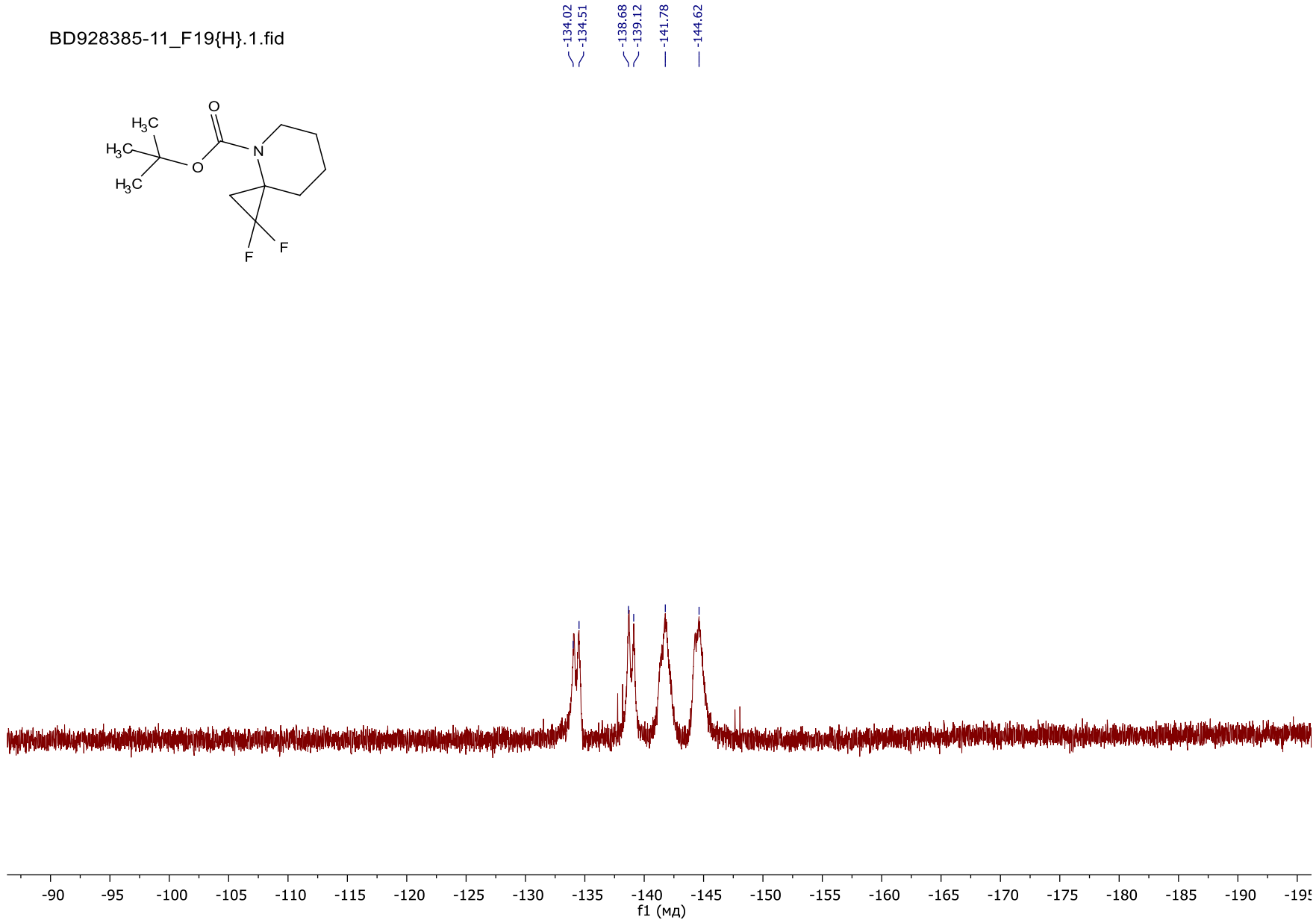
Spectrum 13. *tert*-Butyl 1,1-difluoro-4-azaspiro[2.4]heptane-4-carboxylate **4a**, ^{19}F NMR (376 MHz, $CDCl_3$).



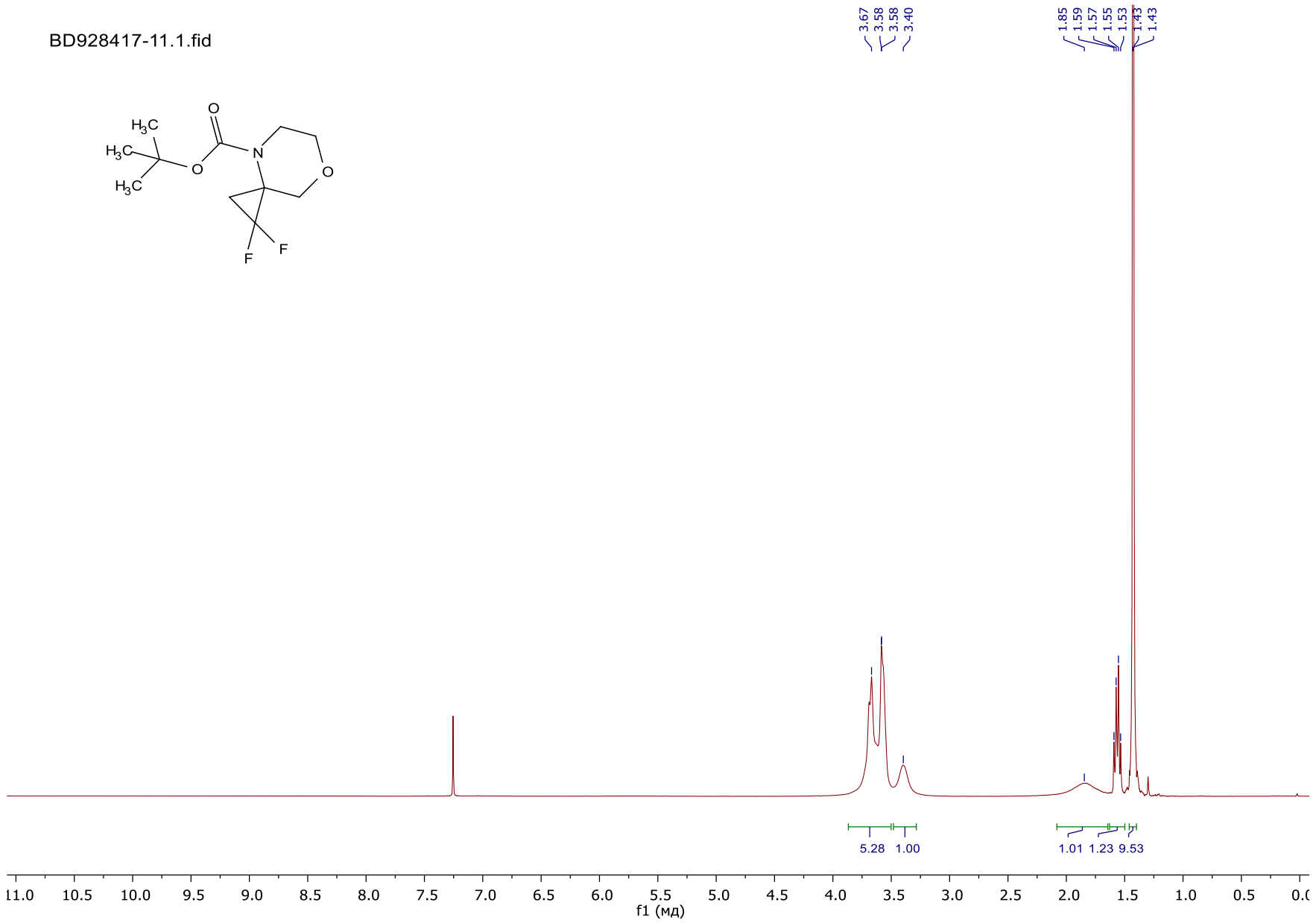
Spectrum 14. *tert*-Butyl 1,1-difluoro-4-azaspiro[2.5]octane-4-carboxylate **4b**, ^{1}H NMR (500 MHz, $CDCl_3$).



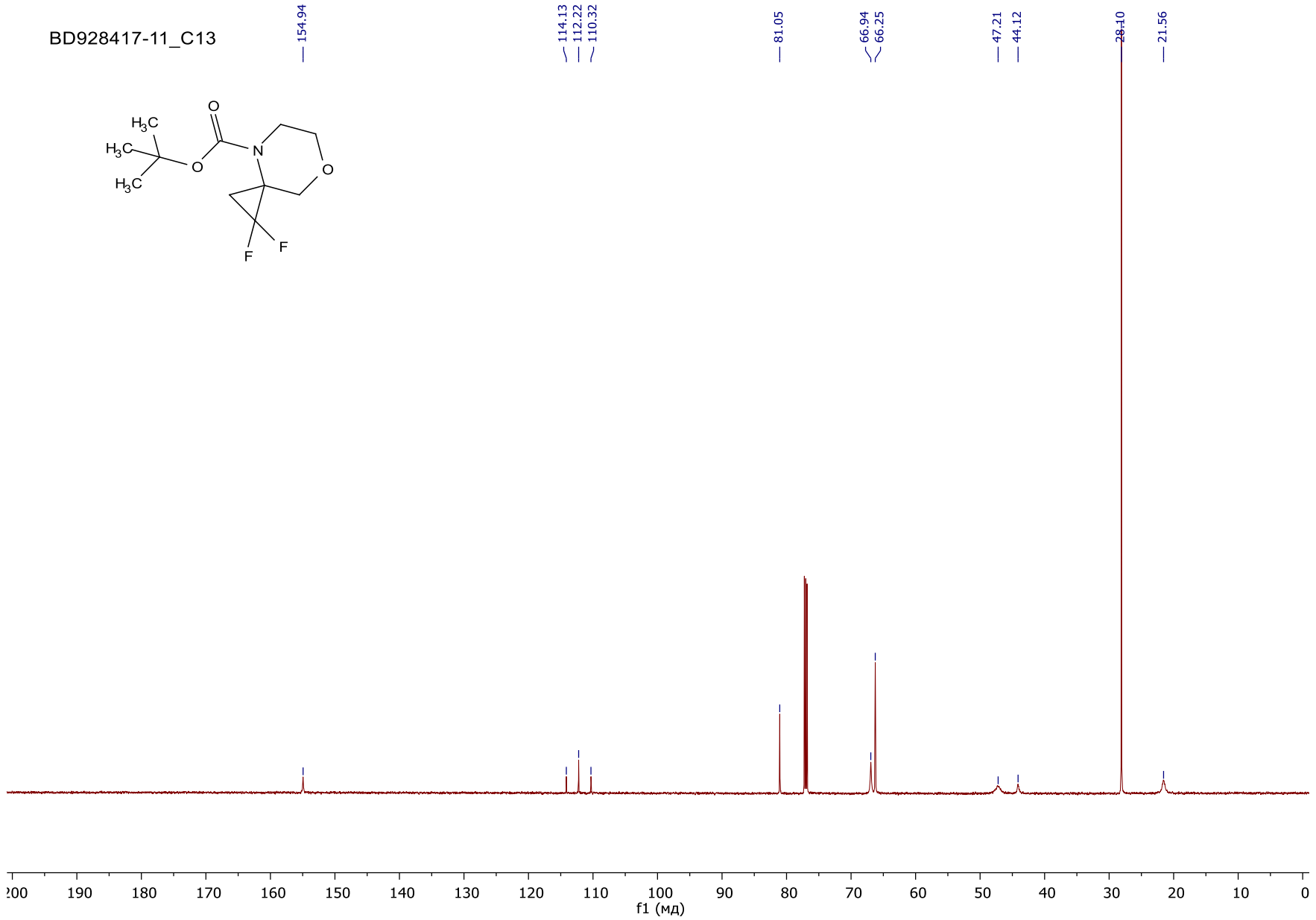
Spectrum 15. *tert*-Butyl 1,1-difluoro-4-azaspiro[2.5]octane-4-carboxylate **4b**, ^{13}C NMR (151 MHz, $CDCl_3$).



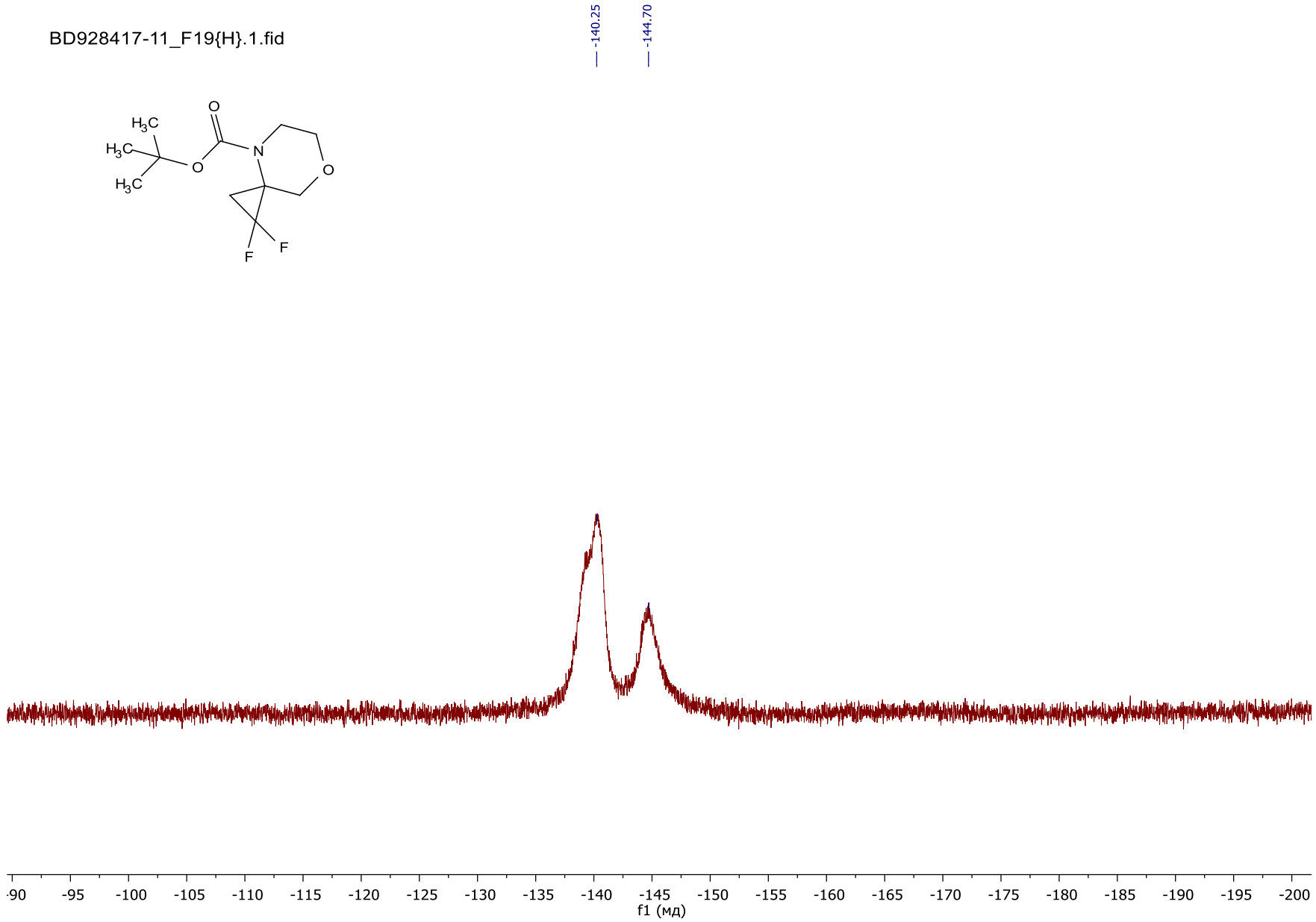
Spectrum 16. *tert*-Butyl 1,1-difluoro-4-azaspiro[2.5]octane-4-carboxylate **4b**, ^{19}F NMR (376 MHz, $CDCl_3$).



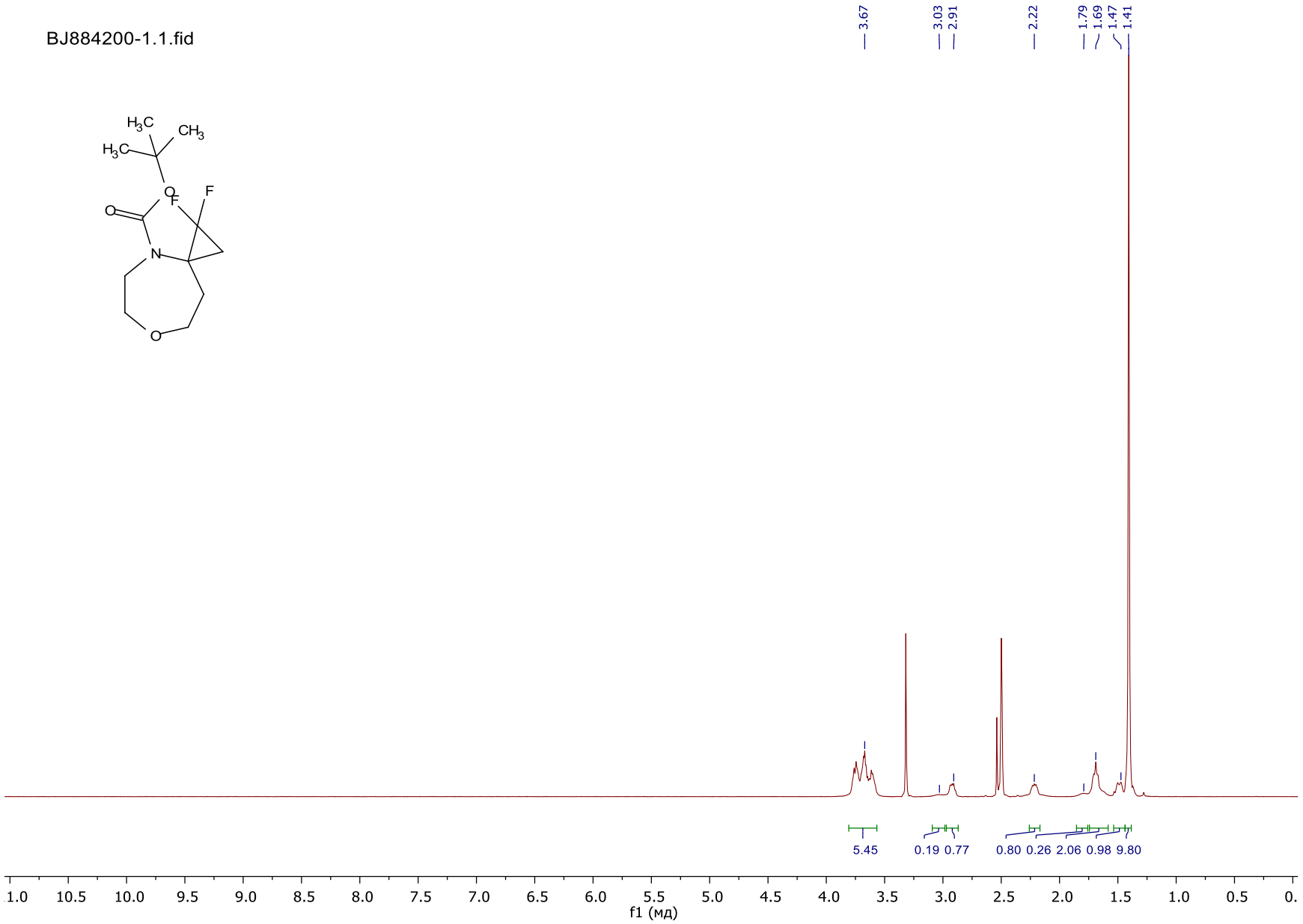
Spectrum 17. *tert*-Butyl 1,1-difluoro-7-oxa-4-azaspiro[2.5]octane-4-carboxylate **4c**, ^{1}H NMR (500 MHz, $CDCl_3$).



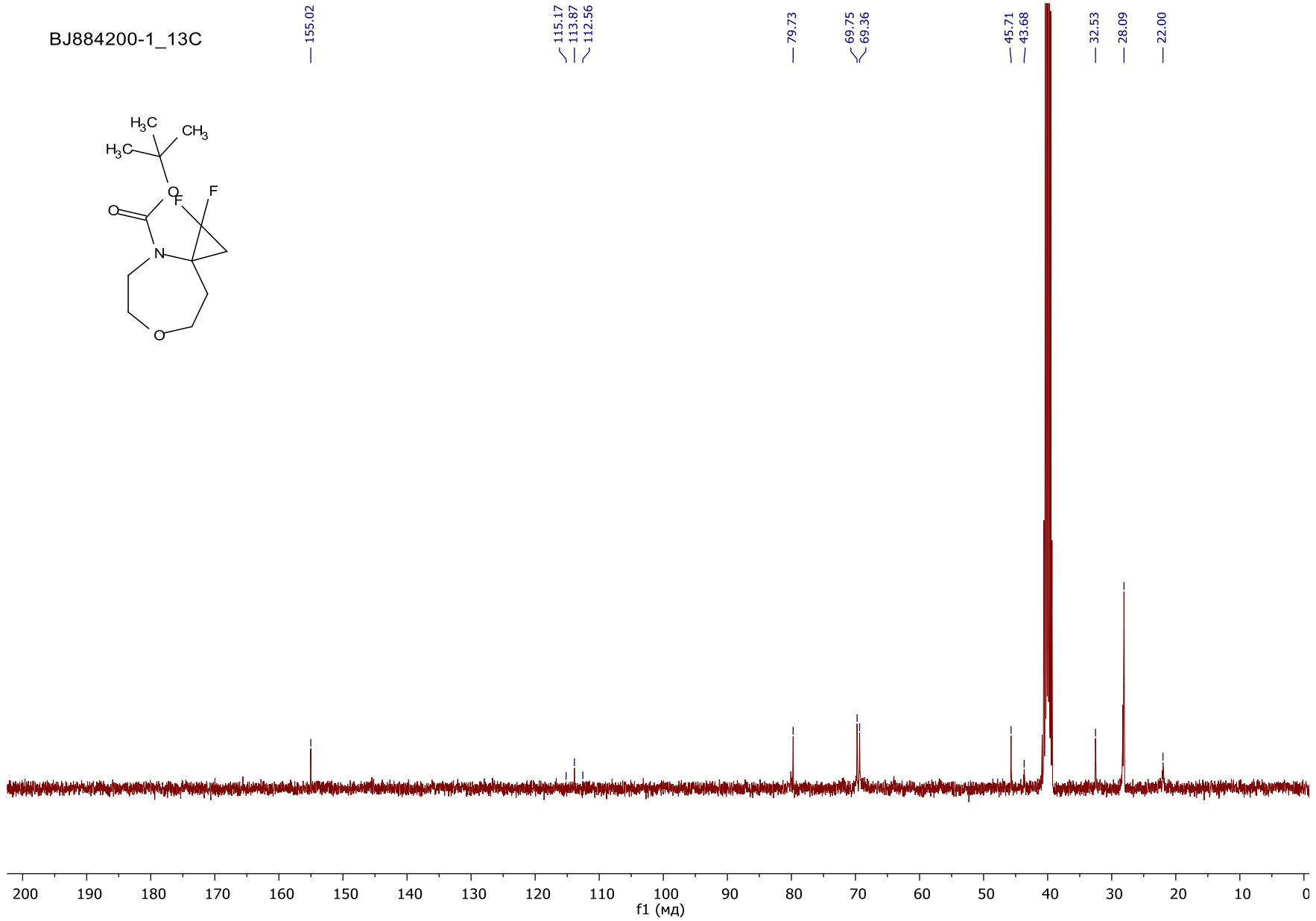
Spectrum 18. *tert*-Butyl 1,1-difluoro-7-oxa-4-azaspiro[2.5]octane-4-carboxylate **4c**, ^{13}C NMR (151 MHz, $CDCl_3$).



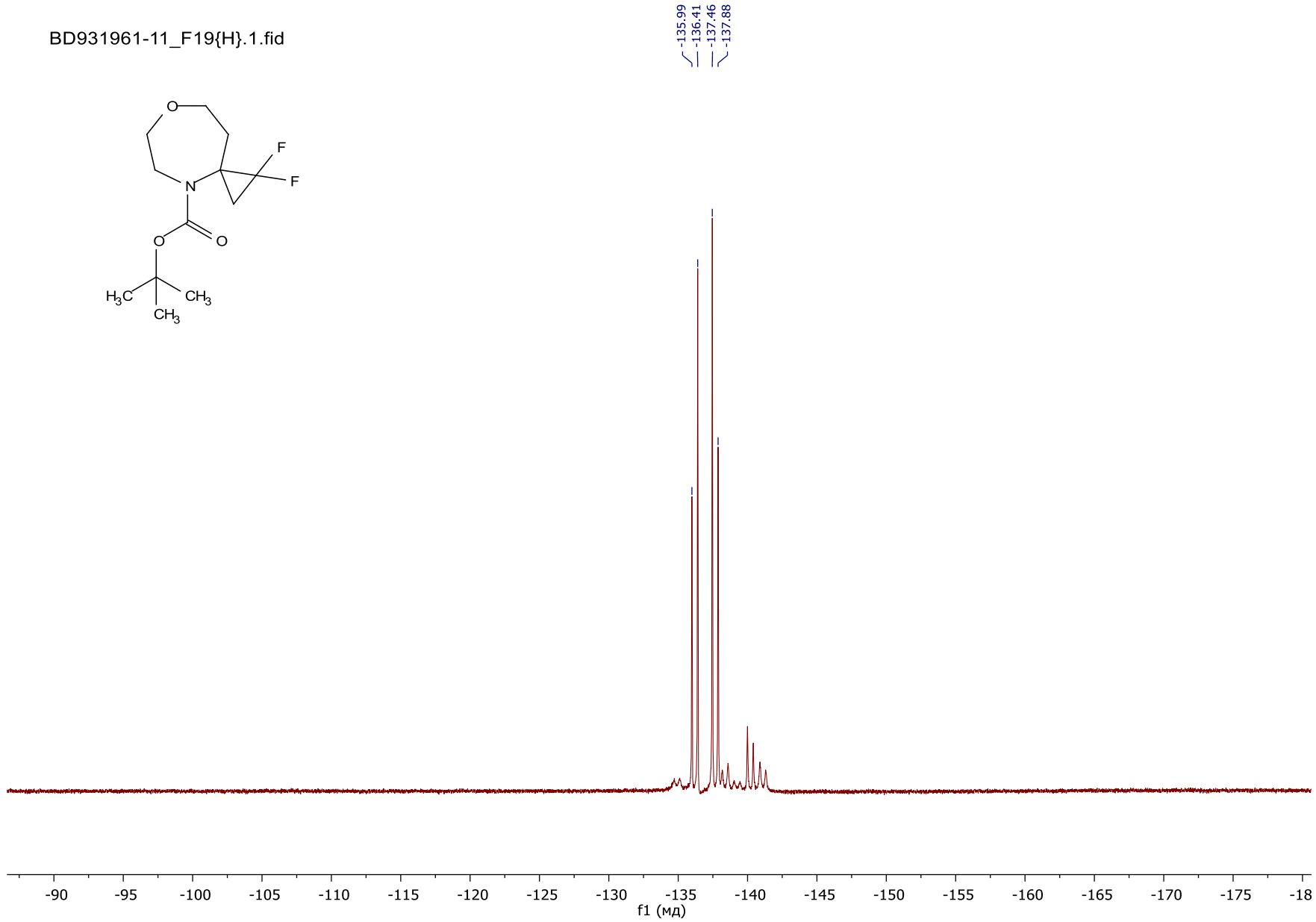
Spectrum 19. *tert*-Butyl 1,1-difluoro-7-oxa-4-azaspiro[2.5]octane-4-carboxylate **4c**, ^{19}F NMR (376 MHz, $CDCl_3$).



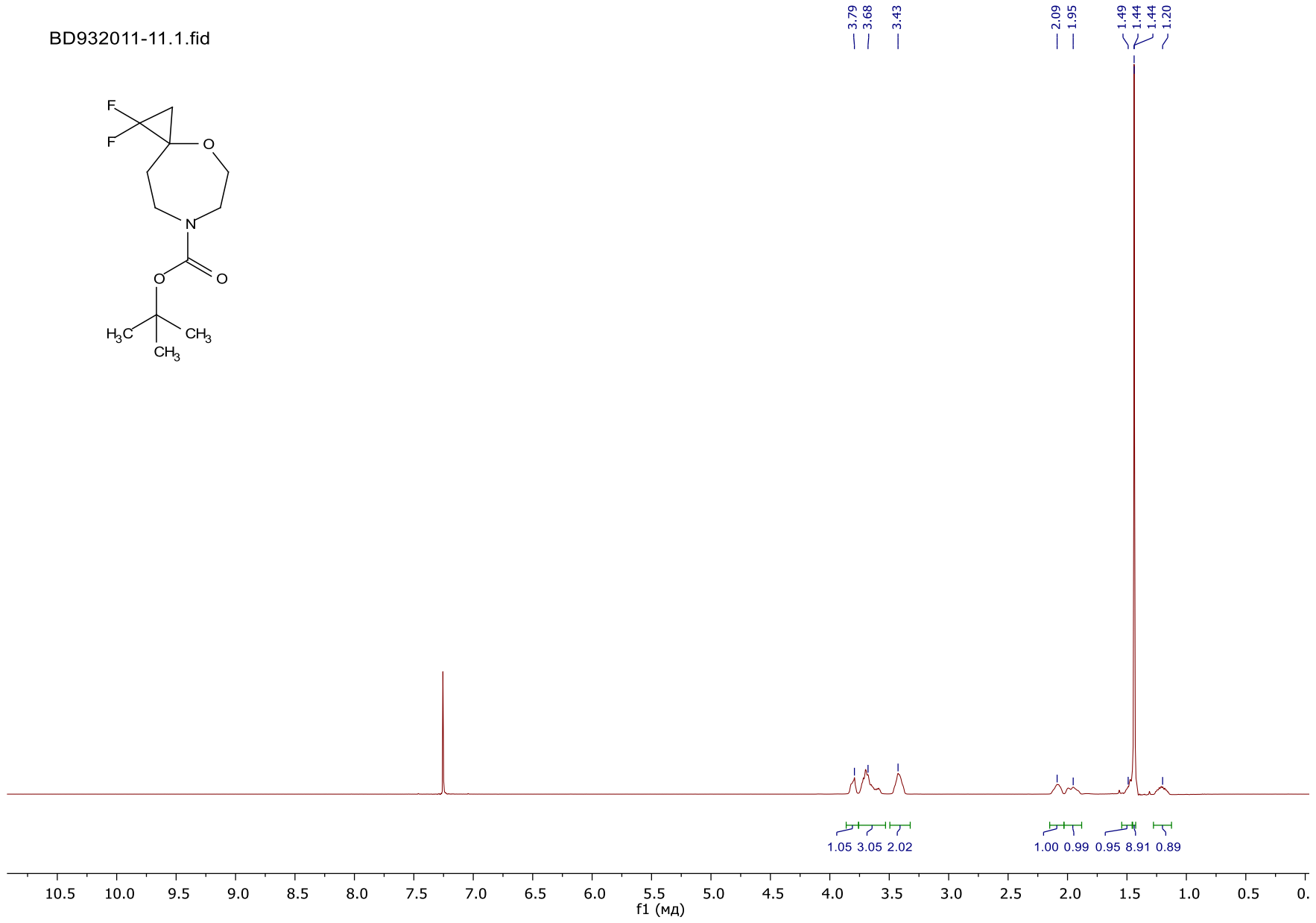
Spectrum 20. *tert*-Butyl 1,1-difluoro-7-oxa-4-azaspiro[2.6]nonane-4-carboxylate **4d**, ^{1}H NMR (500 MHz, DMSO-d_6).



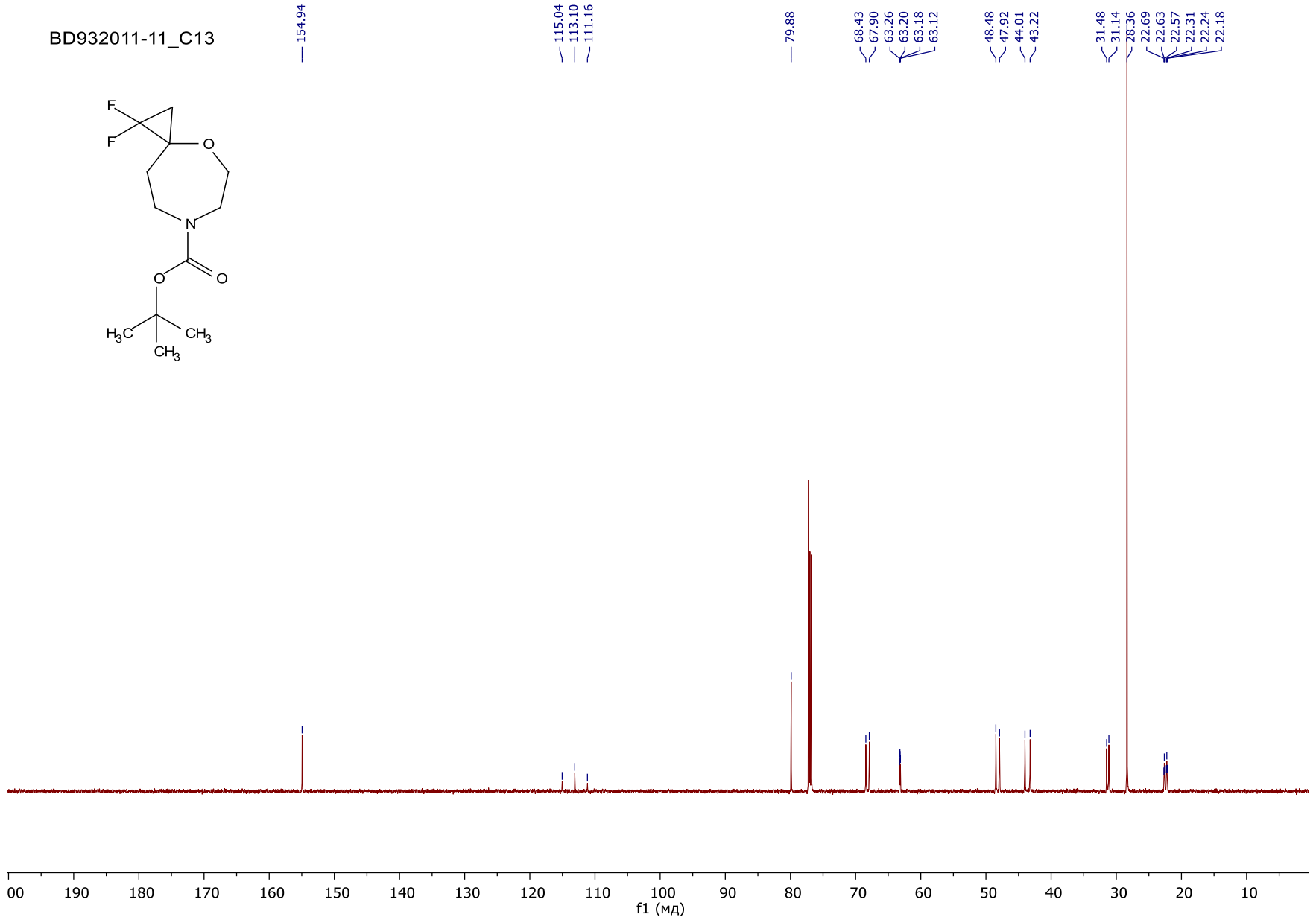
Spectrum 21. *tert*-Butyl 1,1-difluoro-7-oxa-4-azaspiro[2.6]nonane-4-carboxylate **4d**, ^{13}C NMR (151 MHz, DMSO-d_6).



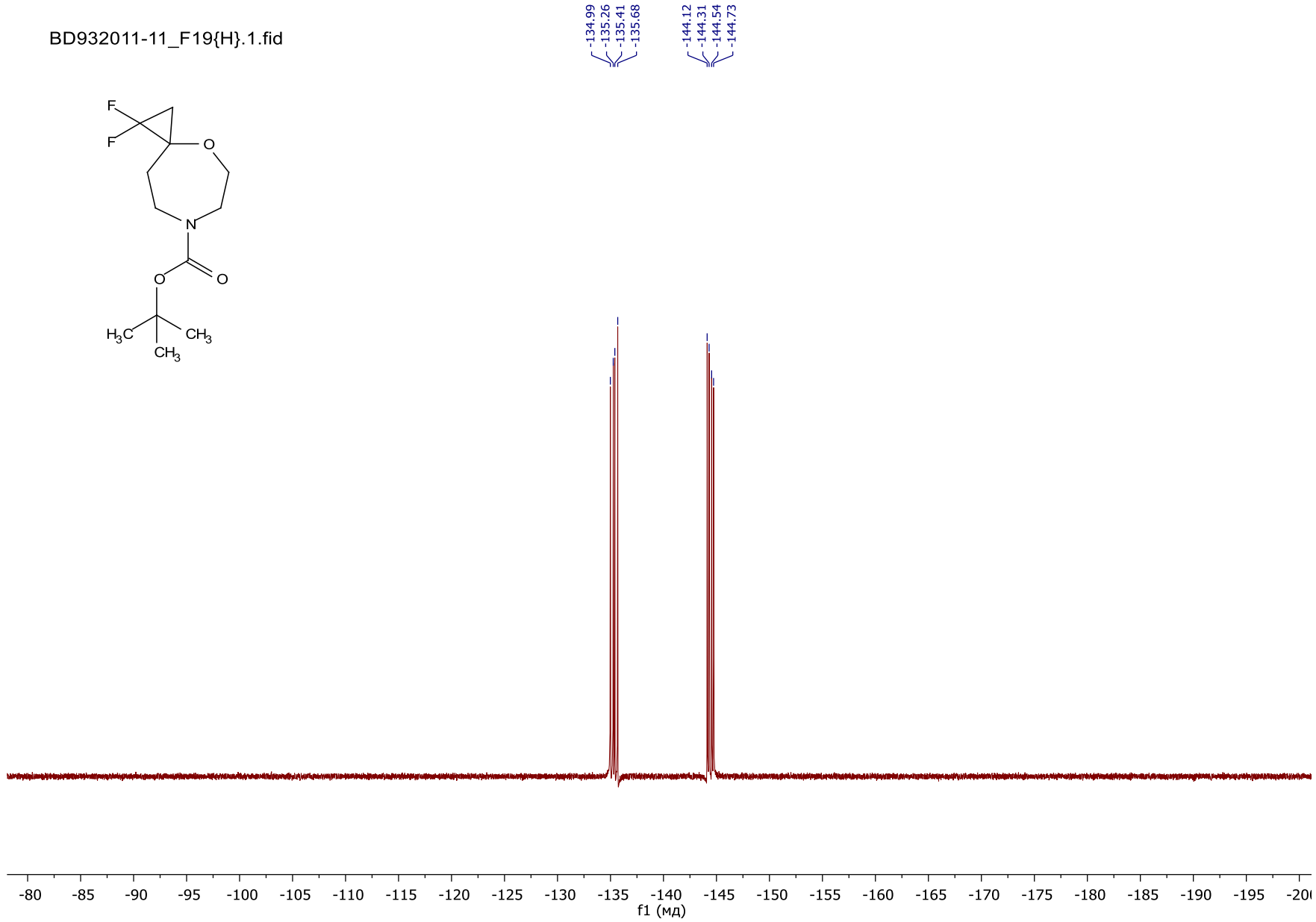
Spectrum 22. *tert*-Butyl 1,1-difluoro-7-oxa-4-azaspiro[2.6]nonane-4-carboxylate **4d**, ^{19}F NMR (376 MHz, $CDCl_3$)



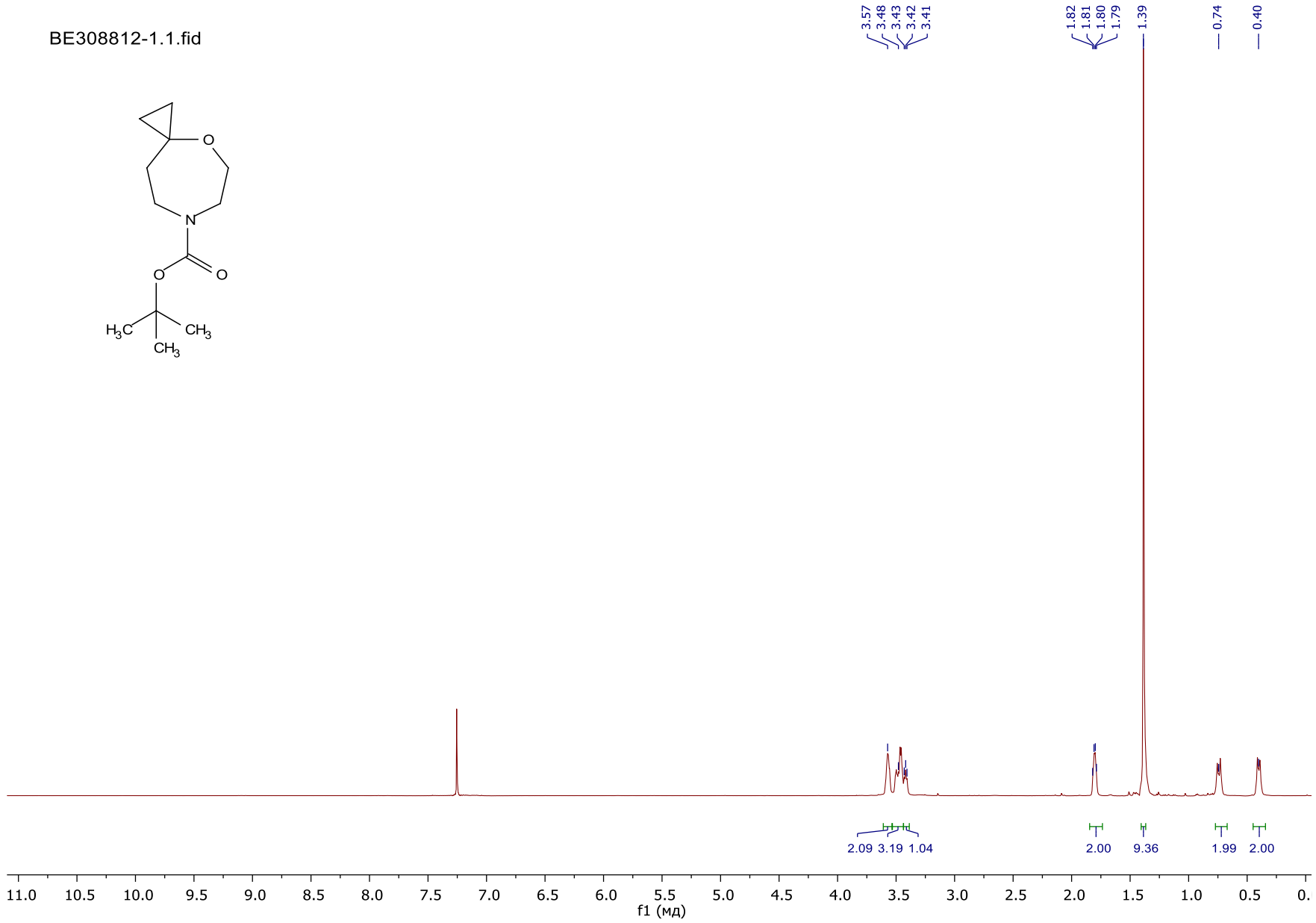
Spectrum 23. *tert*-Butyl 1,1-difluoro-4-oxa-7-azaspiro[2.6]nonane-7-carboxylate **4e**, ^{1}H NMR (500 MHz, $CDCl_3$).



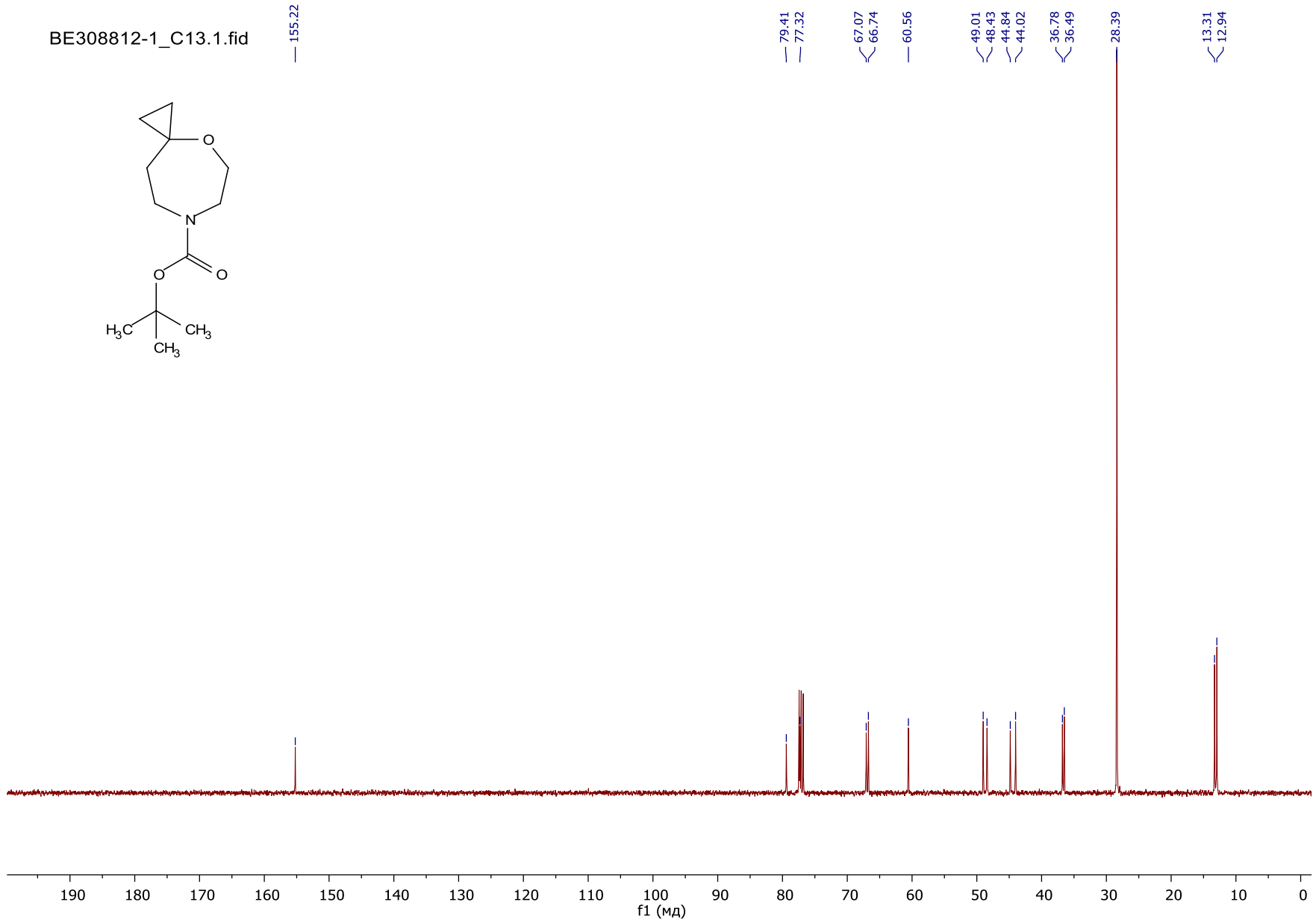
Spectrum 24. *tert*-Butyl 1,1-difluoro-4-oxa-7-azaspiro[2.6]nonane-7-carboxylate **4e**, ^{13}C NMR (151 MHz, $CDCl_3$).



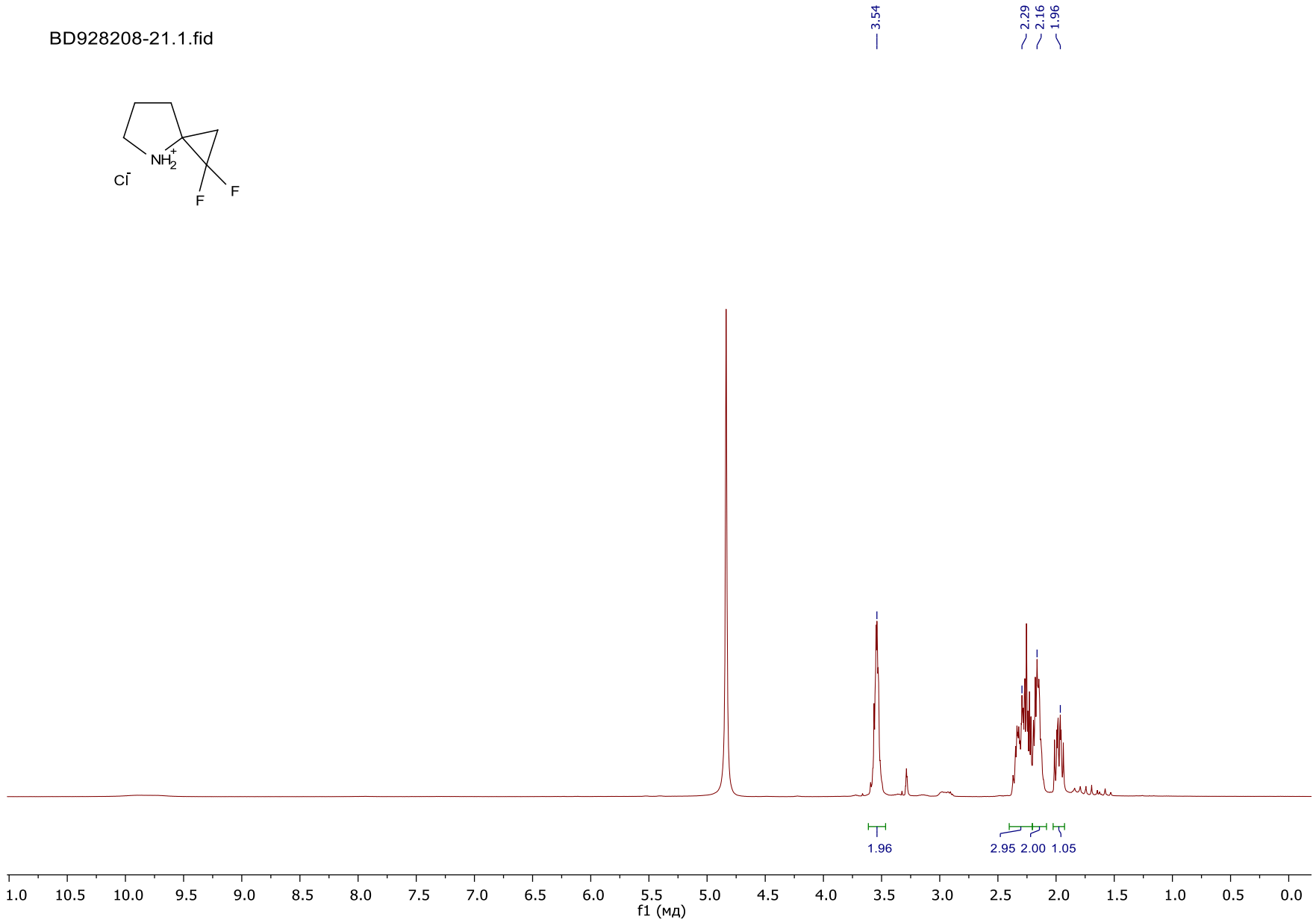
Spectrum 25. *tert*-Butyl 1,1-difluoro-4-oxa-7-azaspiro[2.6]nonane-7-carboxylate **4e**, ^{19}F NMR (376 MHz, $CDCl_3$).



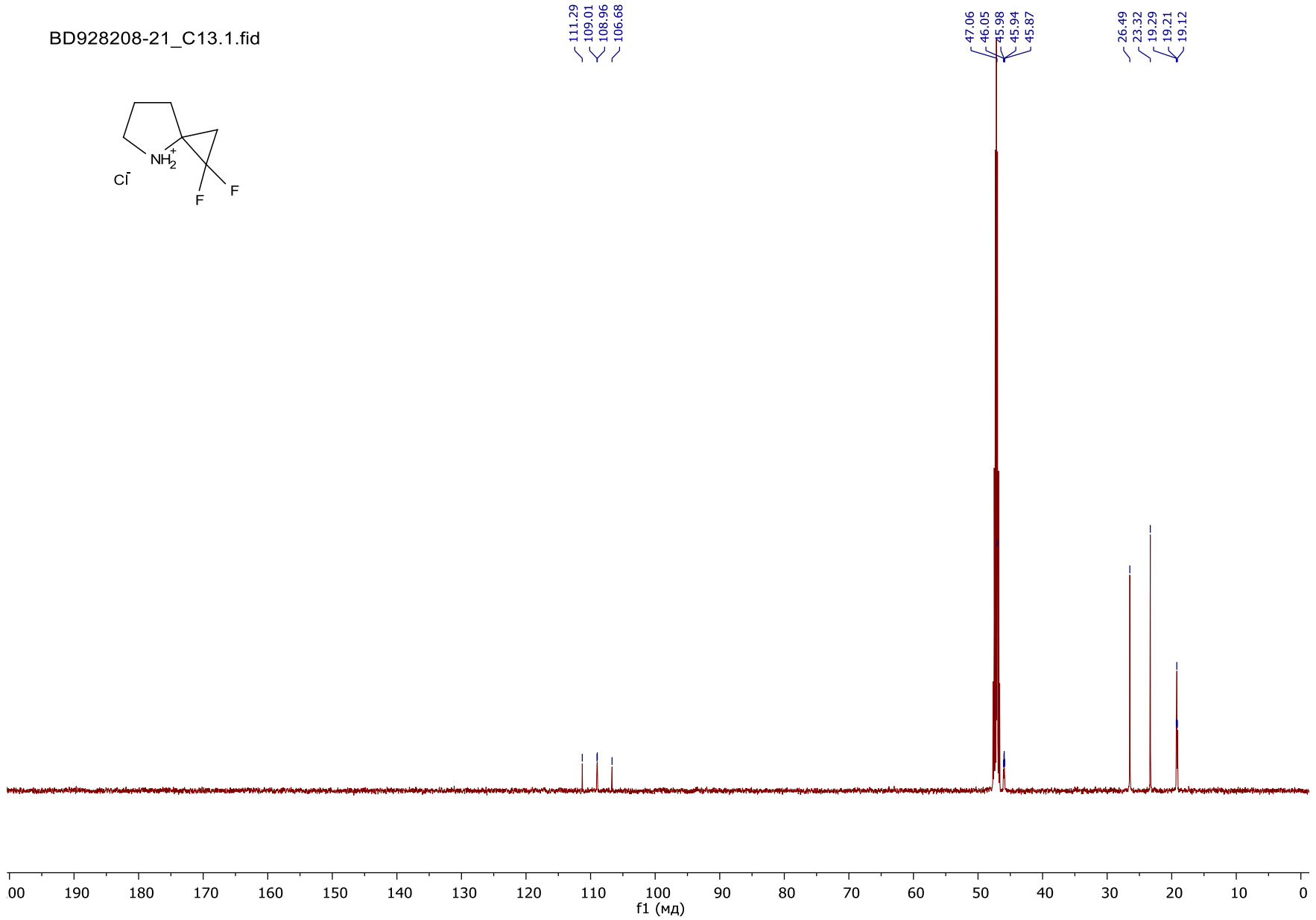
Spectrum 26. *tert*-Butyl 4-oxa-7-azaspiro[2.6]nonane-7-carboxylate **6e**, ^{1}H NMR (500 MHz, $CDCl_3$).



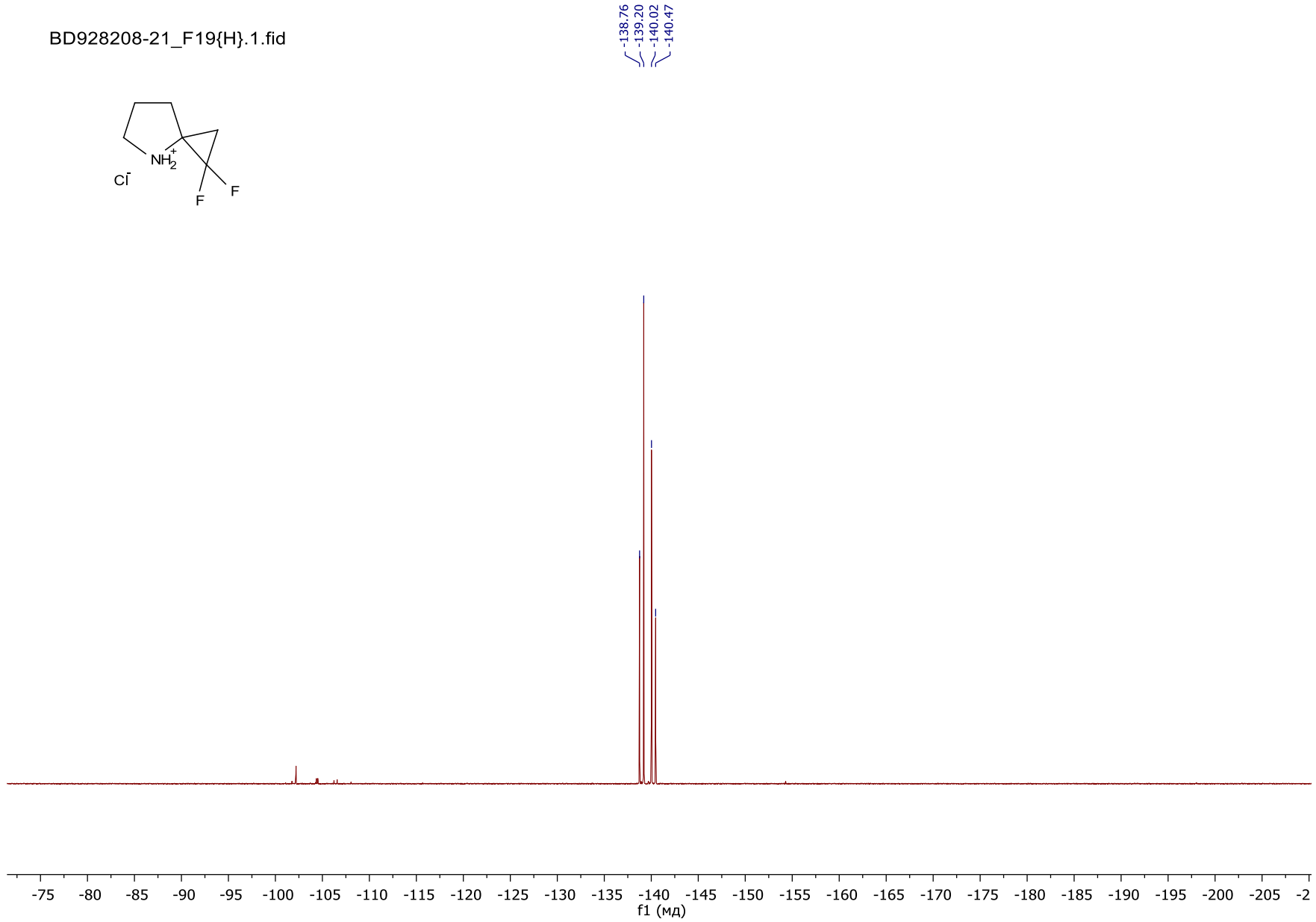
Spectrum 27. *tert*-Butyl 4-oxa-7-azaspiro[2.6]nonane-7-carboxylate **6e**, ^{13}C NMR (101 MHz, $CDCl_3$).



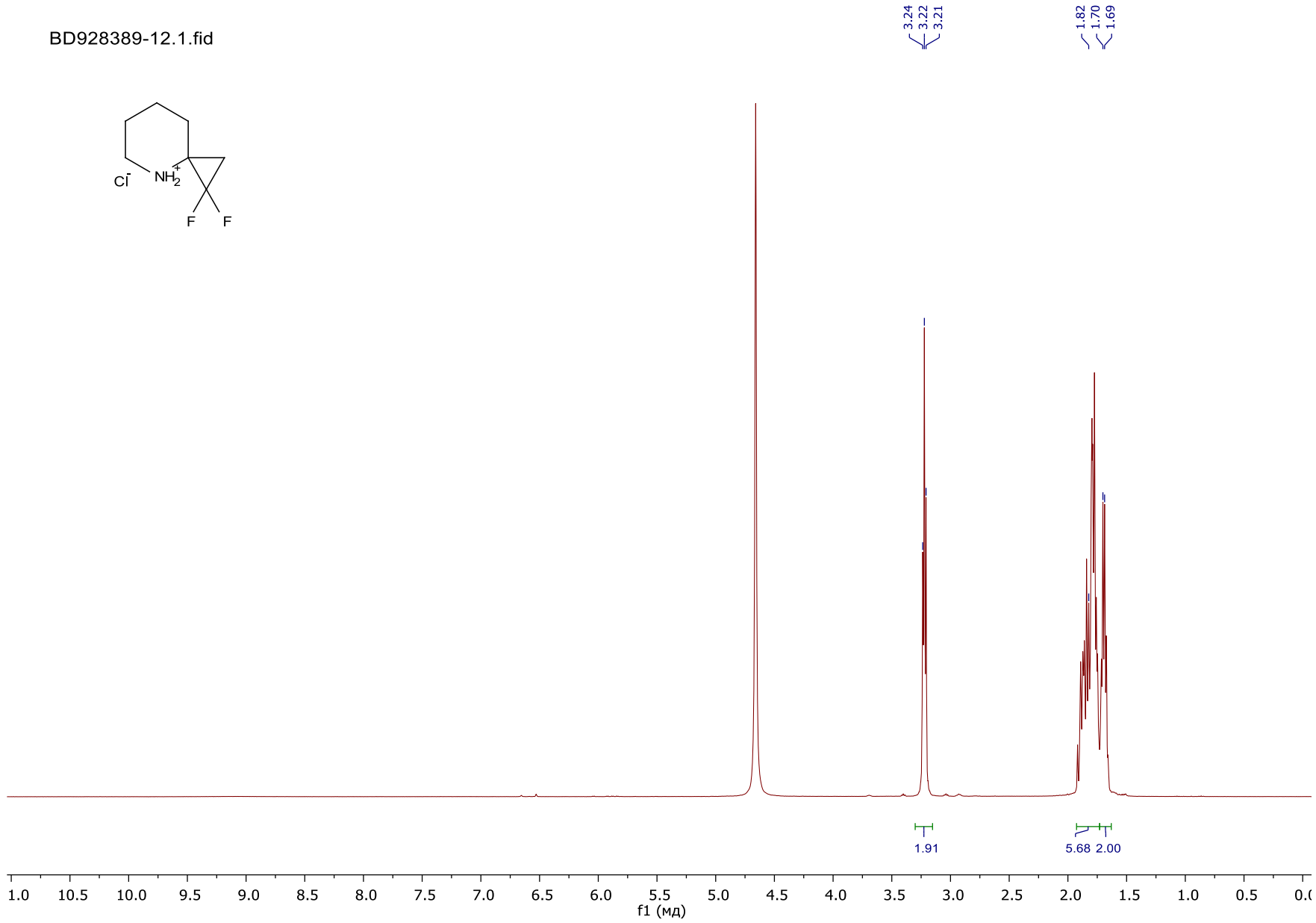
Spectrum 28. 1,1-Difluoro-4-azaspiro[2.4]heptan-4-ium chloride **5a**, ^{1}H NMR (400 MHz, CD_3OD).



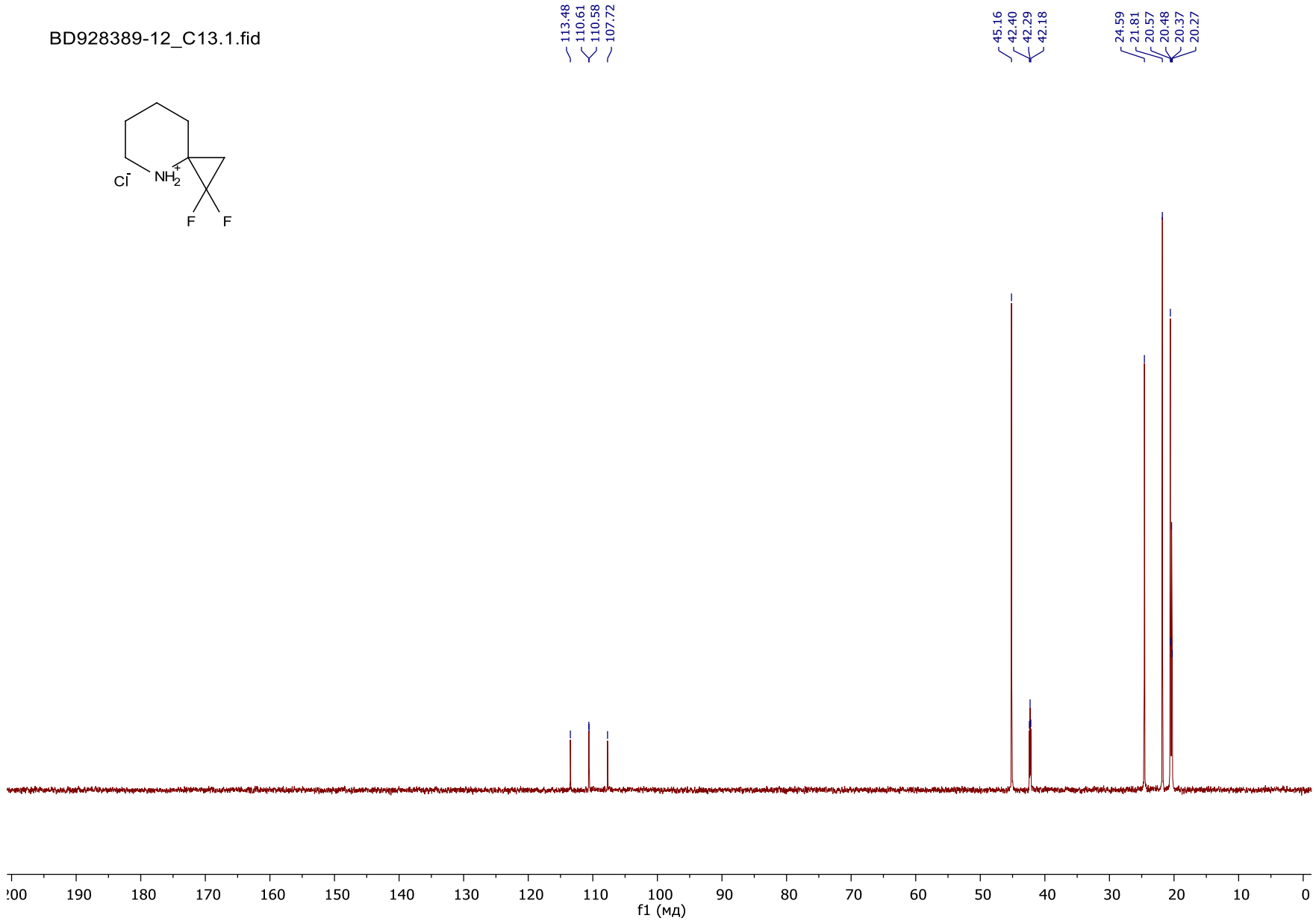
Spectrum 29. 1,1-Difluoro-4-azaspiro[2.4]heptan-4-ium chloride **5a**, ^{13}C NMR (126 MHz, CD_3OD).



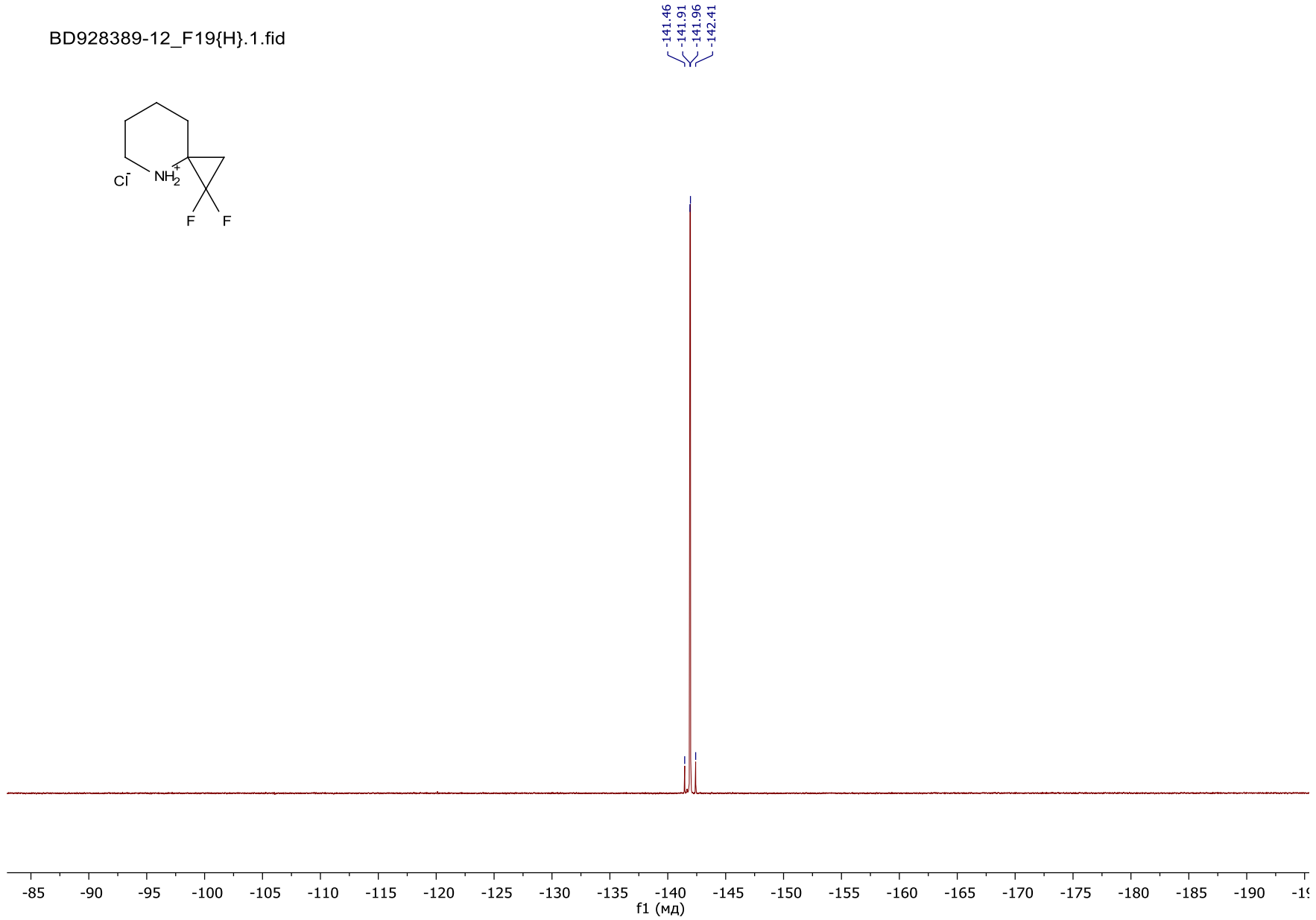
Spectrum 30. 1,1-Difluoro-4-azaspiro[2.4]heptan-4-ium chloride **5a**, ^{19}F NMR (376 MHz, CD_3OD).



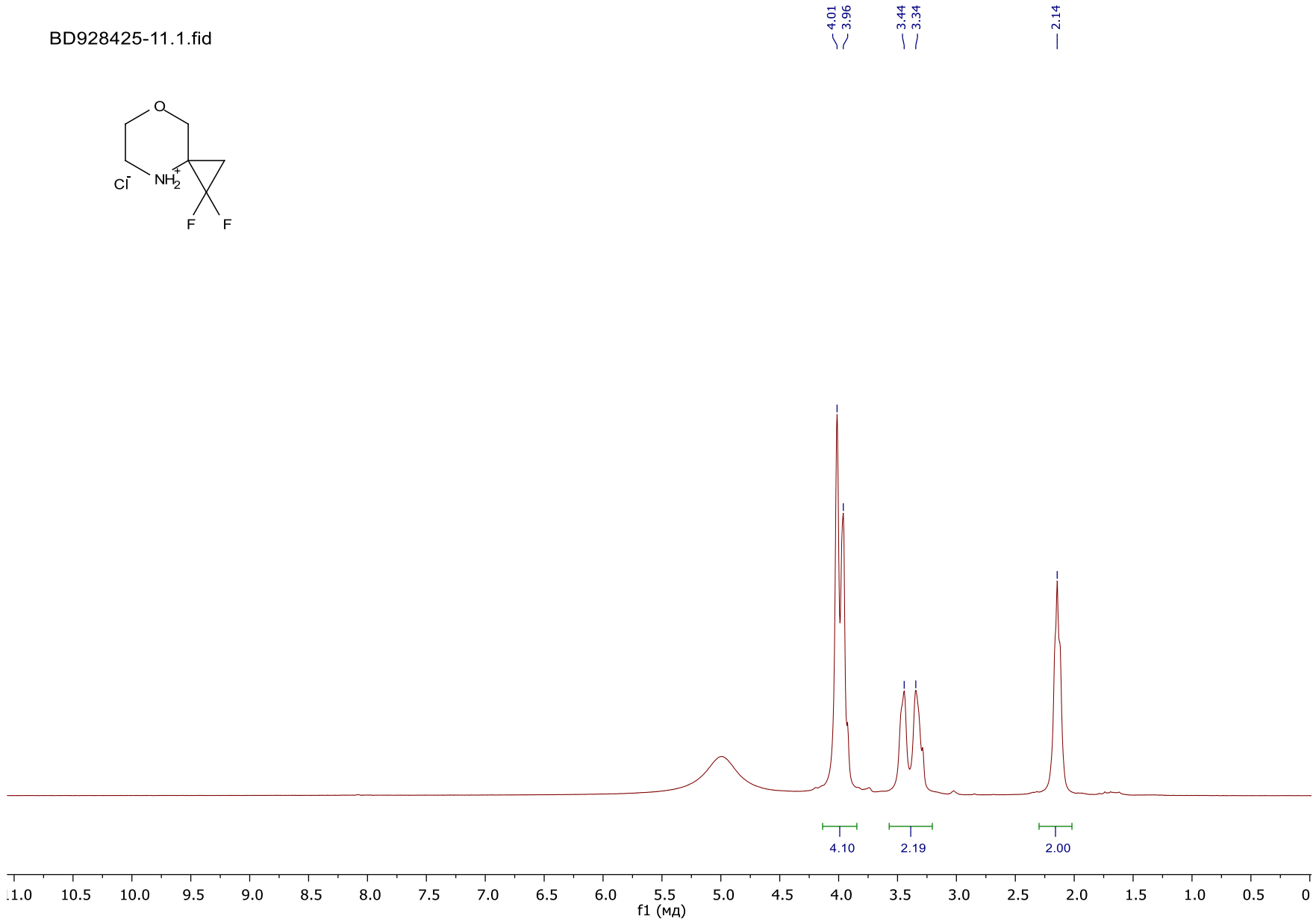
Spectrum 31. 1,1-Difluoro-4-azaspiro[2.5]octan-4-ium chloride **5b**, ^{1}H NMR (400 MHz, D_2O).



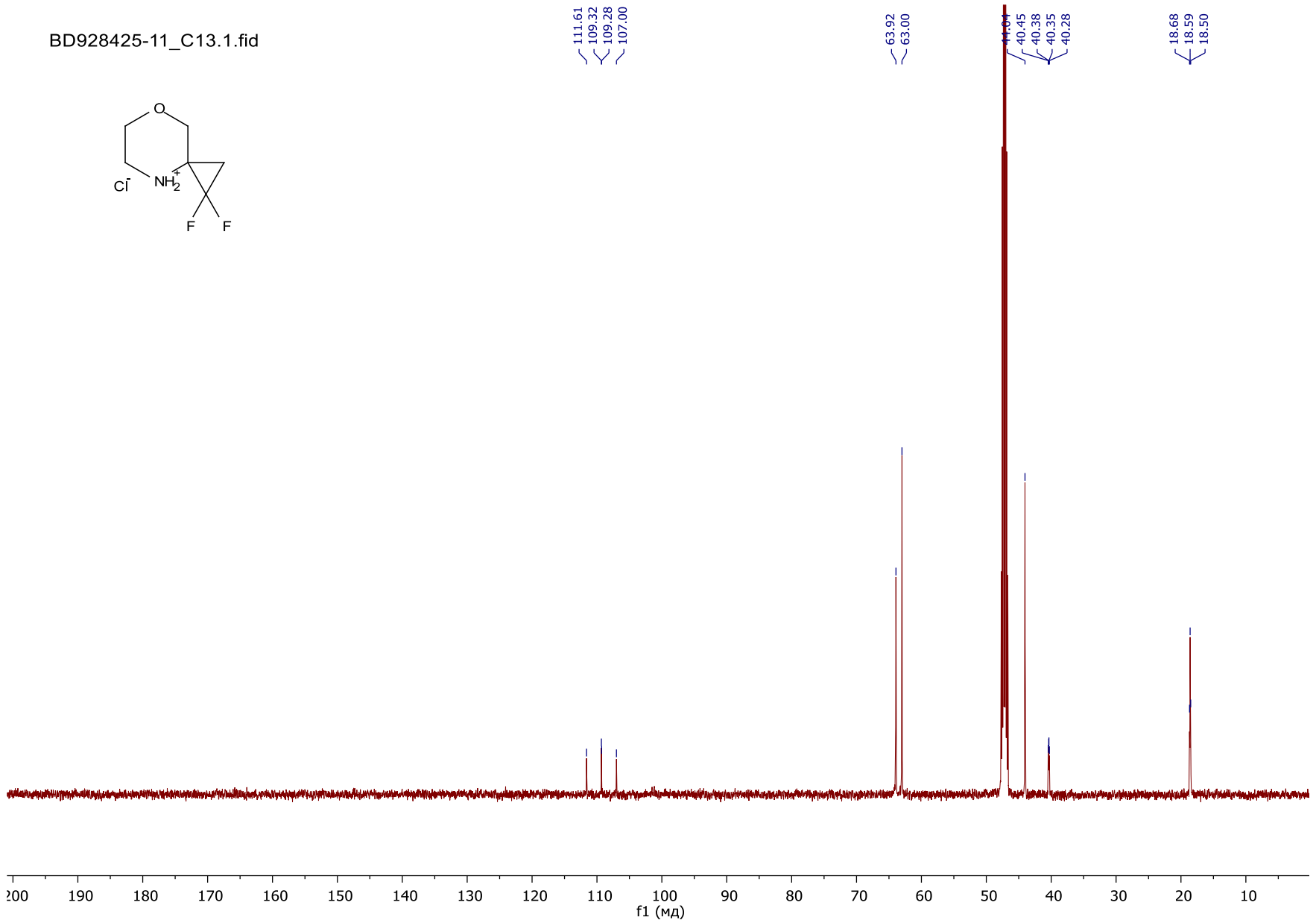
Spectrum 32. 1,1-Difluoro-4-azaspiro[2.5]octan-4-ium chloride **5b**, ^{13}C NMR (101 MHz, D_2O).



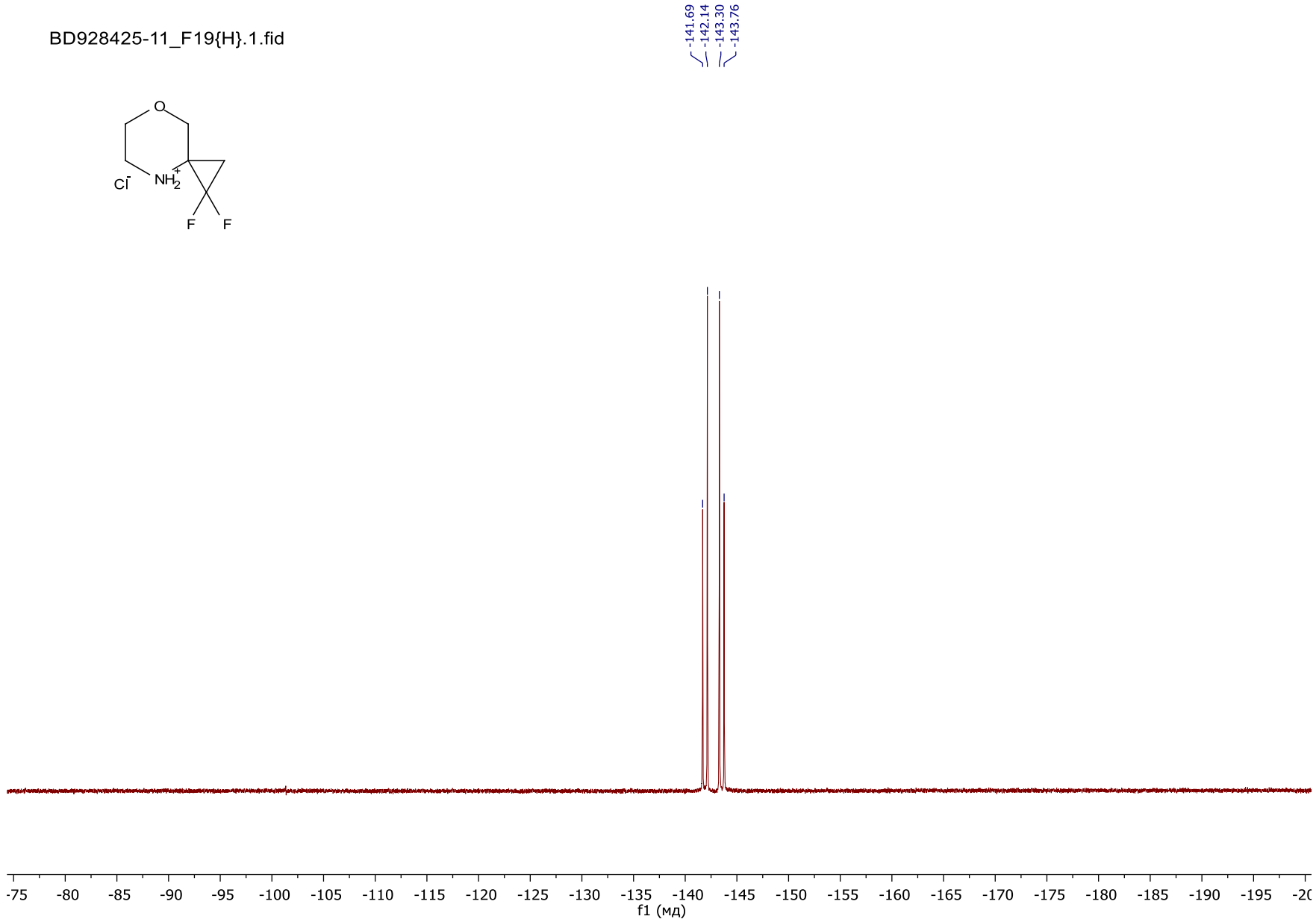
Spectrum 33. 1,1-Difluoro-4-azaspiro[2.5]octan-4-ium chloride **5b**, ^{19}F NMR (376 MHz, D_2O).



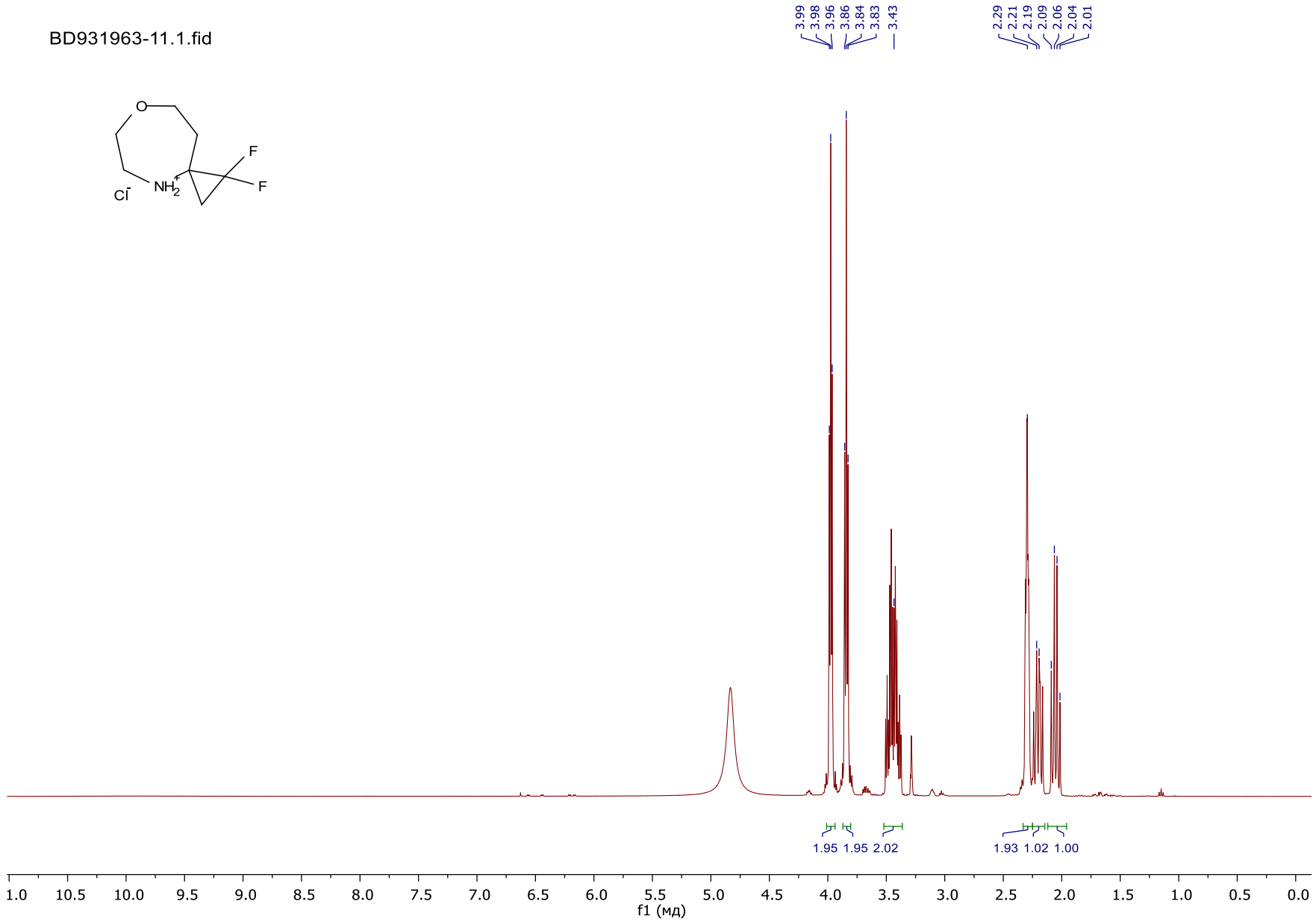
Spectrum 34. 1,1-Difluoro-7-oxa-4-azaspiro[2.5]octan-4-ium chloride **5c**, ^{1}H NMR (400 MHz, CD_3OD).



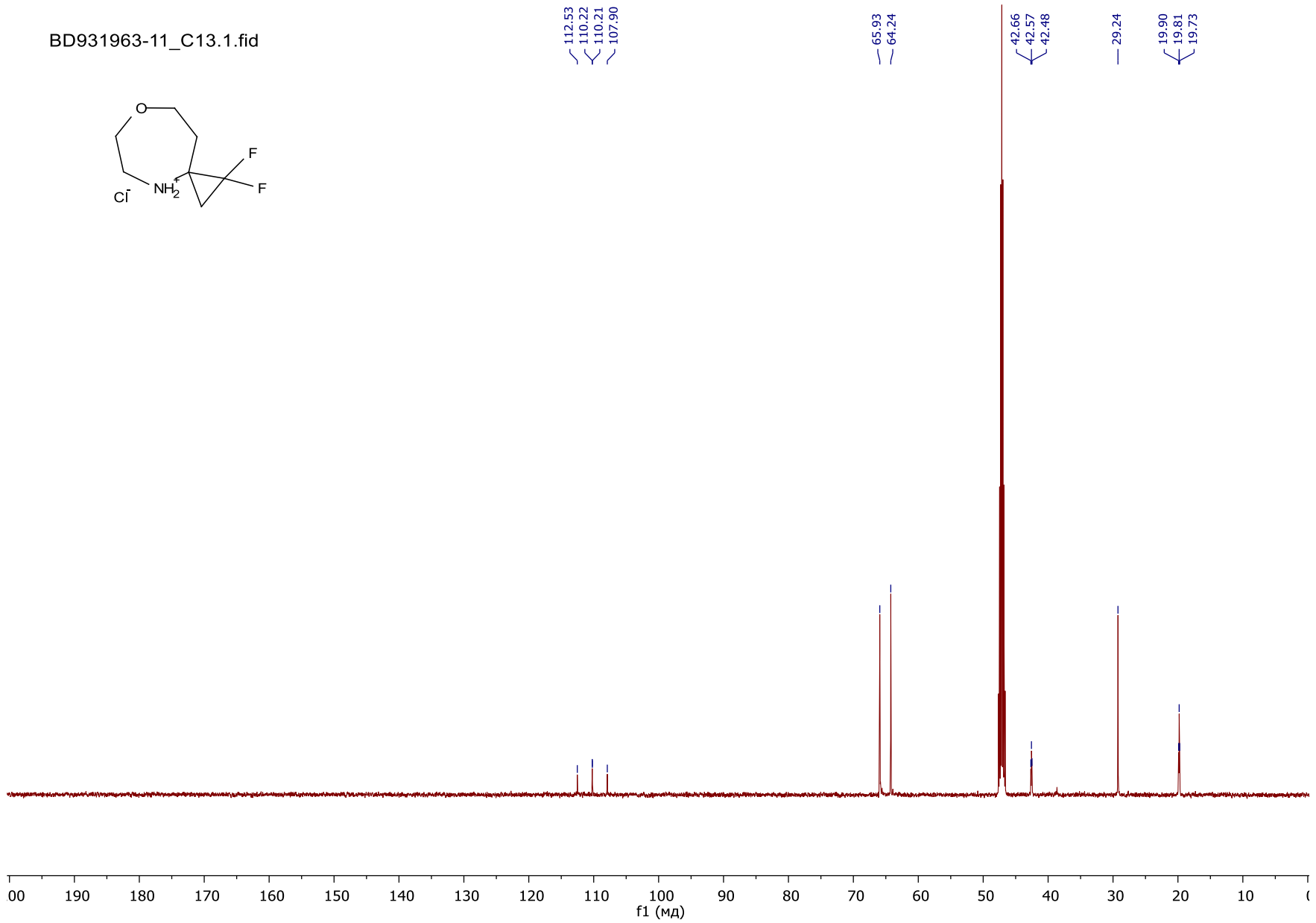
Spectrum 35. 1,1-Difluoro-7-oxa-4-azaspiro[2.5]octan-4-ium chloride **5c**, ^{13}C NMR (126 MHz, CD_3OD).



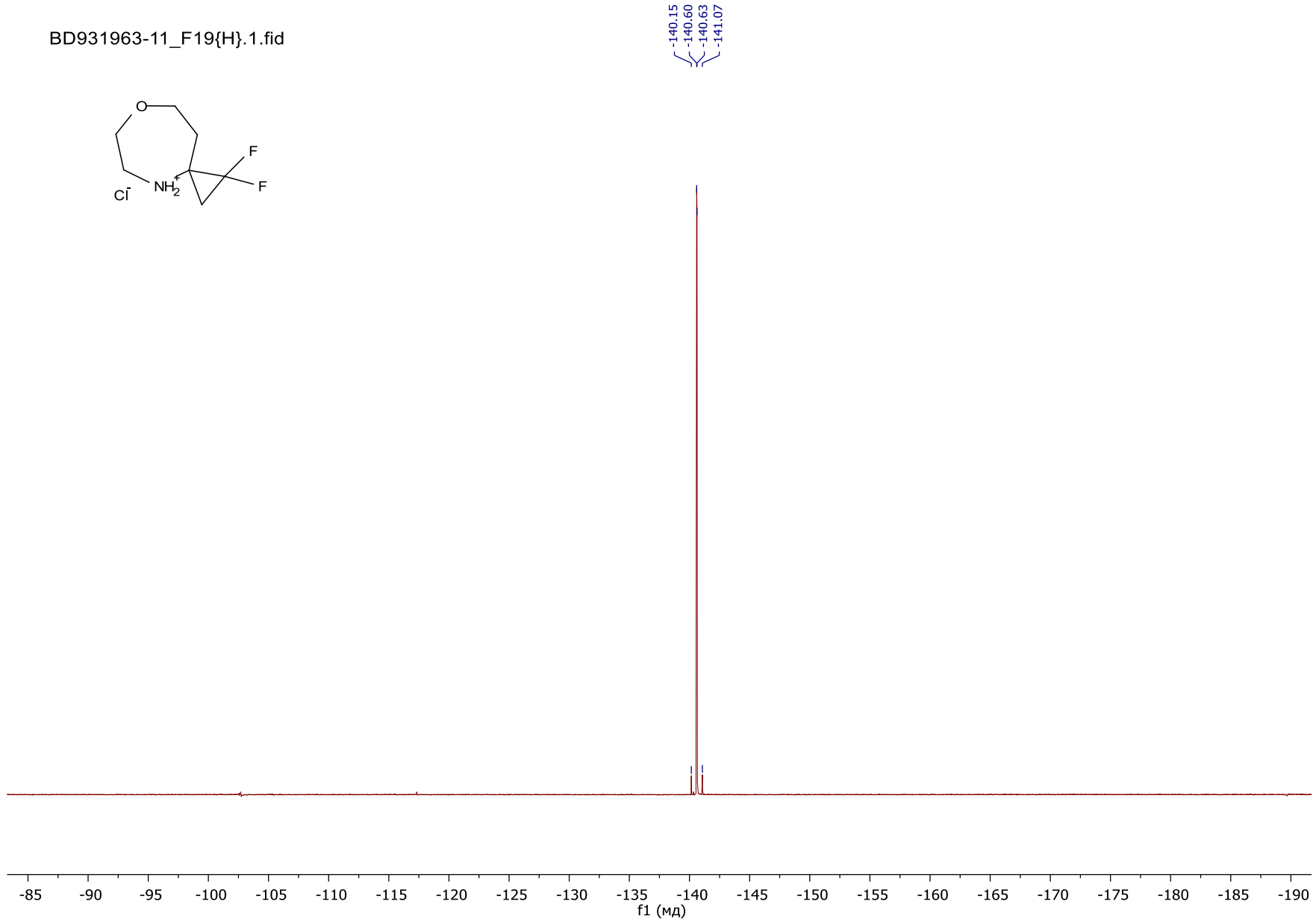
Spectrum 36. 1,1-Difluoro-7-oxa-4-azaspiro[2.5]octan-4-ium chloride **5c**, ^{19}F NMR (376 MHz, CD_3OD).



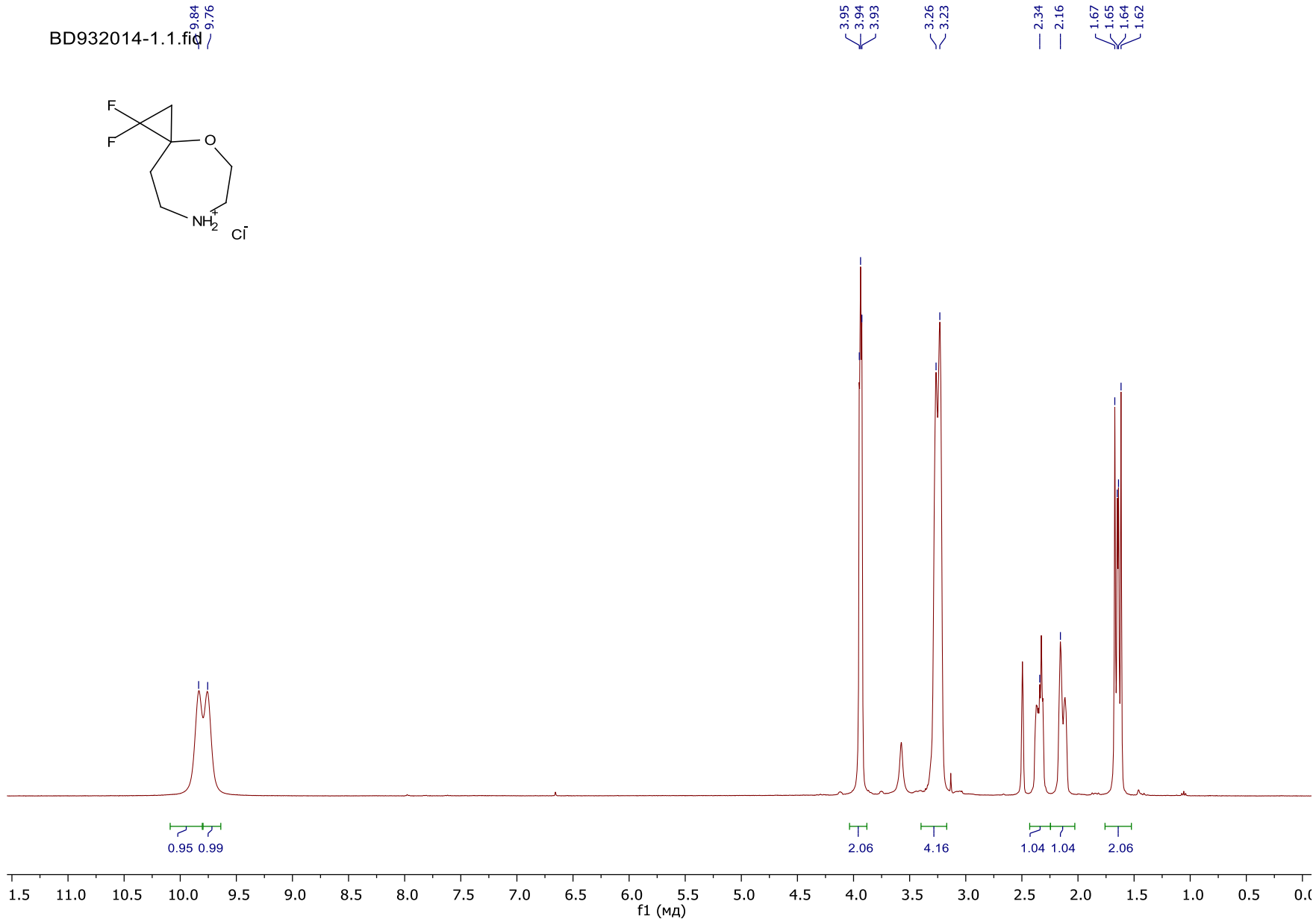
Spectrum 37. 1,1-difluoro-7-oxa-4-azaspiro[2.6]nonan-4-ium chloride **5d**, ^{1}H NMR (400 MHz, CD_3OD).



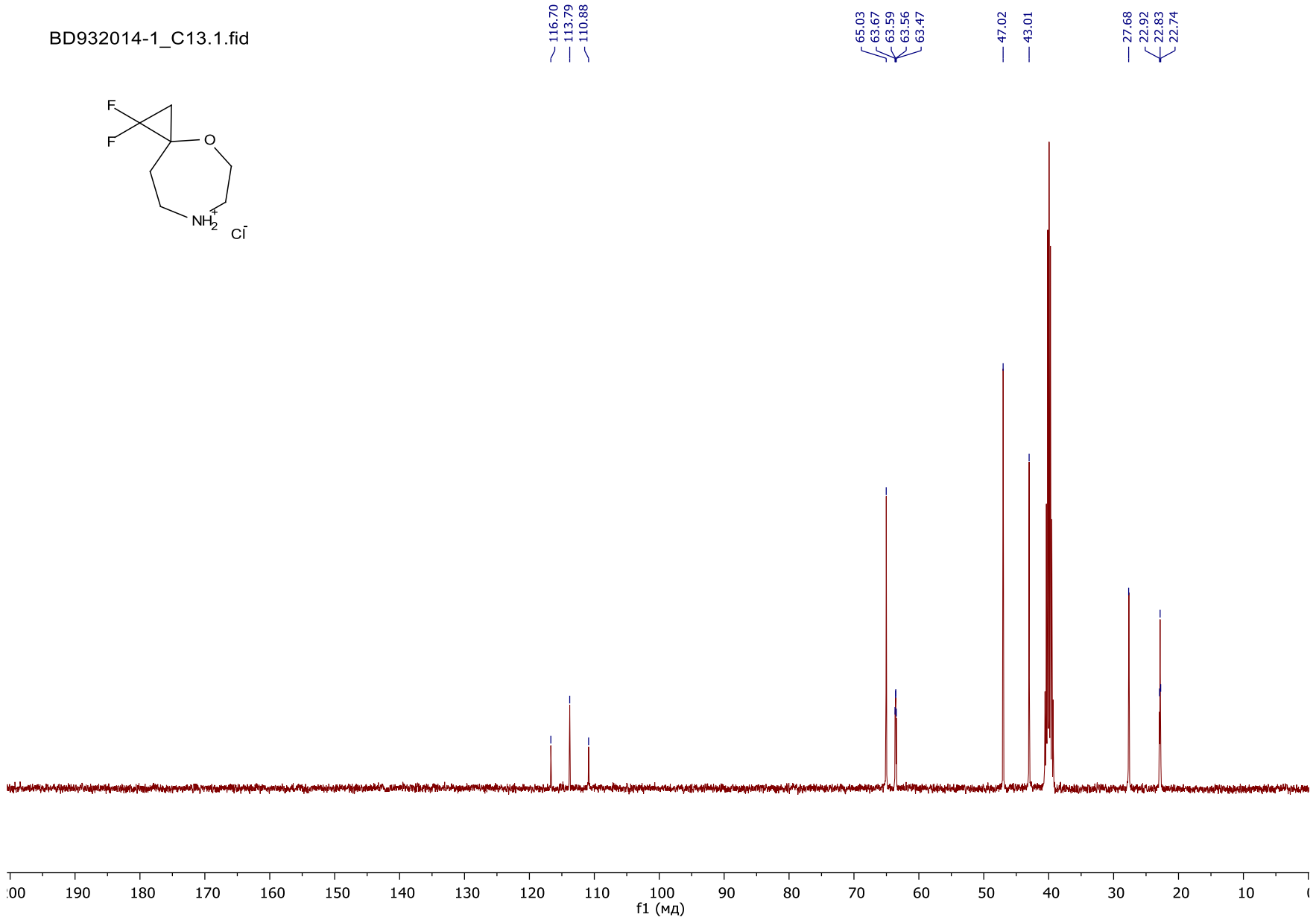
Spectrum 38. 1,1-Difluoro-7-oxa-4-azaspiro[2.6]nonan-4-ium chloride **5d**, ^{13}C NMR (126 MHz, CD_3OD).



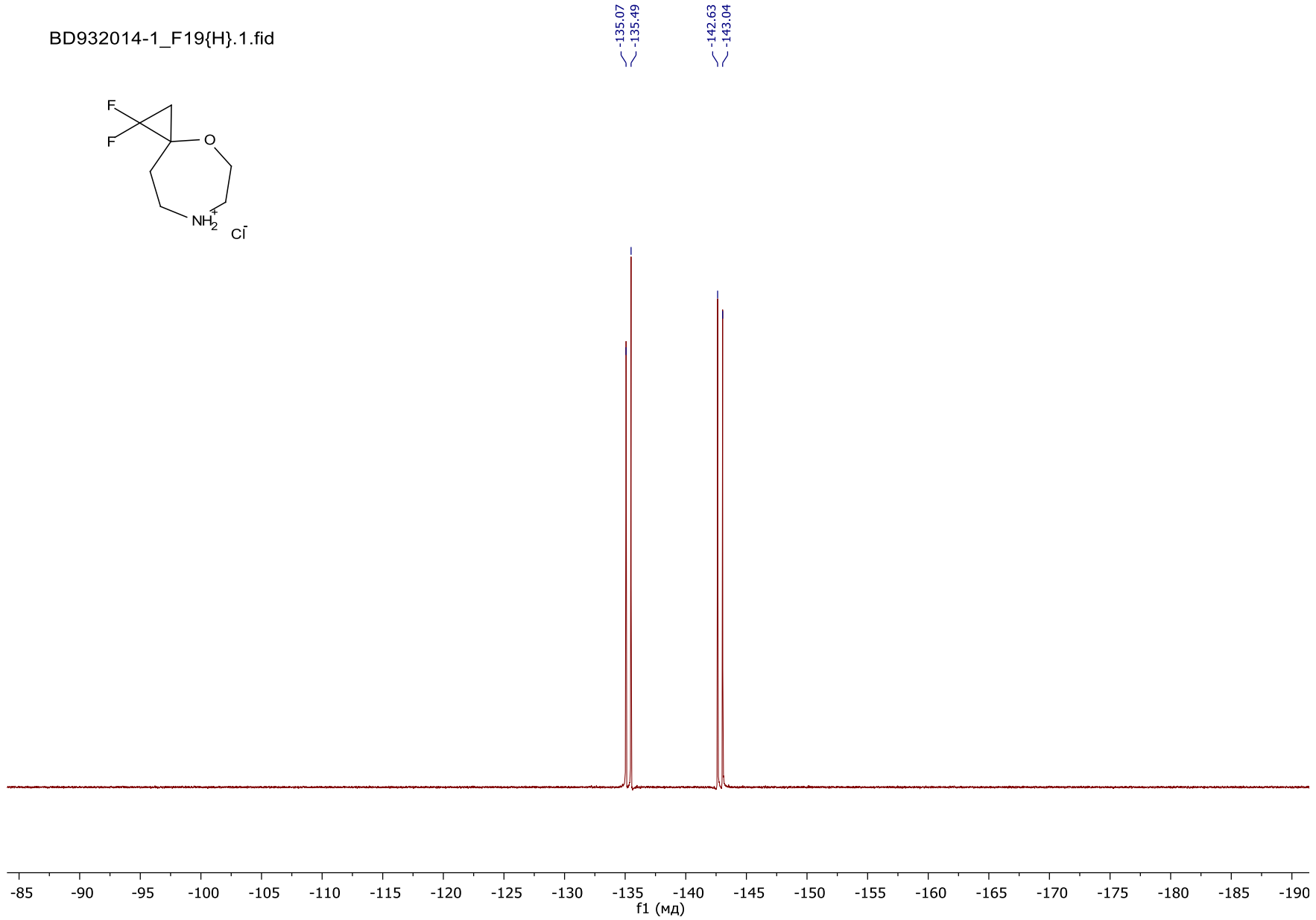
Spectrum 39. 1,1-Difluoro-7-oxa-4-azaspiro[2.6]nonan-4-ium chloride **5d**, ^{19}F NMR (376 MHz, CD_3OD).



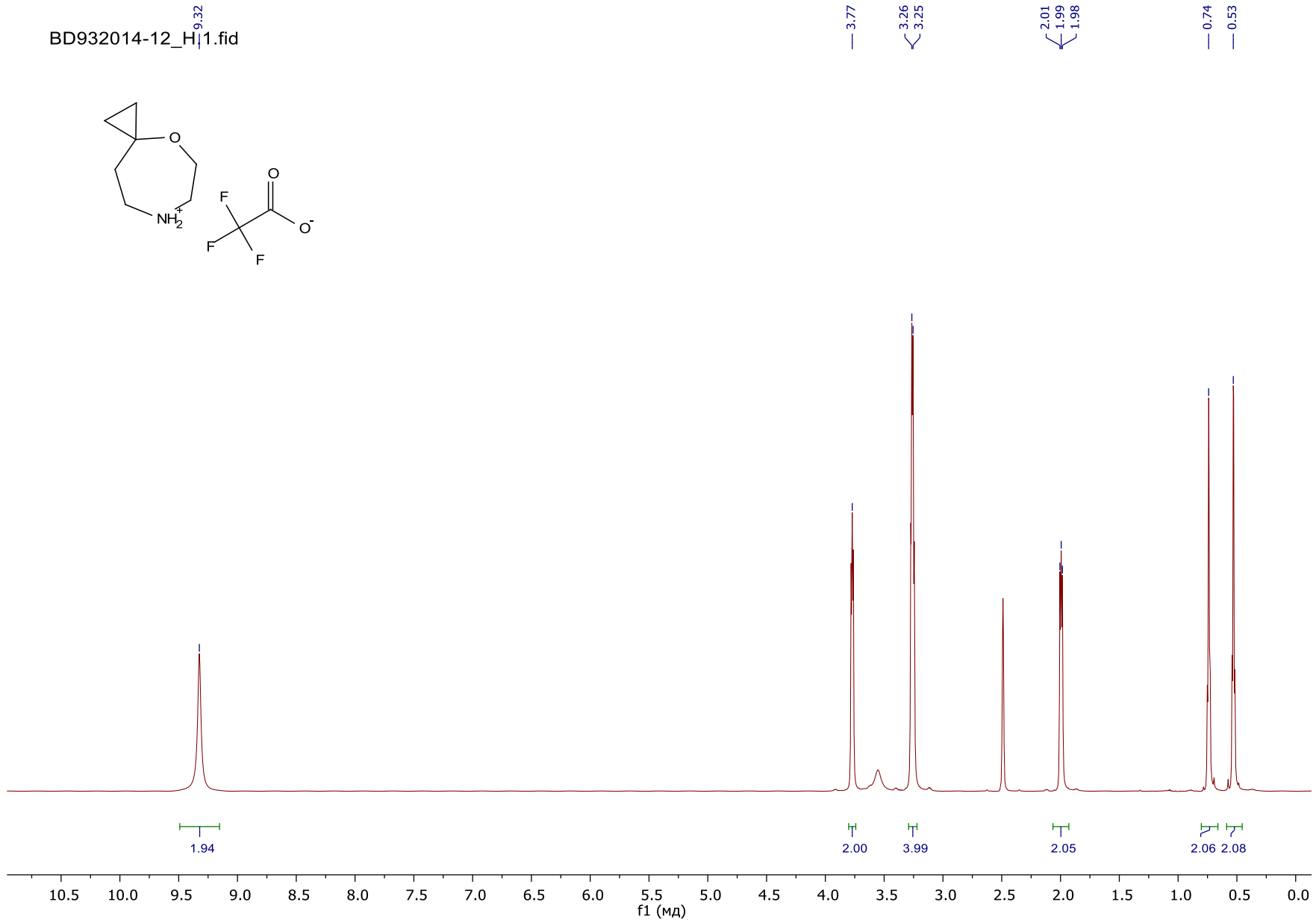
Spectrum 40. 1,1-Difluoro-4-oxa-7-azaspiro[2.6]nonan-7-ium chloride **5e**, ^{1}H NMR (400 MHz, DMSO-d_6).



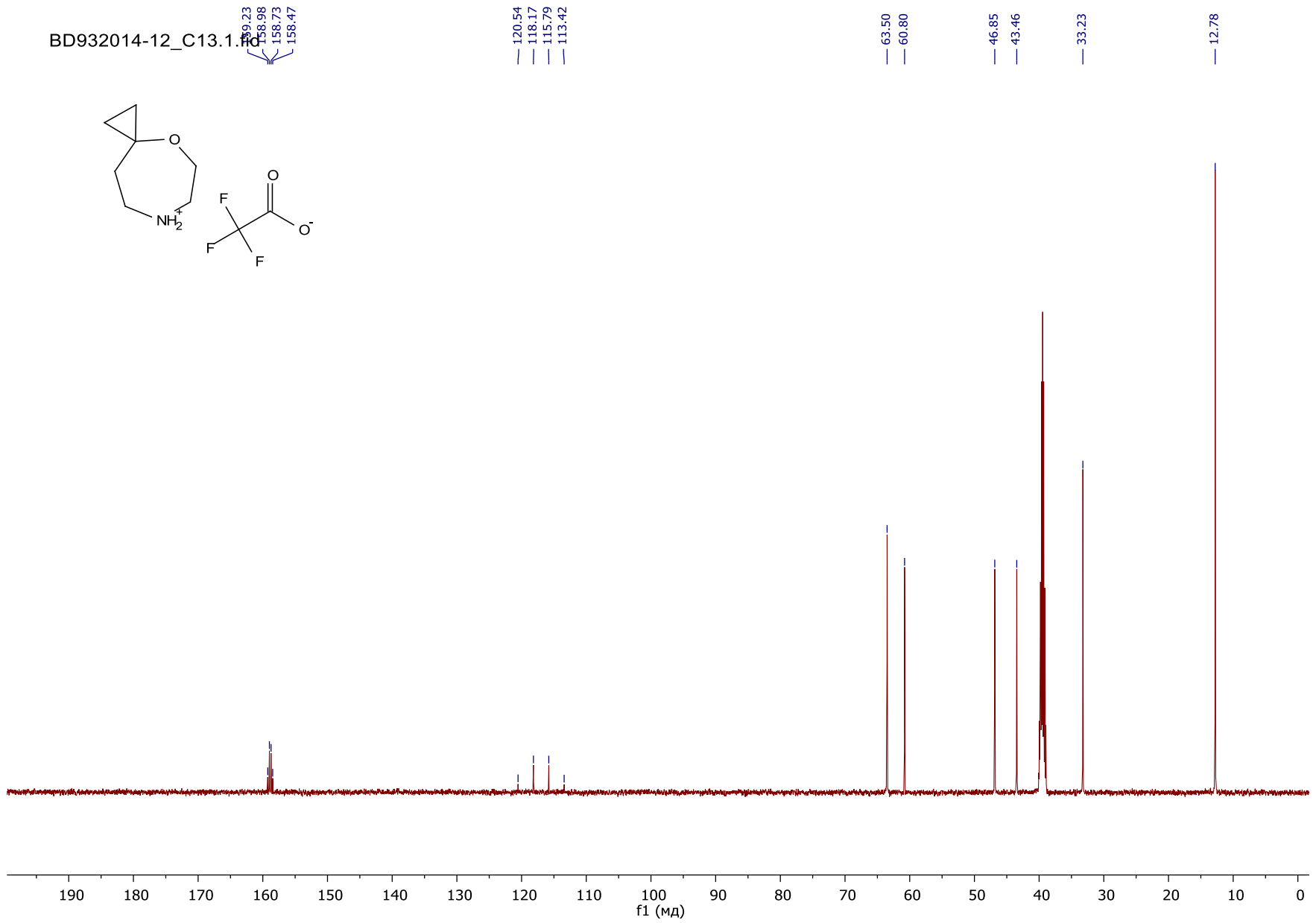
Spectrum 41. 1,1-Difluoro-4-oxa-7-azaspiro[2.6]nonan-7-ium chloride **5e**, ^{13}C NMR (101 MHz, DMSO-d_6).



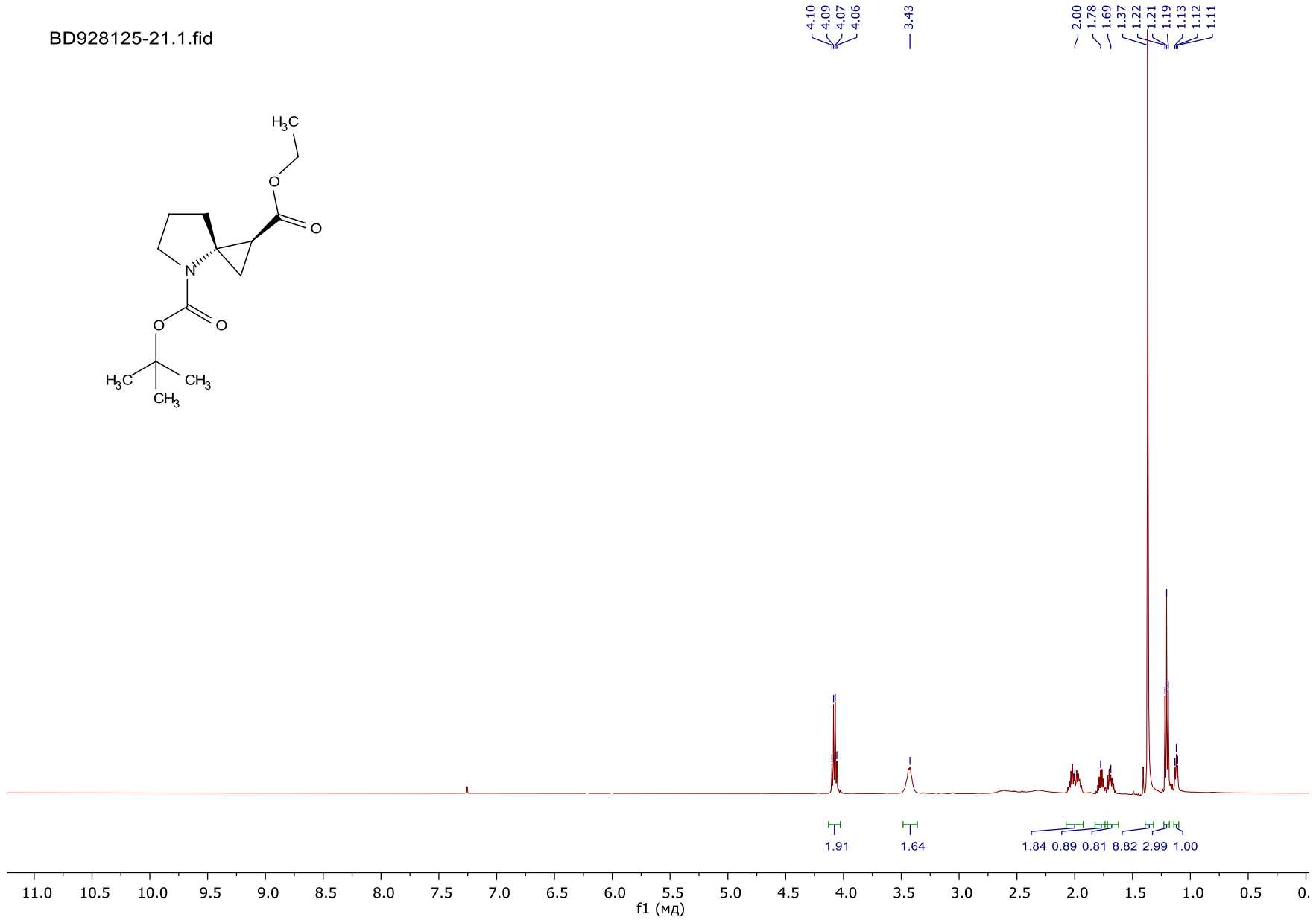
Spectrum 42. 1,1-Difluoro-4-oxa-7-azaspiro[2.6]nonan-7-ium chloride **5e**, ^{19}F NMR (376 MHz, DMSO-d_6).



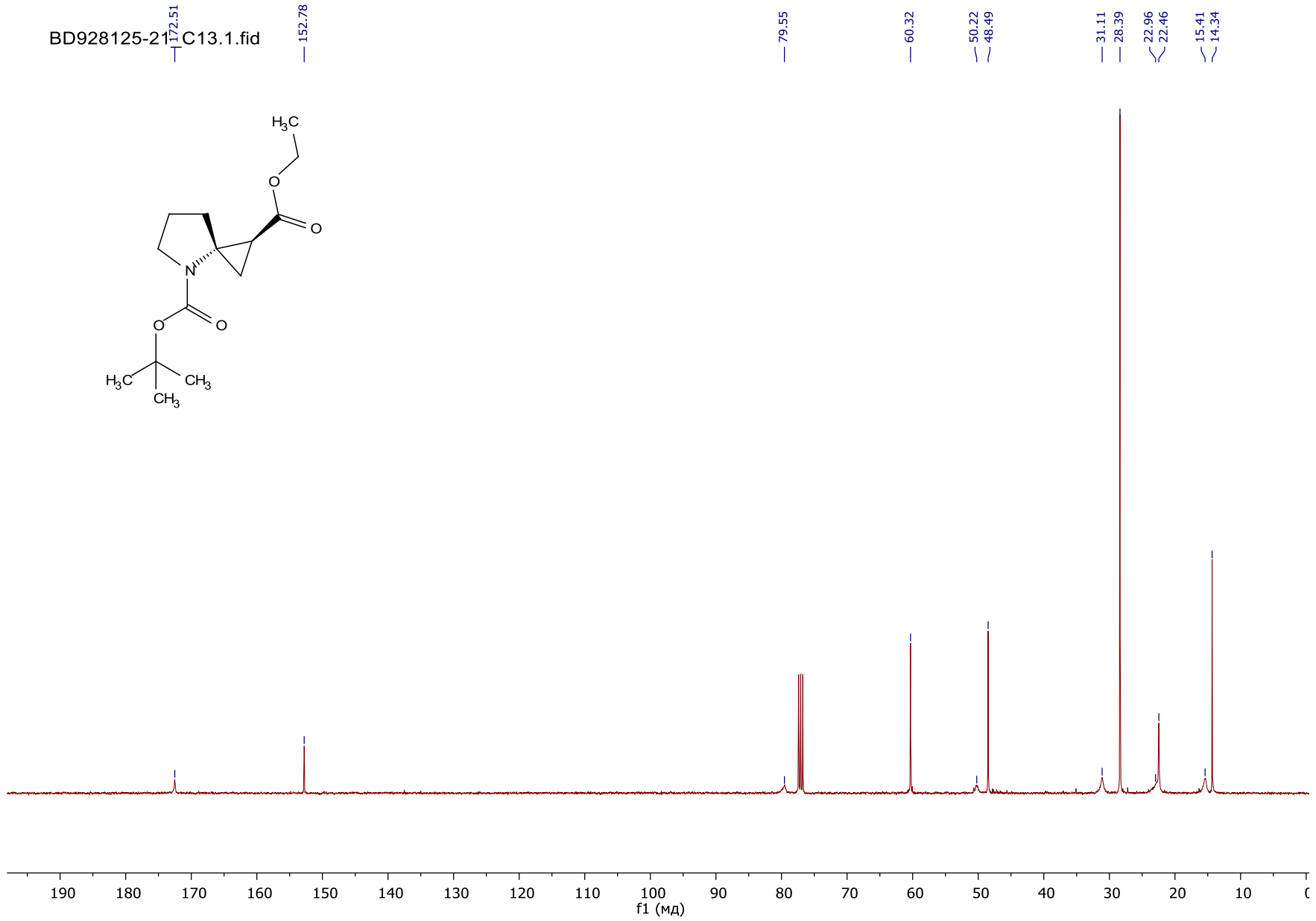
Spectrum 43. 4-Oxa-7-azaspiro[2.6]nonan-7-ium trifluoroacetate **7e**, ^{1}H NMR (500 MHz, DMSO-d_6).



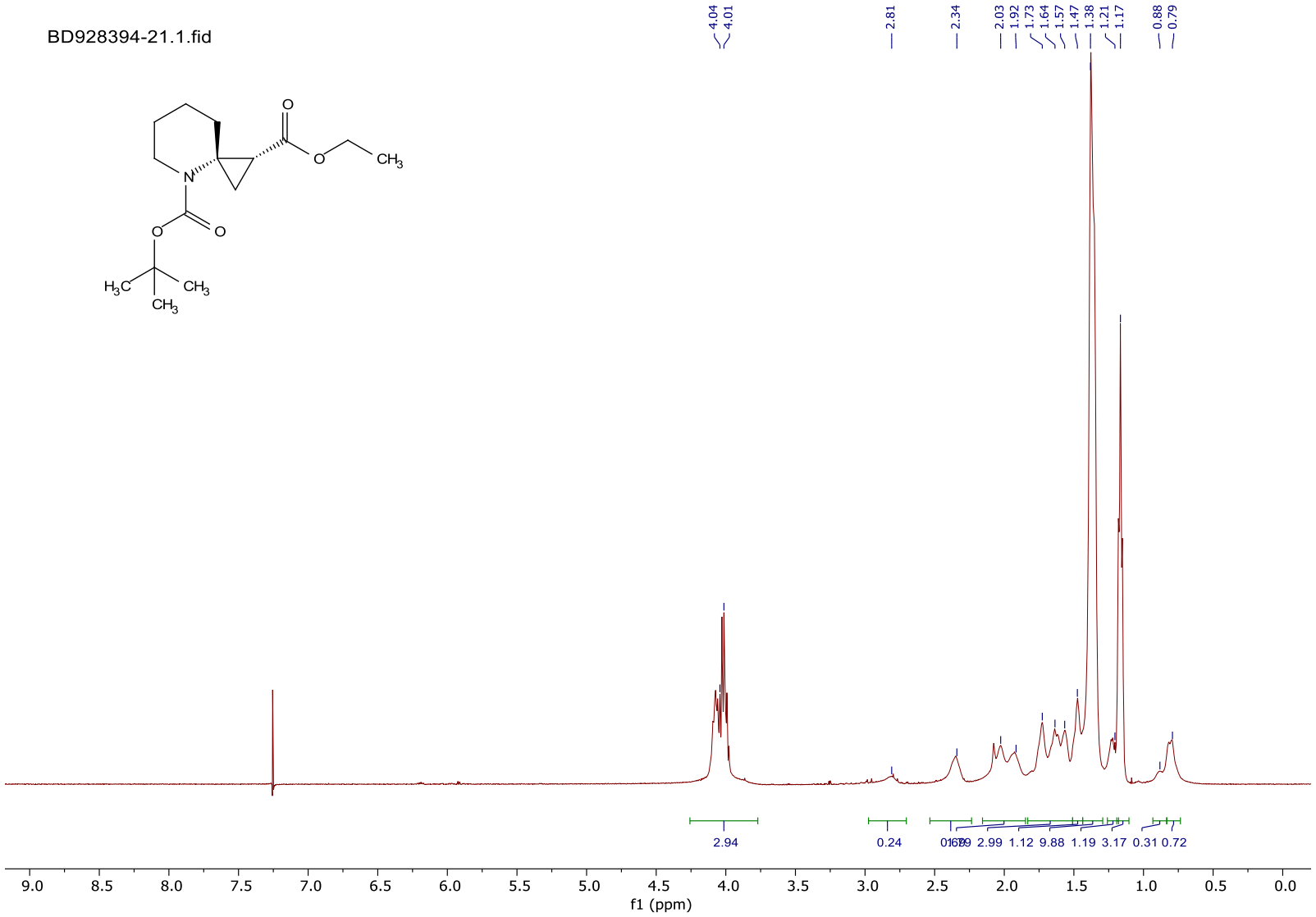
Spectrum 44. 4-Oxa-7-azaspiro[2.6]nonan-7-ium trifluoroacetate **7e**, ^{13}C NMR (126 MHz, DMSO-d_6).



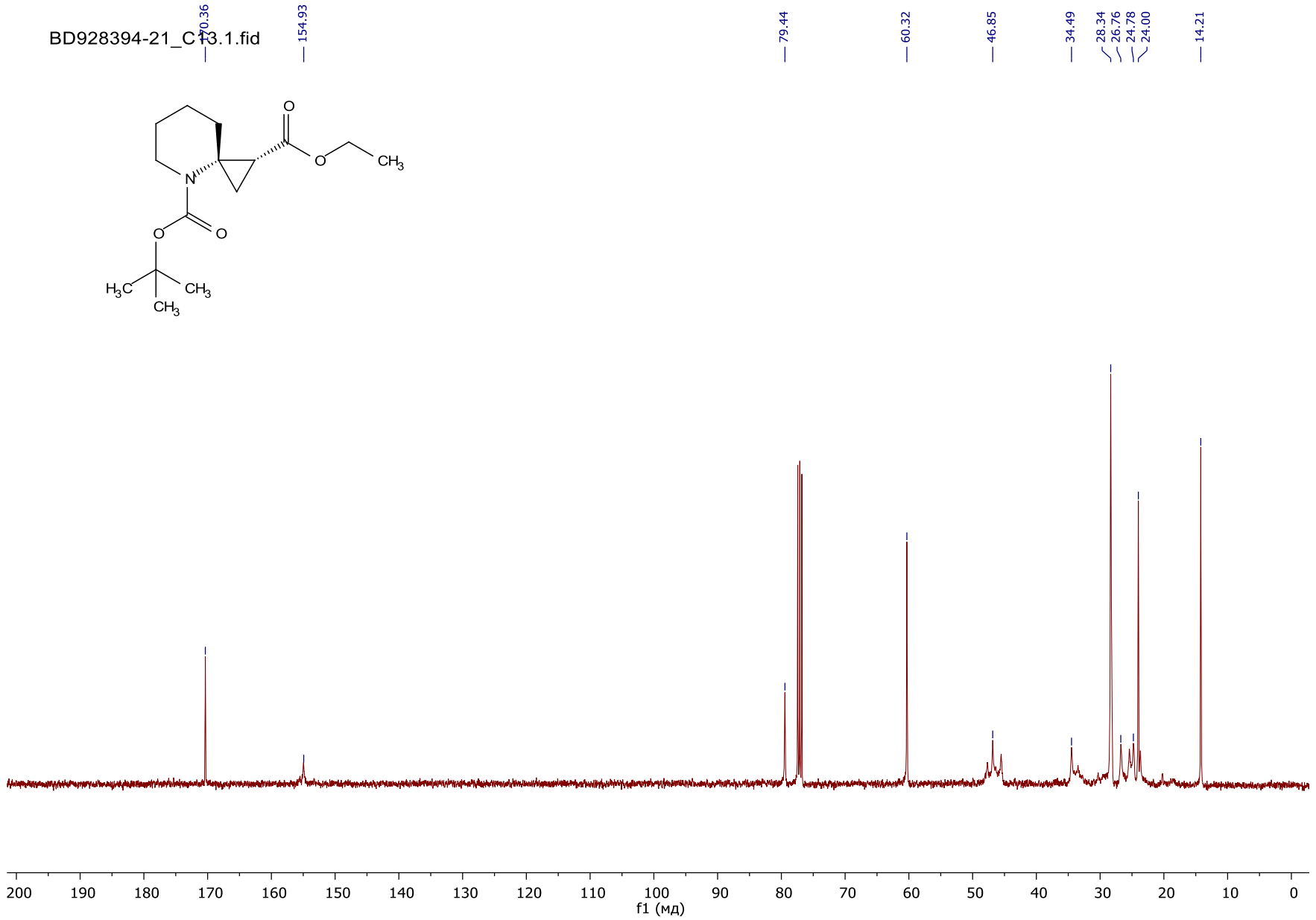
Spectrum 45. 4-*tert*-Butyl 1-ethyl (1*S*,3*S*)-4-azaspiro[2.4]heptane-1,4-dicarboxylate *trans*-**8a**, ^{1}H NMR (500 MHz, $CDCl_3$).



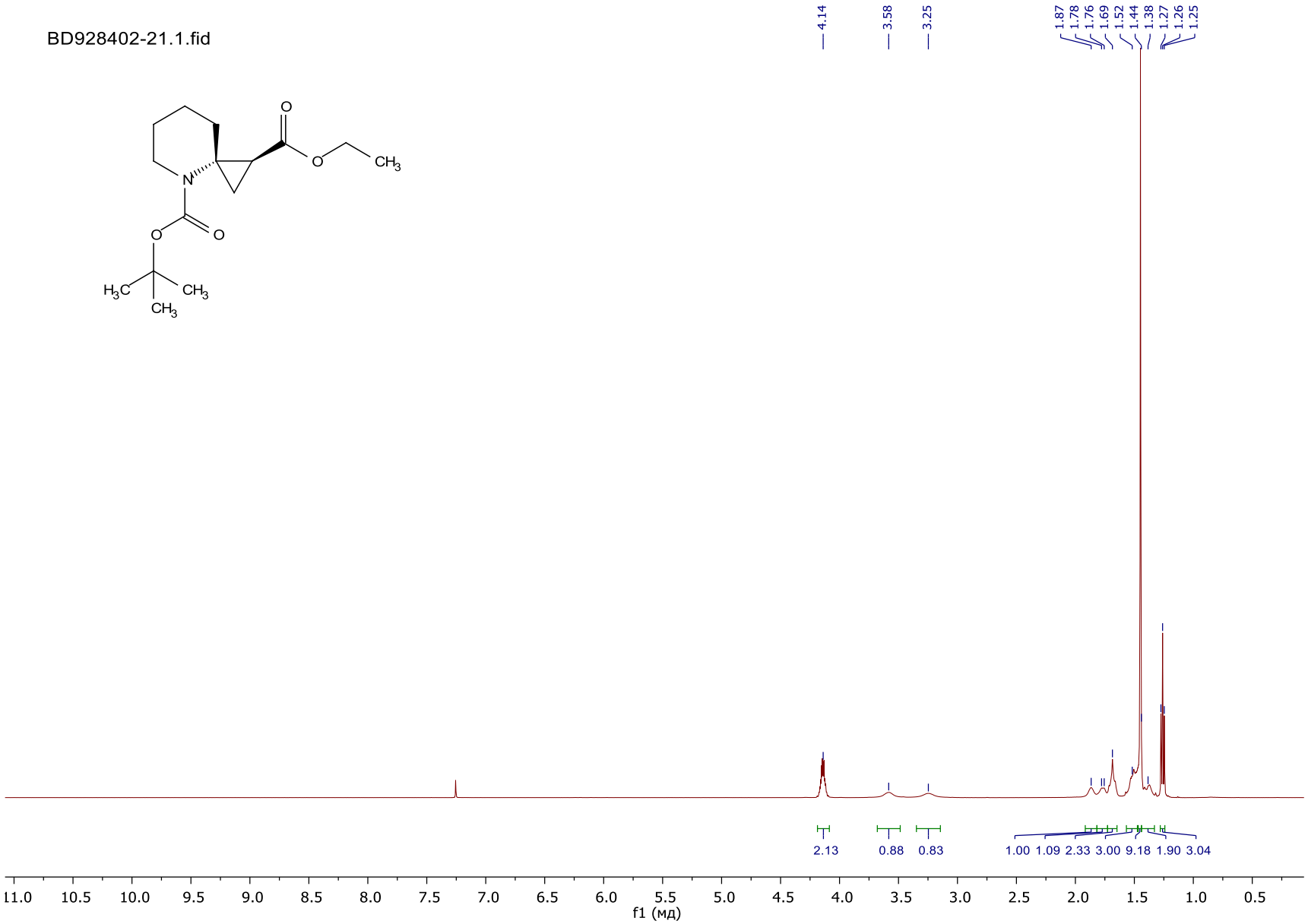
Spectrum 46. 4-*tert*-Butyl 1-ethyl (1*S*,3*S*)-4-azaspiro[2.4]heptane-1,4-dicarboxylate *trans*-**8a**, ^{13}C NMR (101 MHz, $CDCl_3$).



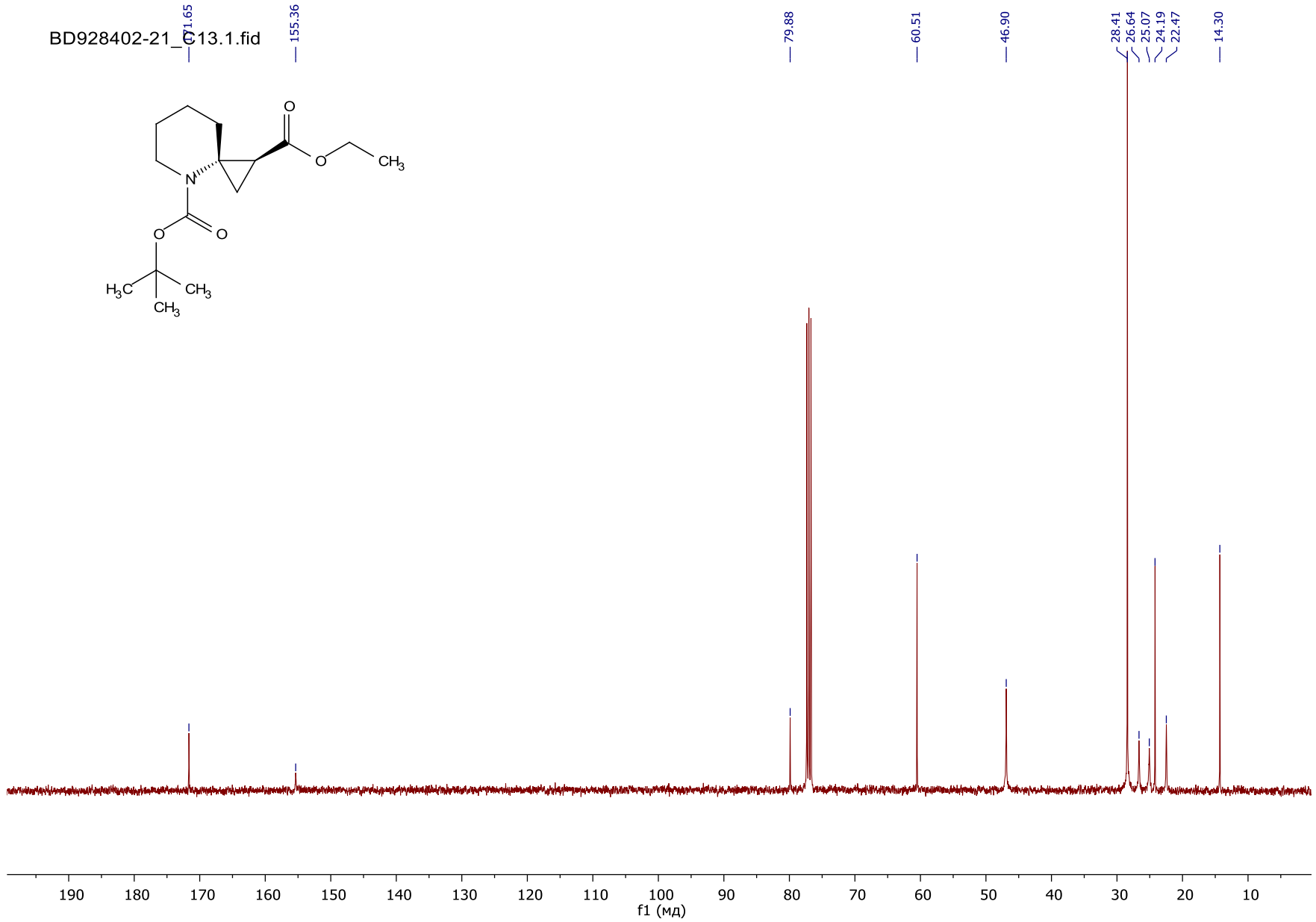
Spectrum 47. 4-*tert*-Butyl 1-ethyl (1*S*,3*R*)-4-azaspiro[2.5]octane-1,4-dicarboxylate *cis*-**8b**, ^{1}H NMR (500 MHz, $CDCl_3$).



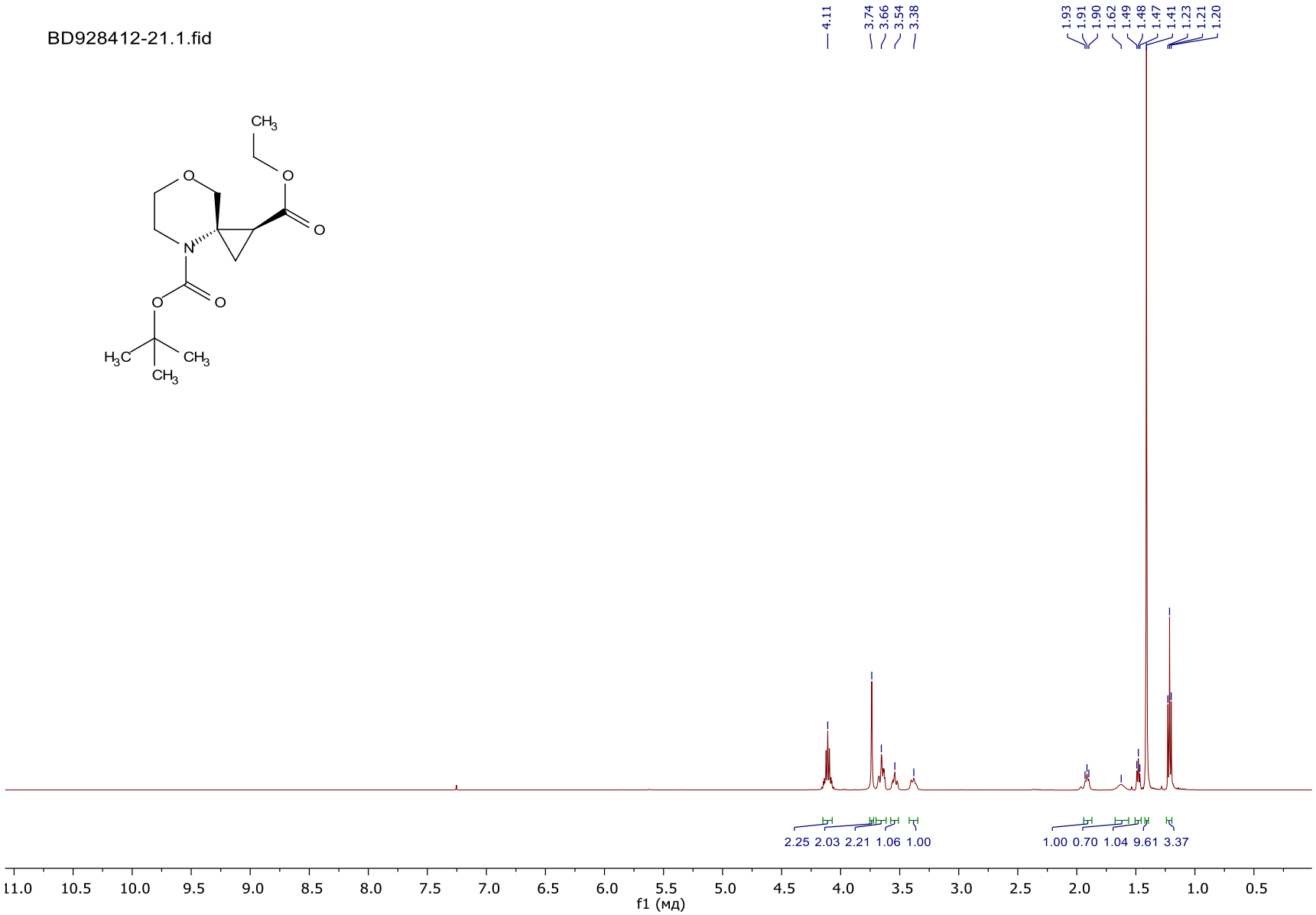
Spectrum 48. 4-*tert*-Butyl 1-ethyl (1*S*,3*R*)-4-azaspiro[2.5]octane-1,4-dicarboxylate *cis*-**8b**, ^{13}C NMR (101 MHz, $CDCl_3$).



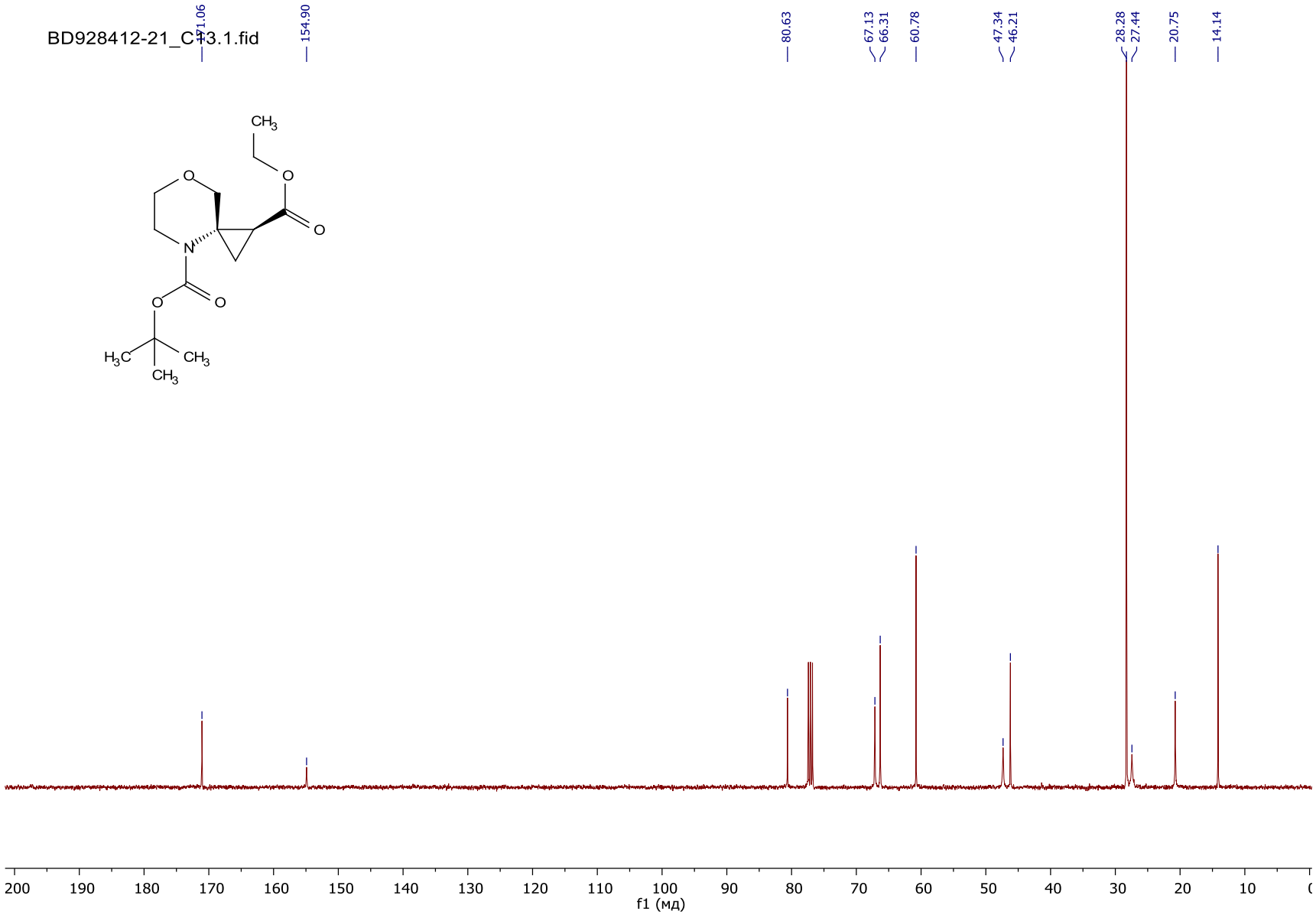
Spectrum 49. 4-*tert*-Butyl 1-ethyl (1*R*,3*R*)-4-azaspiro[2.5]octane-1,4-dicarboxylate *trans*-**8b**, ^{1}H NMR (500 MHz, $CDCl_3$).



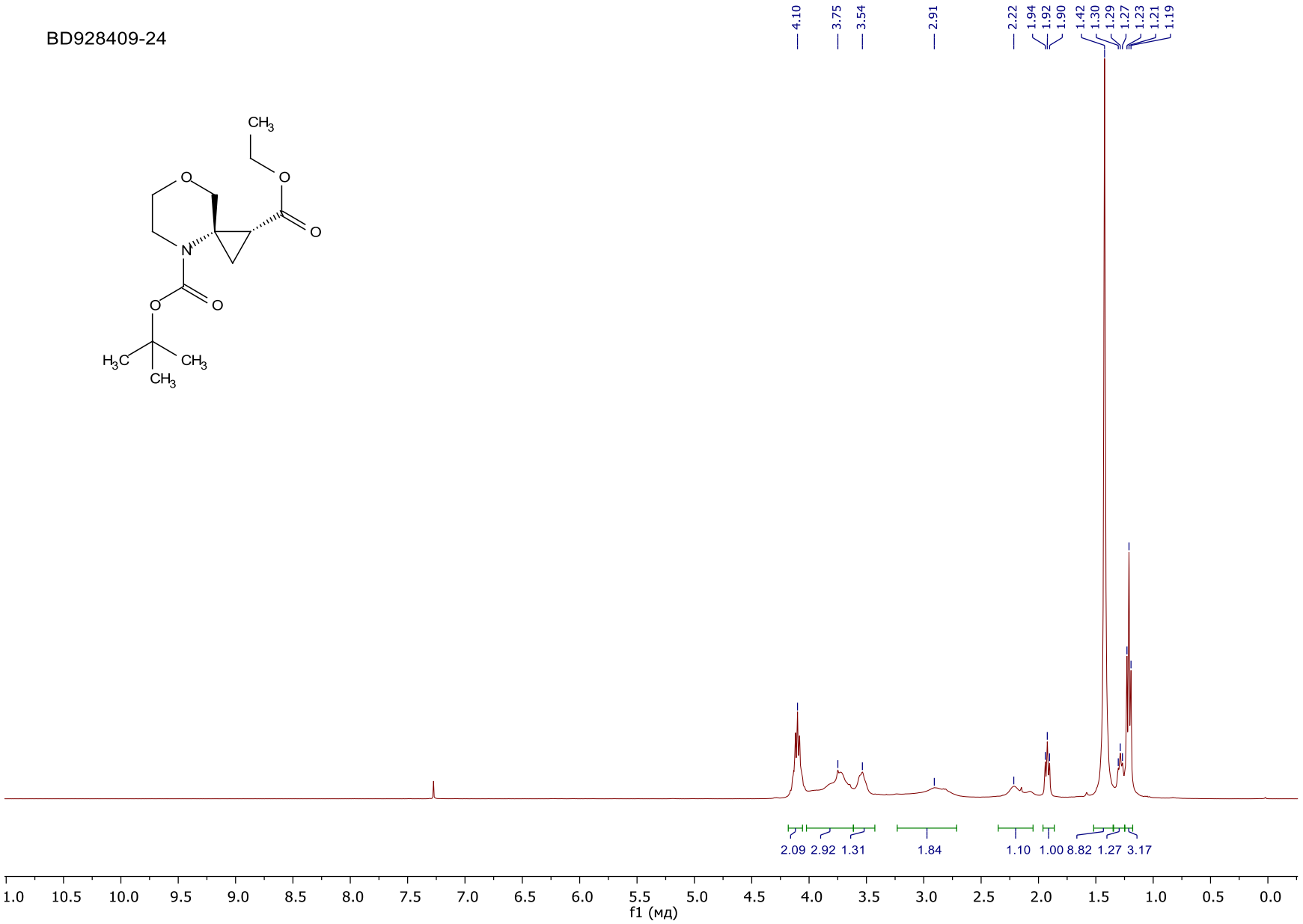
Spectrum 50. 4-*tert*-Butyl 1-ethyl (1*R*,3*R*)-4-azaspiro[2.5]octane-1,4-dicarboxylate *trans*-**8b**, ^{13}C NMR (101 MHz, $CDCl_3$).



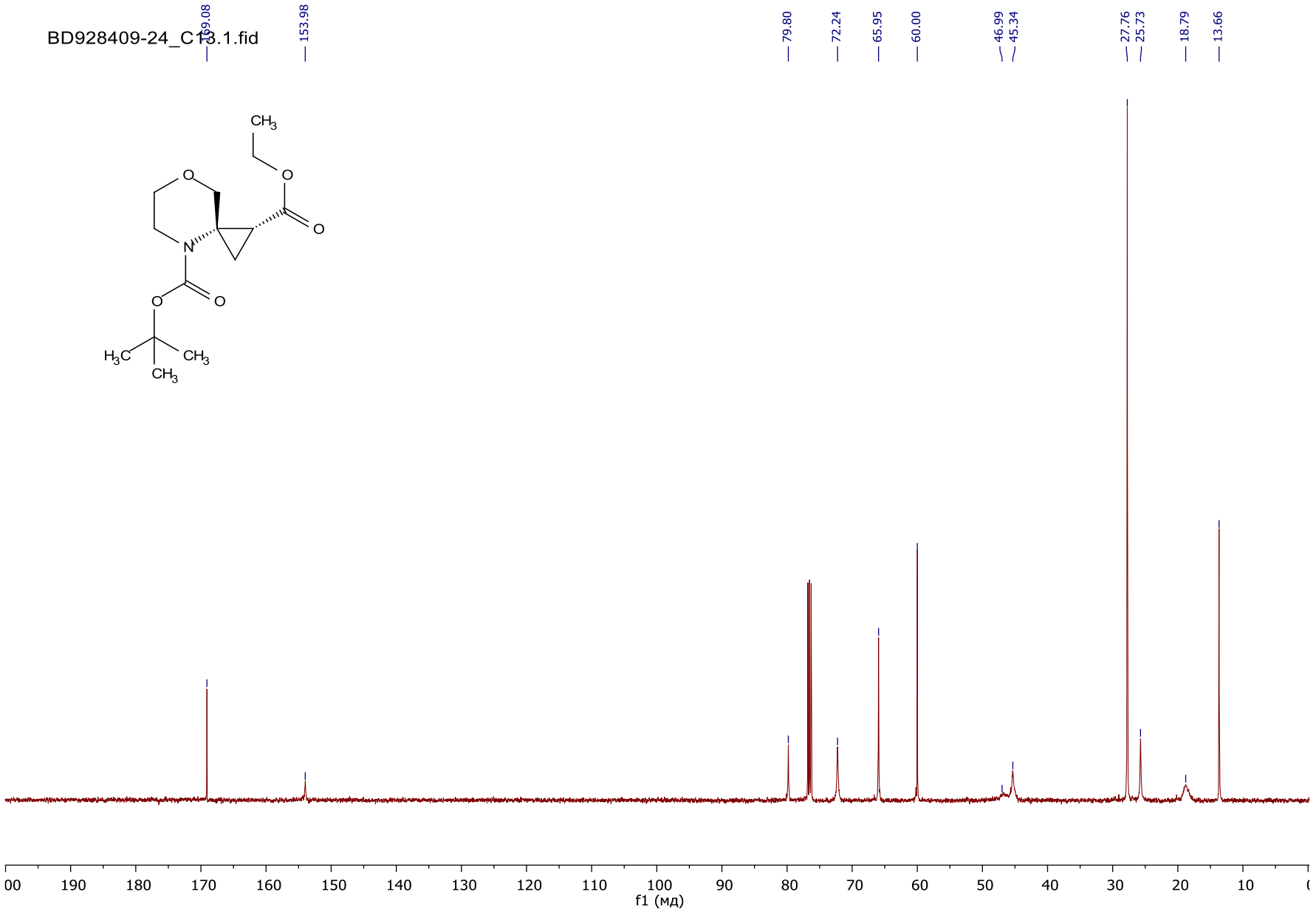
Spectrum 51. 4-*tert*-Butyl 1-ethyl (1*R*,3*R*)-7-oxa-4-azaspiro[2.5]octane-1,4-dicarboxylate *trans*-**8c**, ^{1}H NMR (500 MHz, $CDCl_3$).



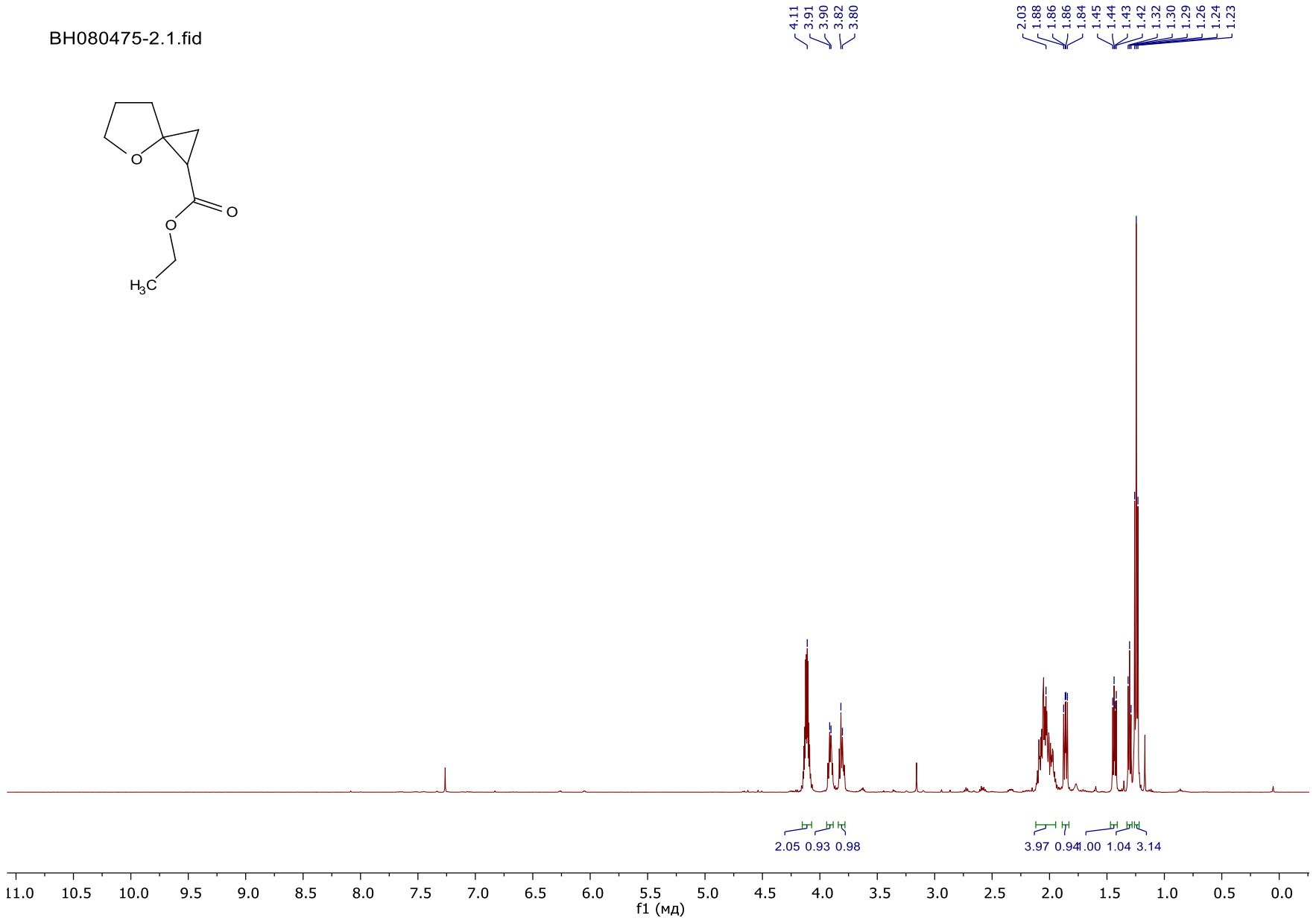
Spectrum 52. 4-*tert*-Butyl 1-ethyl (1*R*,3*R*)-7-oxa-4-azaspiro[2.5]octane-1,4-dicarboxylate *trans*-**8c**, ^{13}C NMR (101 MHz, $CDCl_3$).



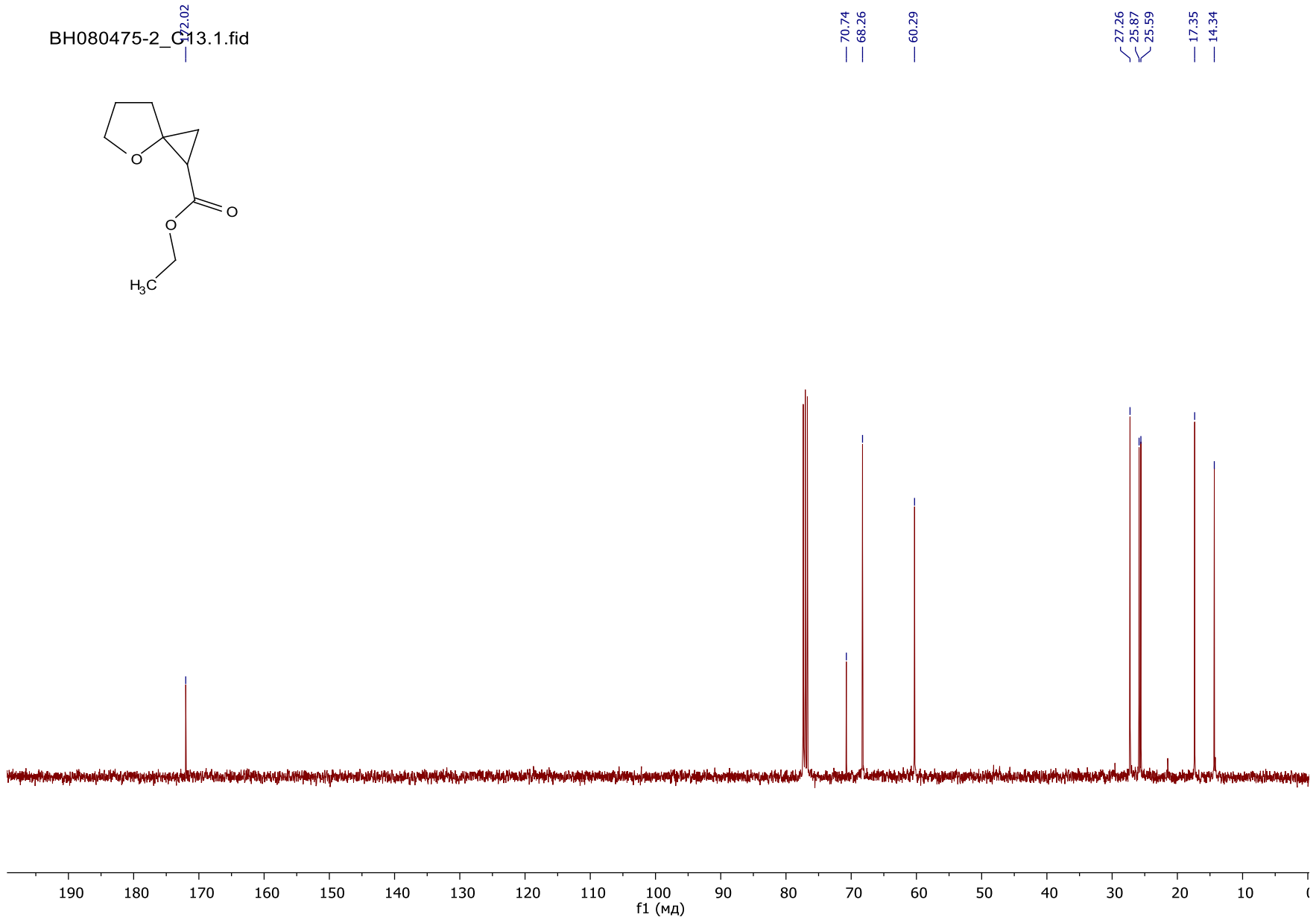
Spectrum 53. 4-*tert*-Butyl 1-ethyl (1*R*,3*S*)-7-oxa-4-azaspiro[2.5]octane-1,4-dicarboxylate *cis*-**8c**, ^{1}H NMR (400 MHz, $CDCl_3$).



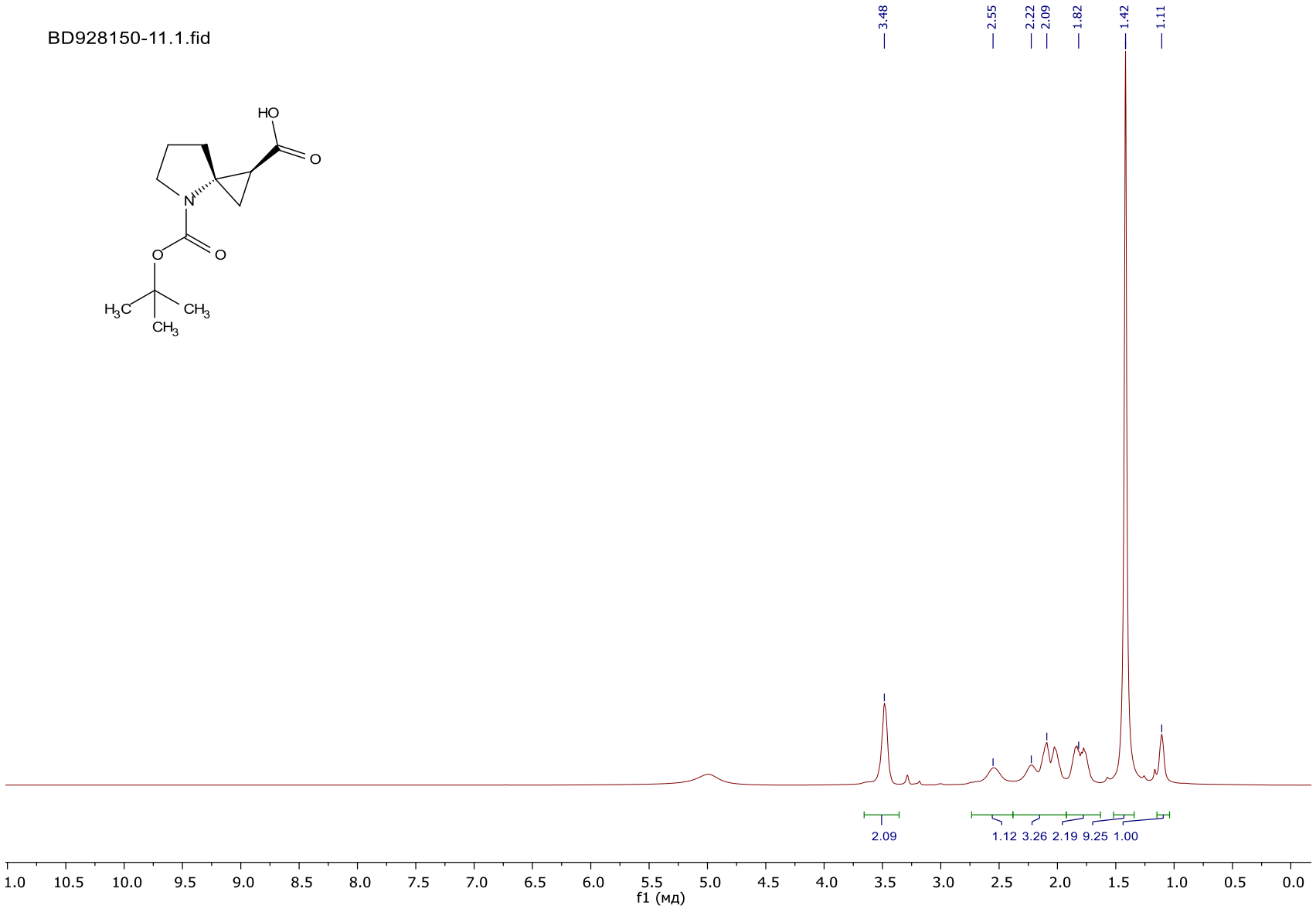
Spectrum 54. 4-*tert*-Butyl 1-ethyl (1*R*,3*S*)-7-oxa-4-azaspiro[2.5]octane-1,4-dicarboxylate *cis*-**8c**, ^{13}C NMR (126 MHz, $CDCl_3$).



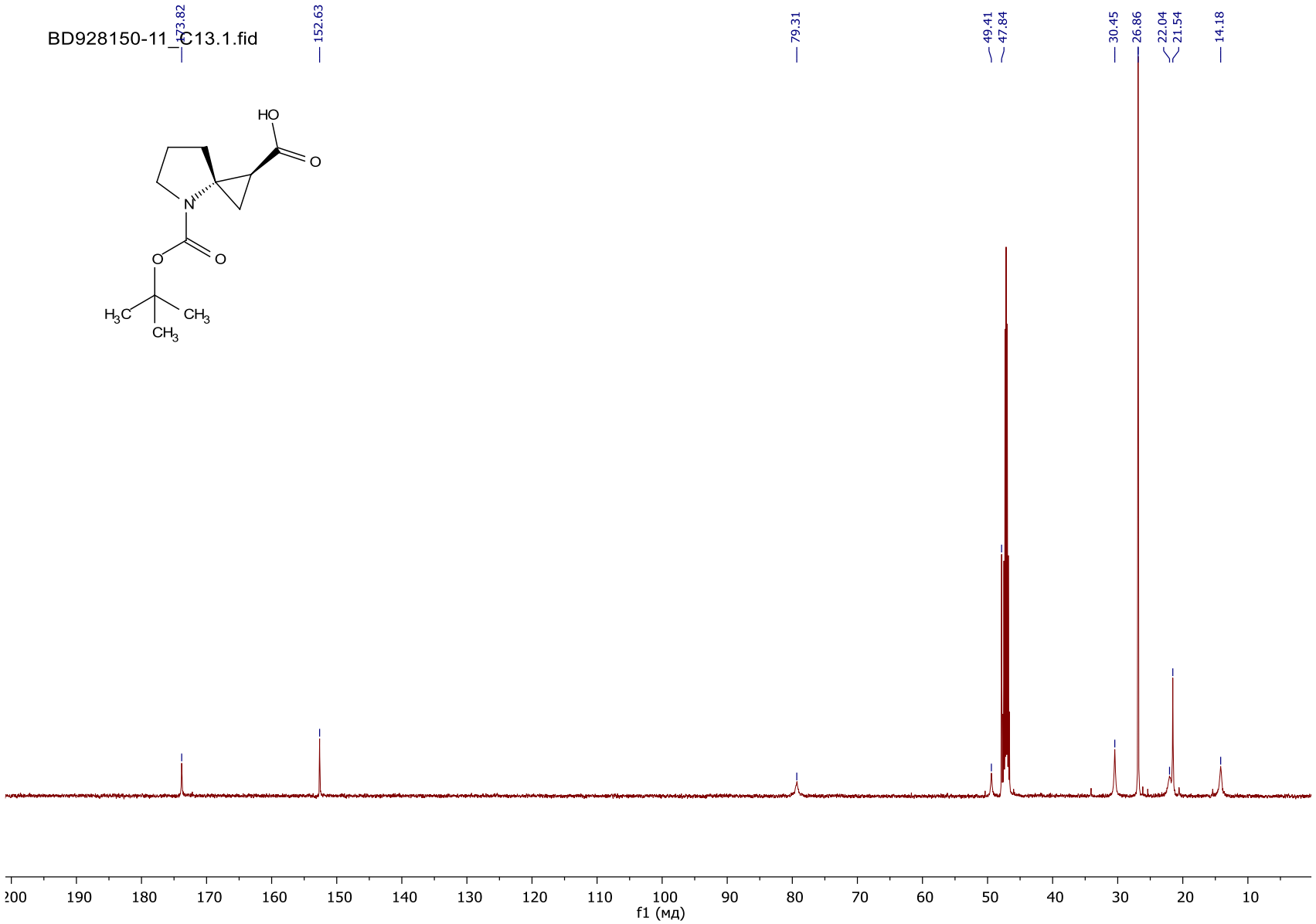
Spectrum 55. Ethyl 4-oxaspiro[2.4]heptane-1-carboxylate **8f**, ^{1}H NMR (500 MHz, $CDCl_3$).



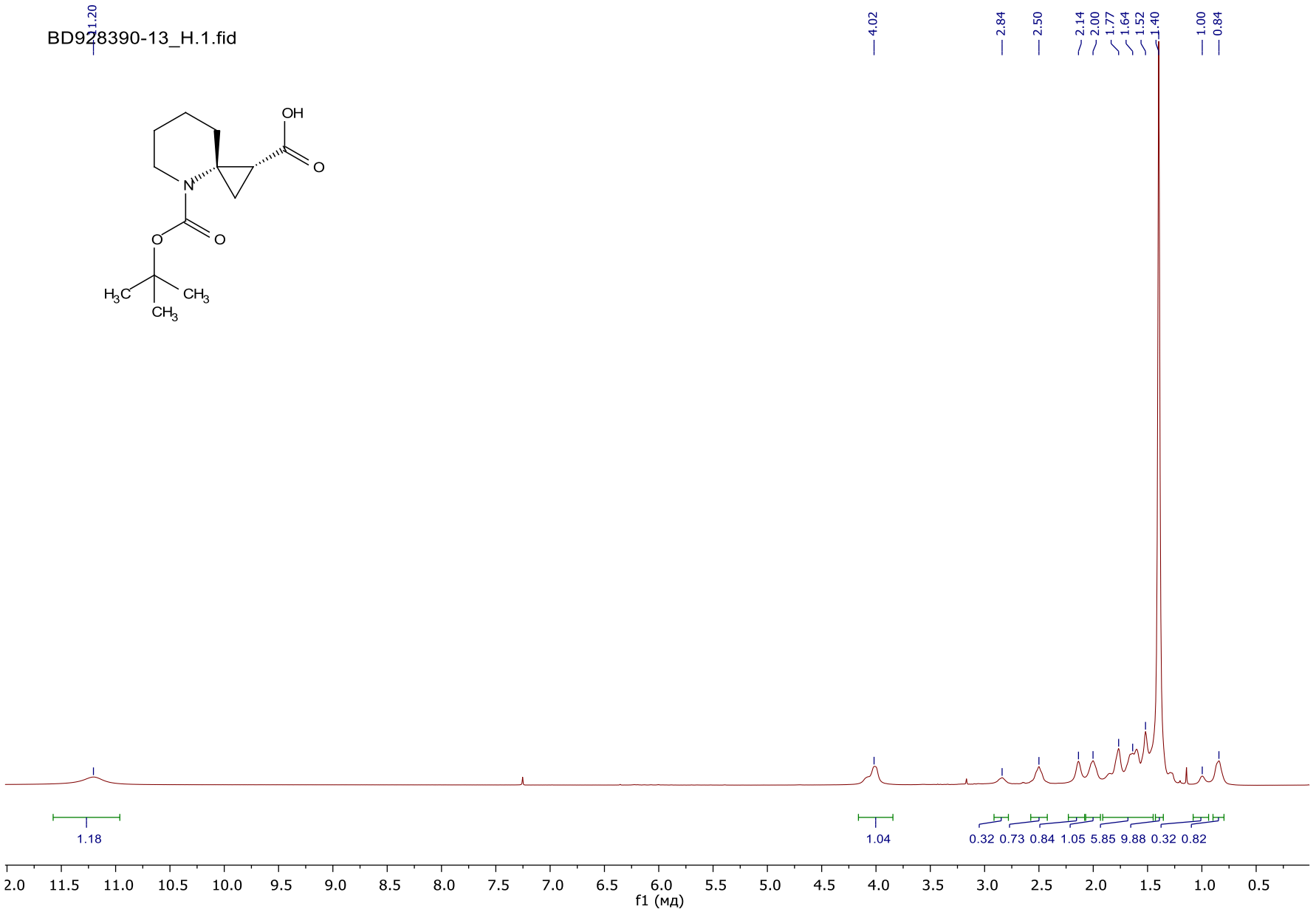
Spectrum 56. Ethyl 4-oxaspiro[2.4]heptane-1-carboxylate **8f**, ^{13}C NMR (101 MHz, $CDCl_3$).



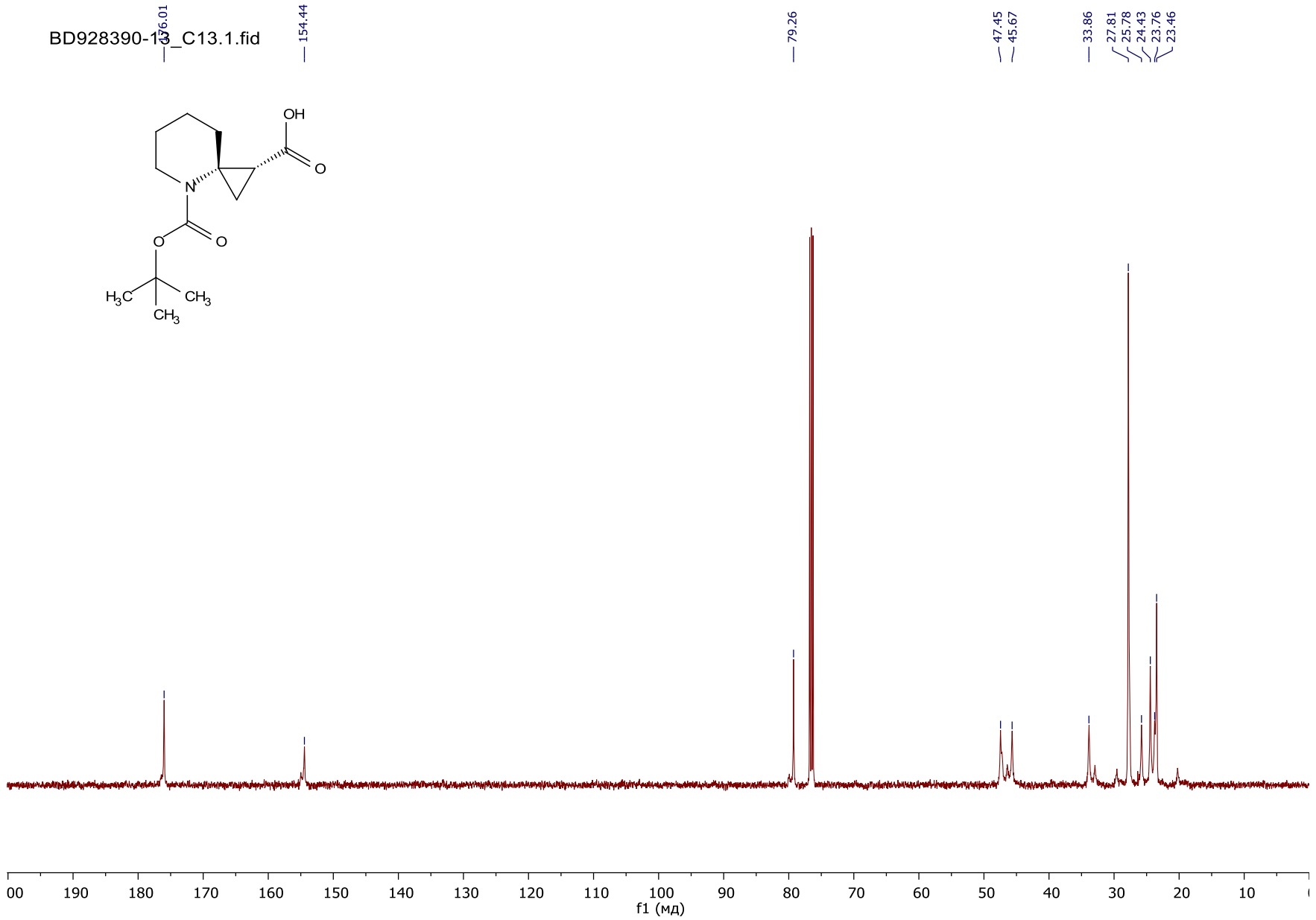
Spectrum 57. (1*S*,3*S*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.4]heptane-1-carboxylic acid *trans*-**9a**, ^{1}H NMR (400 MHz, CD_3OD)



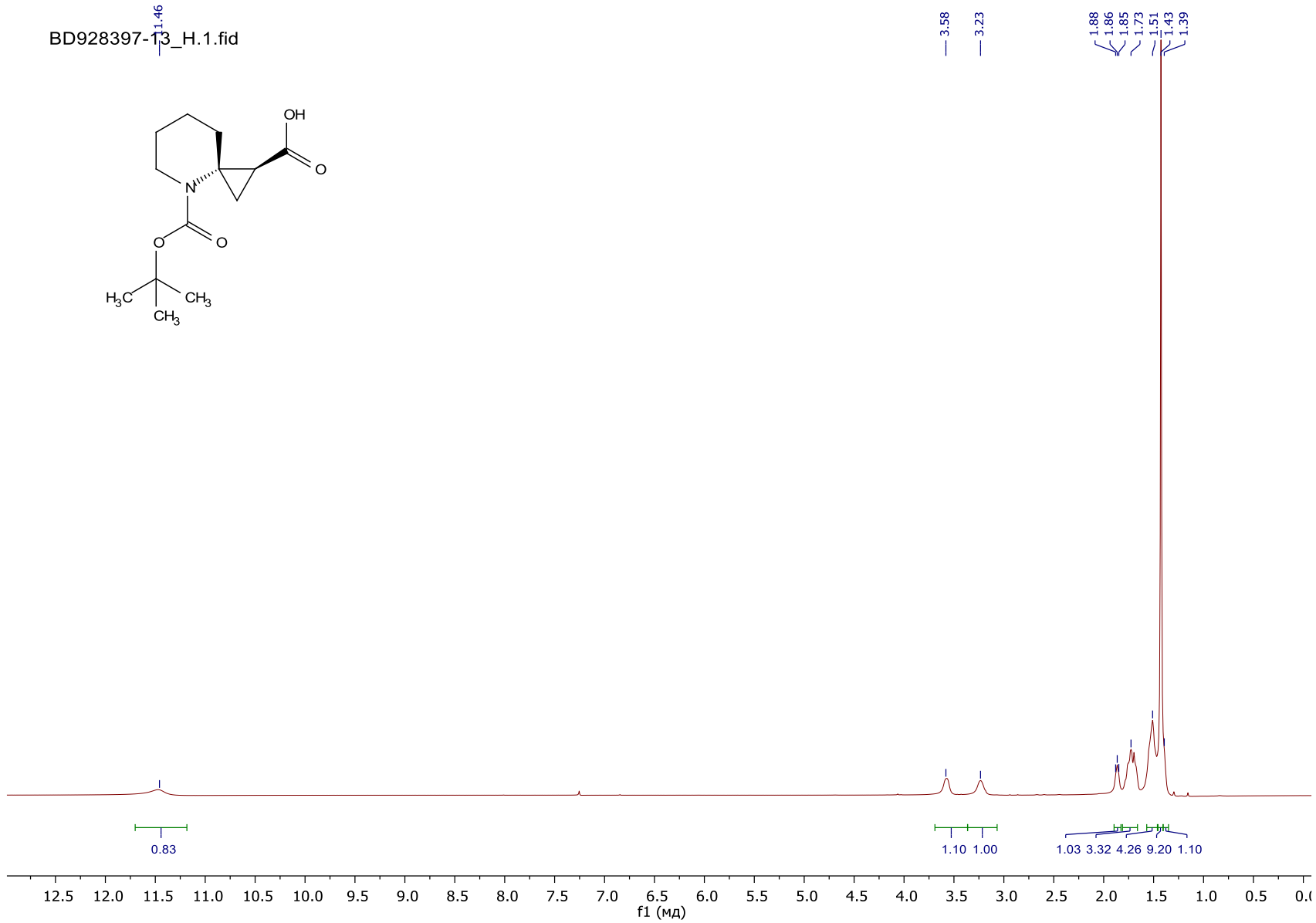
Spectrum 58. (1*S*,3*S*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.4]heptane-1-carboxylic acid *trans*-**9a**, ^{13}C NMR (126 MHz, CD_3OD).



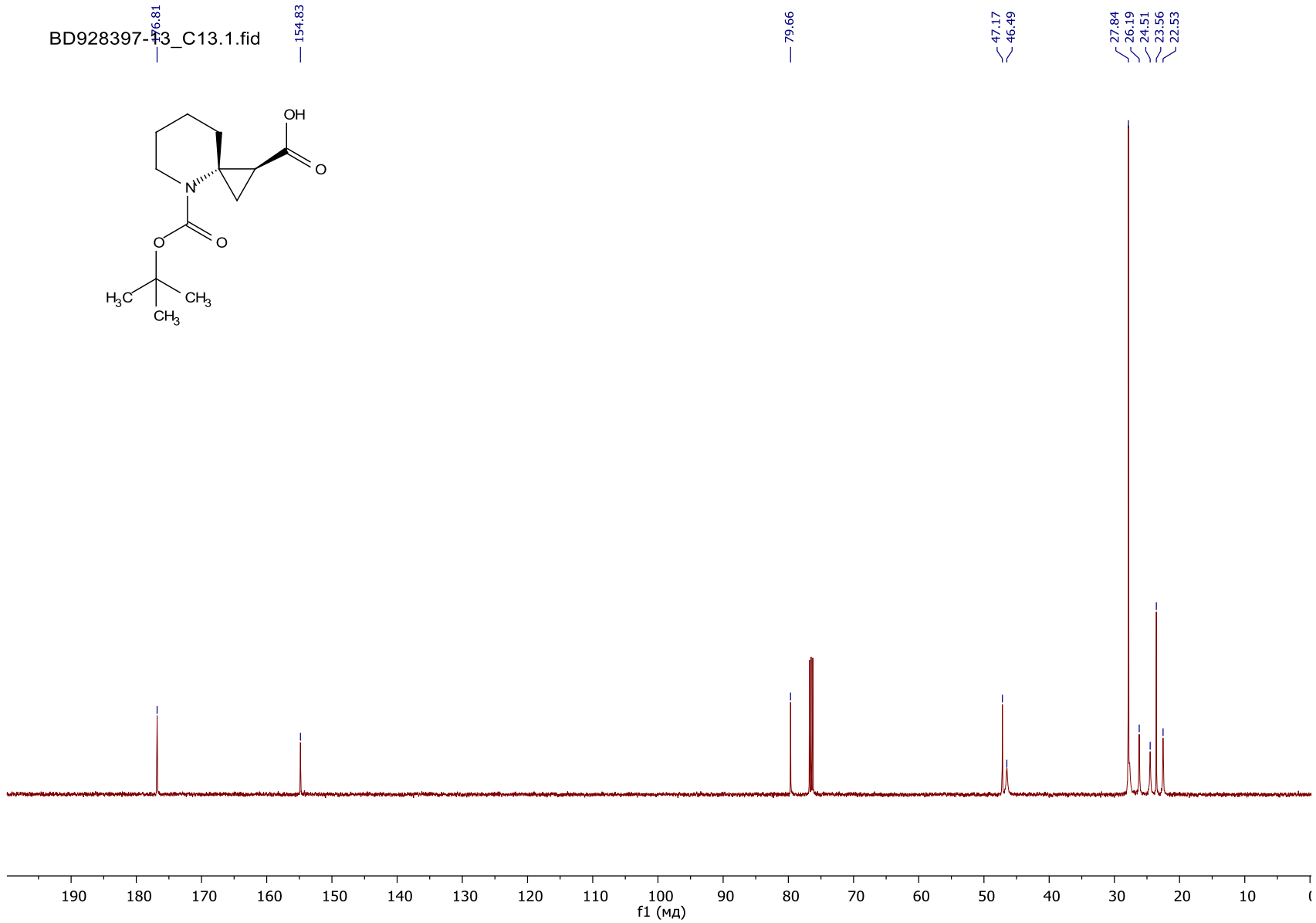
Spectrum 59. (1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.5]octane-1-carboxylic acid *cis*-**9b**, ^{1}H NMR (500 MHz, $CDCl_3$).



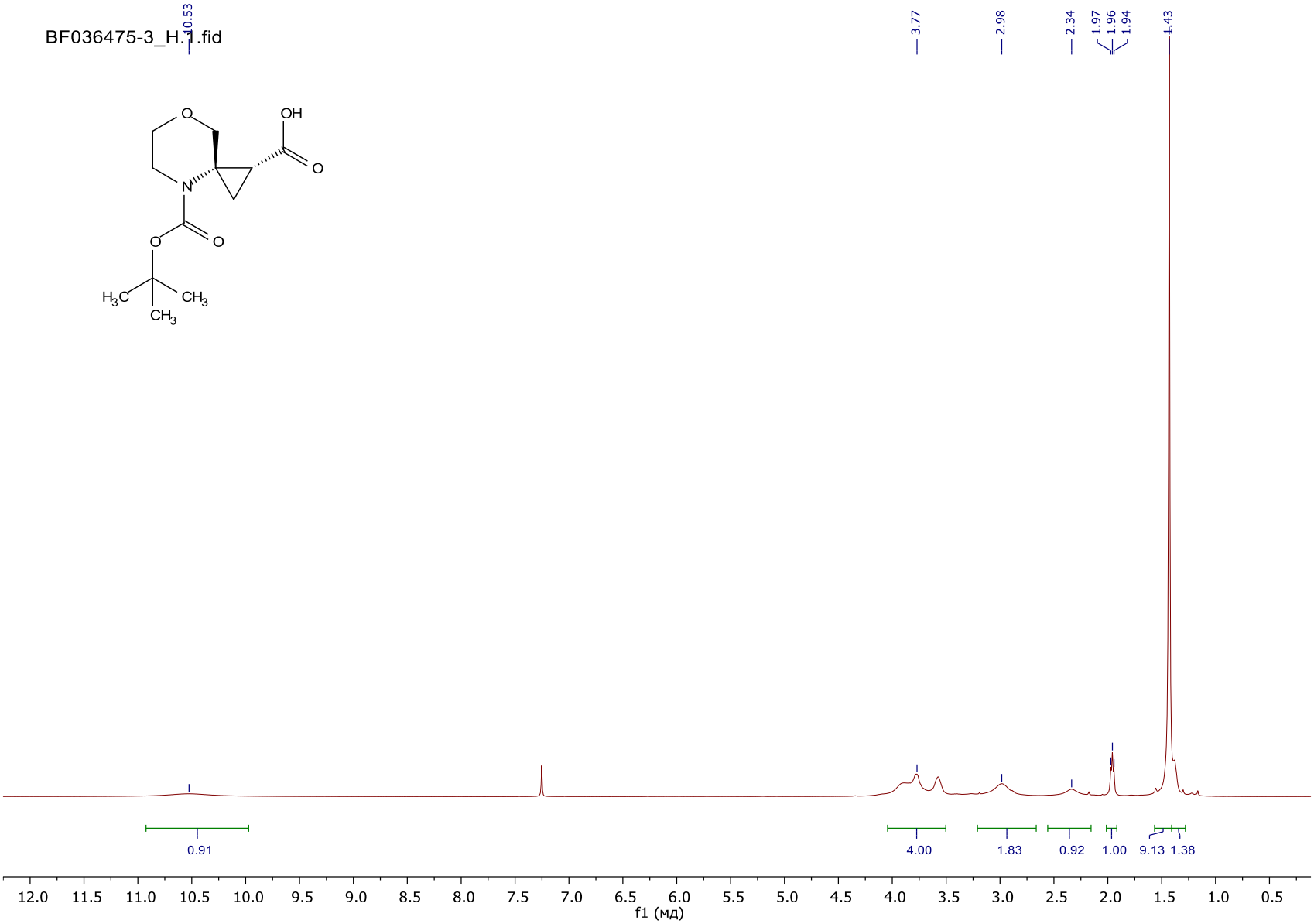
Spectrum 60. (1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.5]octane-1-carboxylic acid *cis*-**9b**, ^{13}C NMR (126 MHz, $CDCl_3$).



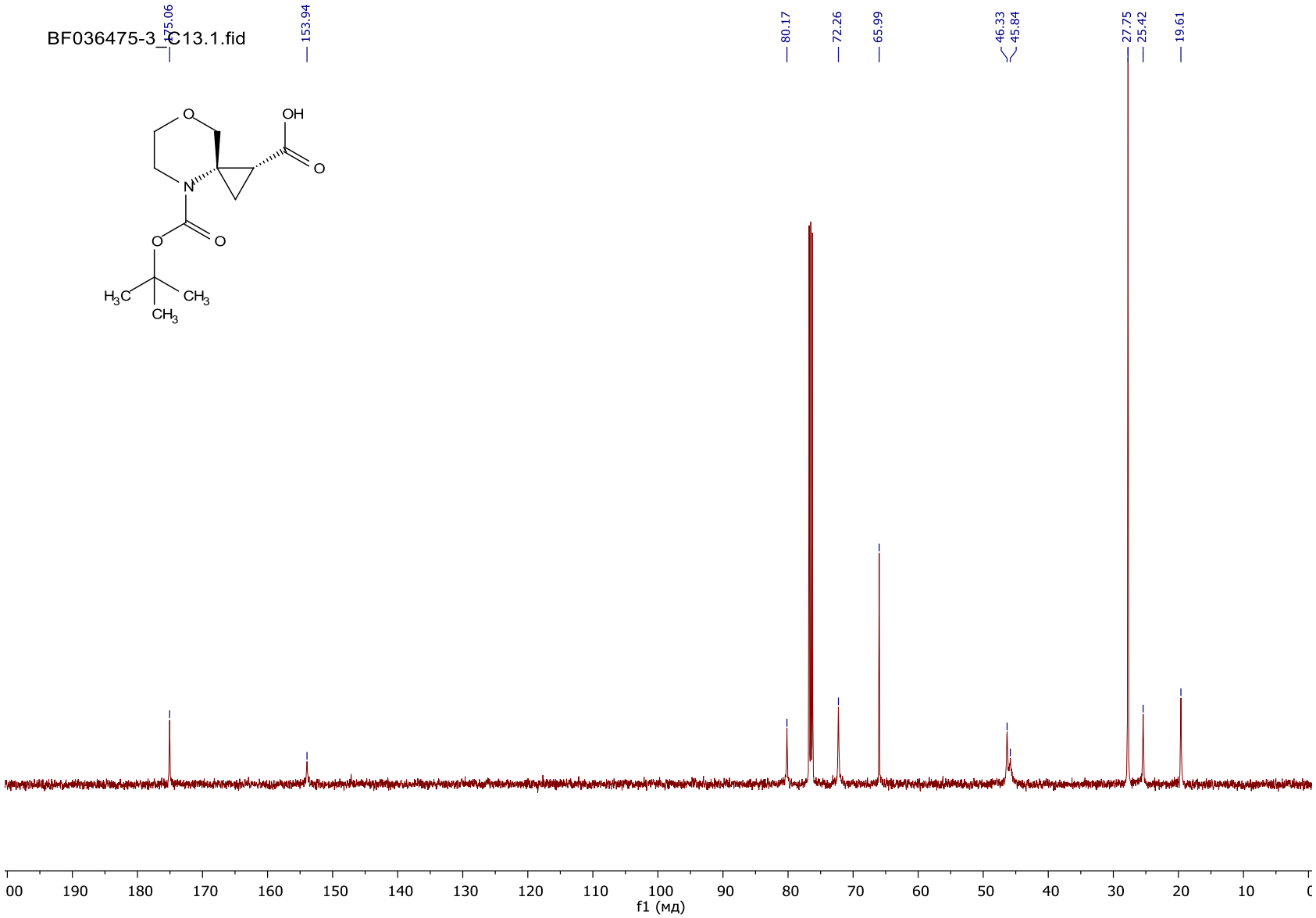
Spectrum 61. (1*R*,3*R*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.5]octane-1-carboxylic acid *trans*-**9b**, ^{1}H NMR (500 MHz, $CDCl_3$).



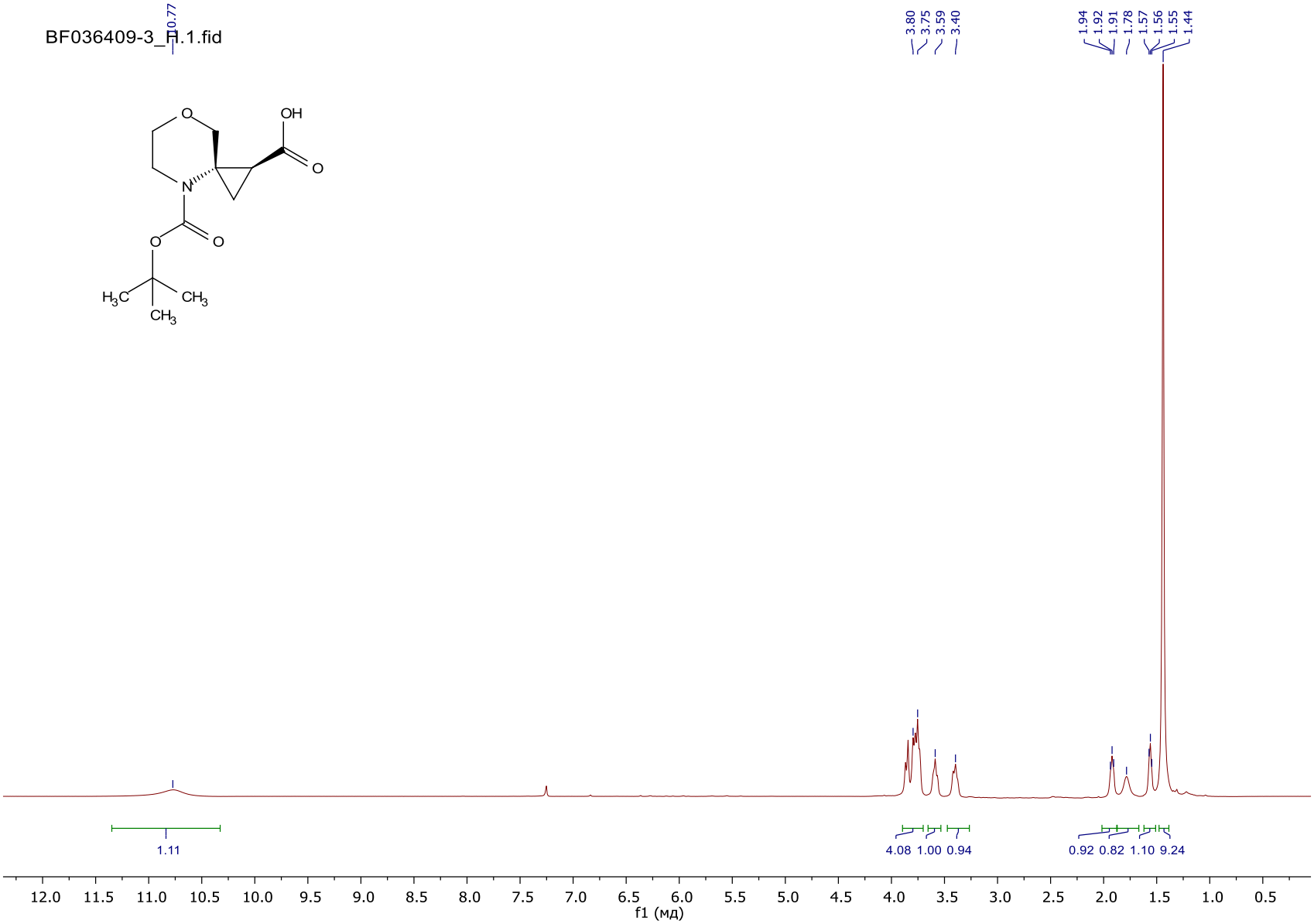
Spectrum 62. (1*R*,3*R*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.5]octane-1-carboxylic acid *trans*-**9b**, ^{13}C NMR (126 MHz, $CDCl_3$).



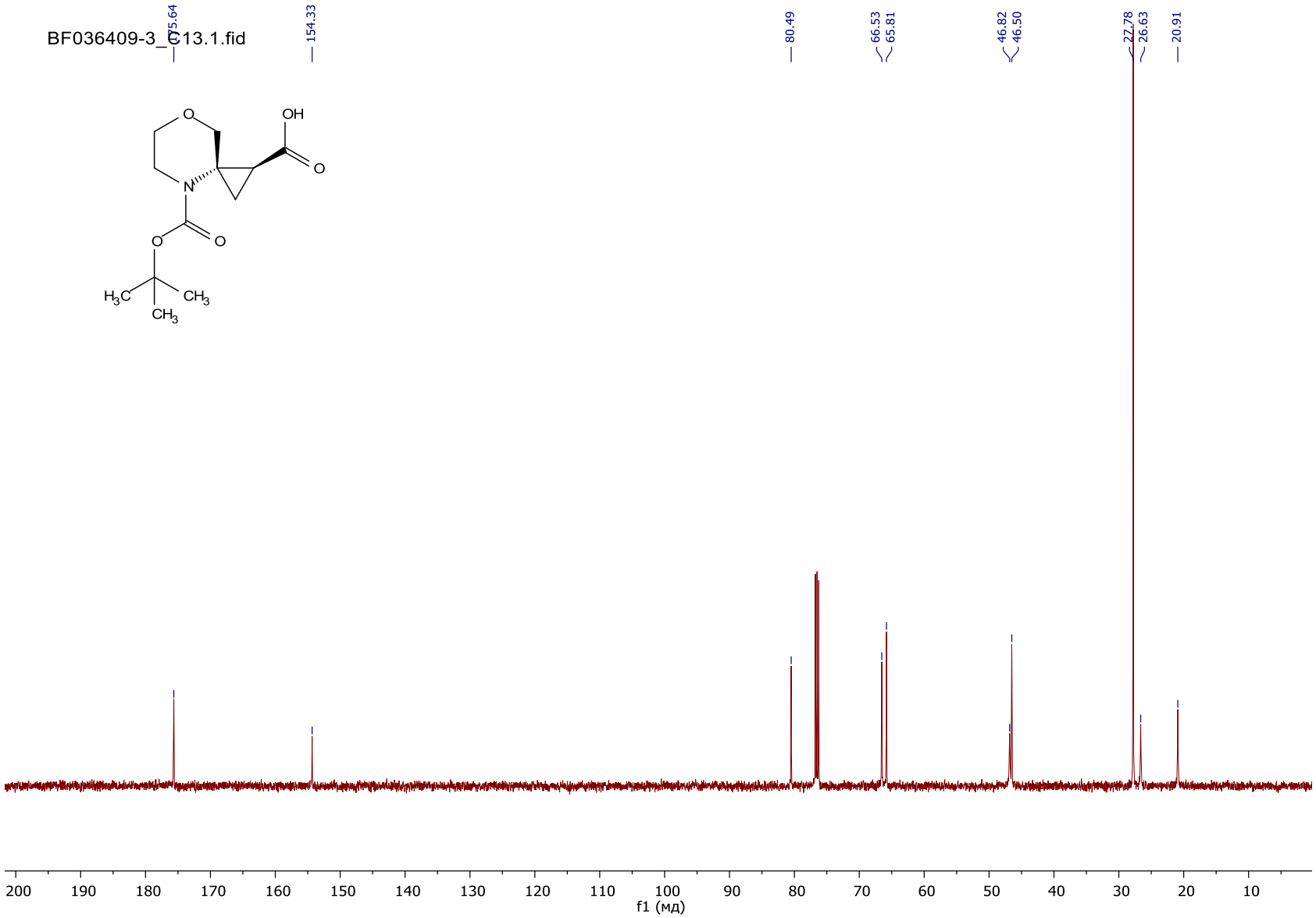
Spectrum 63. (1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-7-oxa-4-azaspiro[2.5]octane-1-carboxylic acid *cis*-**9c**, ^{1}H NMR (500 MHz, $CDCl_3$).



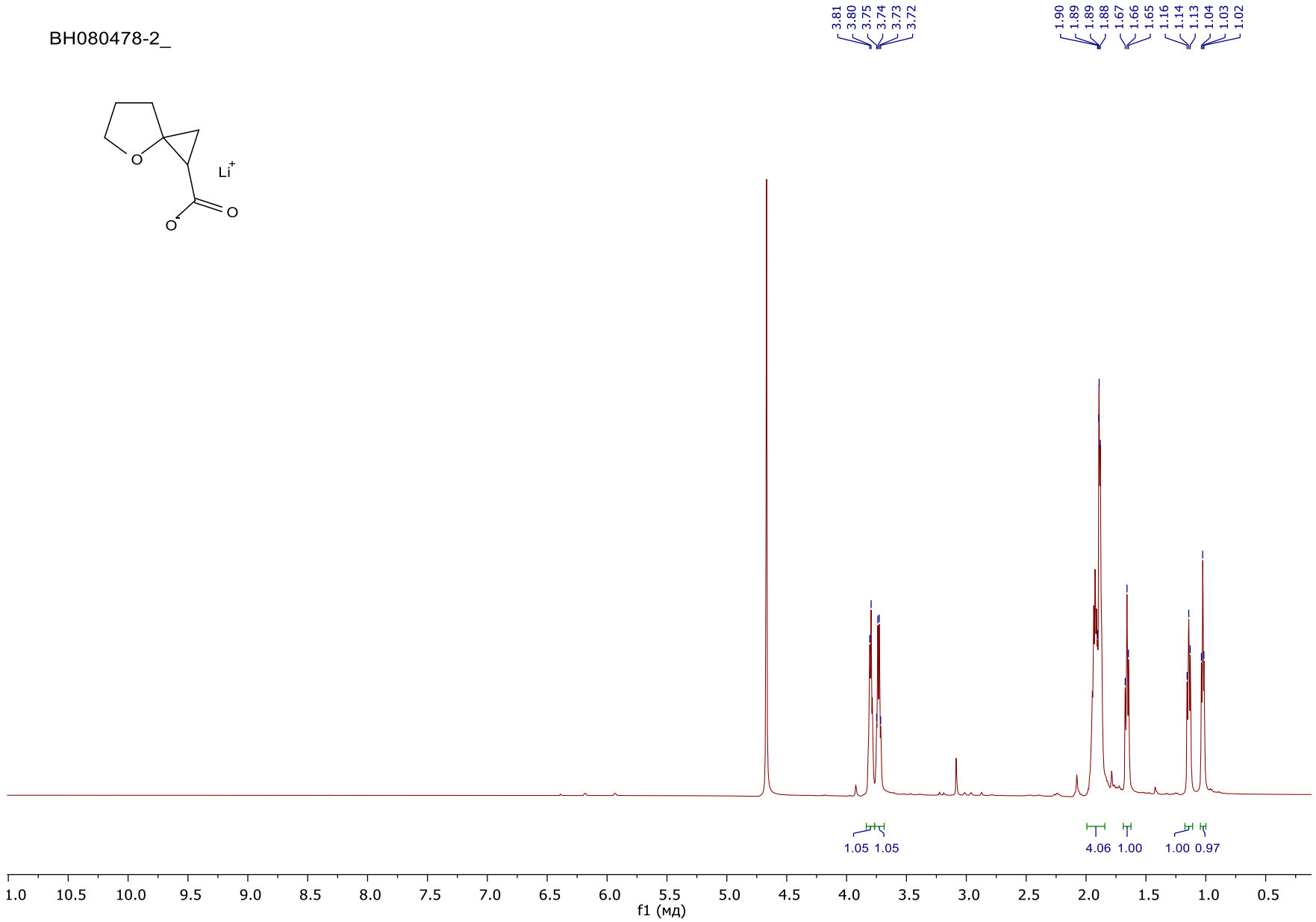
Spectrum 64. (1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-7-oxa-4-azaspiro[2.5]octane-1-carboxylic acid *cis*-**9c**, ^{13}C NMR (126 MHz, $CDCl_3$).



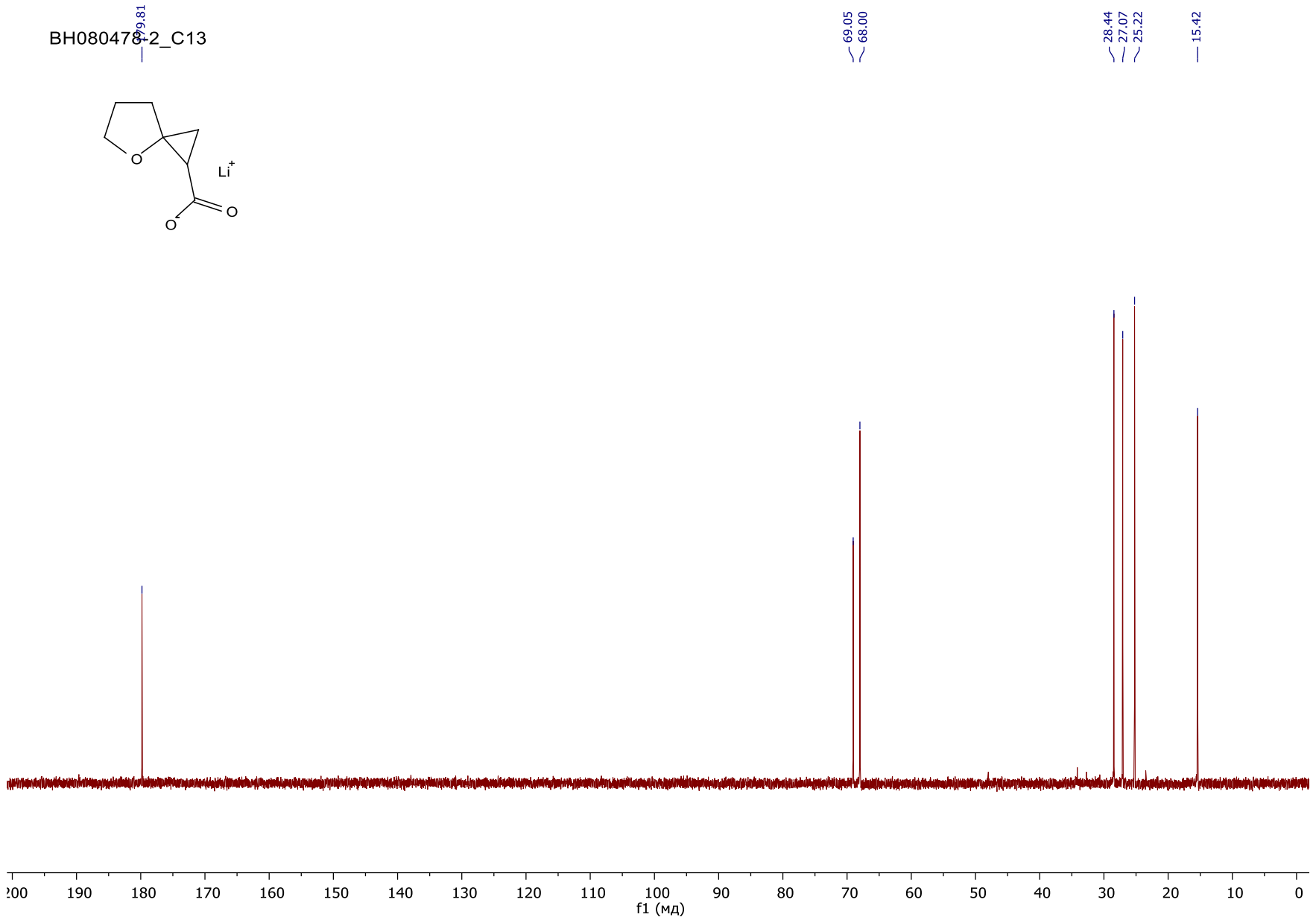
Spectrum 65. (1*R*,3*R*)-4-[(*tert*-butoxy)carbonyl]-7-oxa-4-azaspiro[2.5]octane-1-carboxylic acid *trans*-**9c**, ^{1}H NMR (500 MHz, $CDCl_3$).



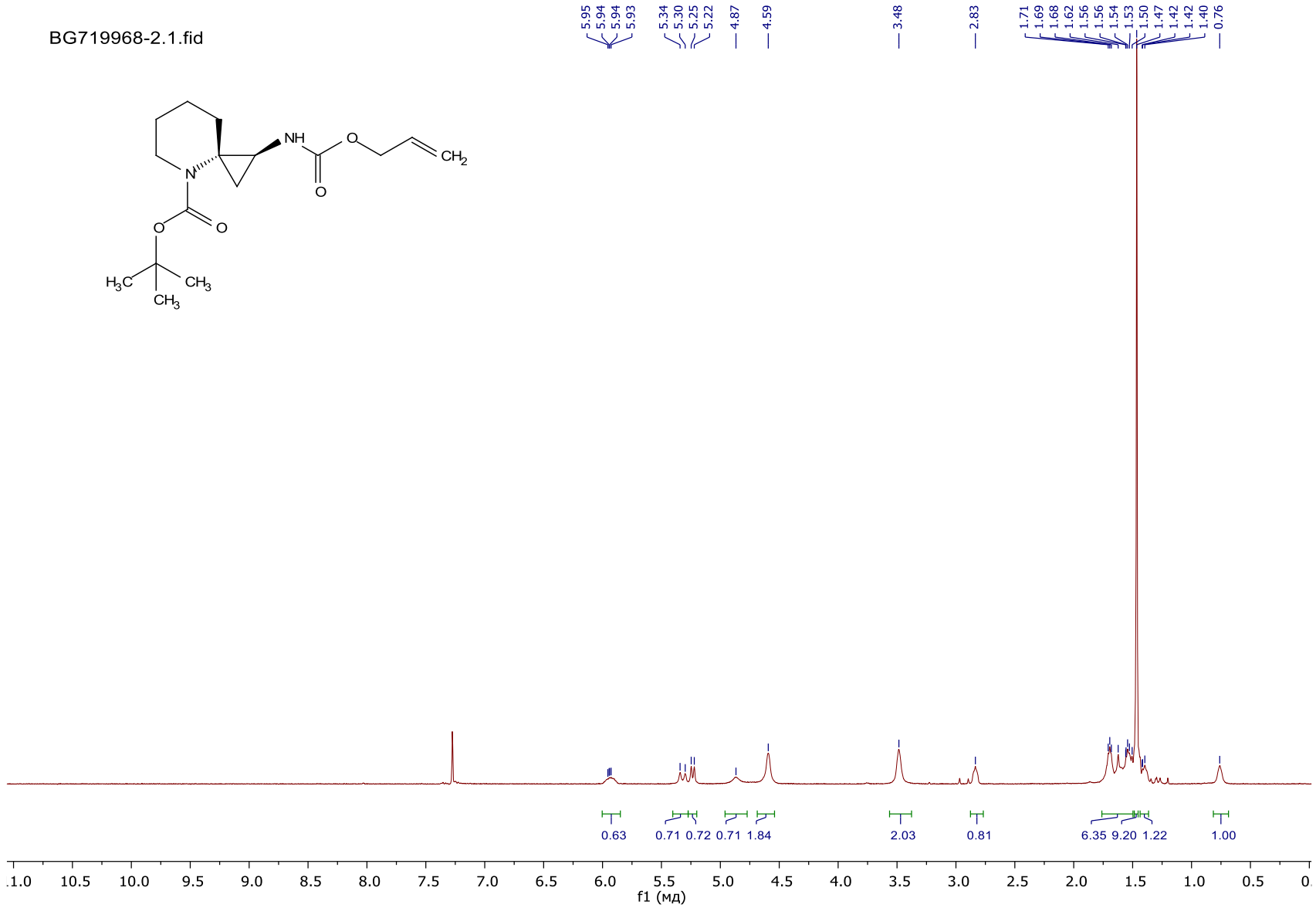
Spectrum 66. (1*R*,3*R*)-4-[(*tert*-butoxy)carbonyl]-7-oxa-4-azaspiro[2.5]octane-1-carboxylic acid *trans*-**9c**, ^{13}C NMR (126 MHz, $CDCl_3$).



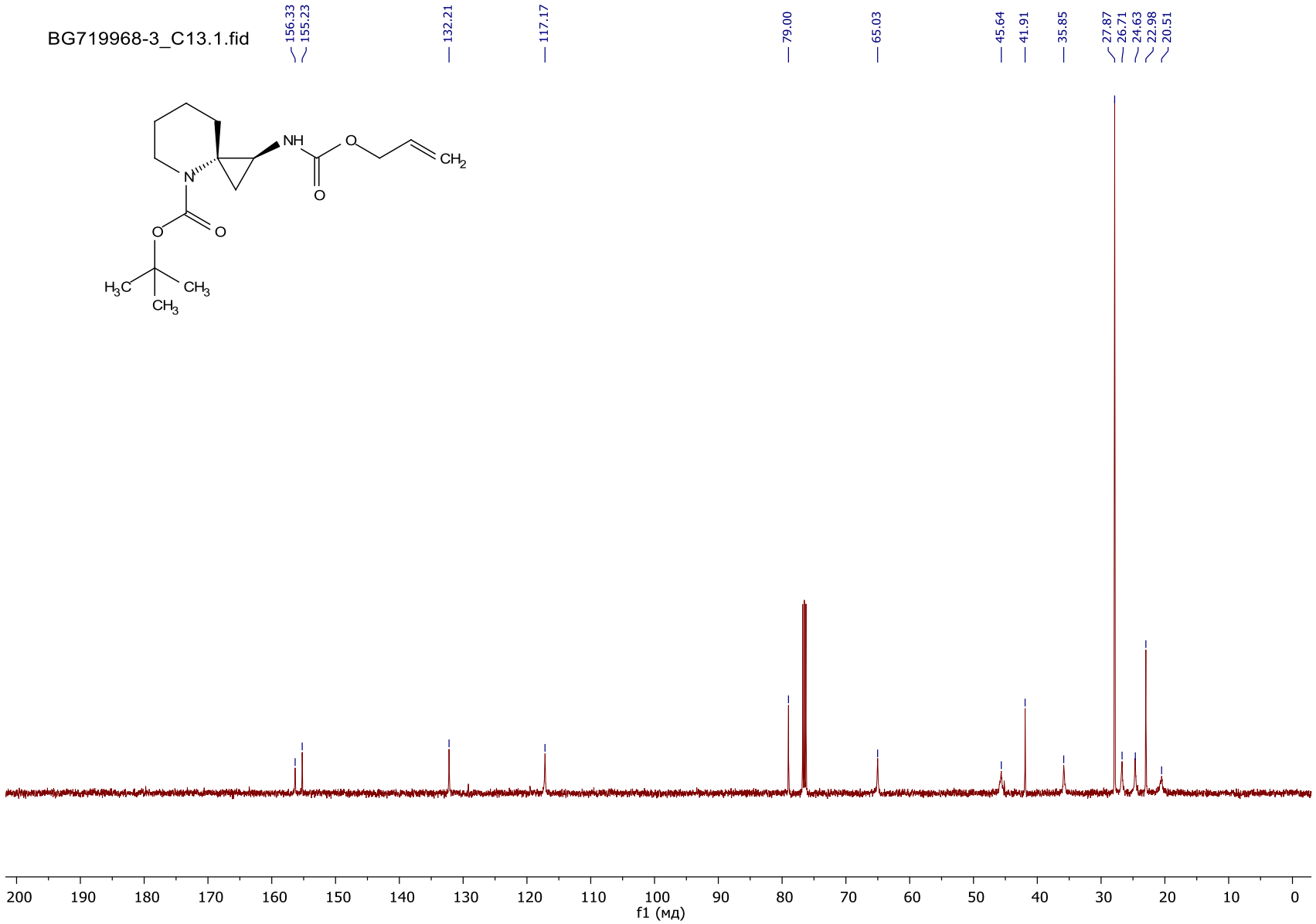
Spectrum 67. Lithium 4-oxaspiro[2.4]heptane-1-carboxylate **9f**, ^{1}H NMR (600 MHz, D_2O).



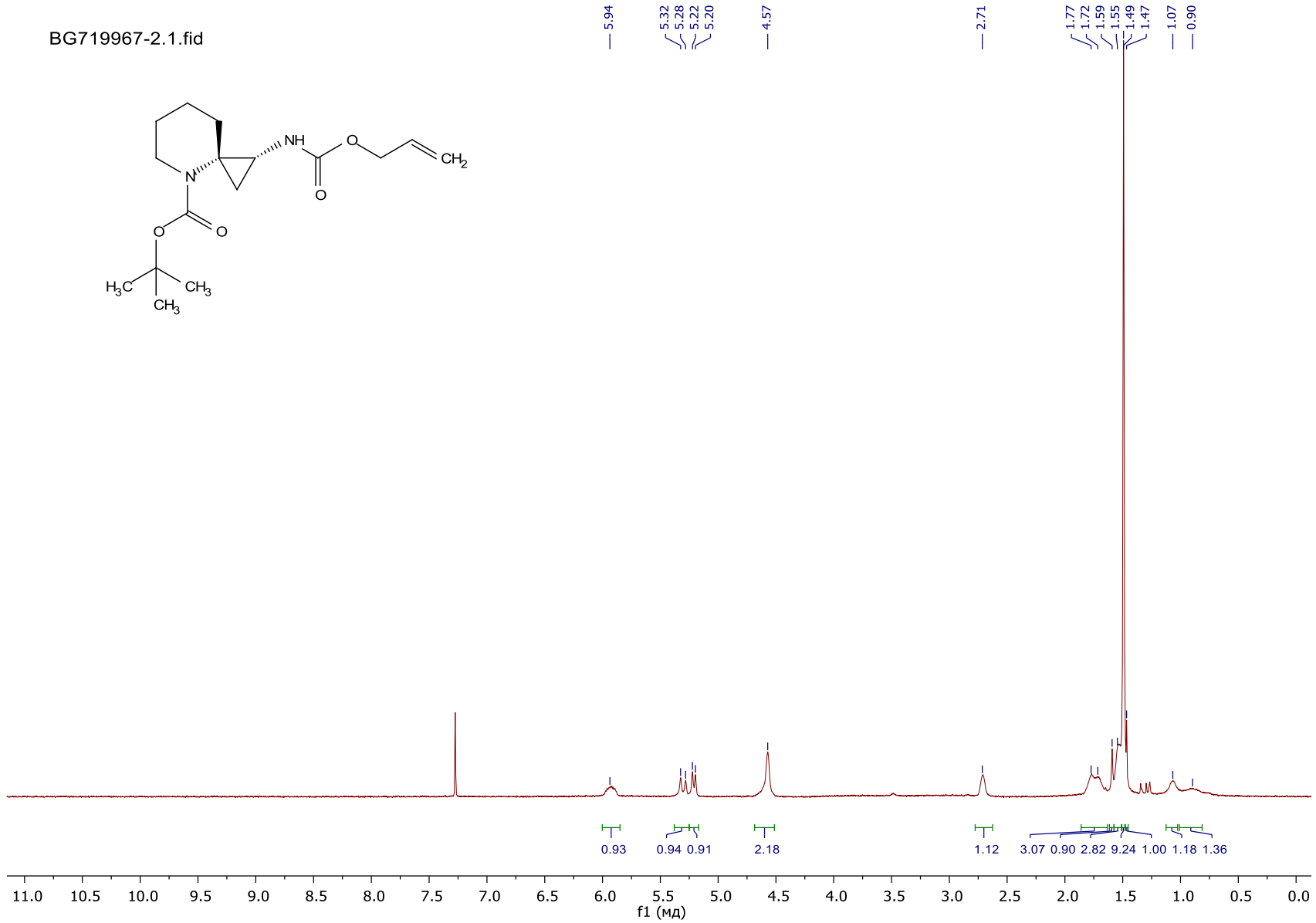
Spectrum 68. Lithium 4-oxaspiro[2.4]heptane-1-carboxylate **9f**, ^{13}C NMR (151 MHz, D_2O).



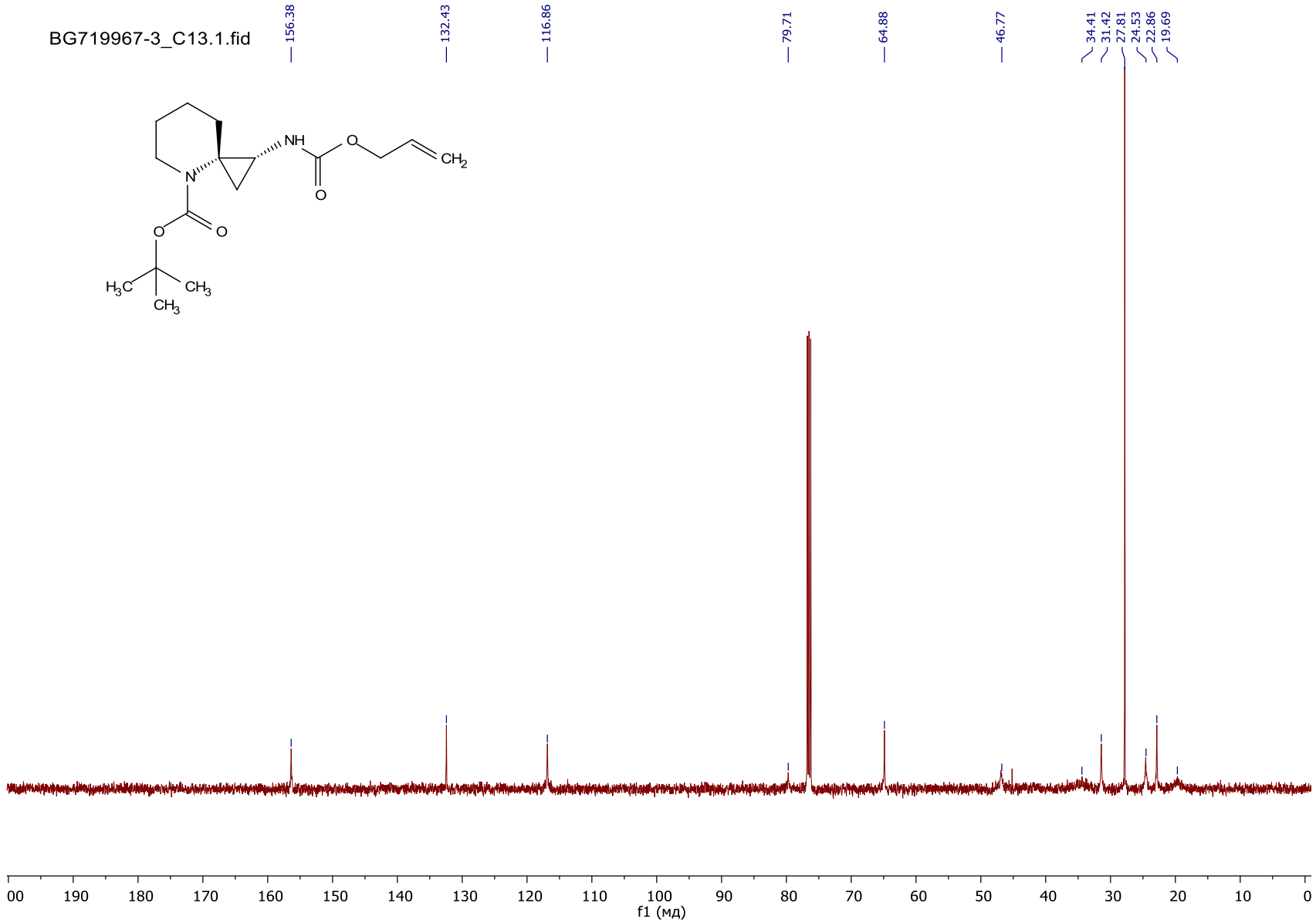
Spectrum 69. *tert*-Butyl (1*S*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate *trans*-**10b**, ^{1}H NMR (400 MHz, $CDCl_3$)



Spectrum 70. *tert*-Butyl (1*S*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate *trans*-**10b**, ^{13}C NMR (126 MHz, $CDCl_3$).

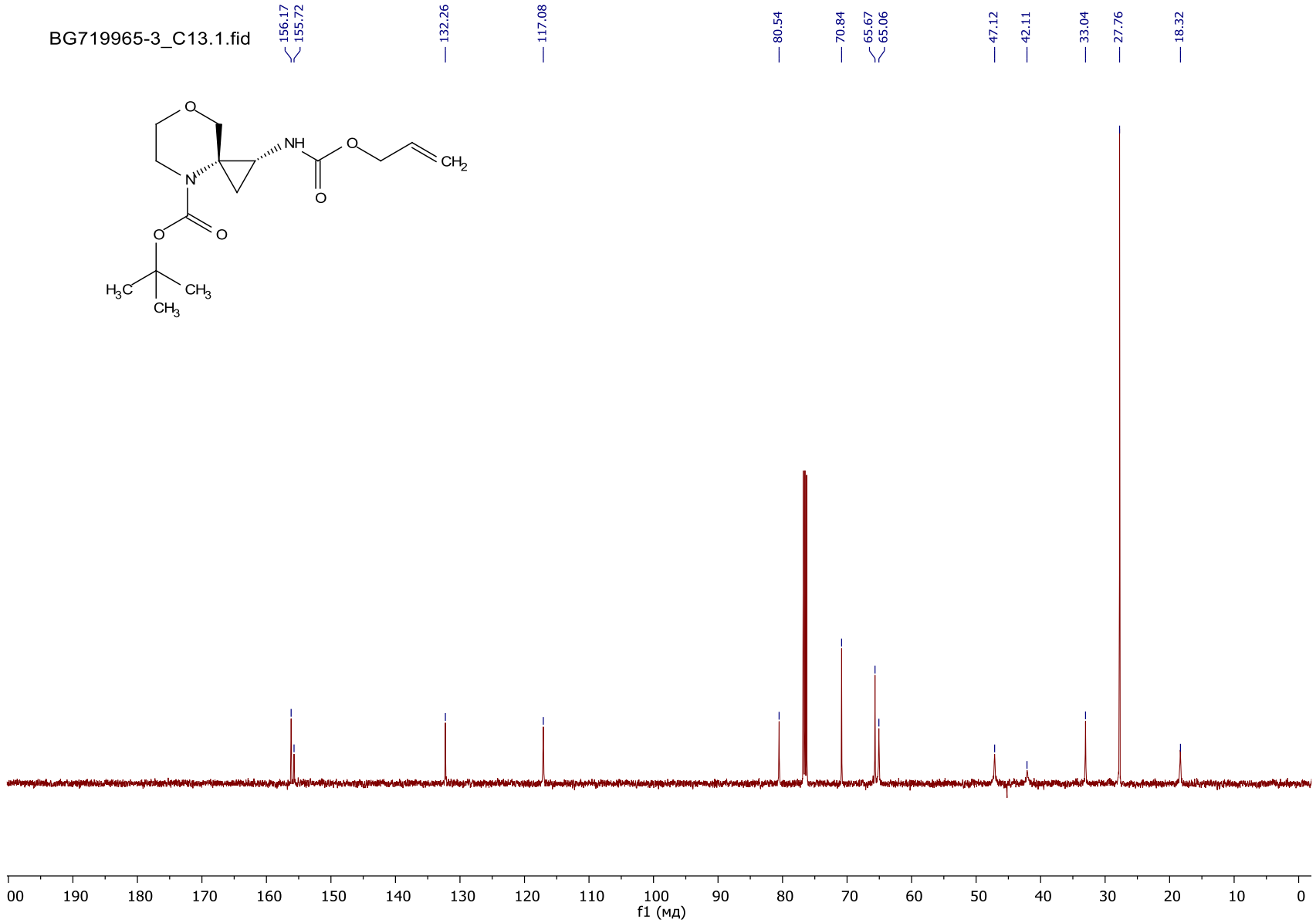


Spectrum 71. *tert*-Butyl (1*R*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate *cis*-**10b**, ^{1}H NMR (400 MHz, $CDCl_3$).

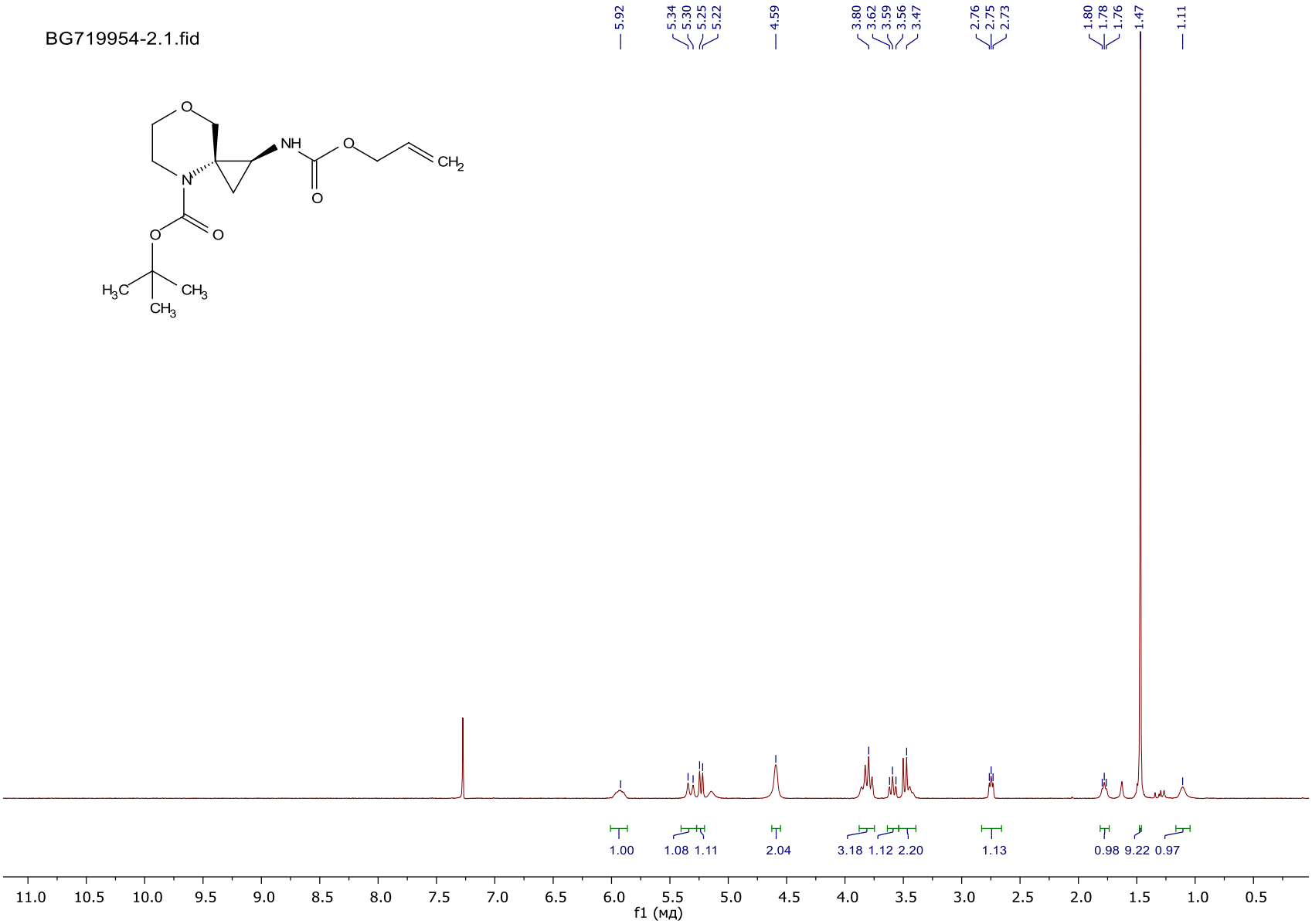


Spectrum 72. *tert*-Butyl (1*R*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate *cis*-**10b**, ^{13}C NMR (126 MHz, $CDCl_3$).

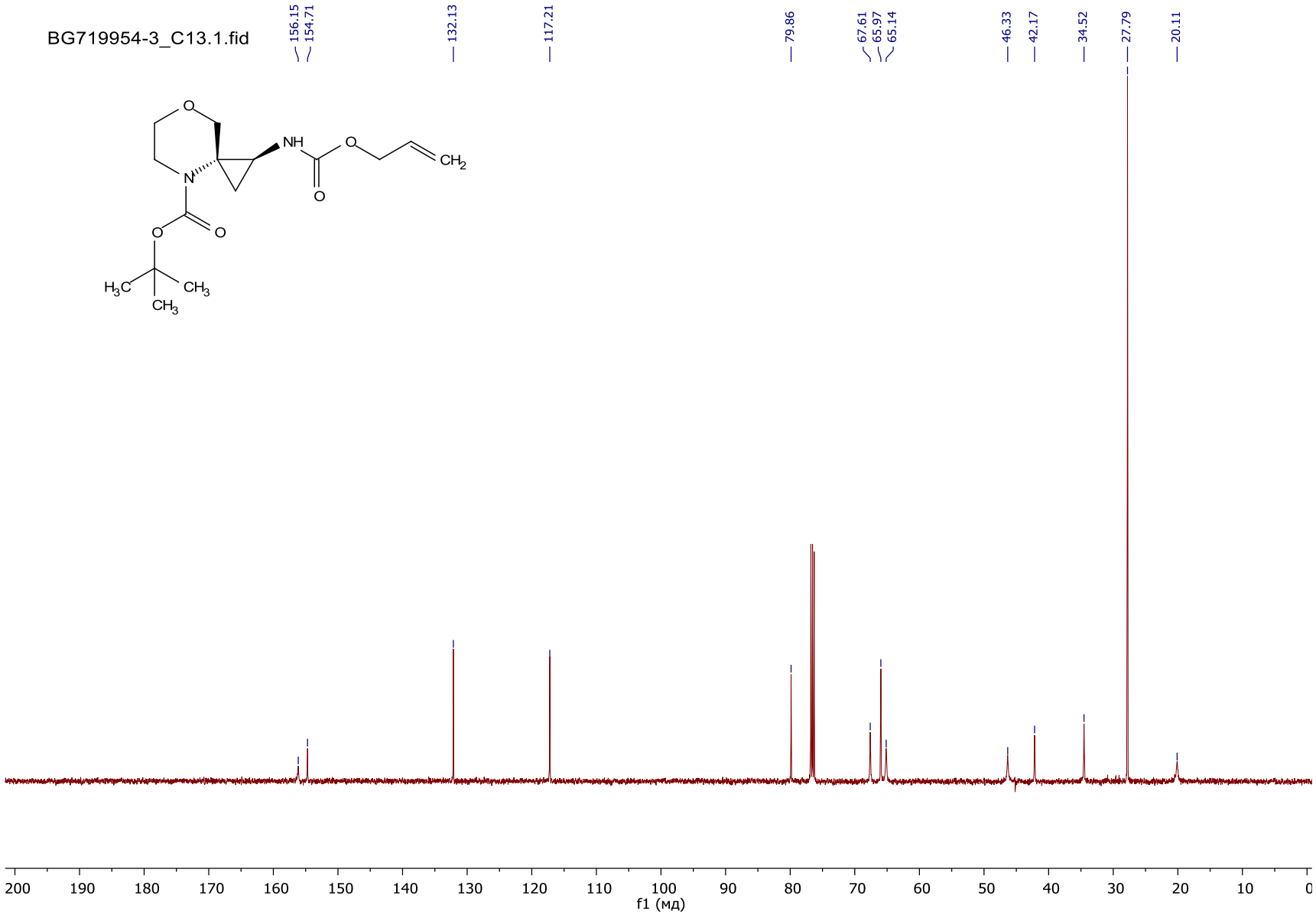
Spectrum 73. *tert*-Butyl (1*R*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *cis*-**10c**, ^{1}H NMR (400 MHz, $CDCl_3$).



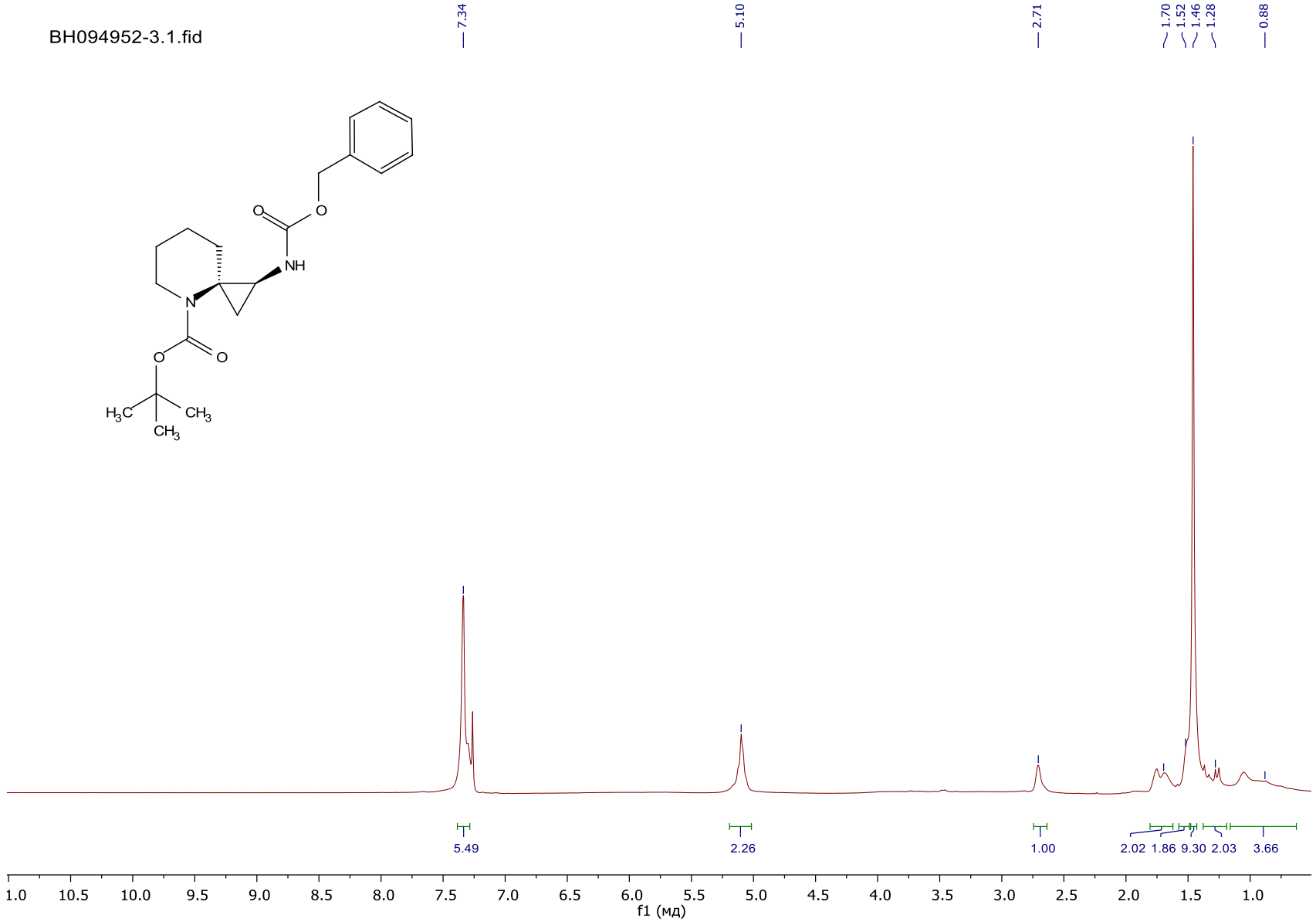
Spectrum 74. *tert*-Butyl (1*R*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *cis*-**10c**, ^{13}C NMR (126 MHz, $CDCl_3$).



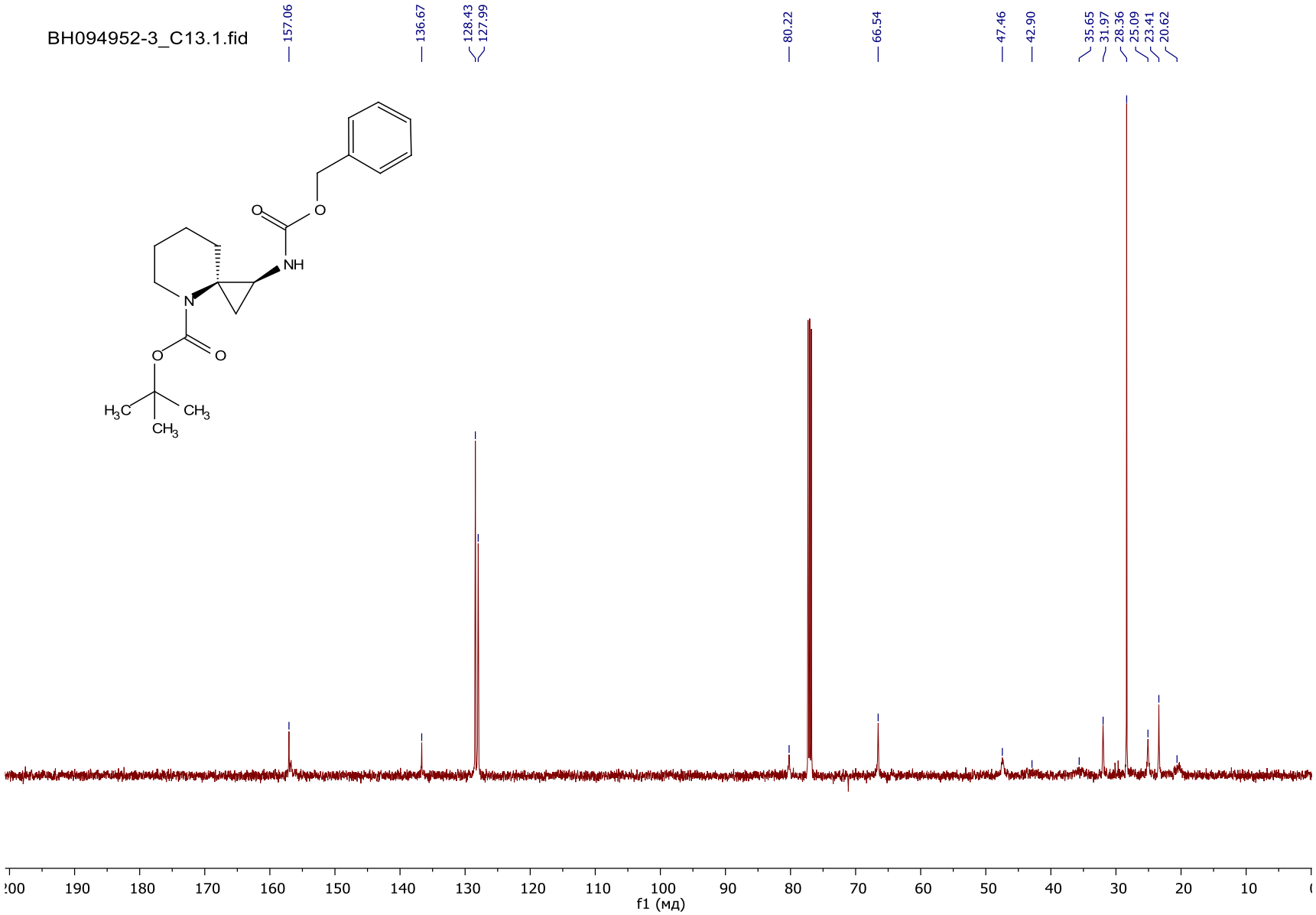
Spectrum 75. *tert*-Butyl (1*S*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *trans*-**10c**, ^{1}H NMR (400 MHz, $CDCl_3$).



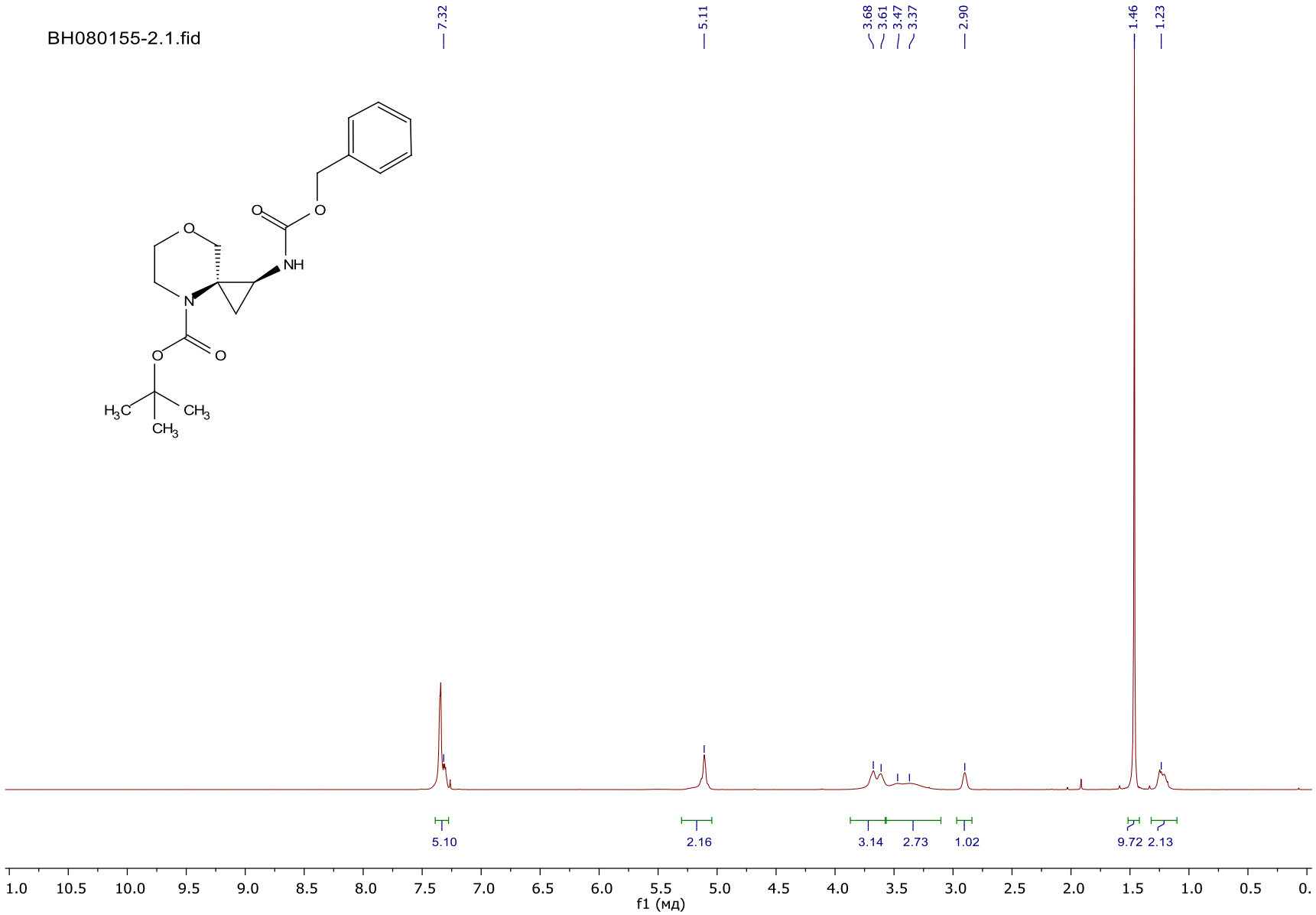
Spectrum 76. *tert*-Butyl (1*S*,3*S*)-1-{[(prop-2-en-1-yloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *trans*-**10c**, ^{13}C NMR (126 MHz, $CDCl_3$).



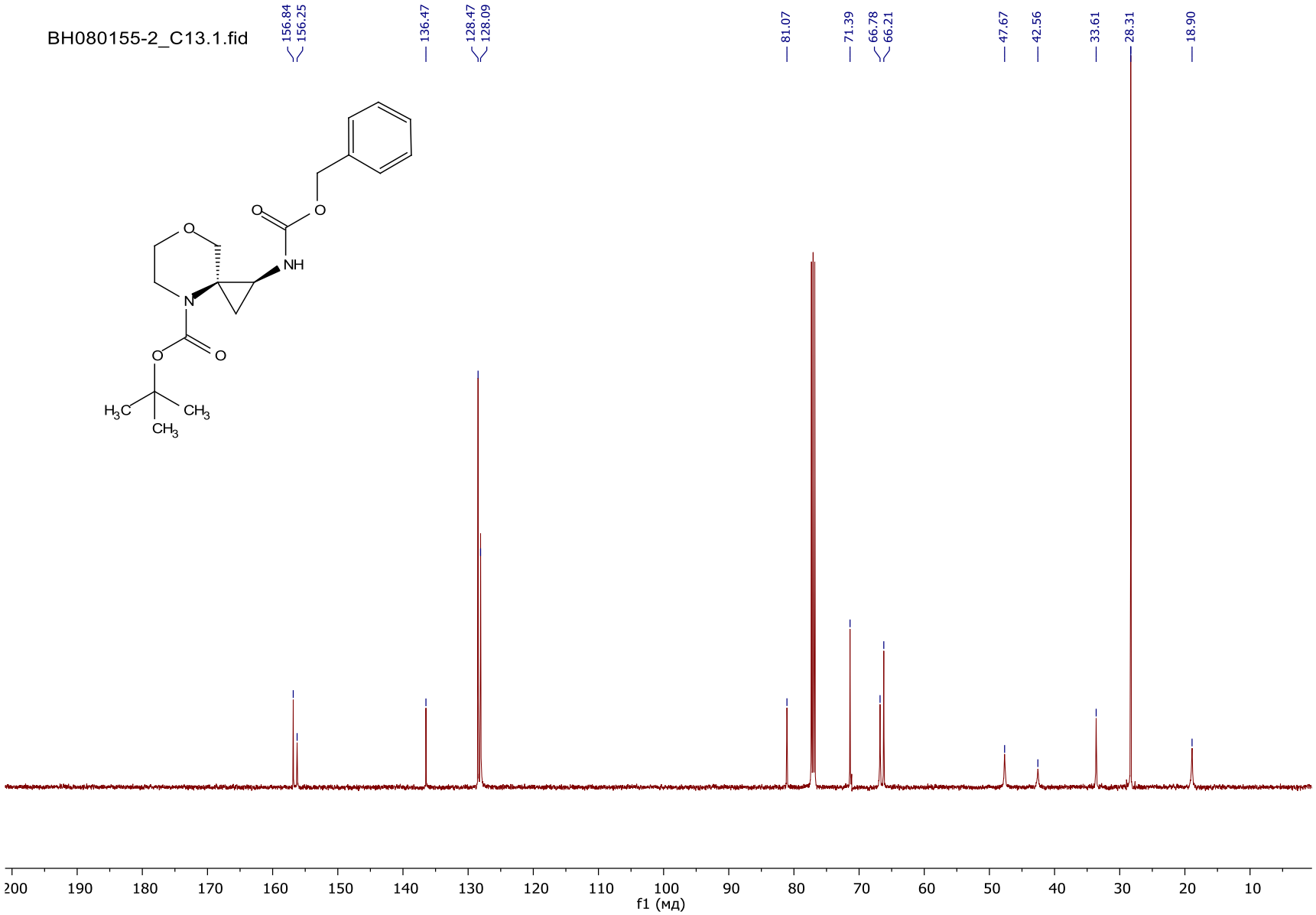
Spectrum 77. *tert*-Butyl (1*S*,3*R*)-1-{[(benzyloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate *cis*-**11b**, ^{1}H NMR (500 MHz, $CDCl_3$).



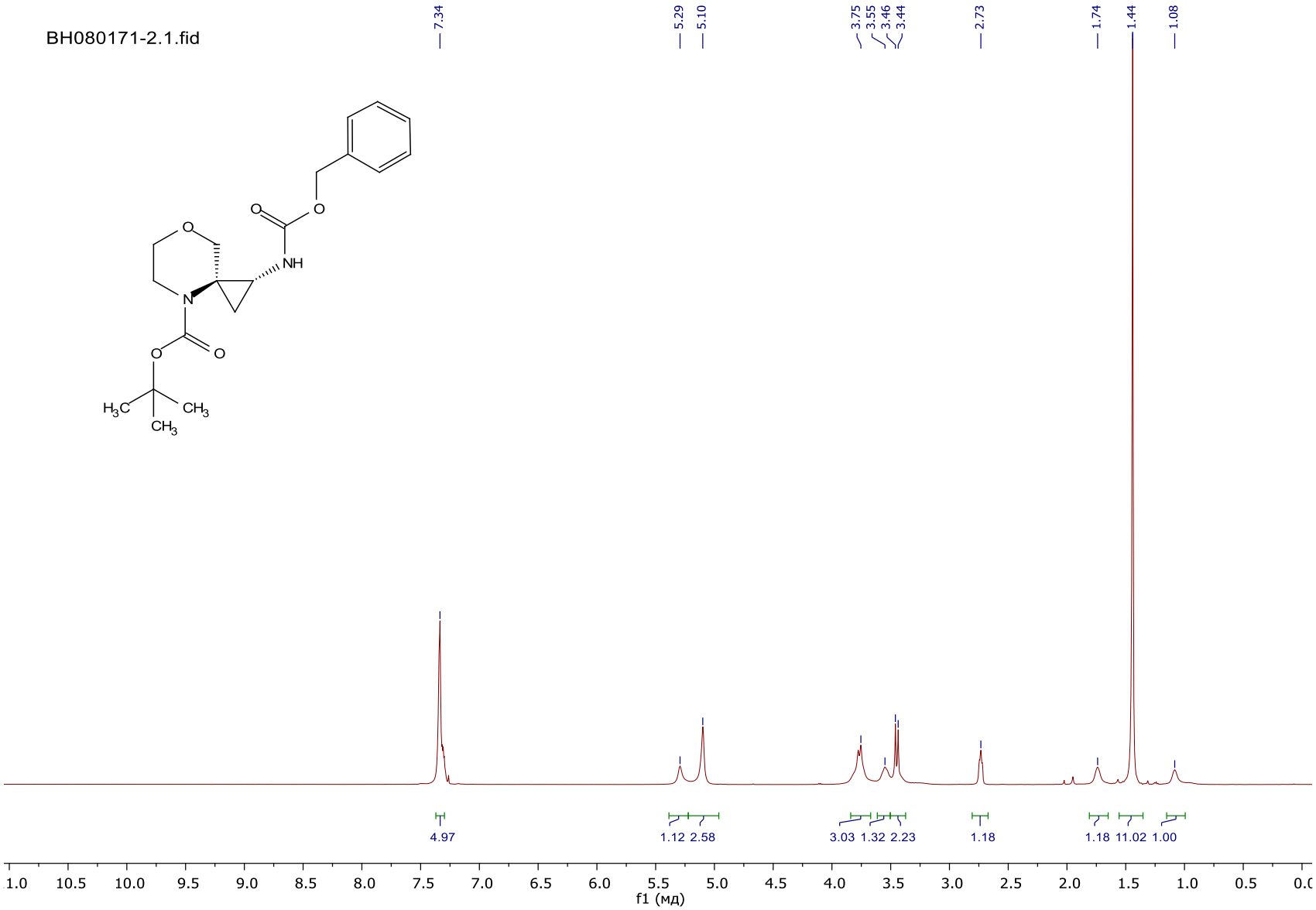
Spectrum 78. *tert*-Butyl (1*S*,3*R*)-1-{[(benzyloxy)carbonyl]amino}-4-azaspiro[2.5]octane-4-carboxylate *cis*-**11b**, ^{13}C NMR (126 MHz, $CDCl_3$).



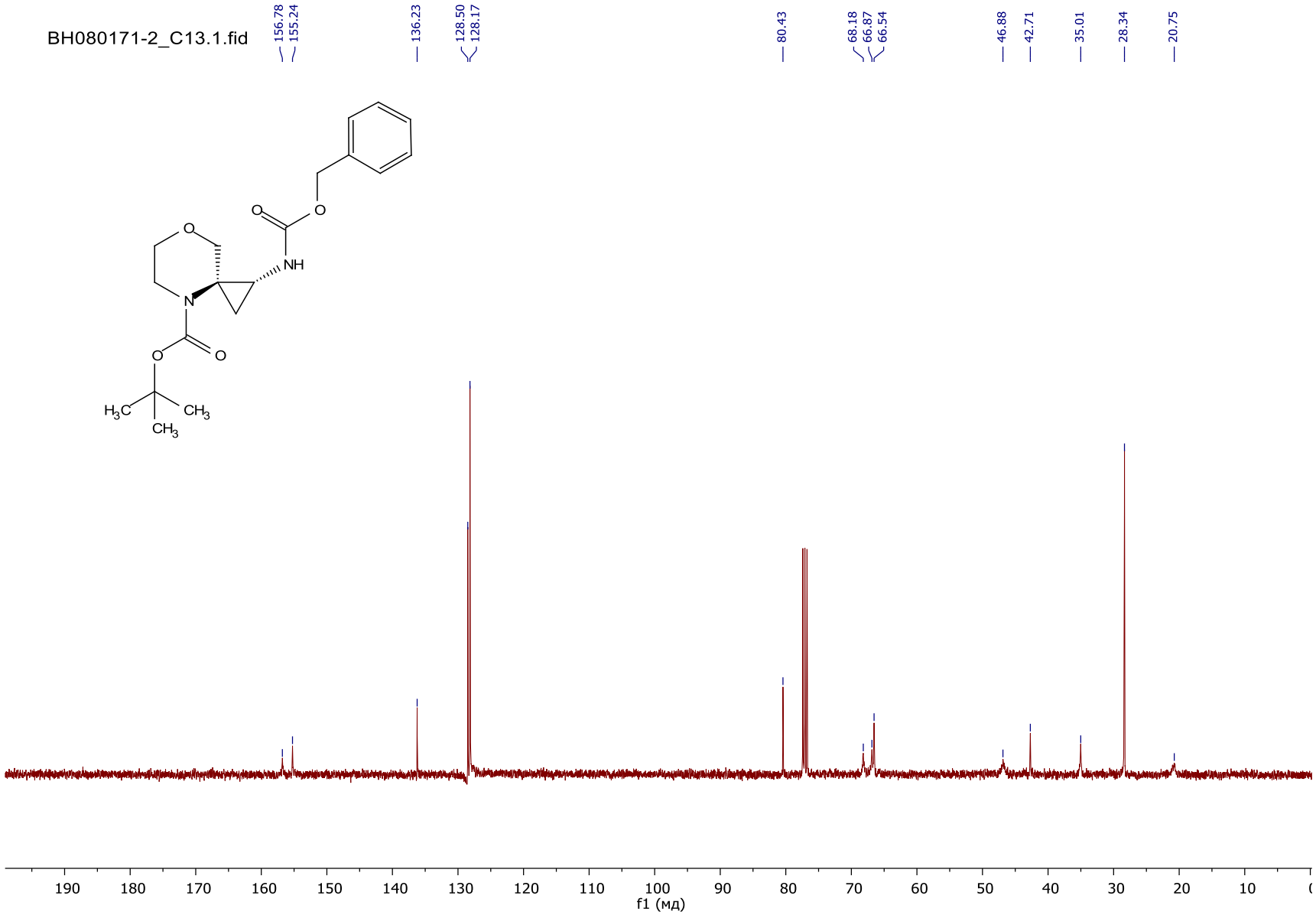
Spectrum 79. *tert*-Butyl (1*R*,3*S*)-1-{[(benzyloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *cis*-**11c**, ^{1}H NMR (500 MHz, $CDCl_3$).



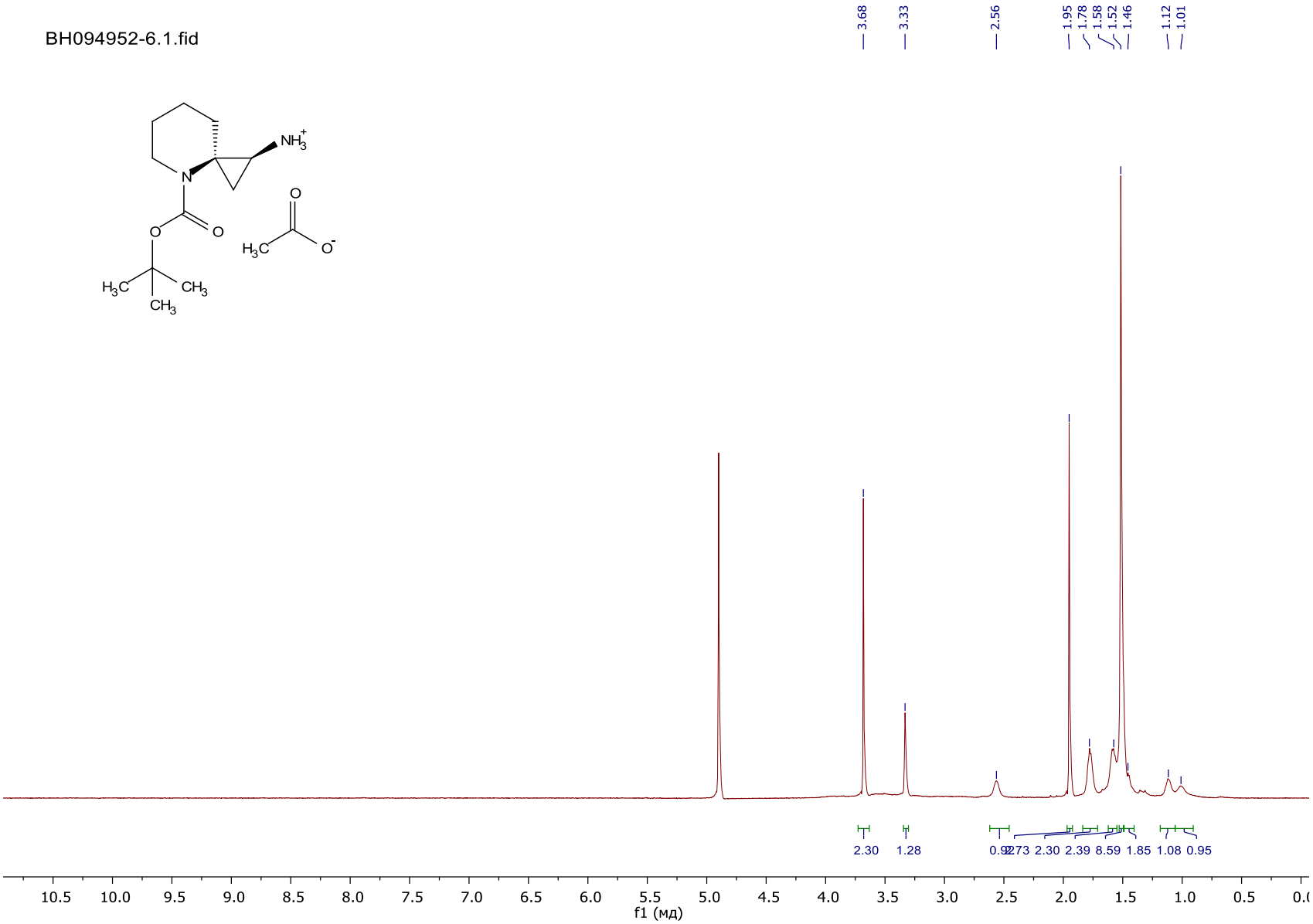
Spectrum 80. *tert*-Butyl (1*R*,3*S*)-1-{[(benzyloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *cis*-**11c**, ^{13}C NMR (126 MHz, $CDCl_3$).



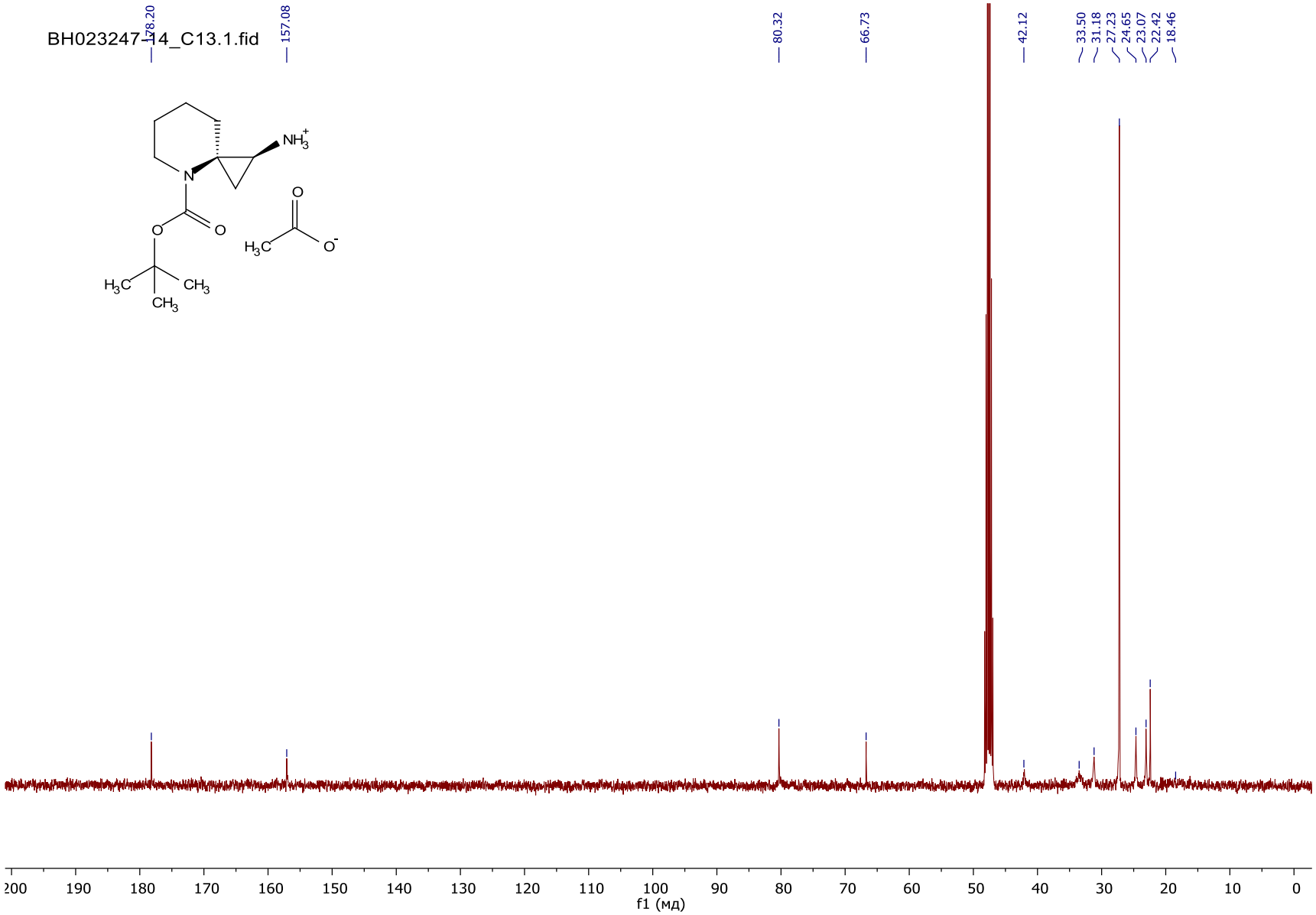
Spectrum 81. *tert*-Butyl (1*S*,3*S*)-1-{[(benzyloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *trans*-**11c**, ^{1}H NMR (500 MHz, $CDCl_3$).



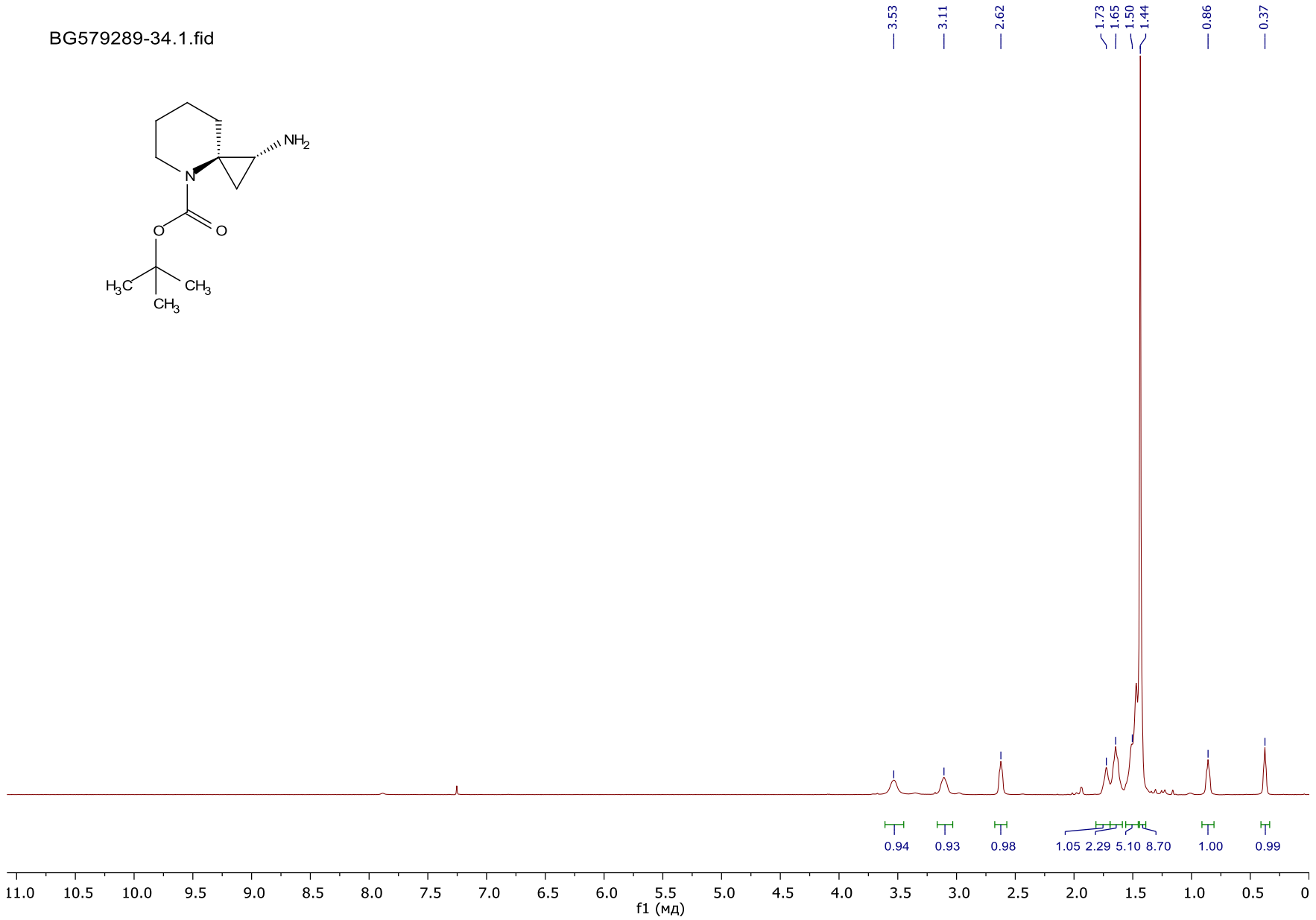
Spectrum 82. *tert*-Butyl (1*S*,3*S*)-1-{[(benzyloxy)carbonyl]amino}-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *trans*-**11c**, ^{13}C NMR (101 MHz, $CDCl_3$).



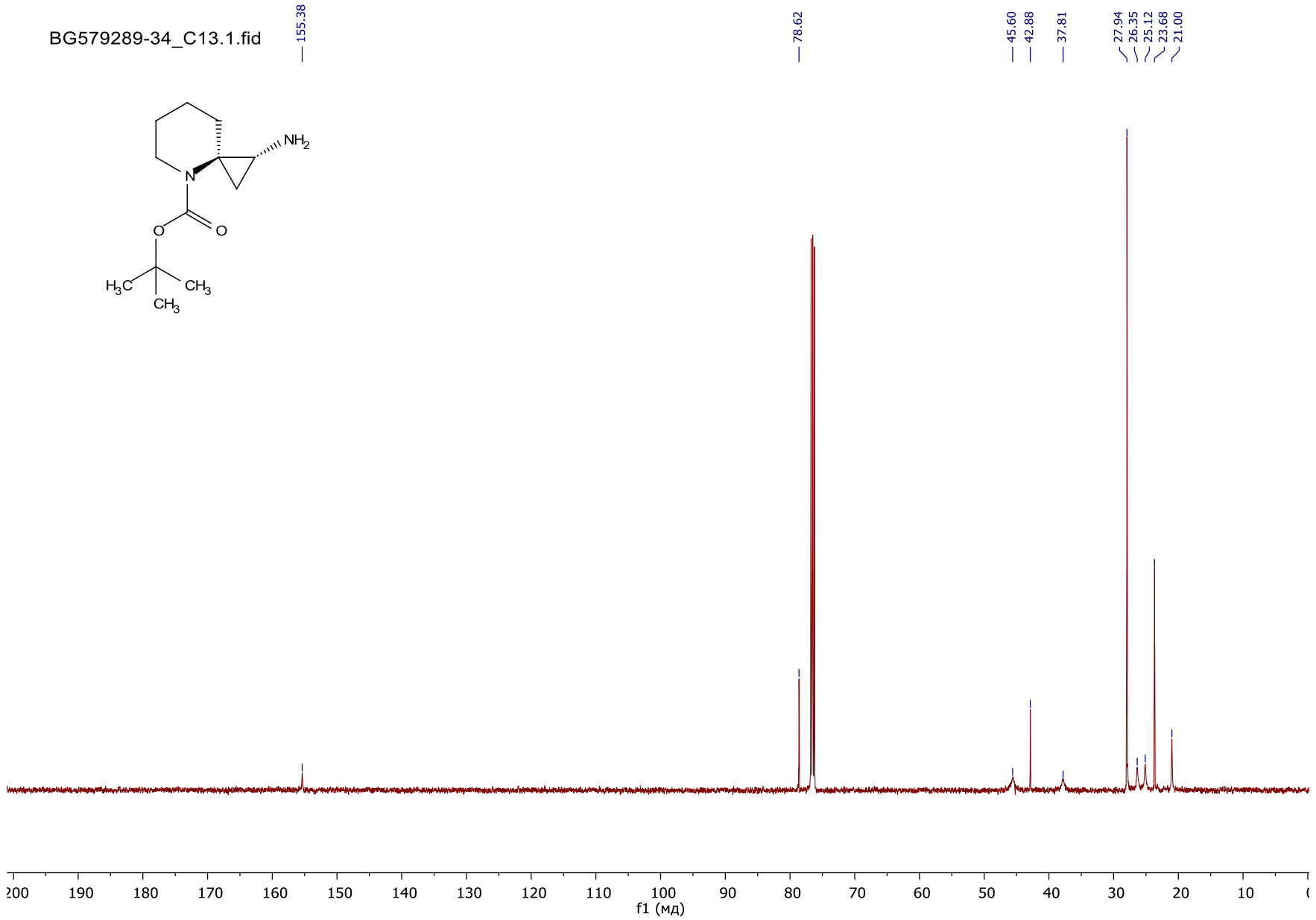
Spectrum 83. (1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.5]octan-1-aminium acetate *cis*-**12b**, ^{1}H NMR (500 MHz, CD_3OD).



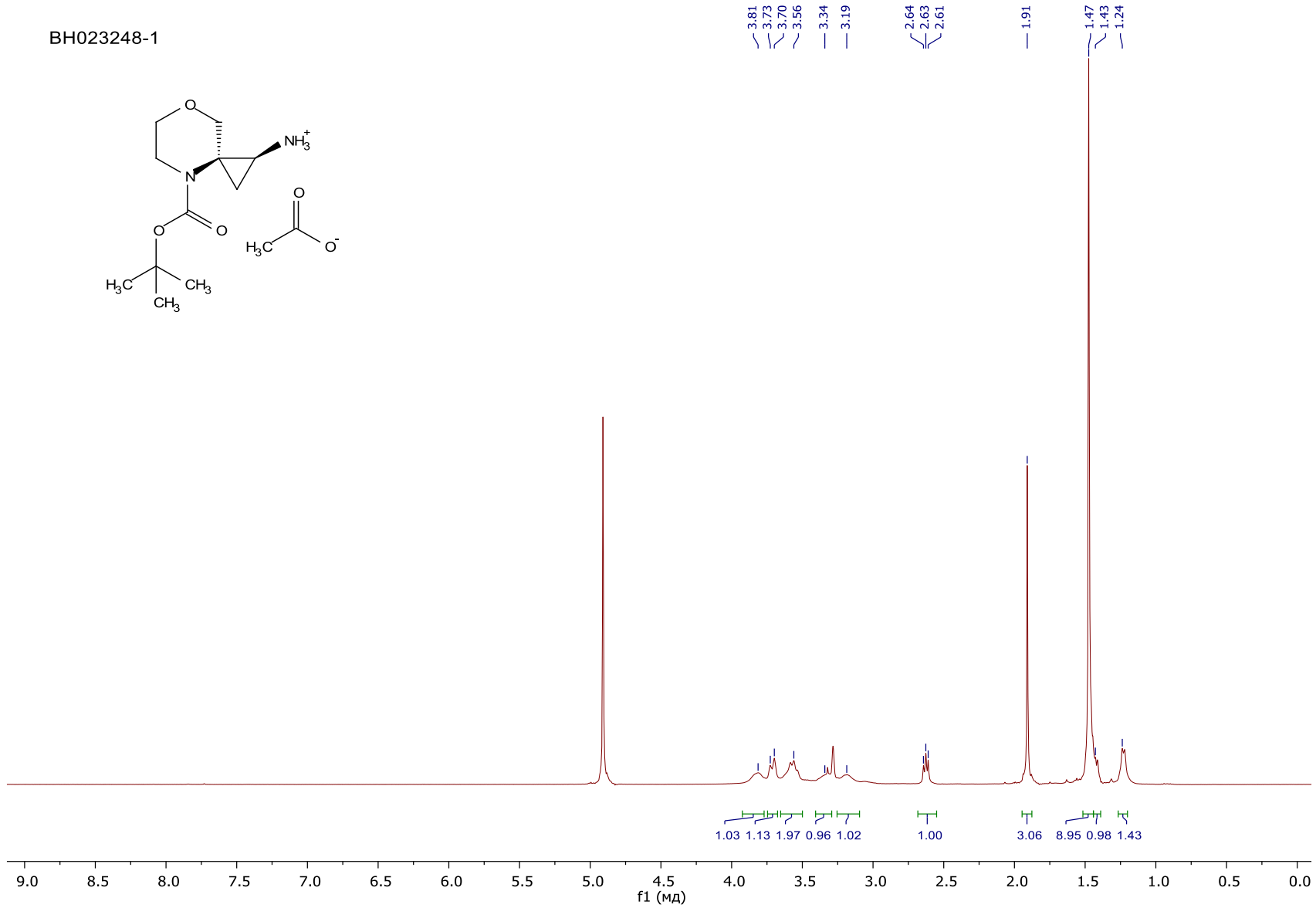
Spectrum 84. (1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-4-azaspiro[2.5]octan-1-aminium acetate *cis*-**12b**, ^{13}C NMR (101 MHz, CD_3OD).



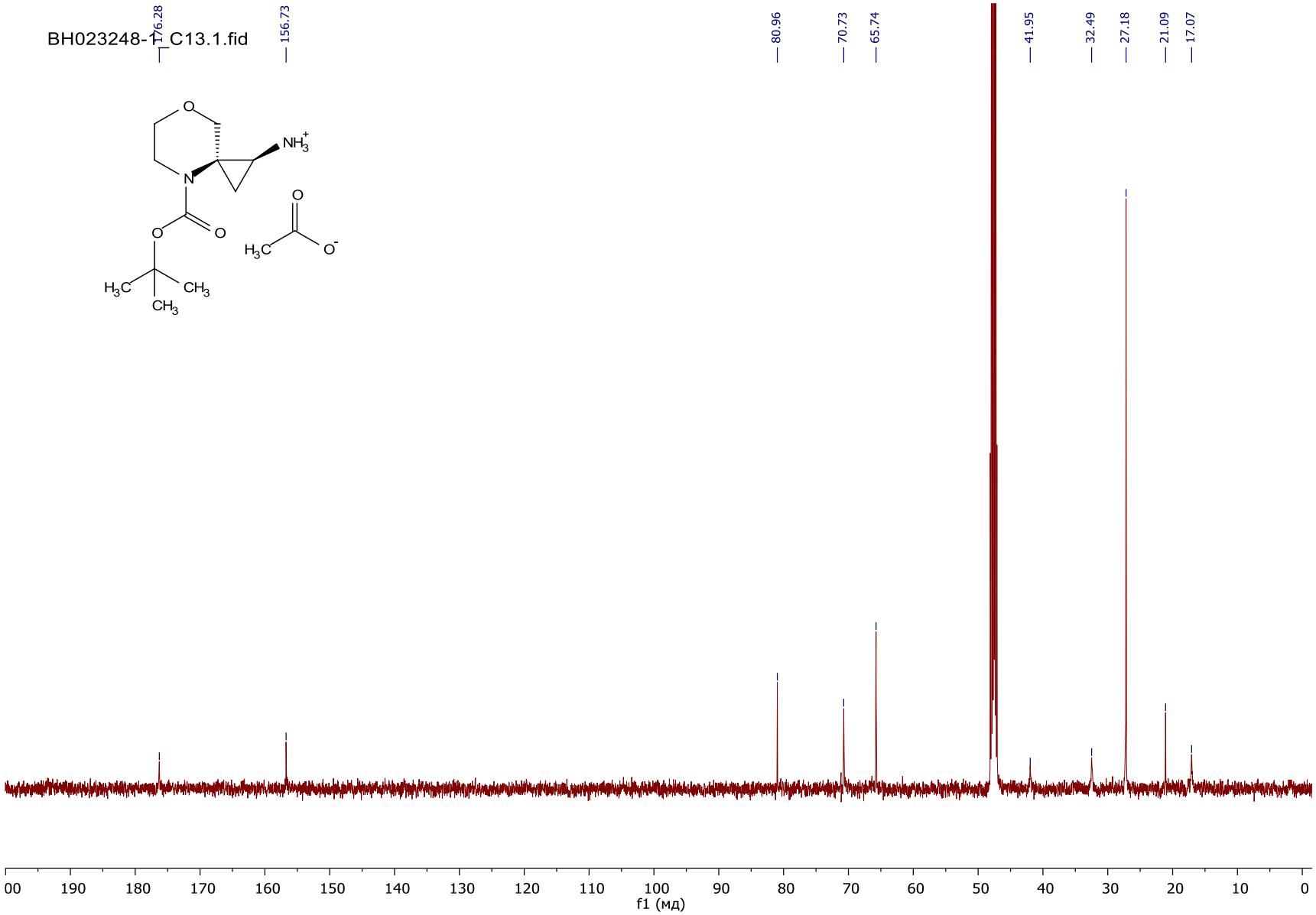
Spectrum 85. *tert*-Butyl (1*S*,3*S*)-1-amino-4-azaspiro[2.5]octane-4-carboxylate *trans*-**12b**, ^{1}H NMR (500 MHz, $CDCl_3$).



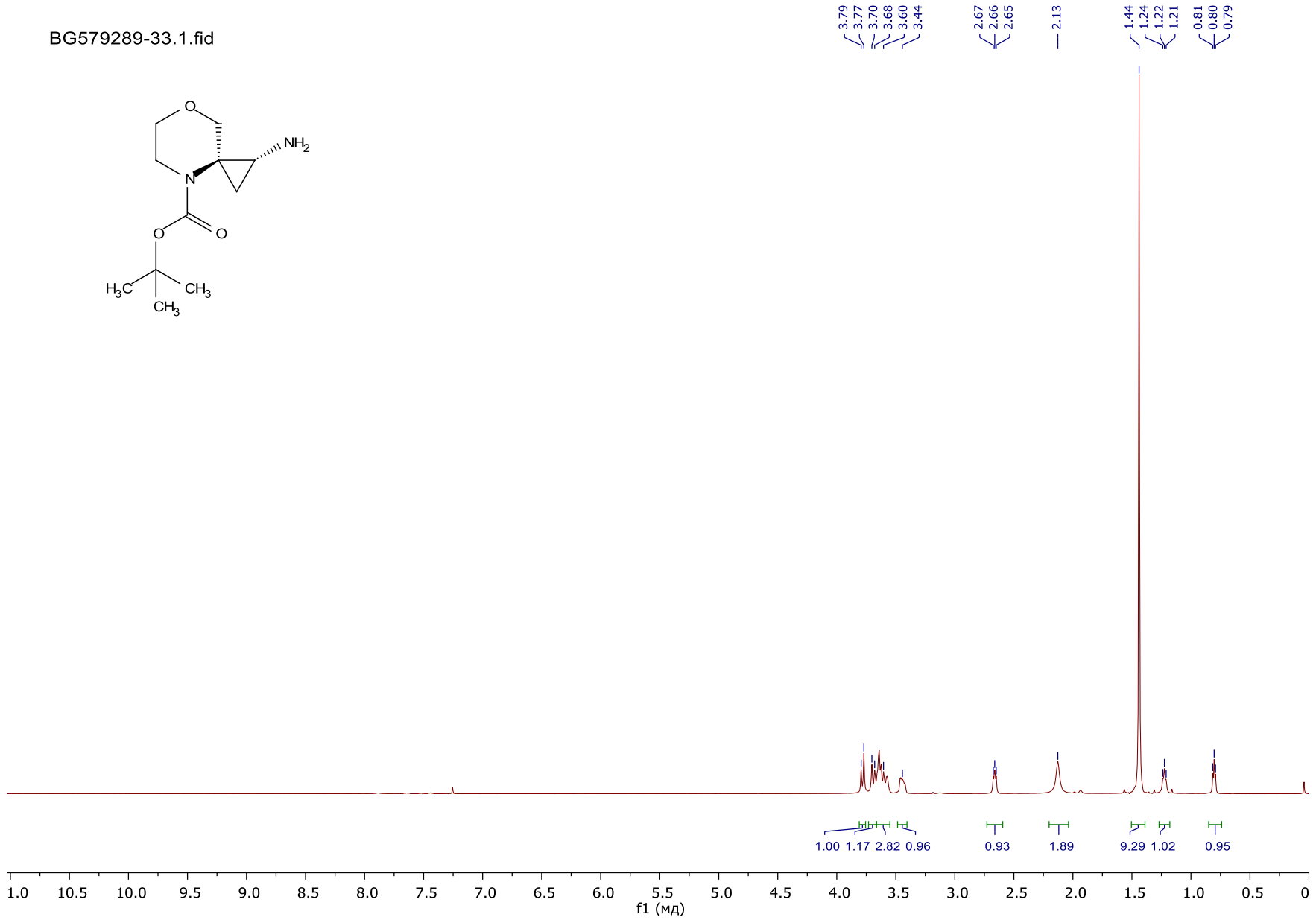
Spectrum 86. *tert*-Butyl (1*S*,3*S*)-1-amino-4-azaspiro[2.5]octane-4-carboxylate *trans*-**12b**, ^{13}C NMR (126 MHz, $CDCl_3$).



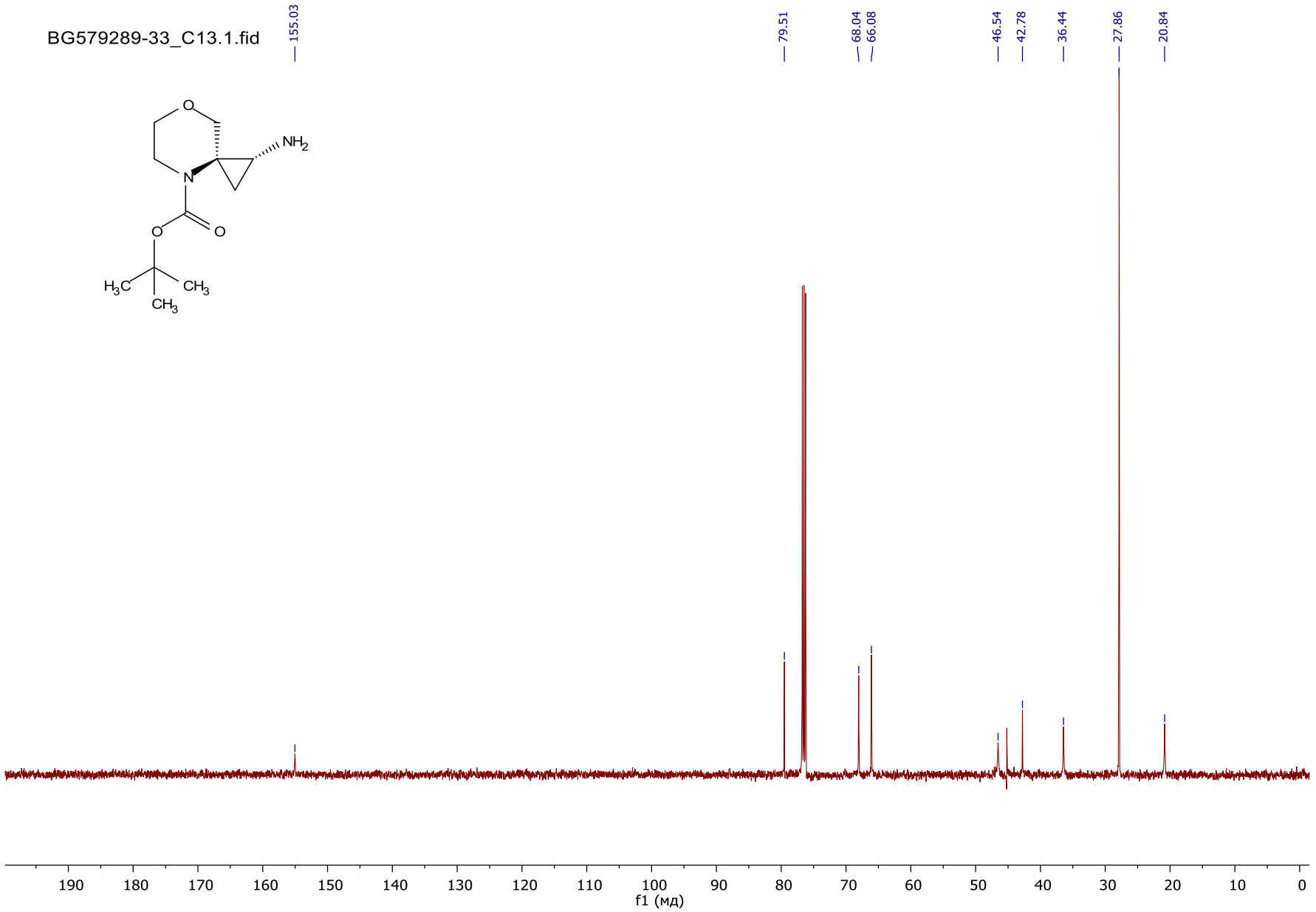
Spectrum 87. (1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-7-oxa-4-azaspiro[2.5]octan-1-aminium acetate *cis*-**12c**, ^{1}H NMR (400 MHz, CD_3OD).



Spectrum 88. (1*R*,3*S*)-4-[(*tert*-butoxy)carbonyl]-7-oxa-4-azaspiro[2.5]octan-1-aminium acetate *cis*-**12c**, ^{13}C NMR (126 MHz, CD_3OD).



Spectrum 89. *tert*-Butyl (1*R*,3*R*)-1-amino-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *trans*-**12c**, ^{1}H NMR (500 MHz, $CDCl_3$).



Spectrum 90. *tert*-Butyl (1*R*,3*R*)-1-amino-7-oxa-4-azaspiro[2.5]octane-4-carboxylate *trans*-**12c**, ^{13}C NMR (126 MHz, $CDCl_3$).

ORTEP diagrams

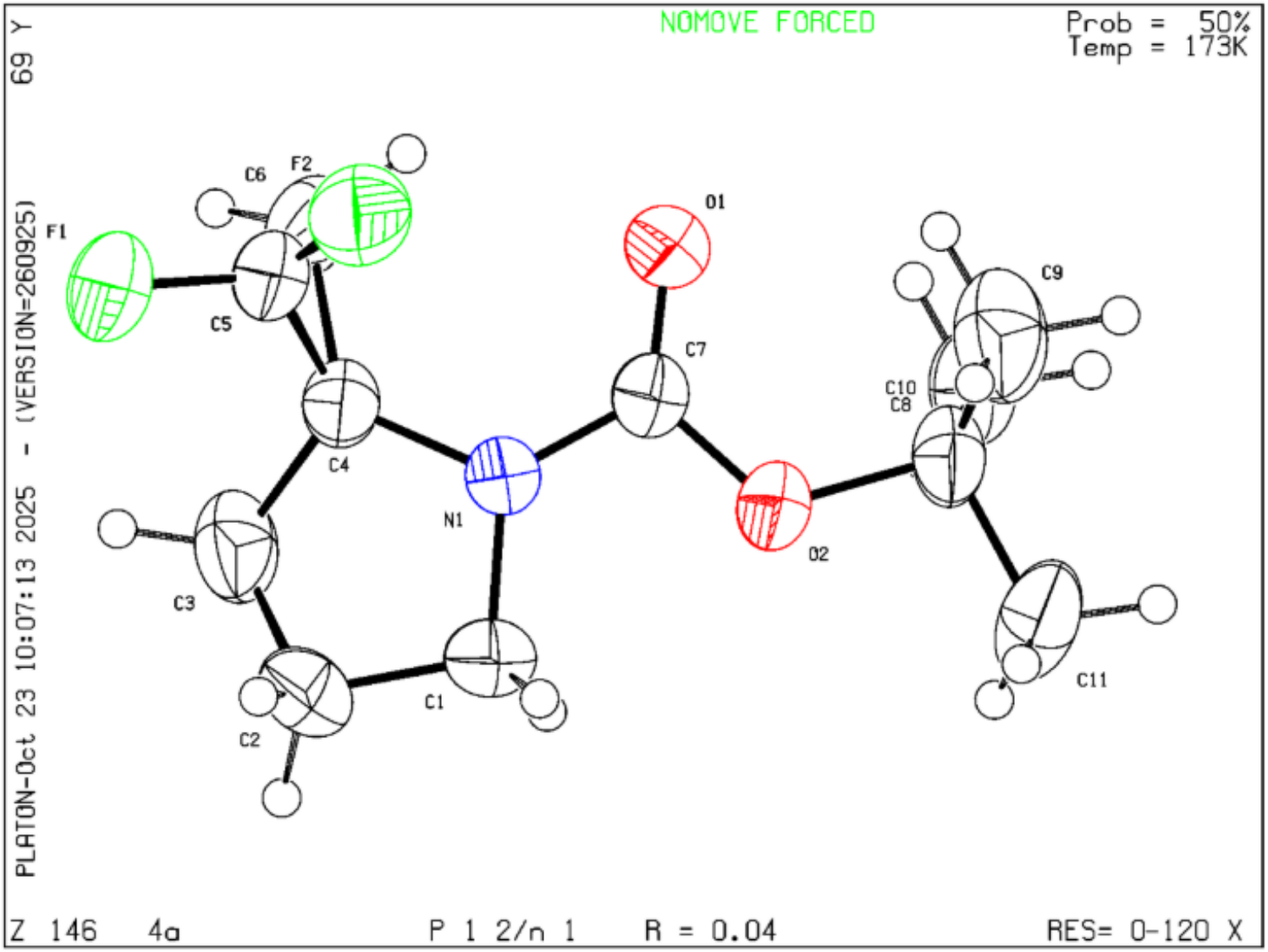


Figure 1. ORTEP diagram of compound **4a**.

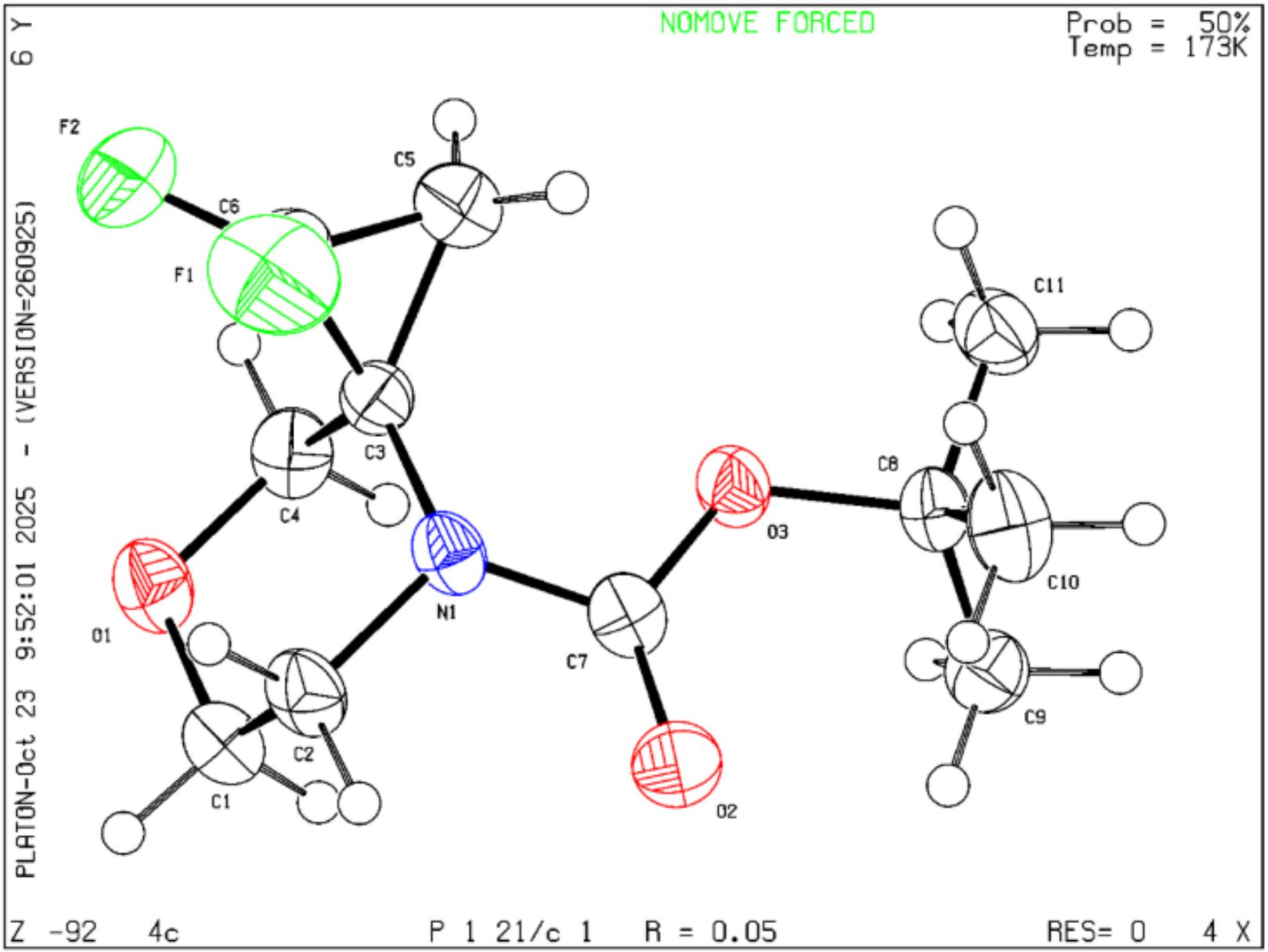


Figure 2. ORTEP diagram of compound **4c**.

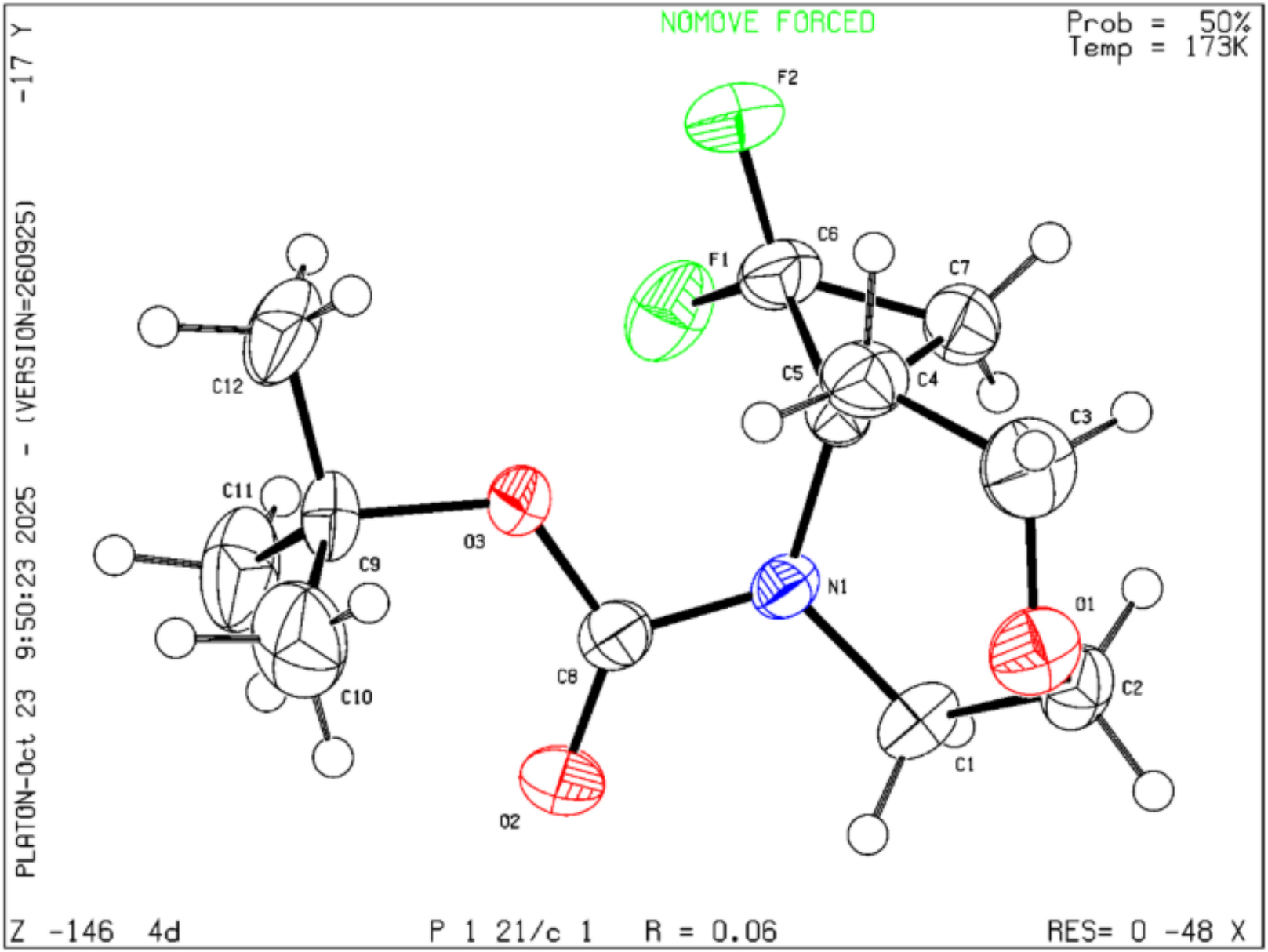


Figure 3. ORTEP diagram of compound **4d**.

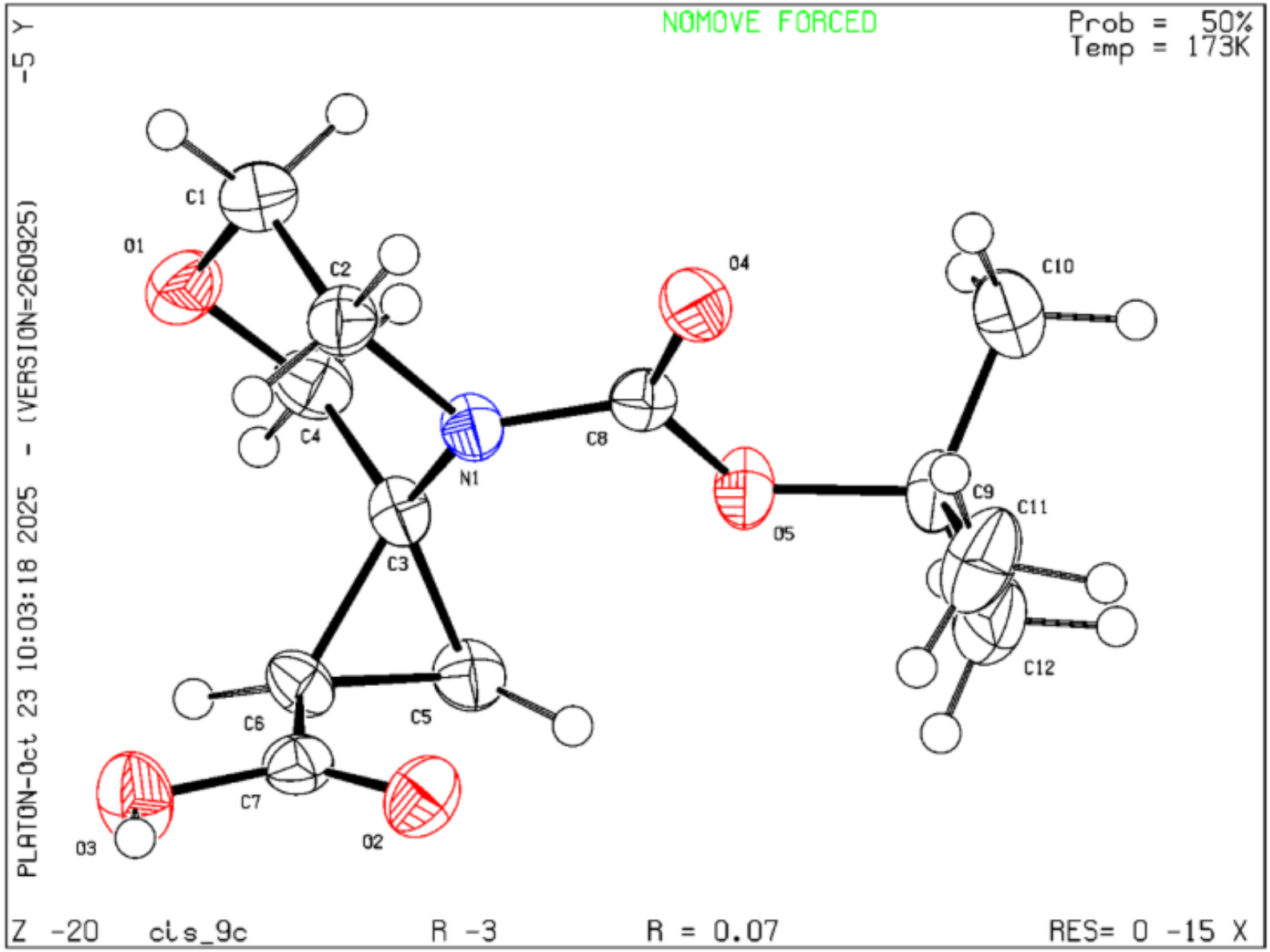


Figure 4. ORTEP diagram of compound *cis*-**9c**.

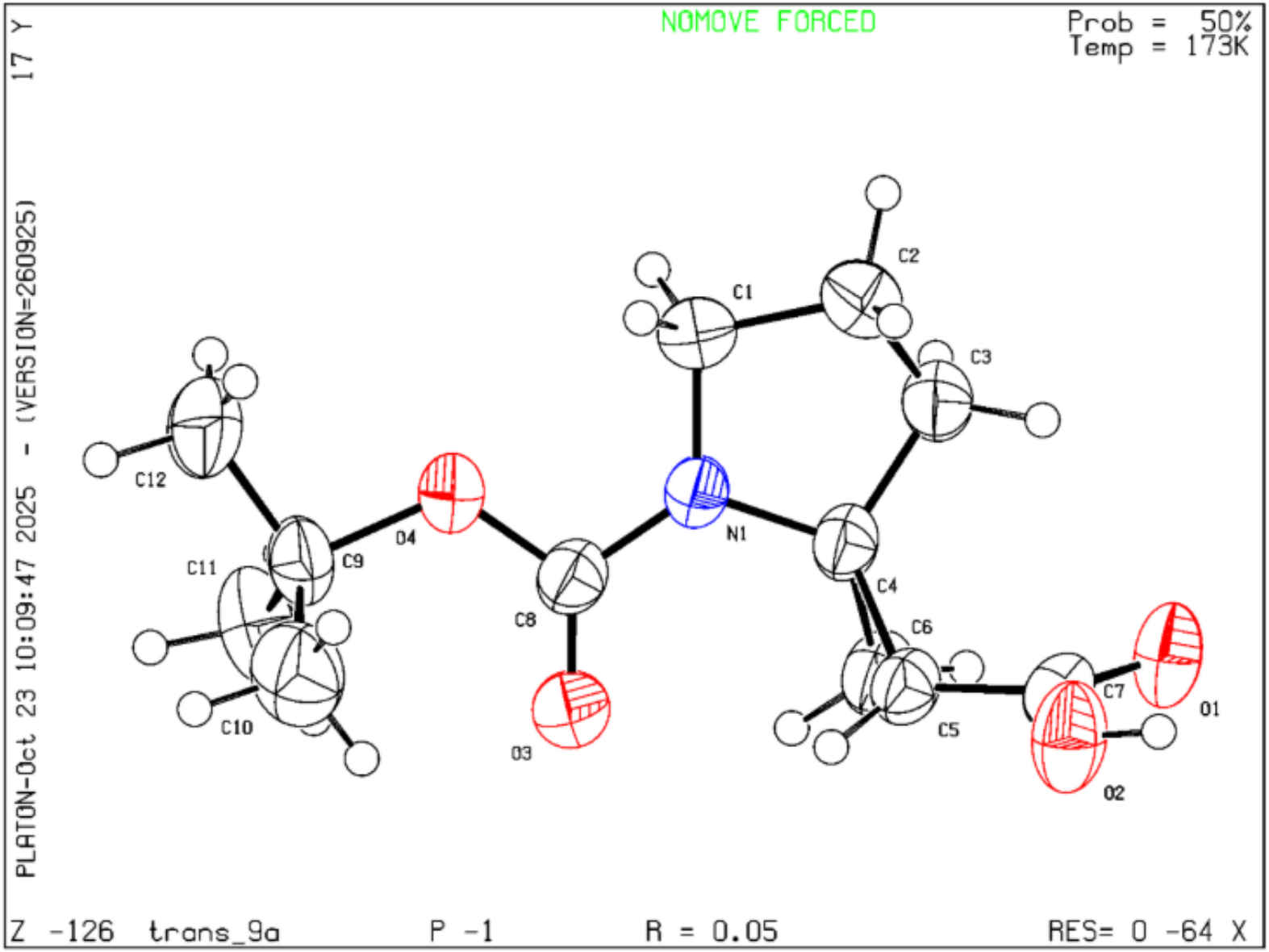


Figure 5. ORTEP diagram of compound *trans*-**9a**.

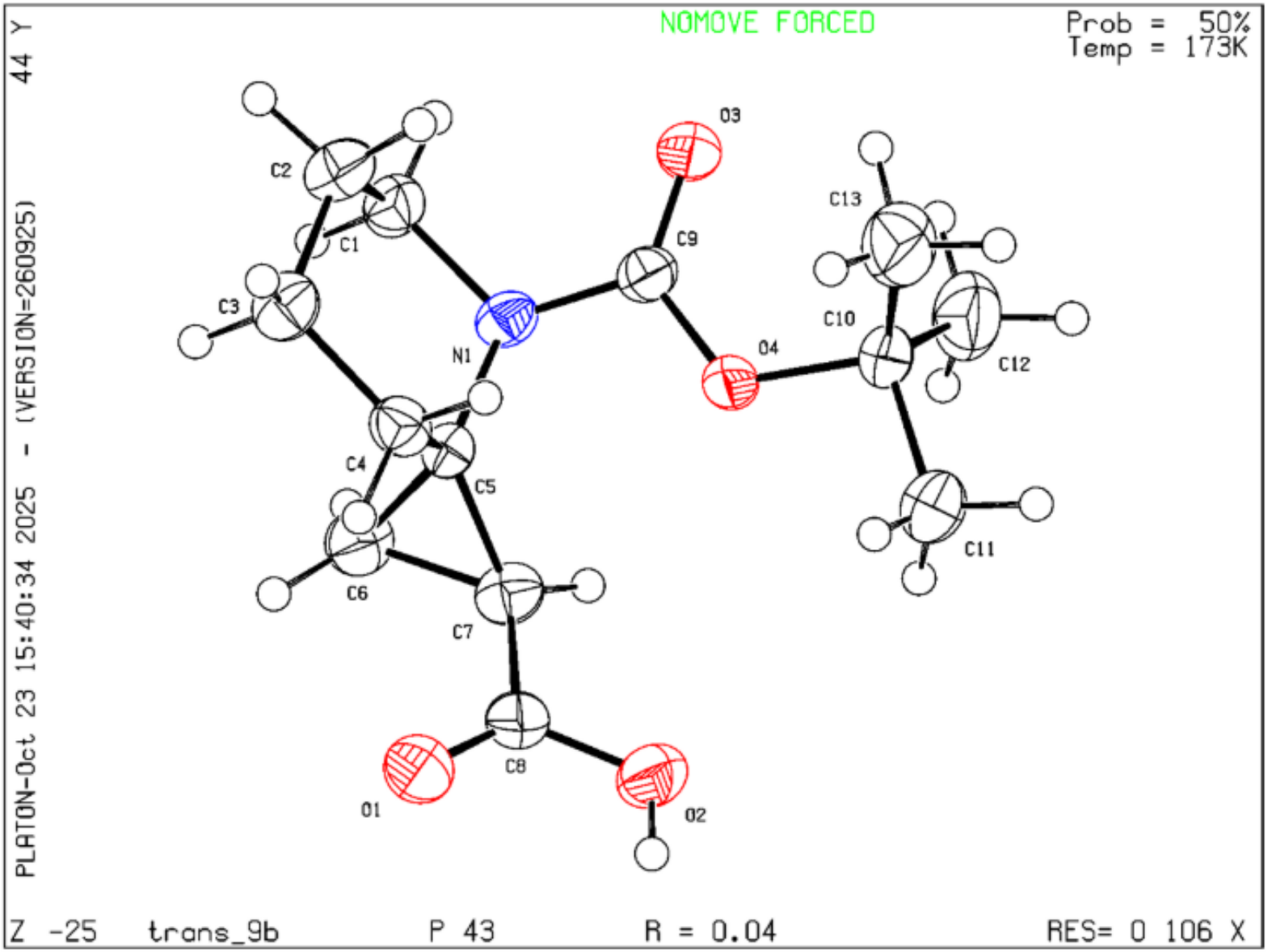


Figure 6. ORTEP diagram of compound *trans*-**9b**.

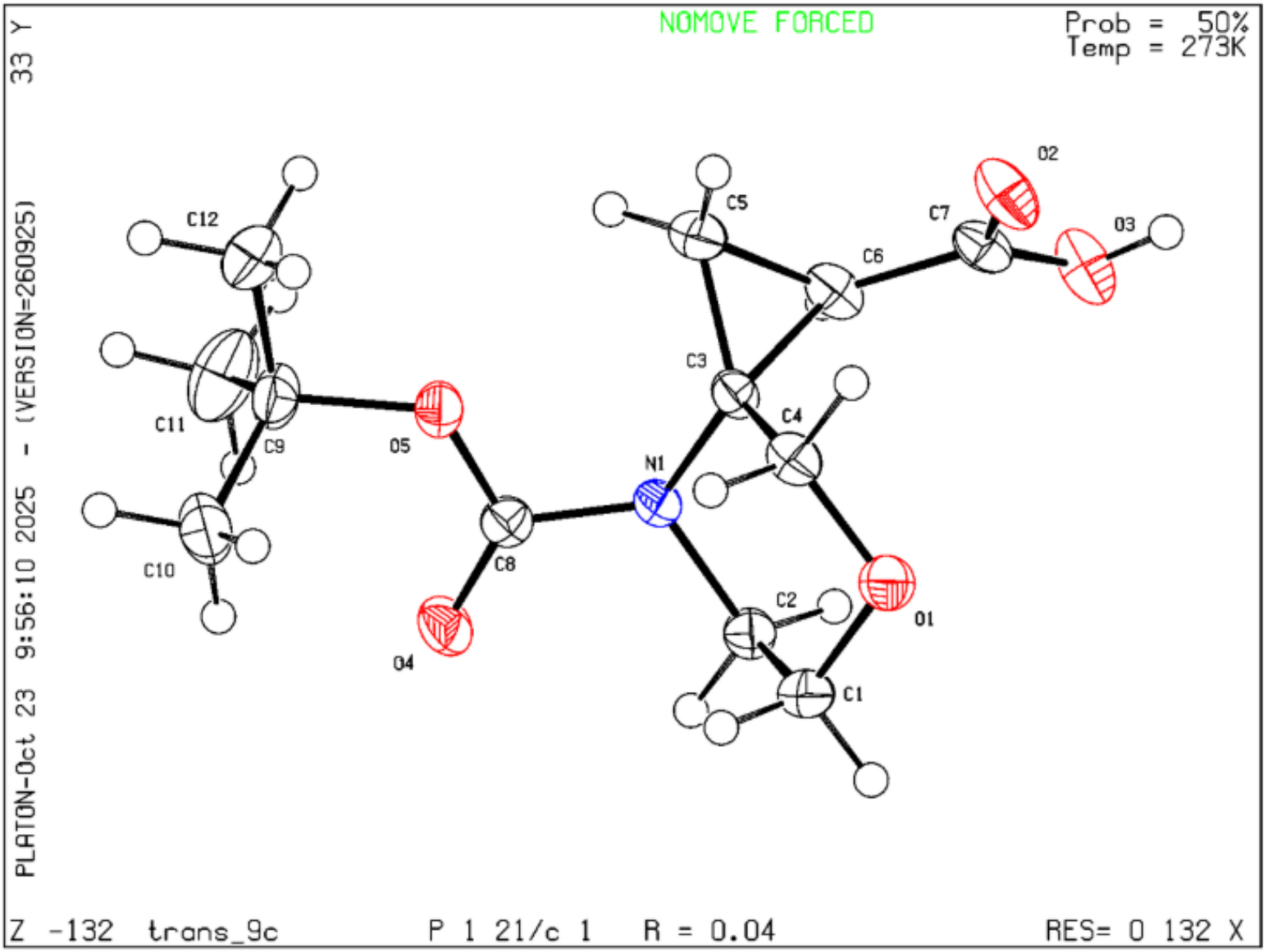


Figure 7. ORTEP diagram of compound *trans*-**9c**.

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