

### **Multigram Synthesis of 2-Azabicyclo[2.1.1]hexane-1-Carboxylates (2,4-Methanoprolines) – Promising Bicyclic Proline Analogs**

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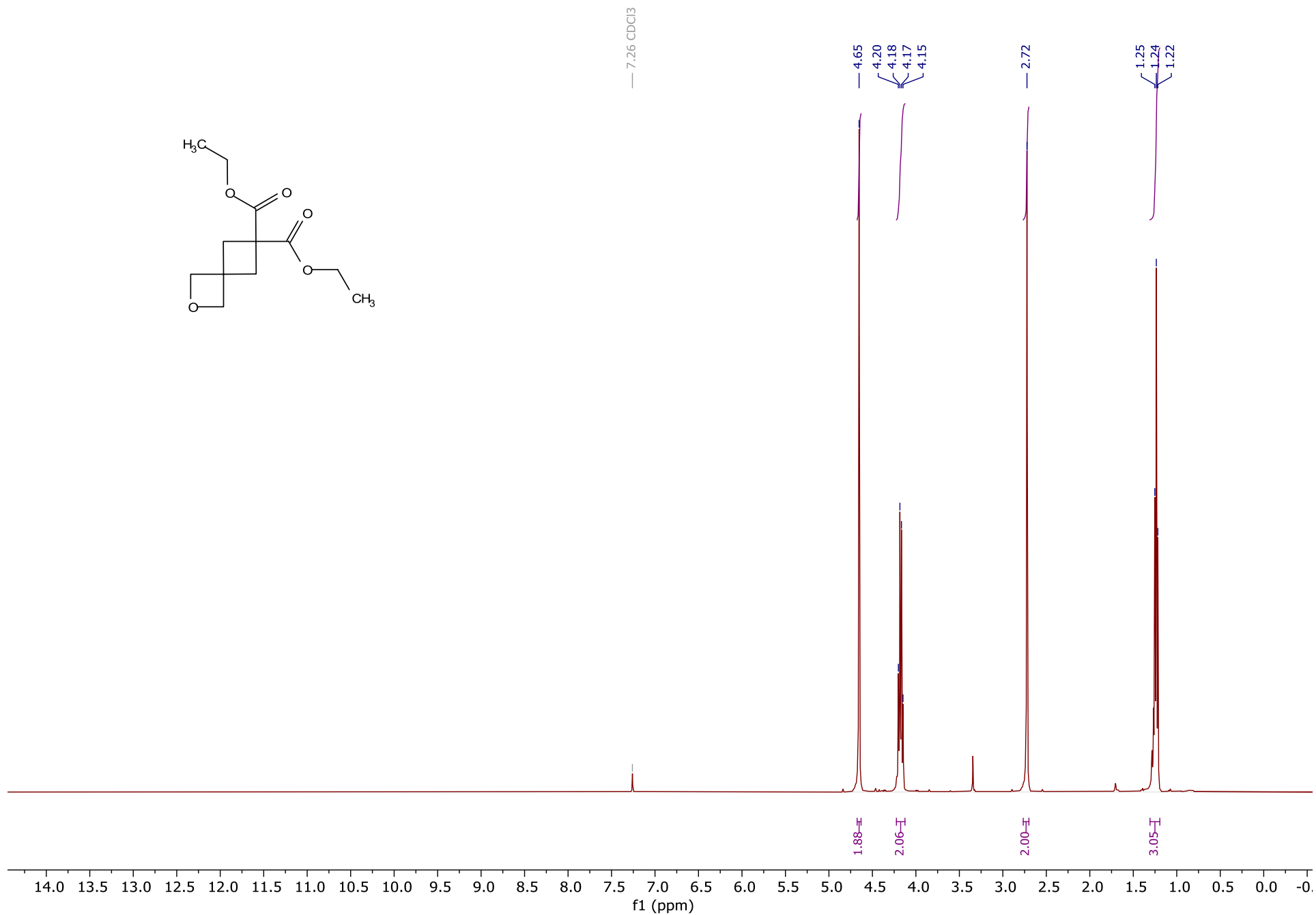


Figure 1. Diethyl 2-oxaspiro[3.3]heptane-6,6-dicarboxylate **13**, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

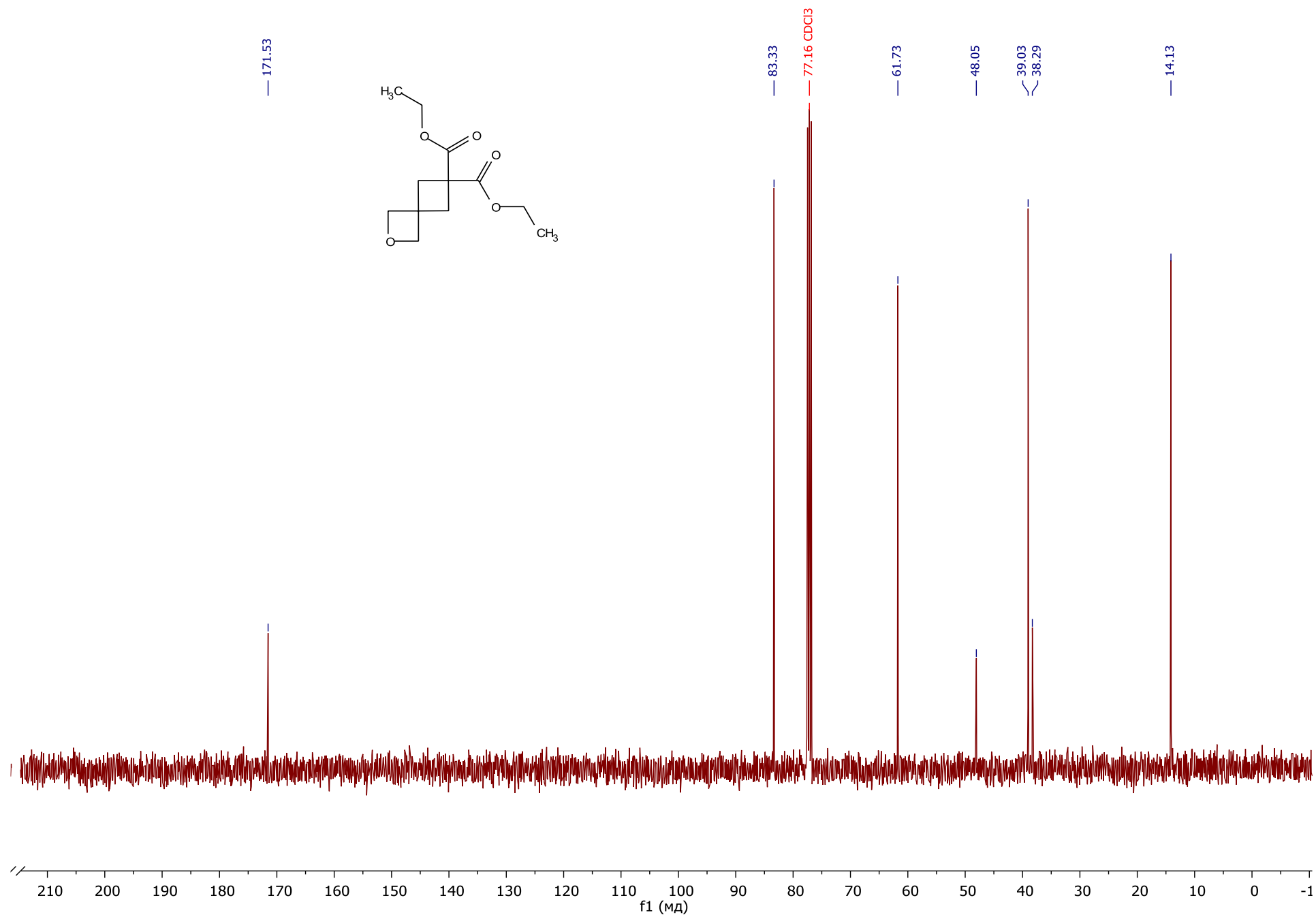


Figure 2. Diethyl 2-oxaspiro[3.3]heptane-6,6-dicarboxylate **13**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ).

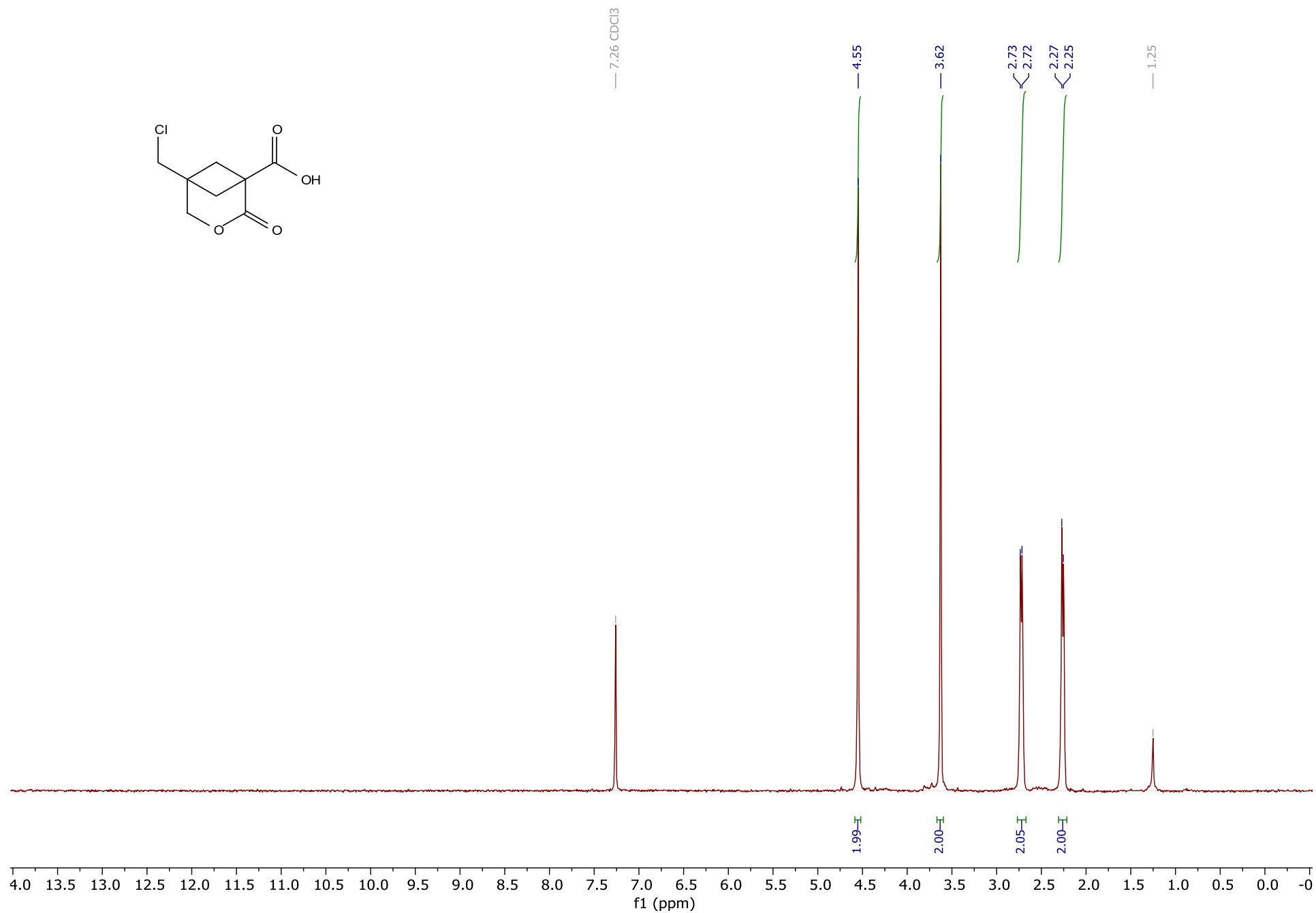


Figure 3. 5-(Chloromethyl)-2-oxo-3-oxabicyclo[3.1.1]heptane-1-carboxylic acid **7**,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

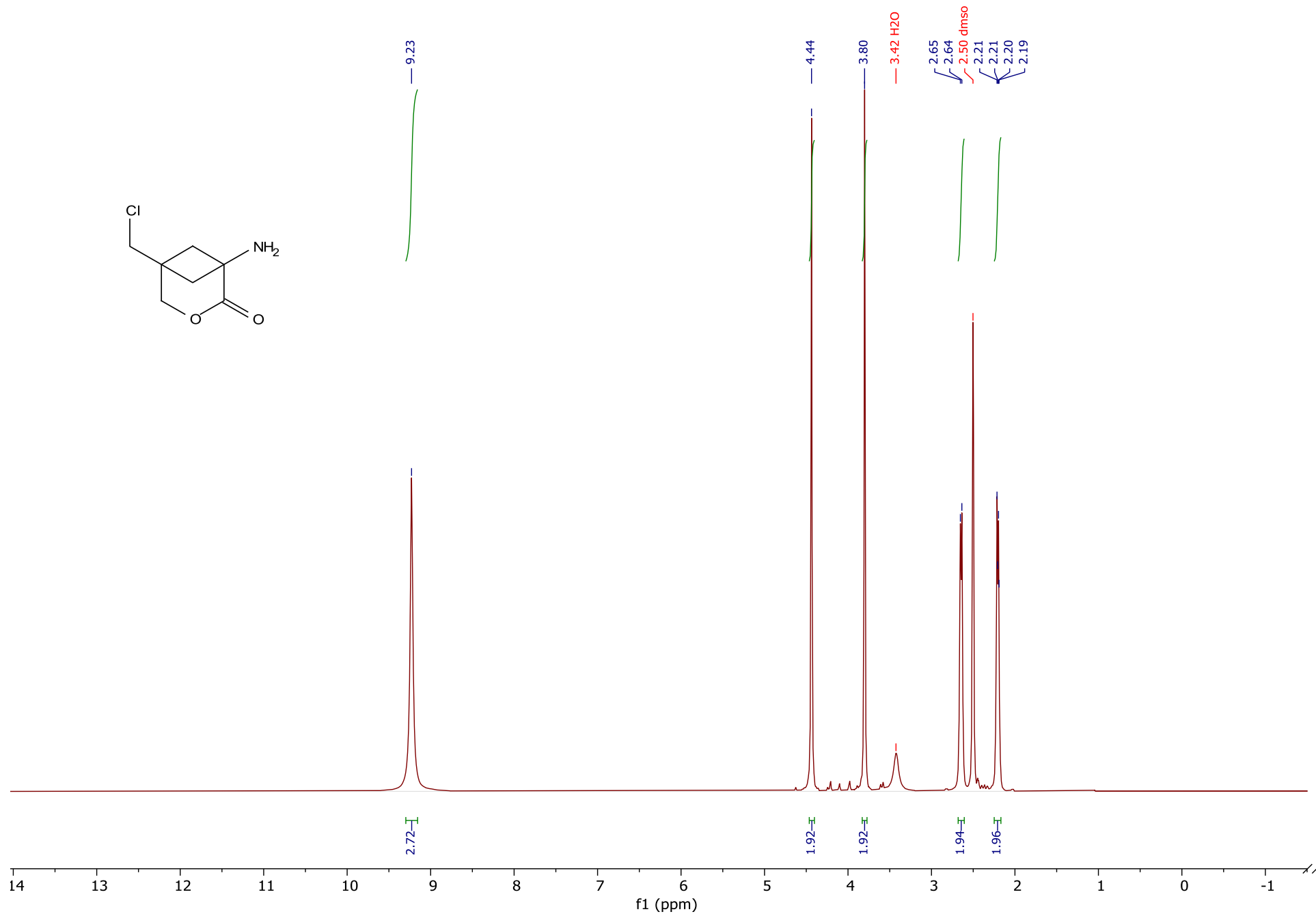


Figure 4. 1-Amino-5-(chloromethyl)-3-oxabicyclo[3.1.1]heptan-2-one hydrochloride **14**, <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>)



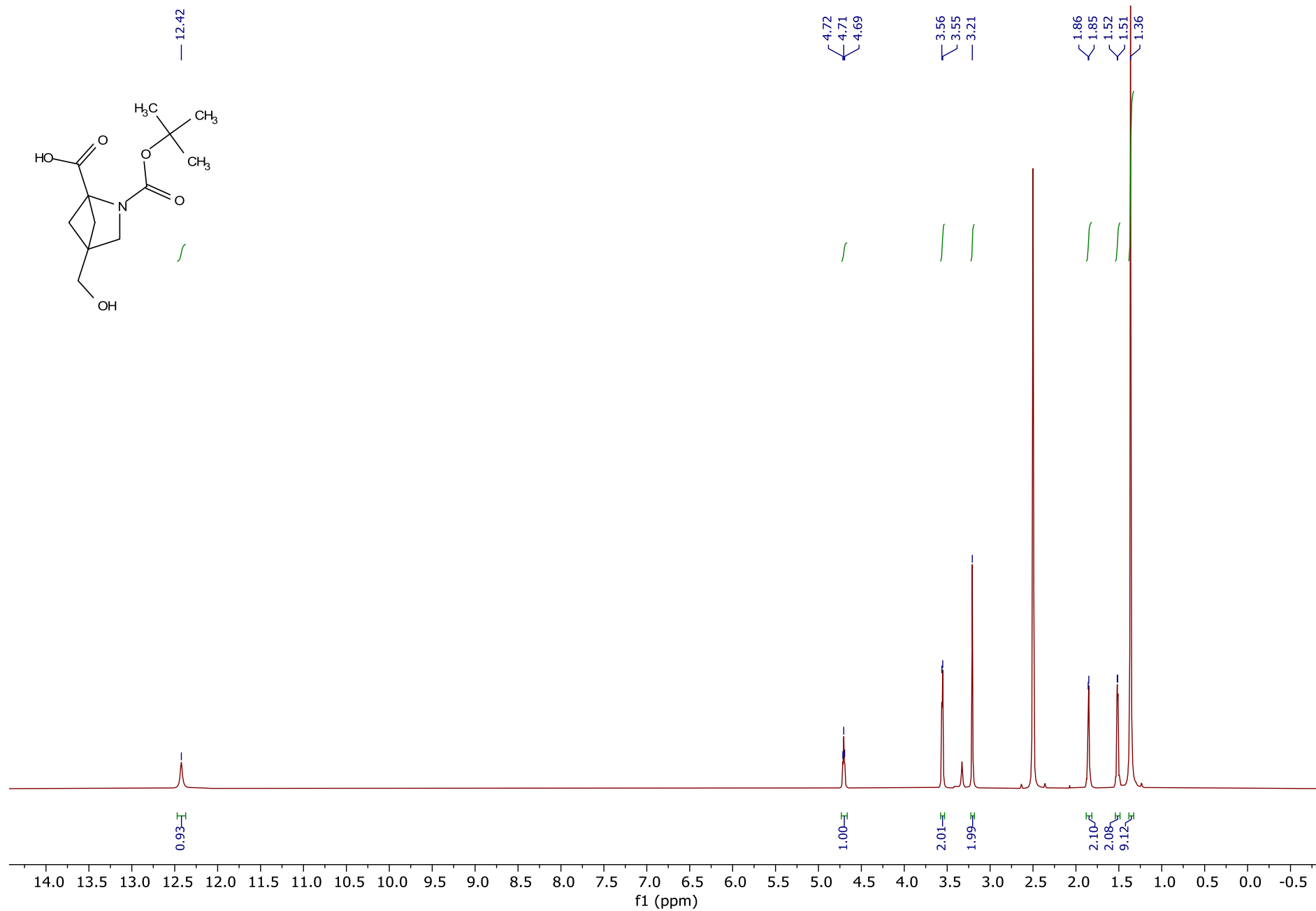


Figure 5. 2-(*tert*-Butoxycarbonyl)-4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **6**, <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>).

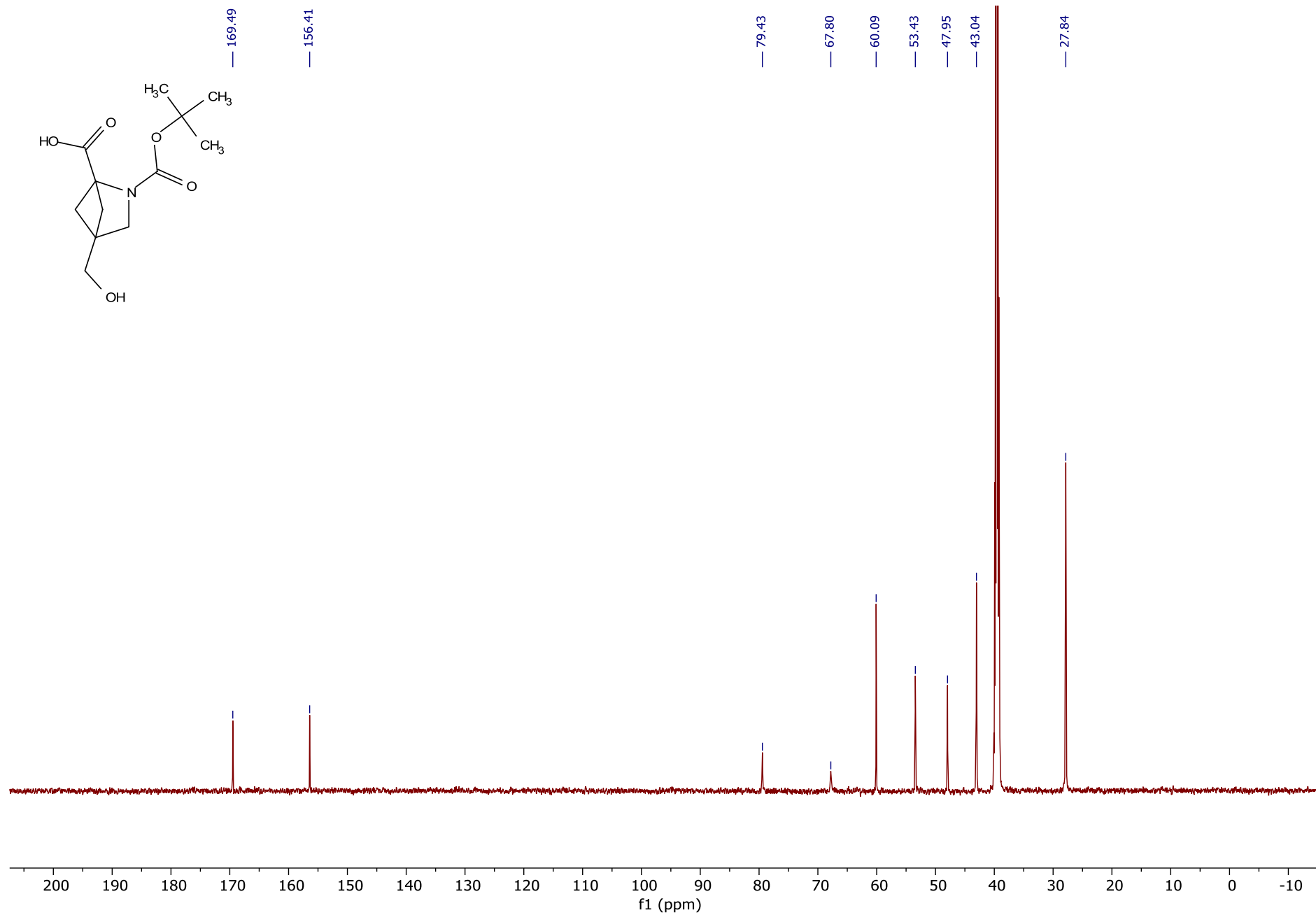


Figure 6. 2-(*tert*-Butoxycarbonyl)-4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **6**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz, DMSO- $d_6$ ).

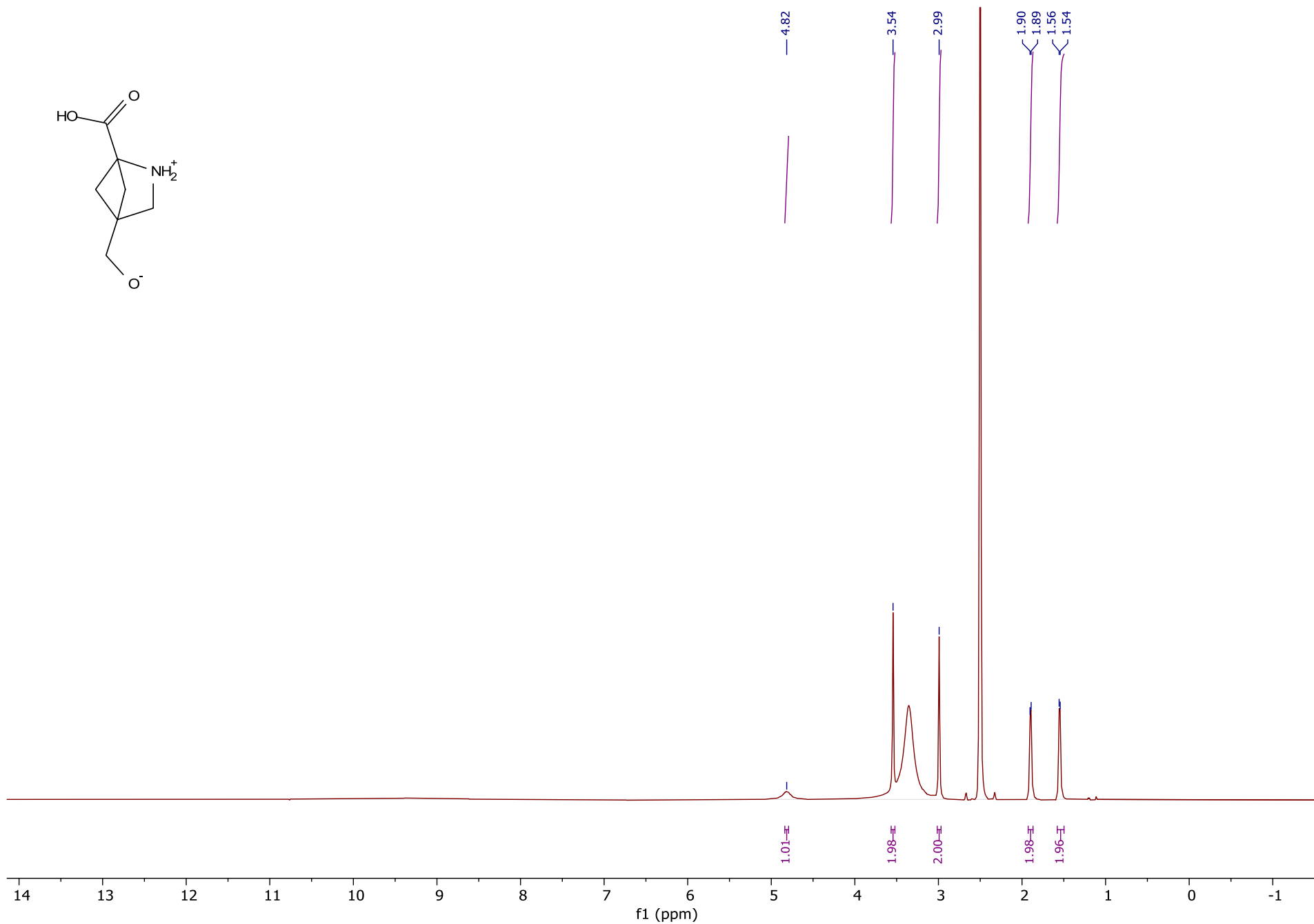
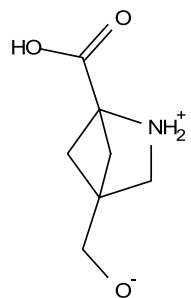


Figure 7. 4-(Hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **16**, <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>).

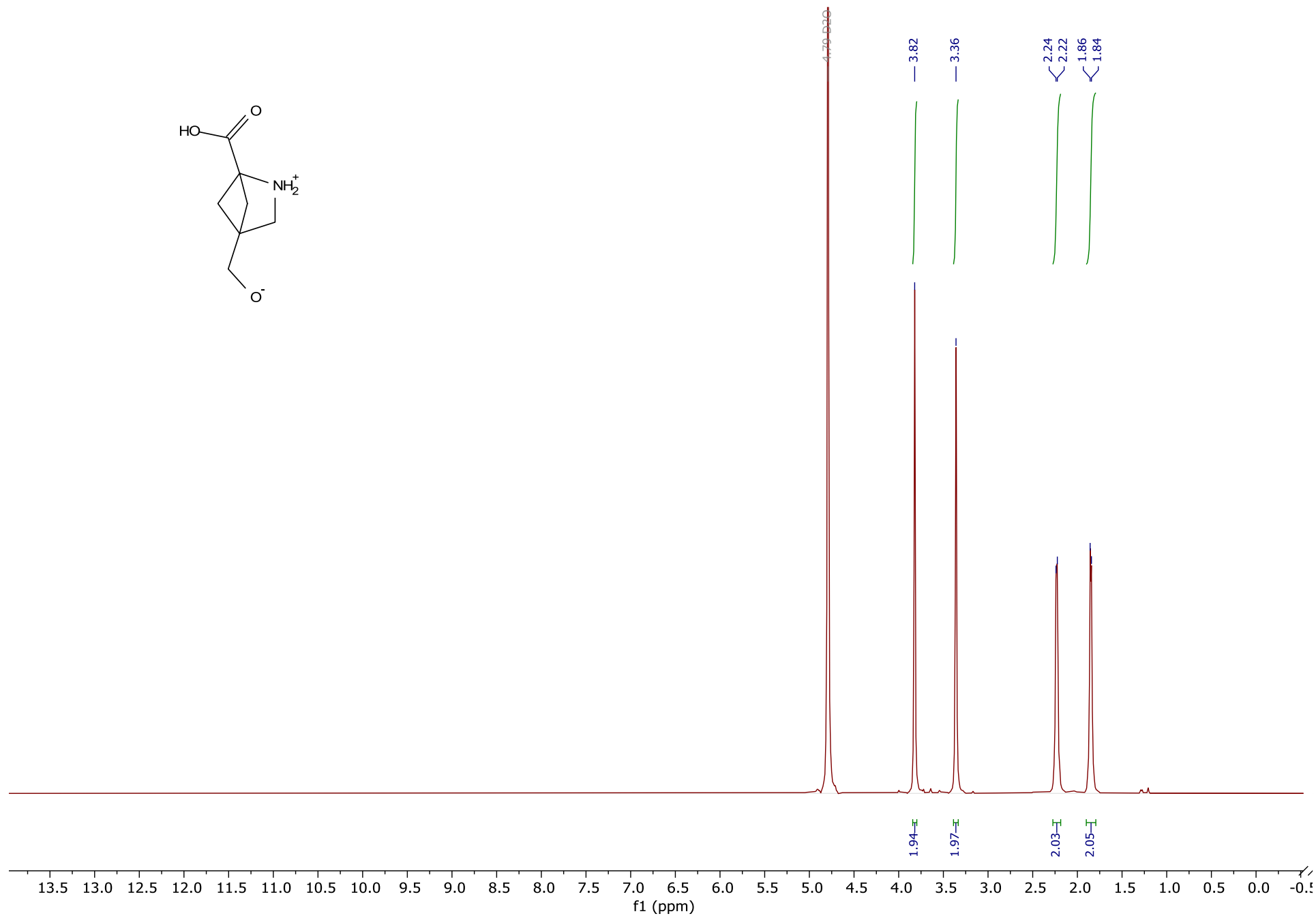
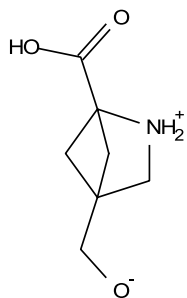


Figure 8. 4-(Hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **16**. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O)

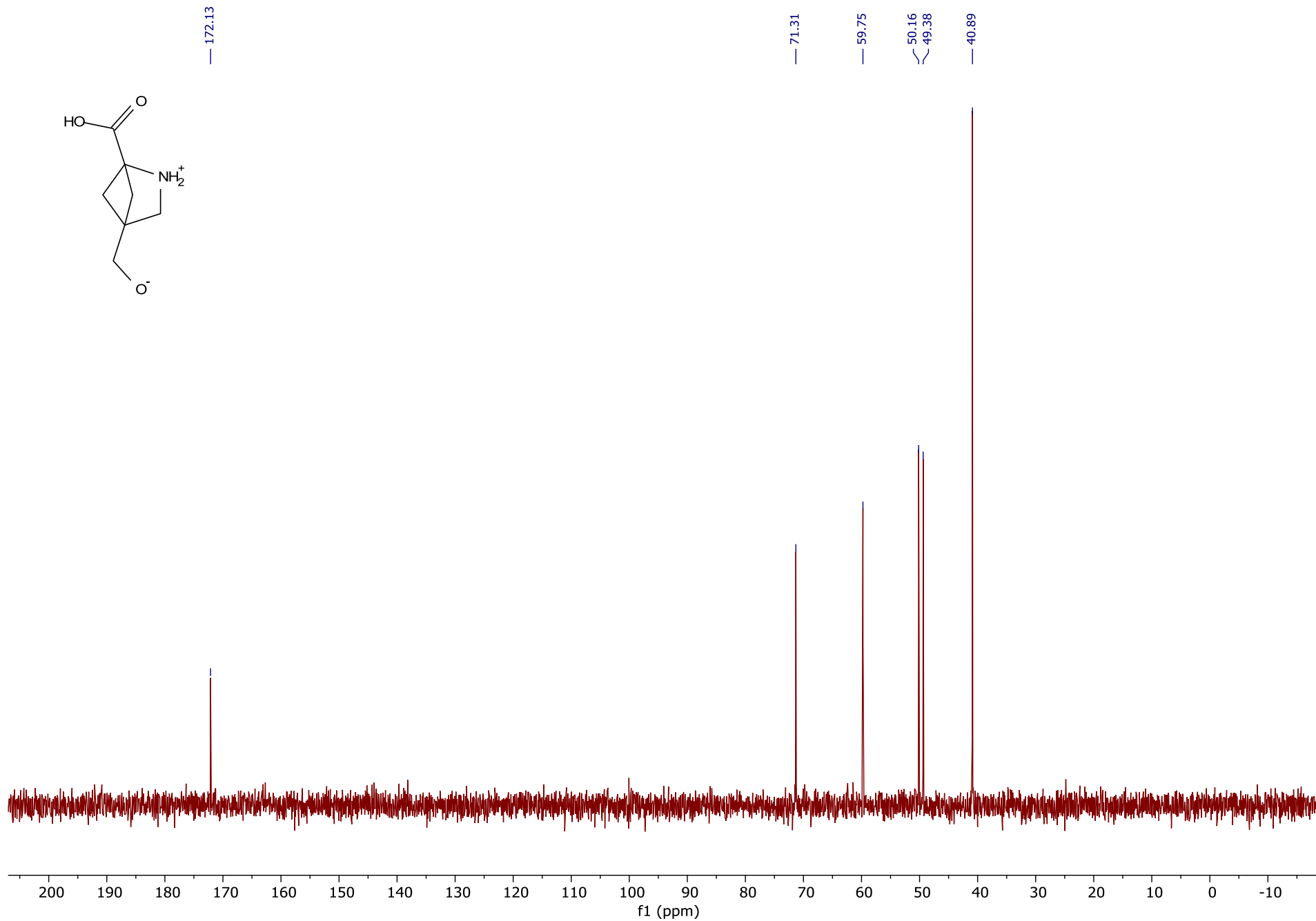


Figure 9. 4-(Hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **16**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{D}_2\text{O}$ ).

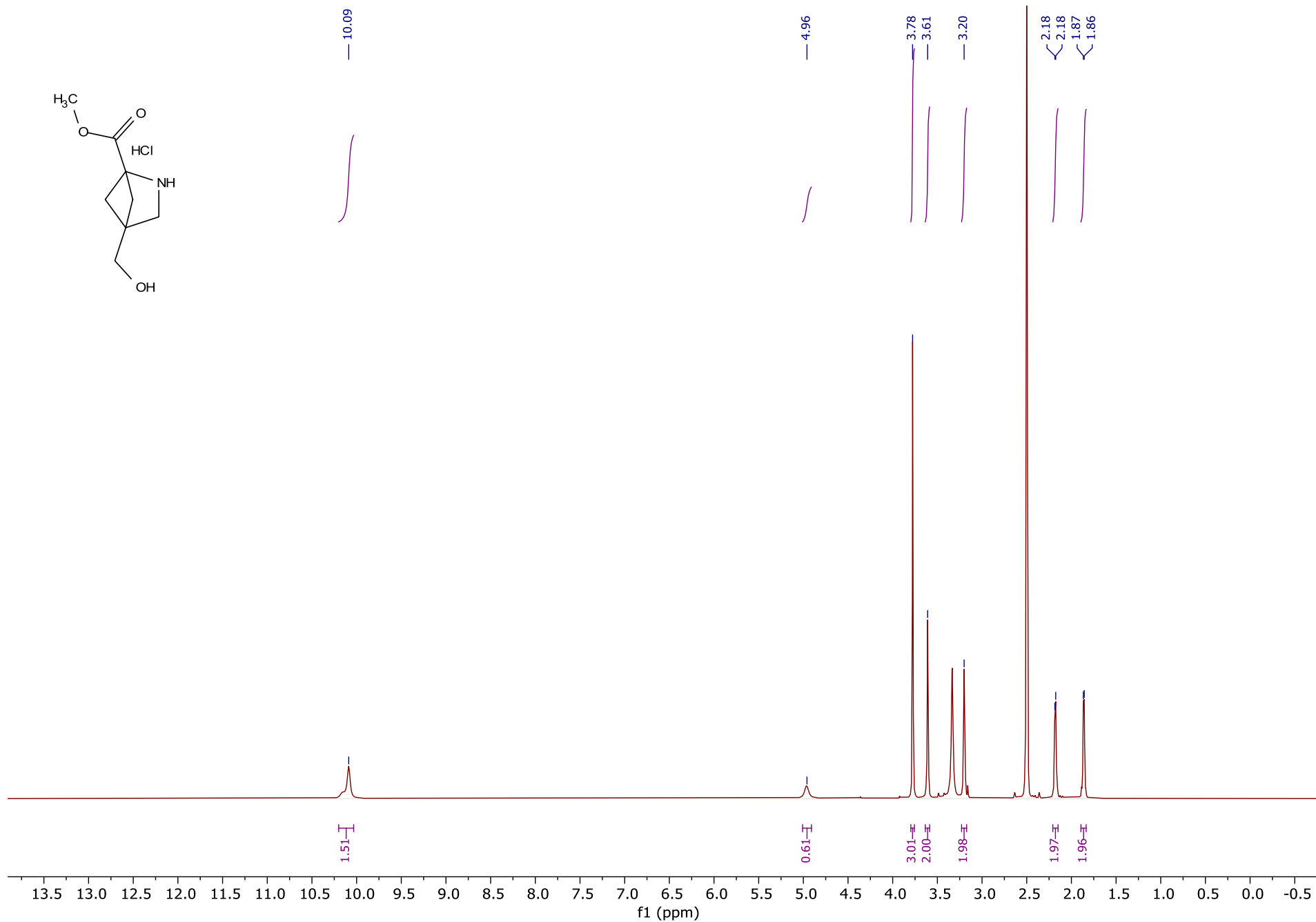


Figure 10. Methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **17**, <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>).

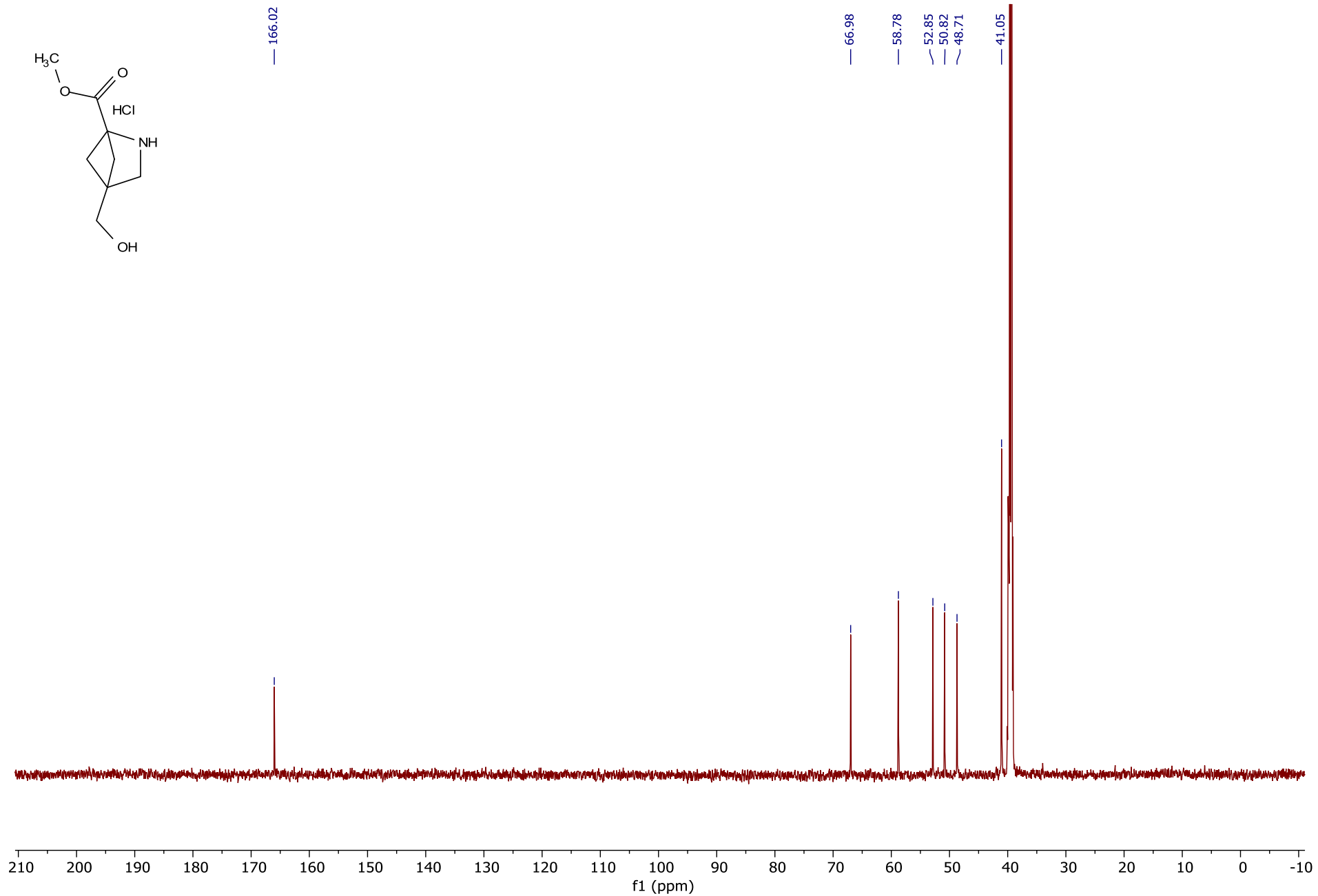


Figure 11. Methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **17**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{DMSO}-d_6$ ).

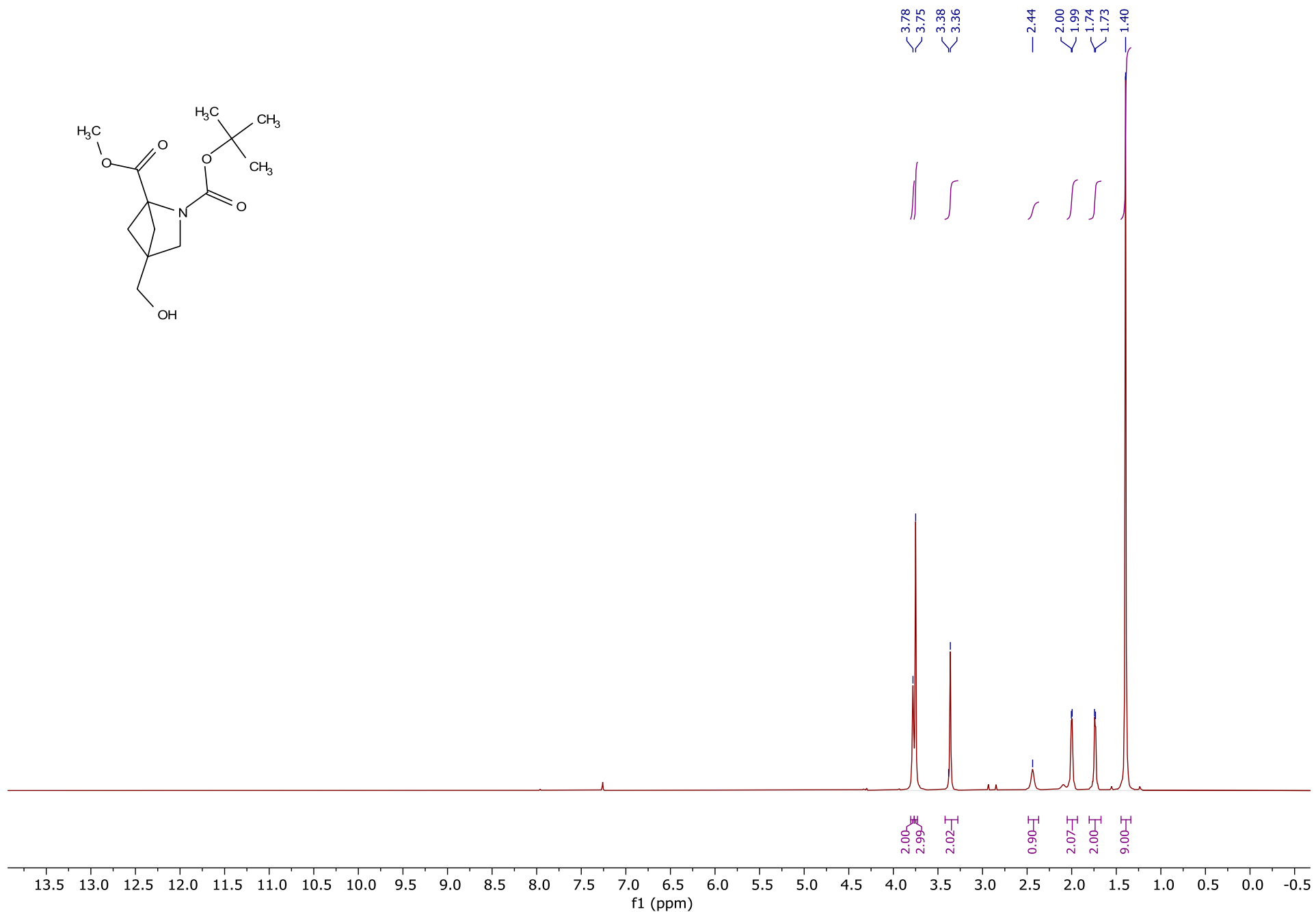


Figure 12. 2-(*tert*-Butyl) 1-methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **18**,  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ).



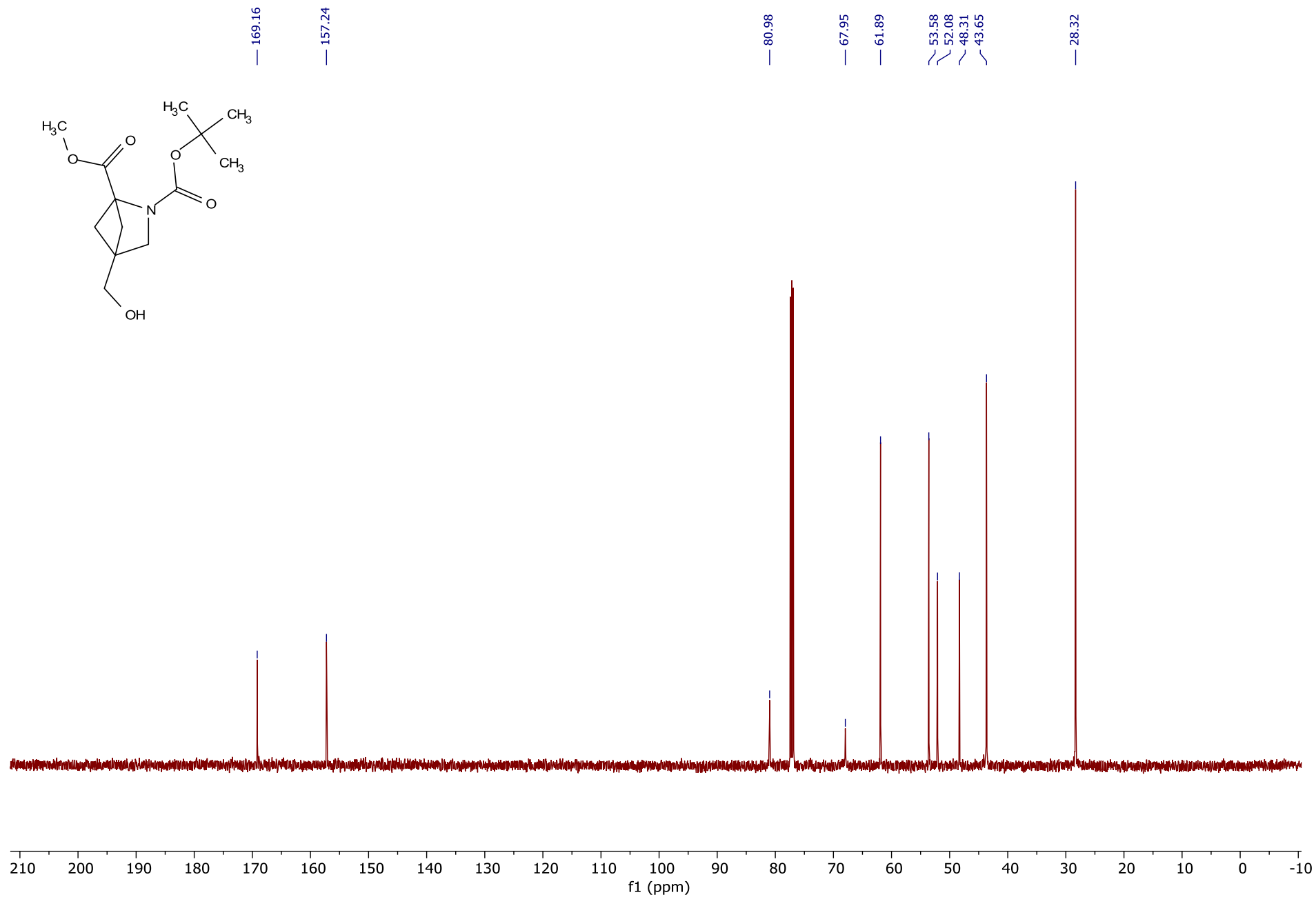


Figure 13. 2-(*tert*-Butyl) 1-methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **18**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ ).

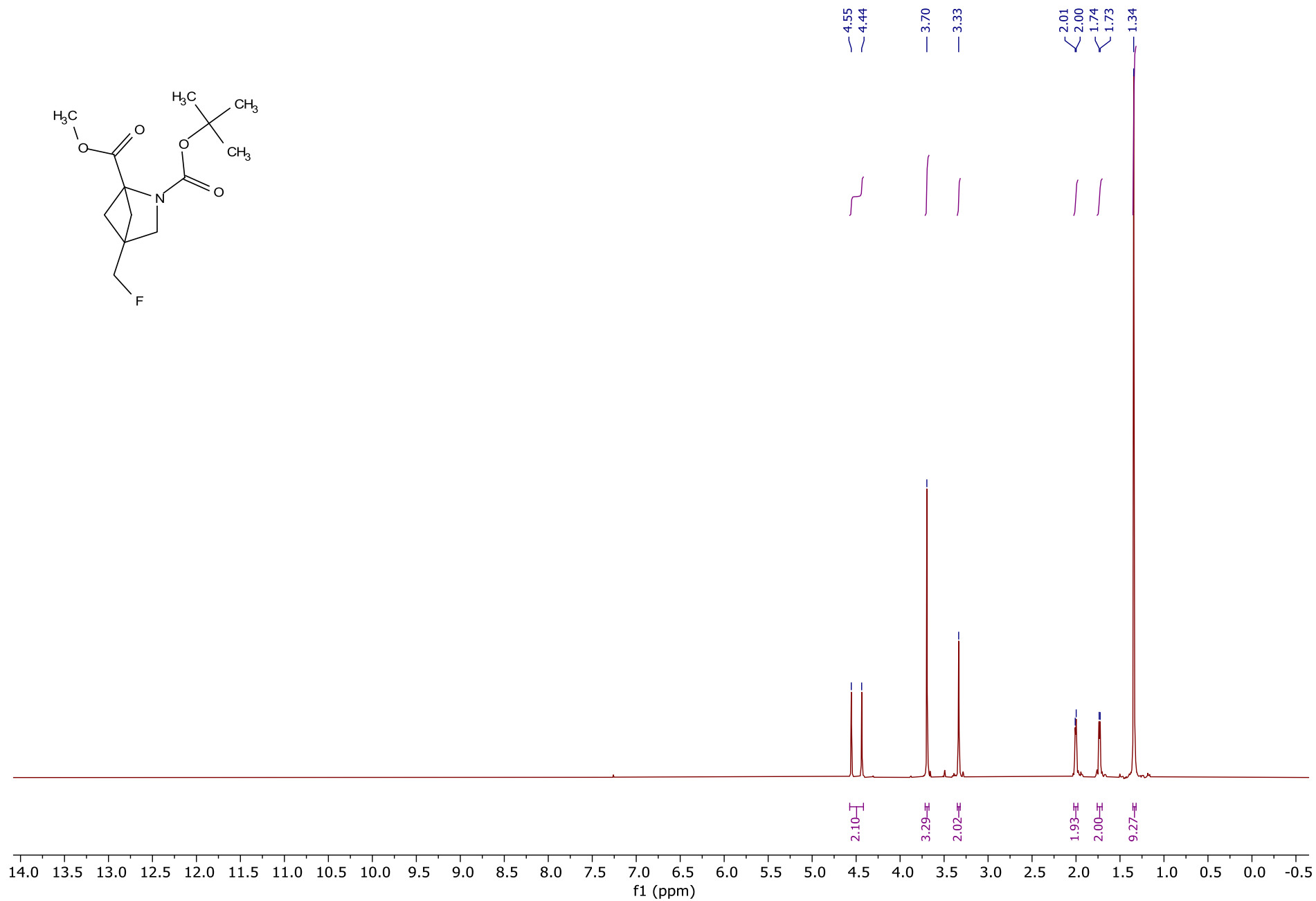


Figure 14. 2-(*tert*-Butyl) 1-methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **19**, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

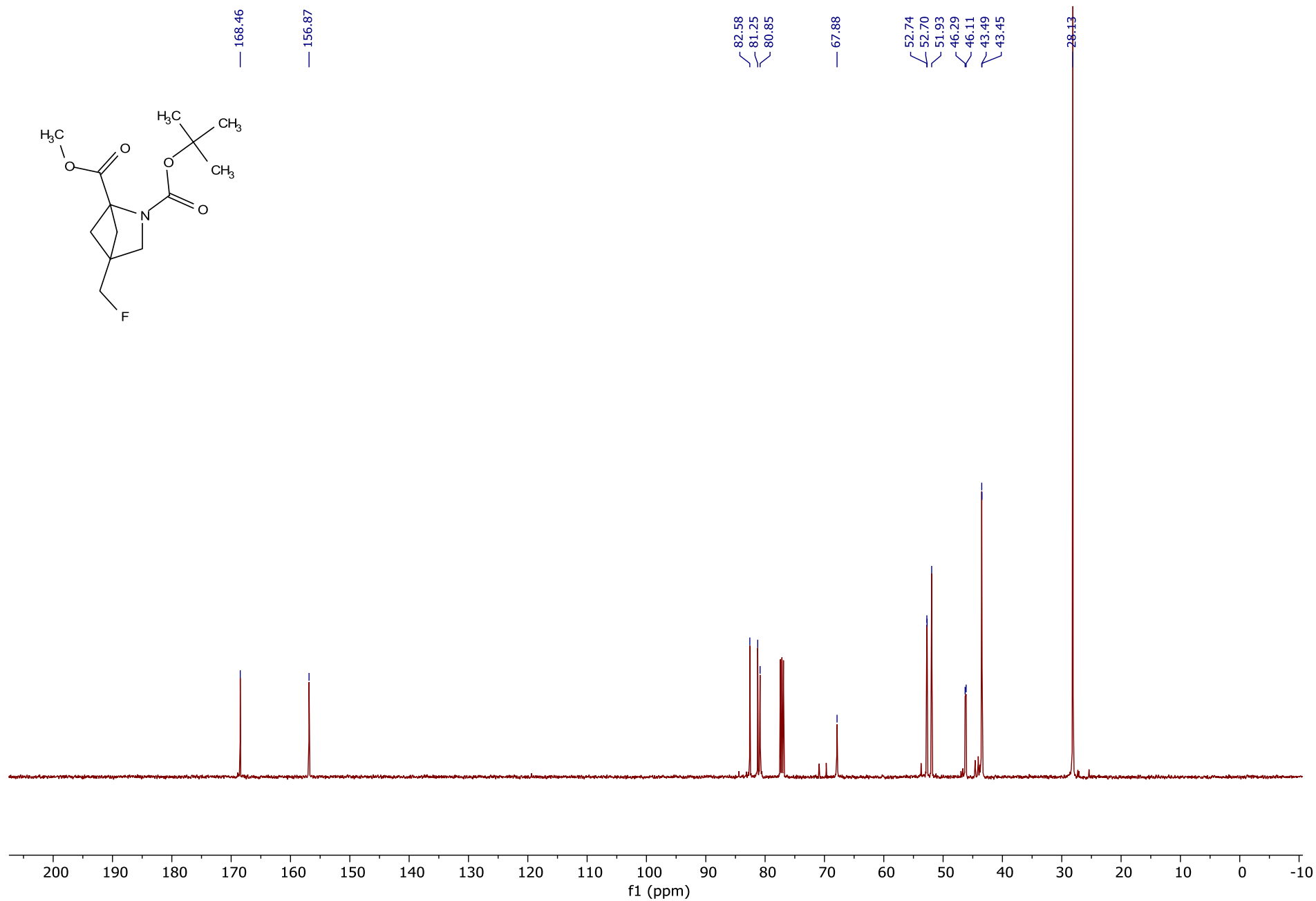


Figure 15. 2-(*tert*-Butyl) 1-methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **19**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ ).

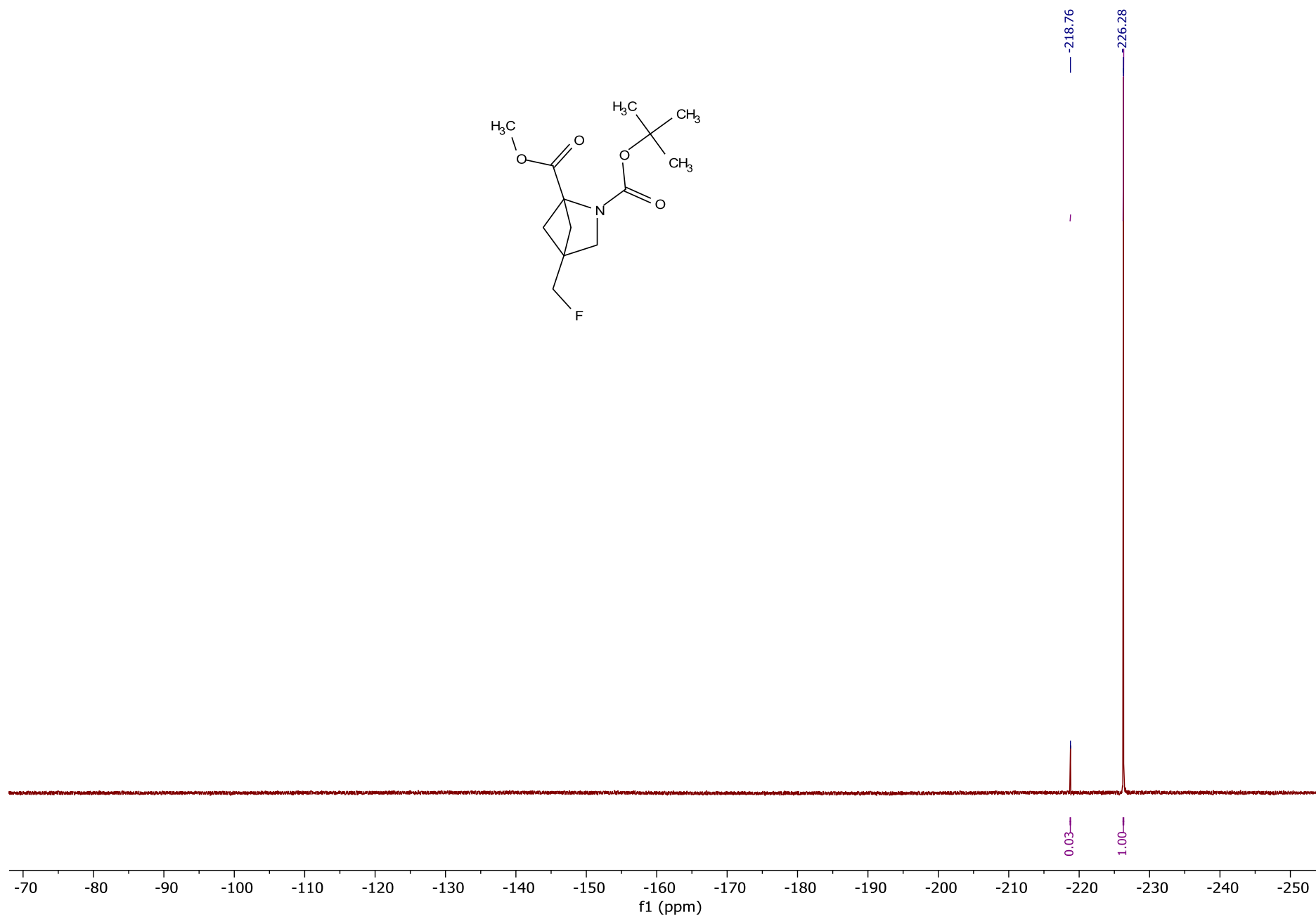


Figure 16. 2-(*tert*-Butyl) 1-methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **19**,  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{DMSO-}d_6$ ).

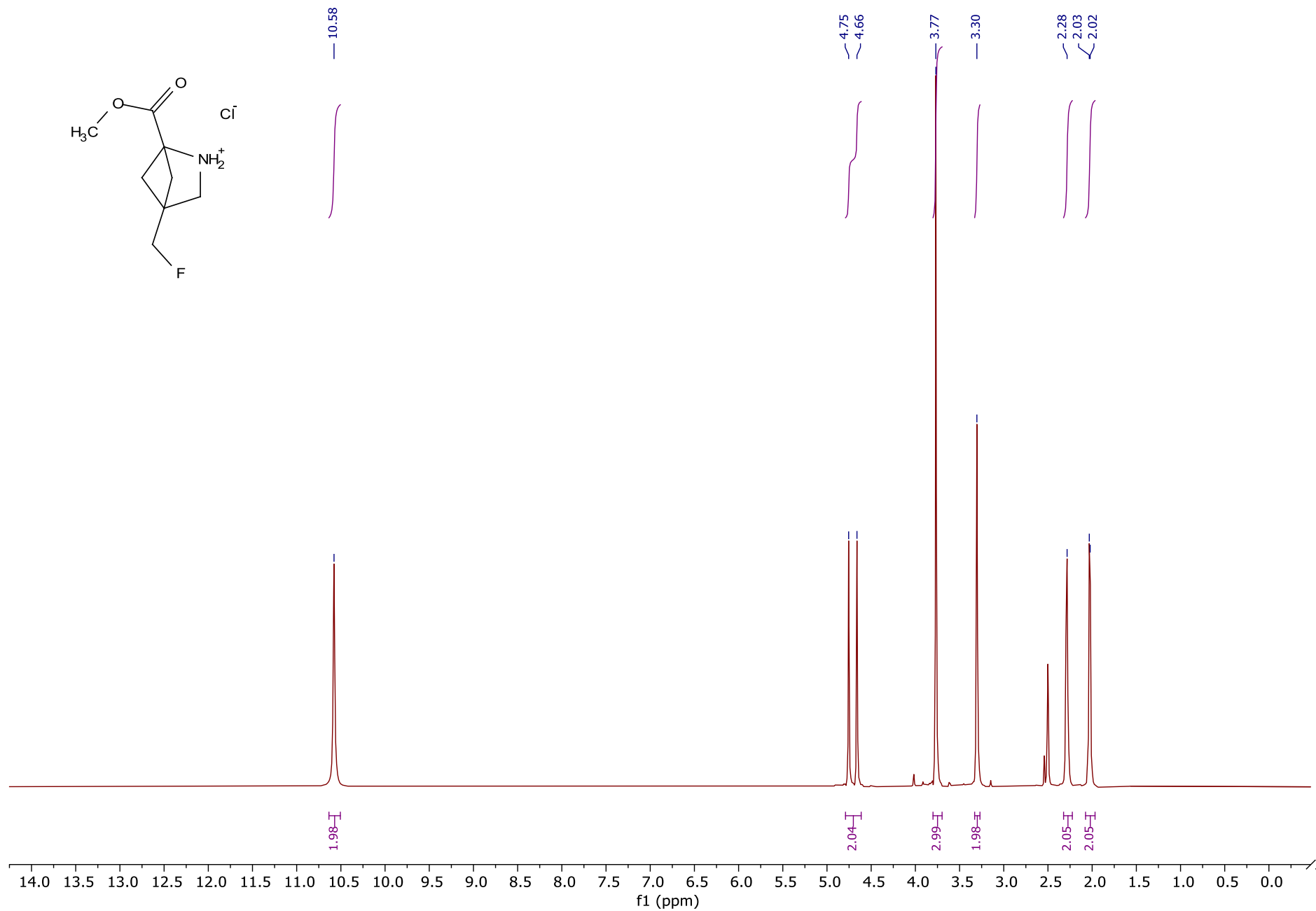


Figure 17. Methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **20**, <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>).

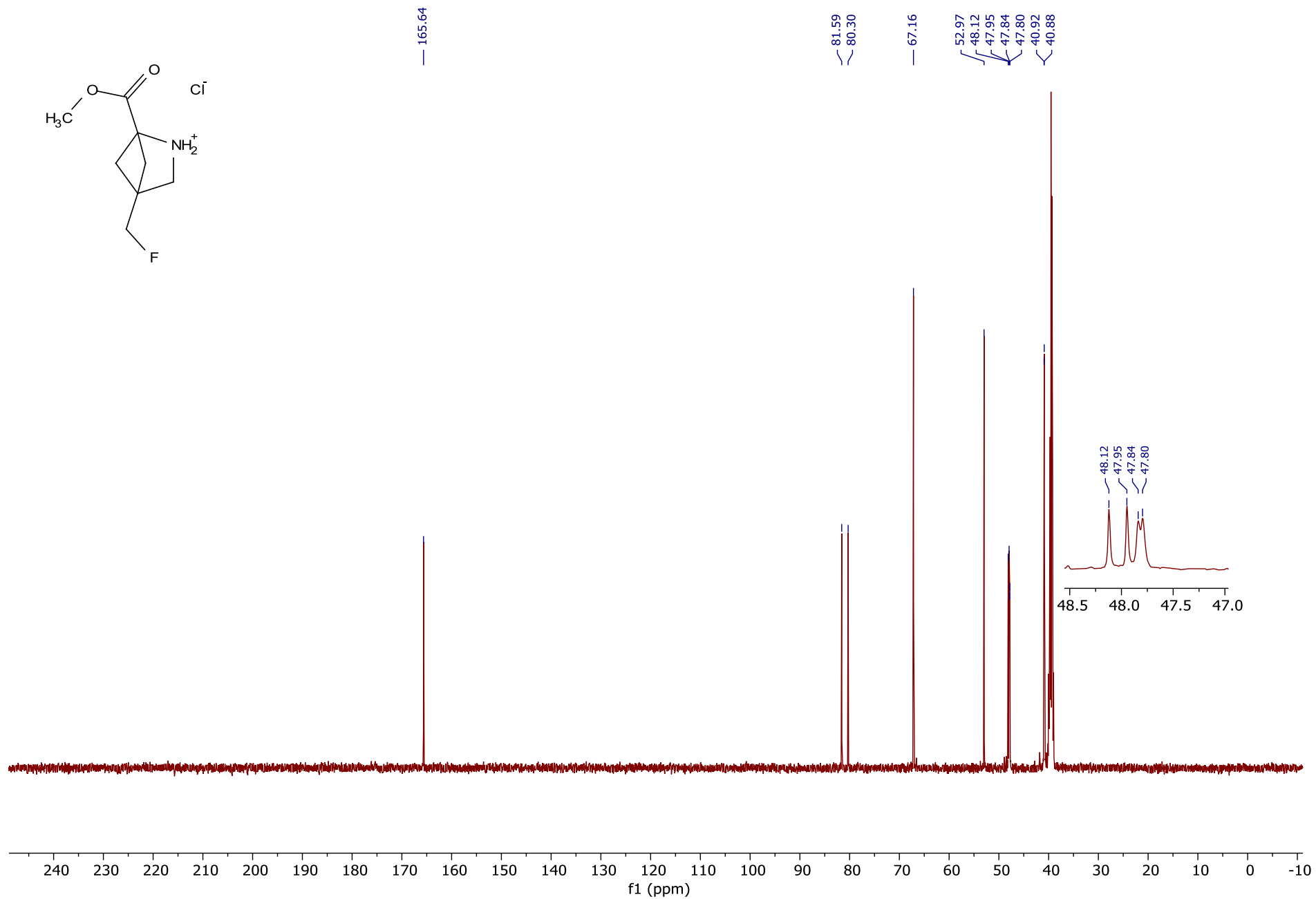


Figure 18. Methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **20**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{DMSO-}d_6$ ).

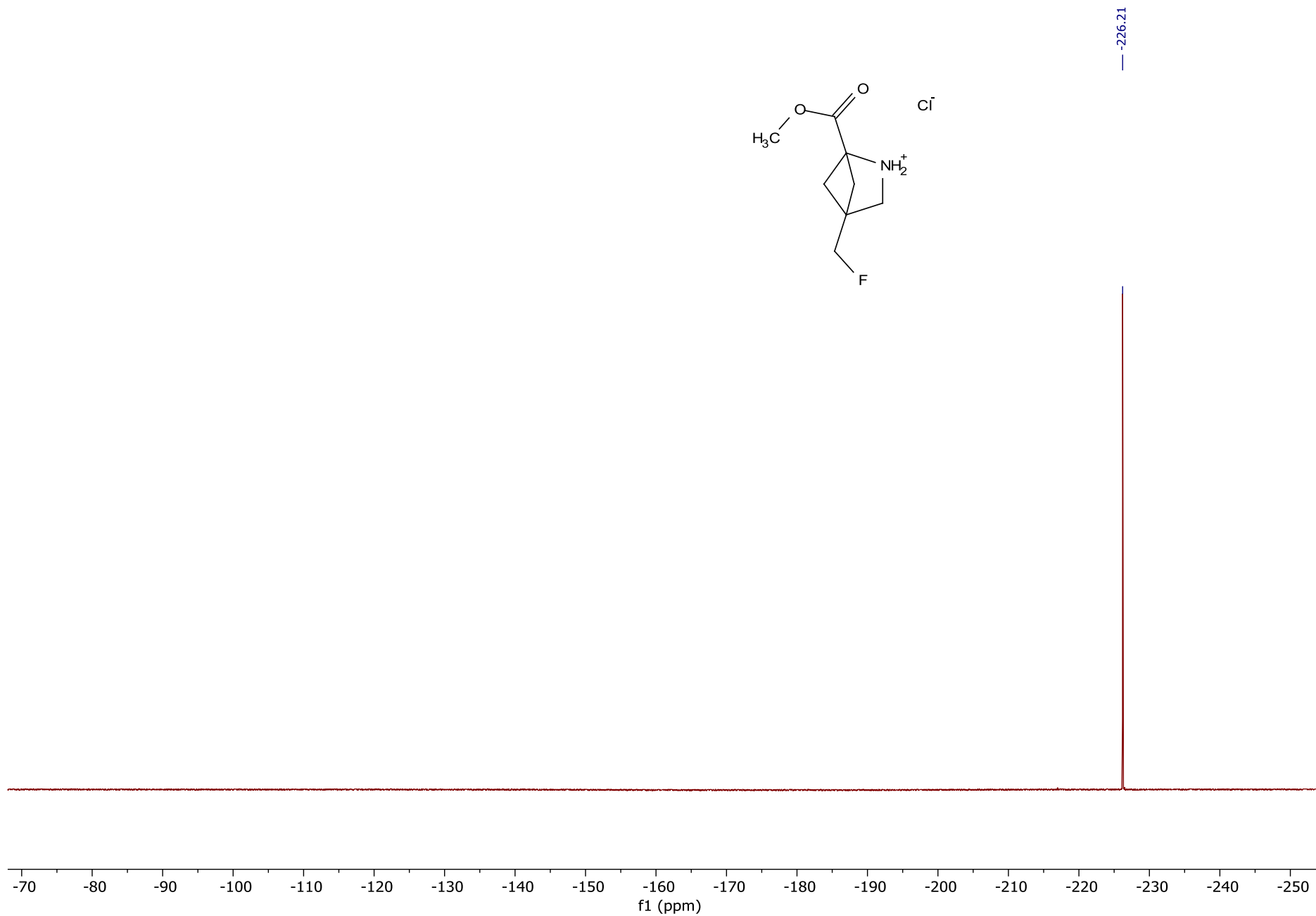


Figure 19. Methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **20**,  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{DMSO-d}_6$ ).

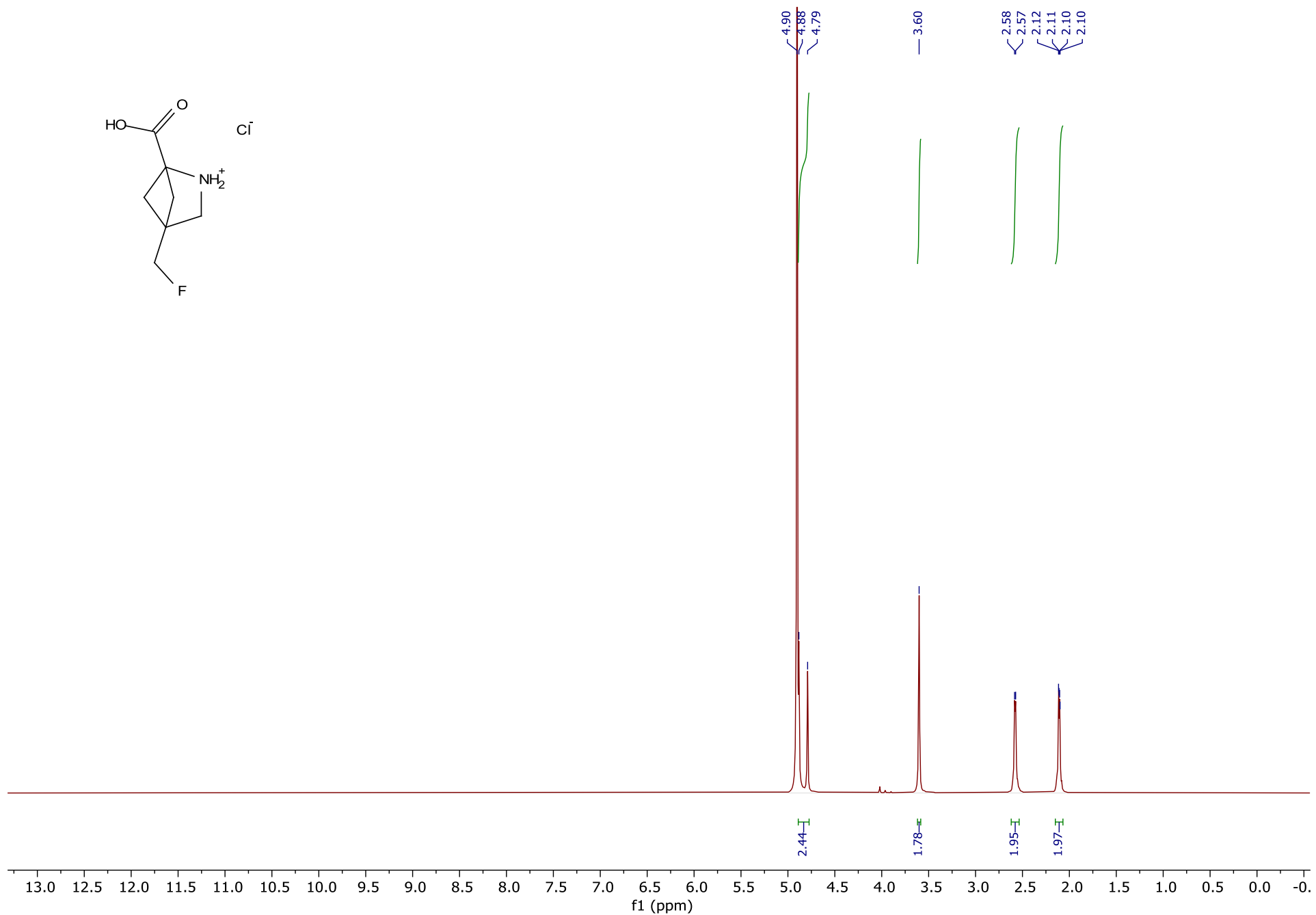


Figure 20. 4-(Fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **21**, <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O).



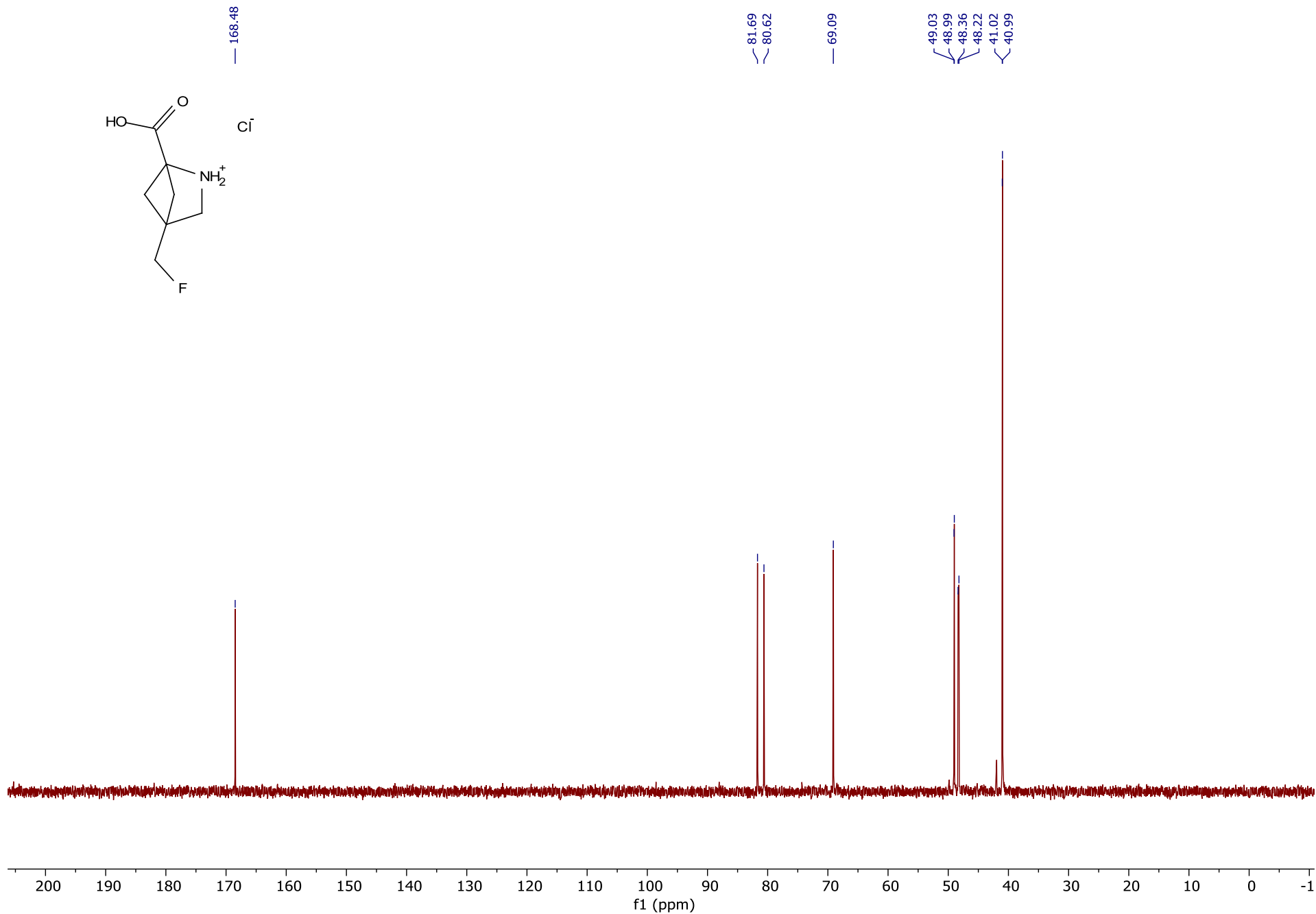


Figure 21. 4-(Fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **21**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{DMSO-}d_6$ ).

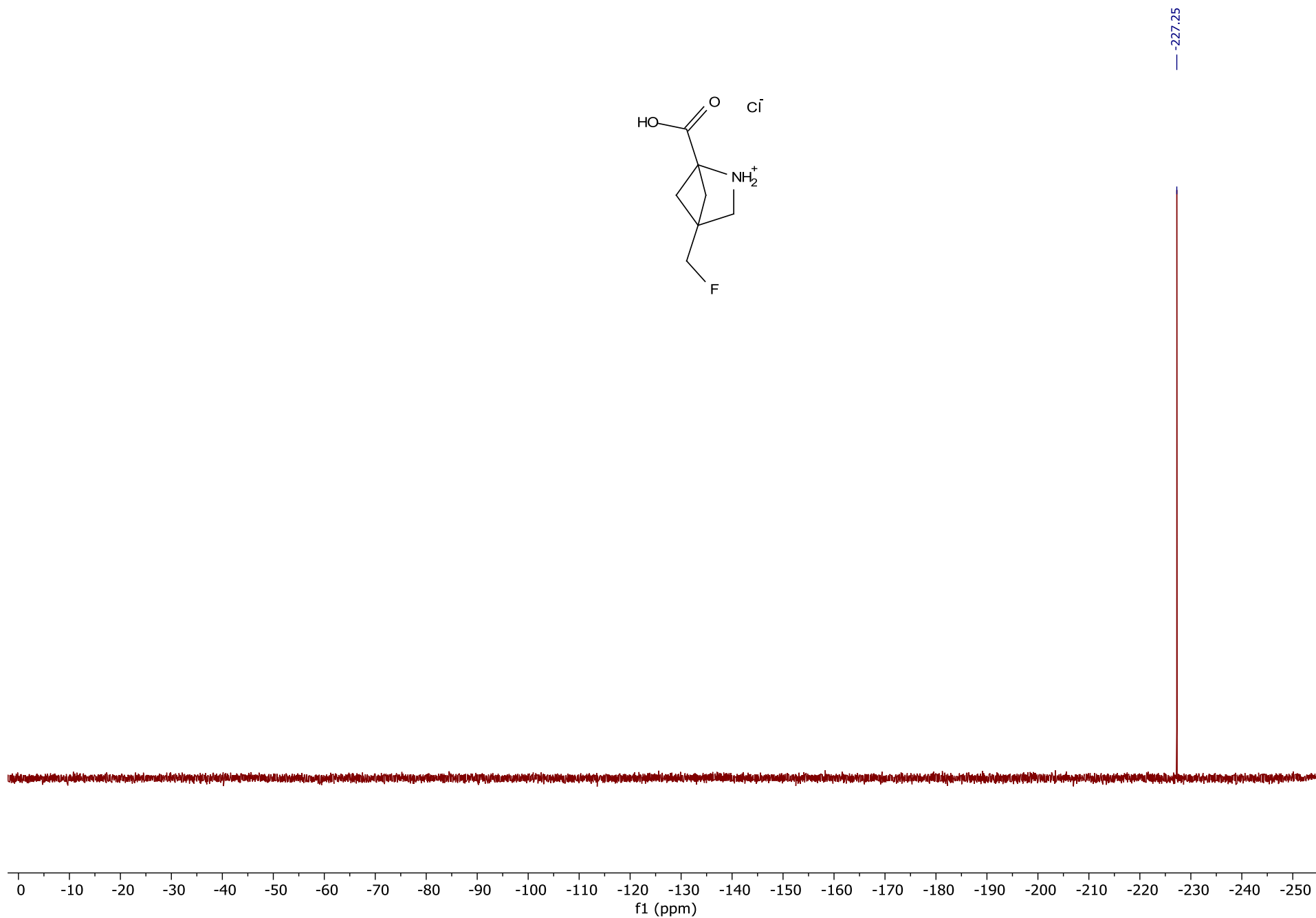


Figure 22. 4-(Fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **21**,  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{DMSO-}d_6$ ).

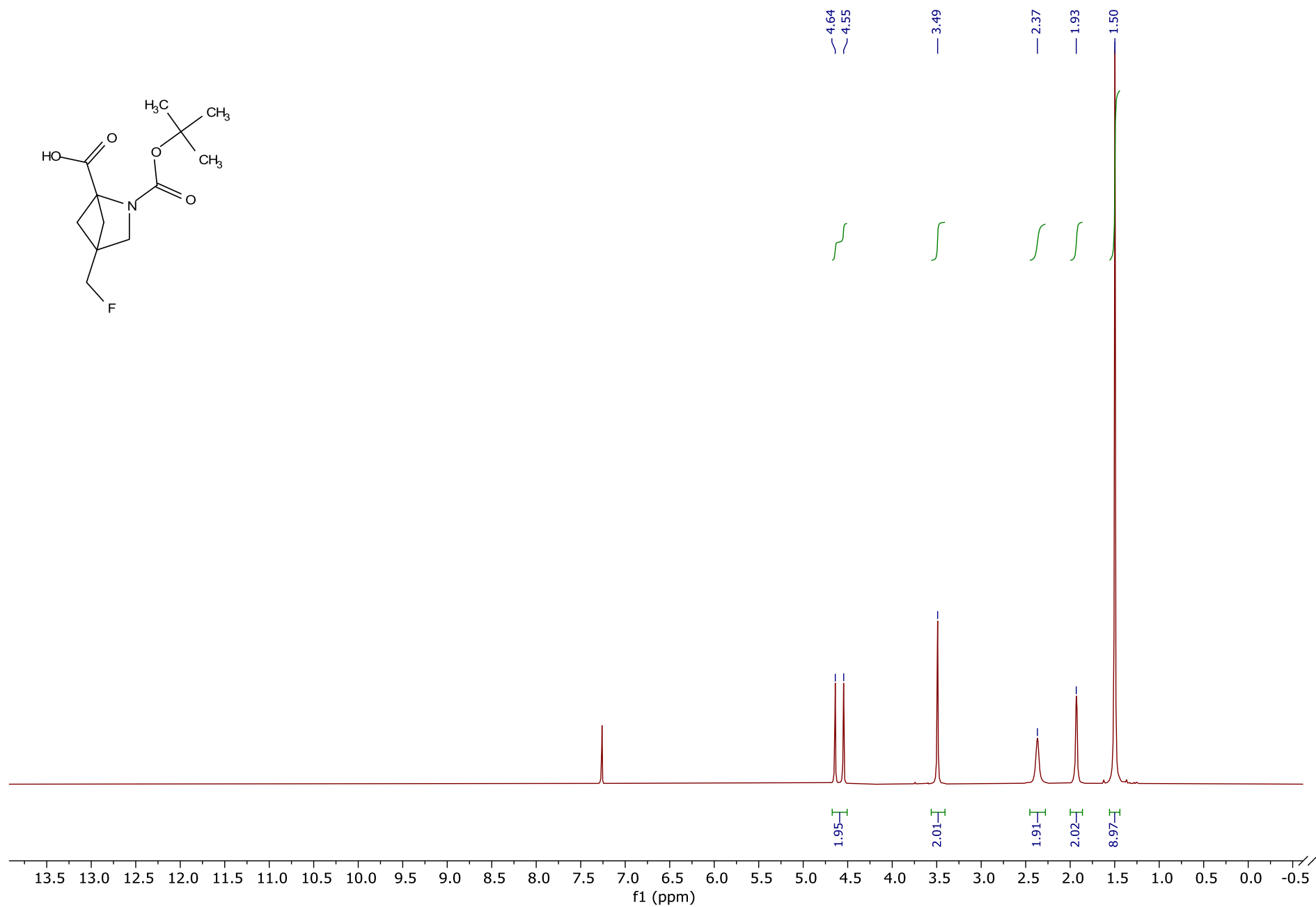


Figure 23. 2-(*tert*-Butoxycarbonyl)-4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **22**, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>).

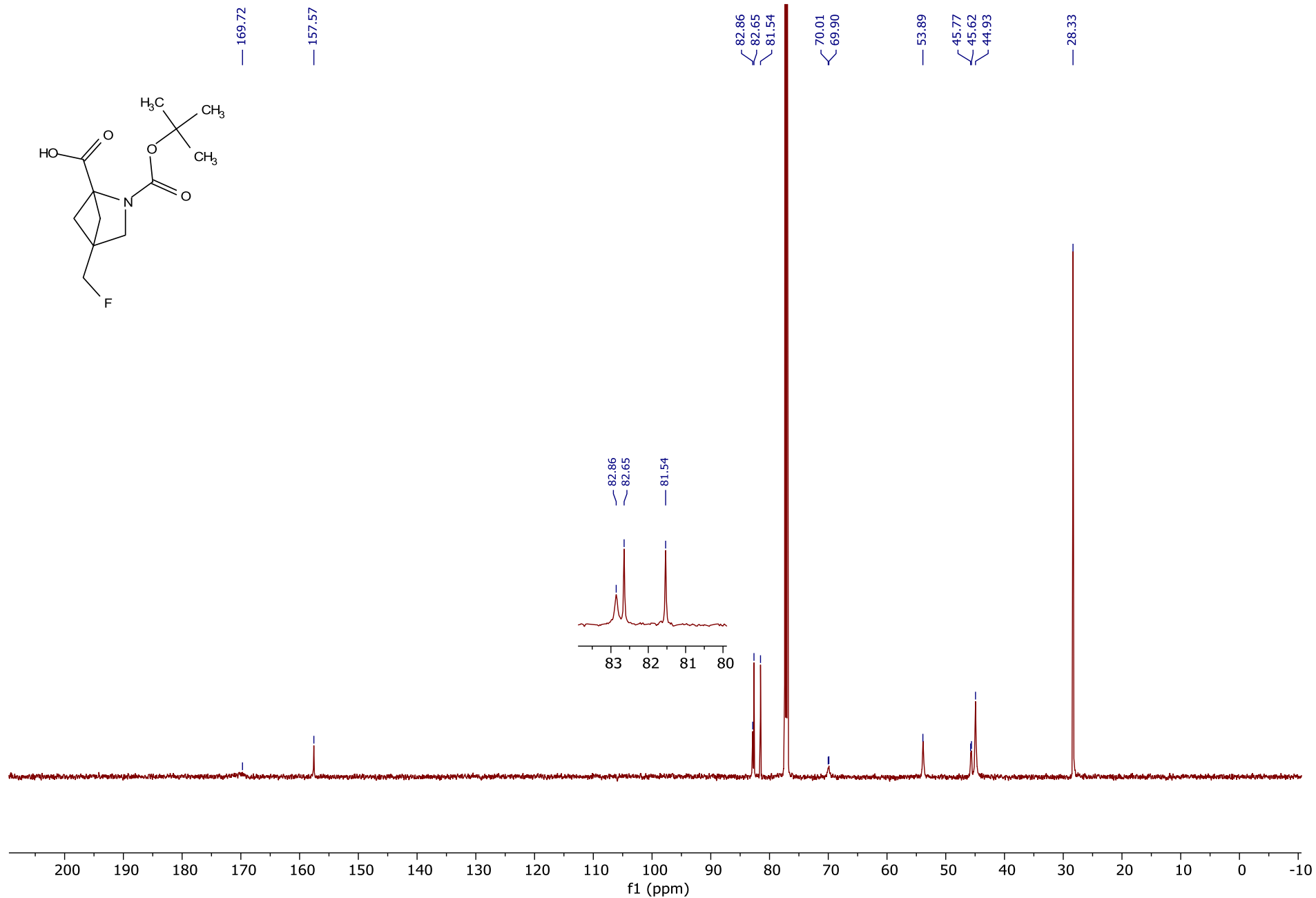


Figure 24. 2-(*tert*-Butoxycarbonyl)-4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **22**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{CDCl}_3$ ).

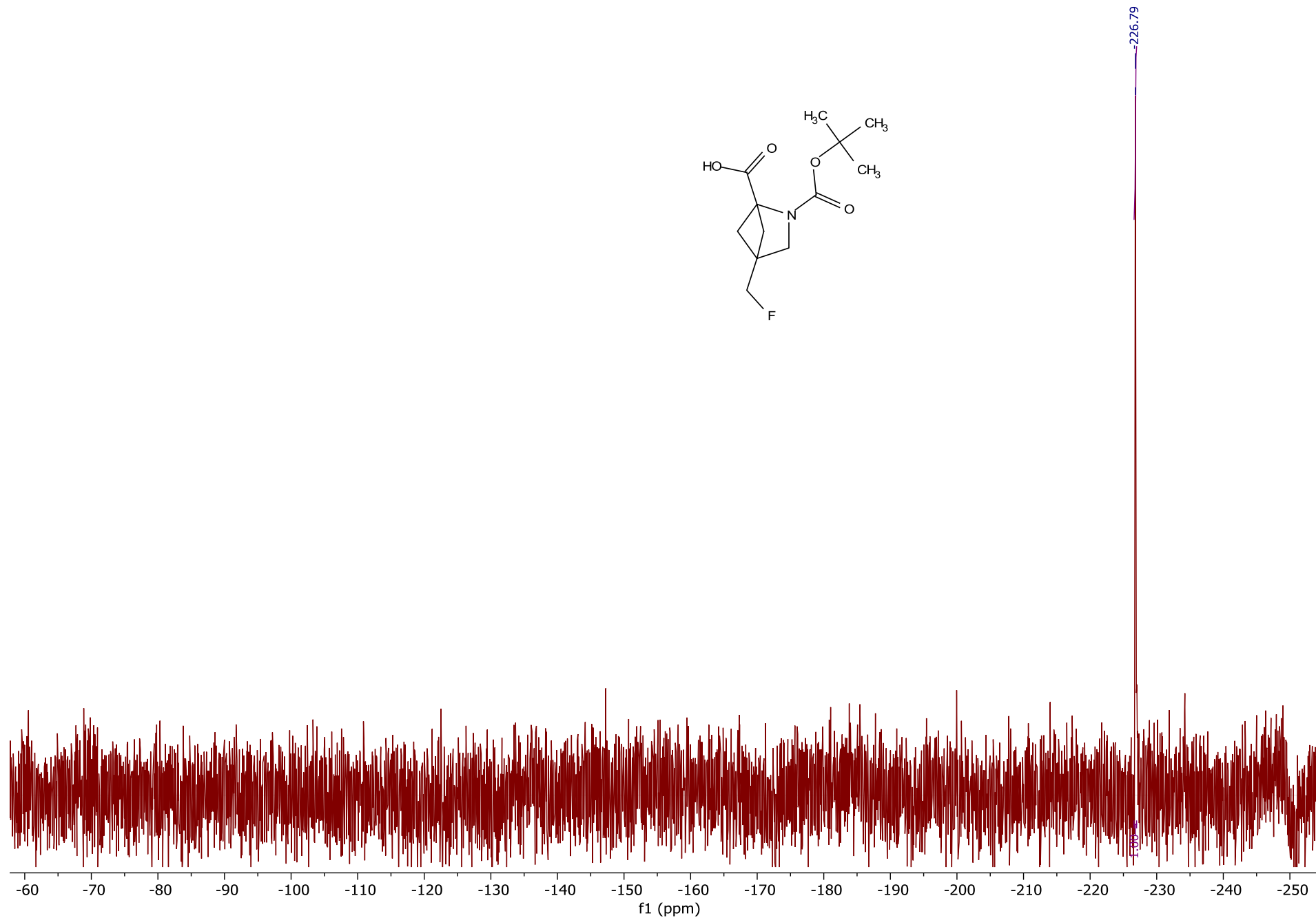
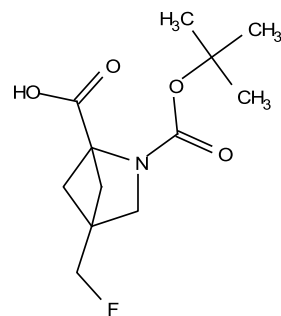


Figure 25. 2-(*tert*-Butoxycarbonyl)-4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **22**,  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ ).

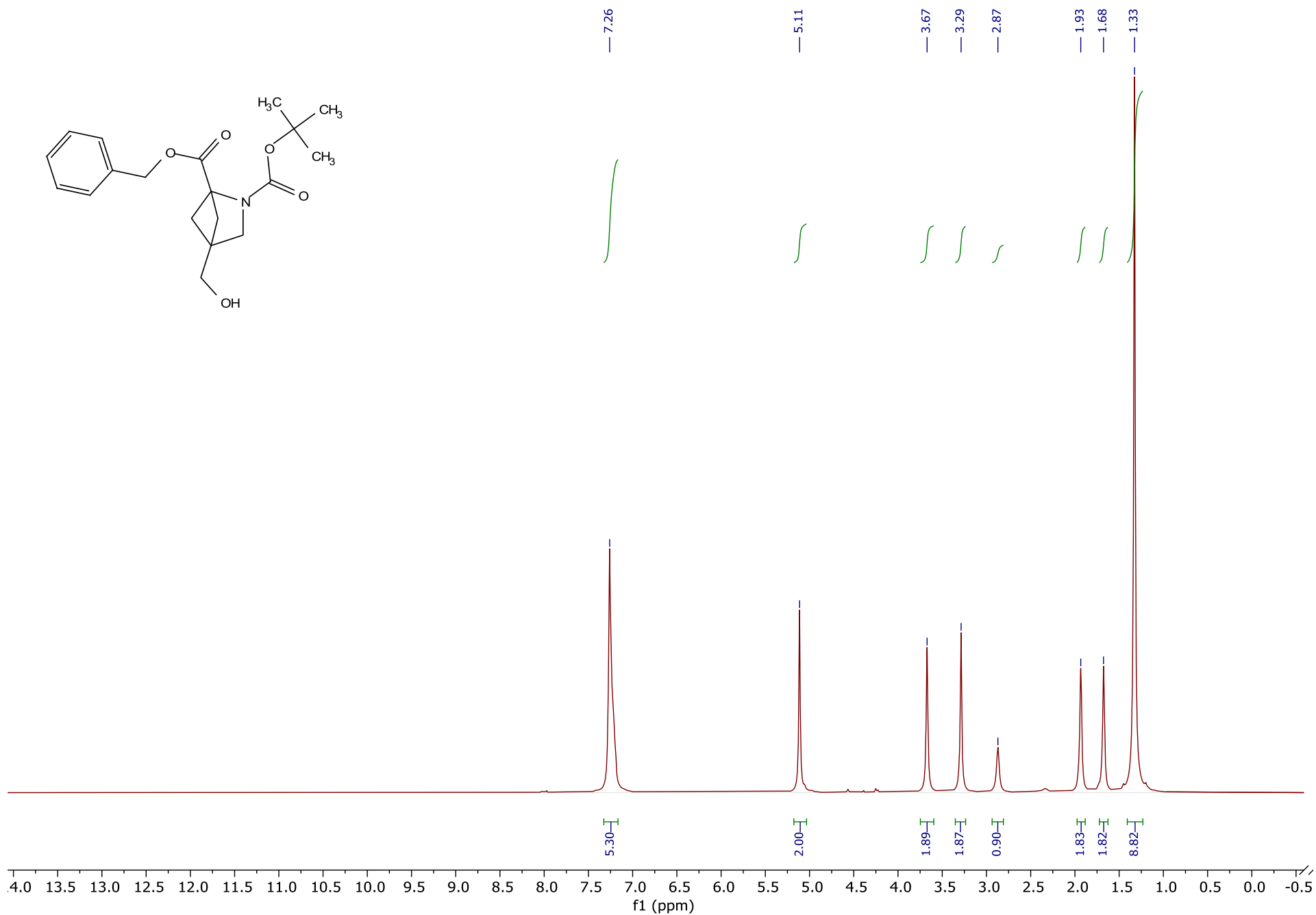


Figure 26. 1-Benzyl 2-(*tert*-butyl) 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **23**, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>).

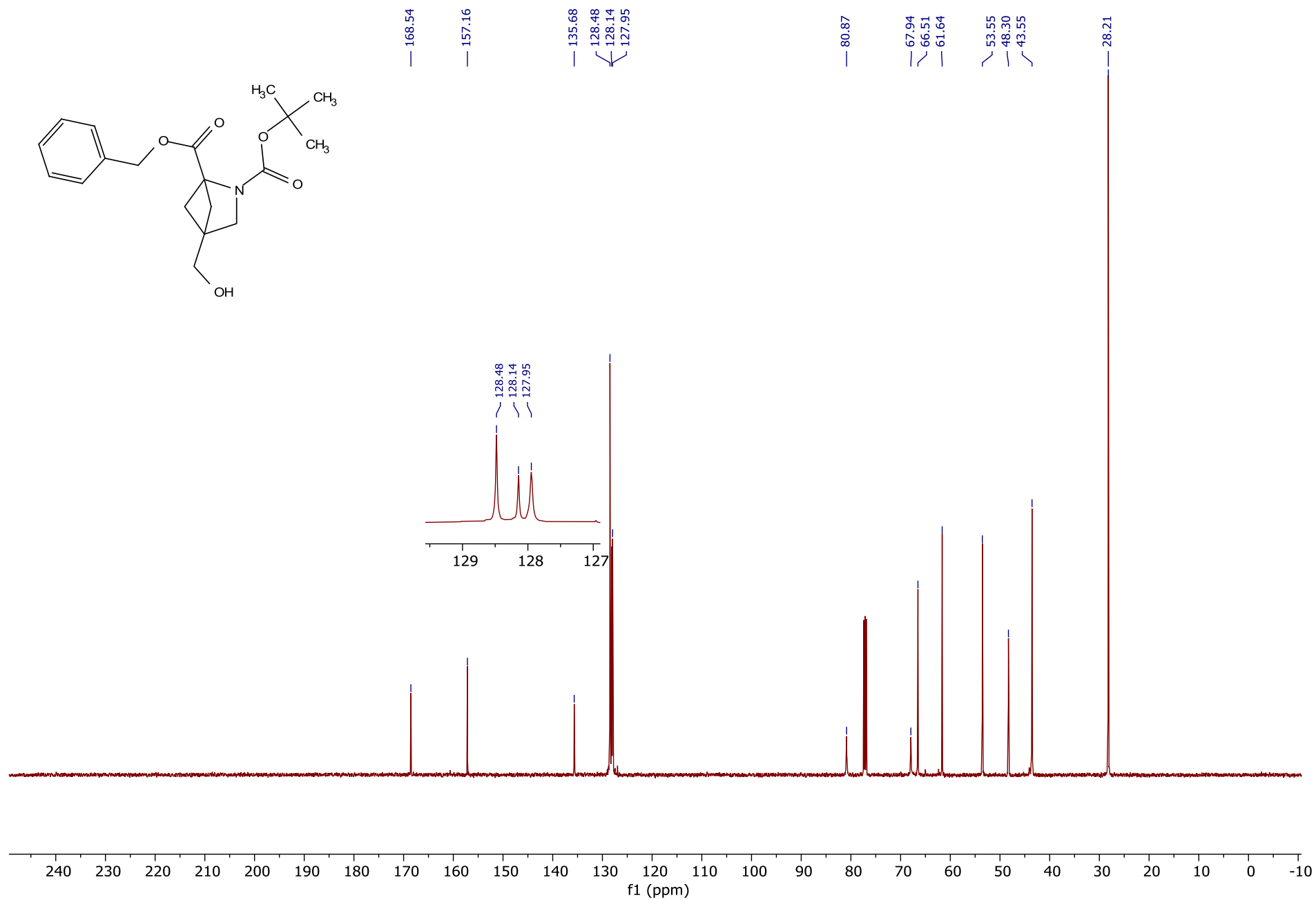


Figure 27. 1-Benzyl 2-(*tert*-butyl) 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **23**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ ).

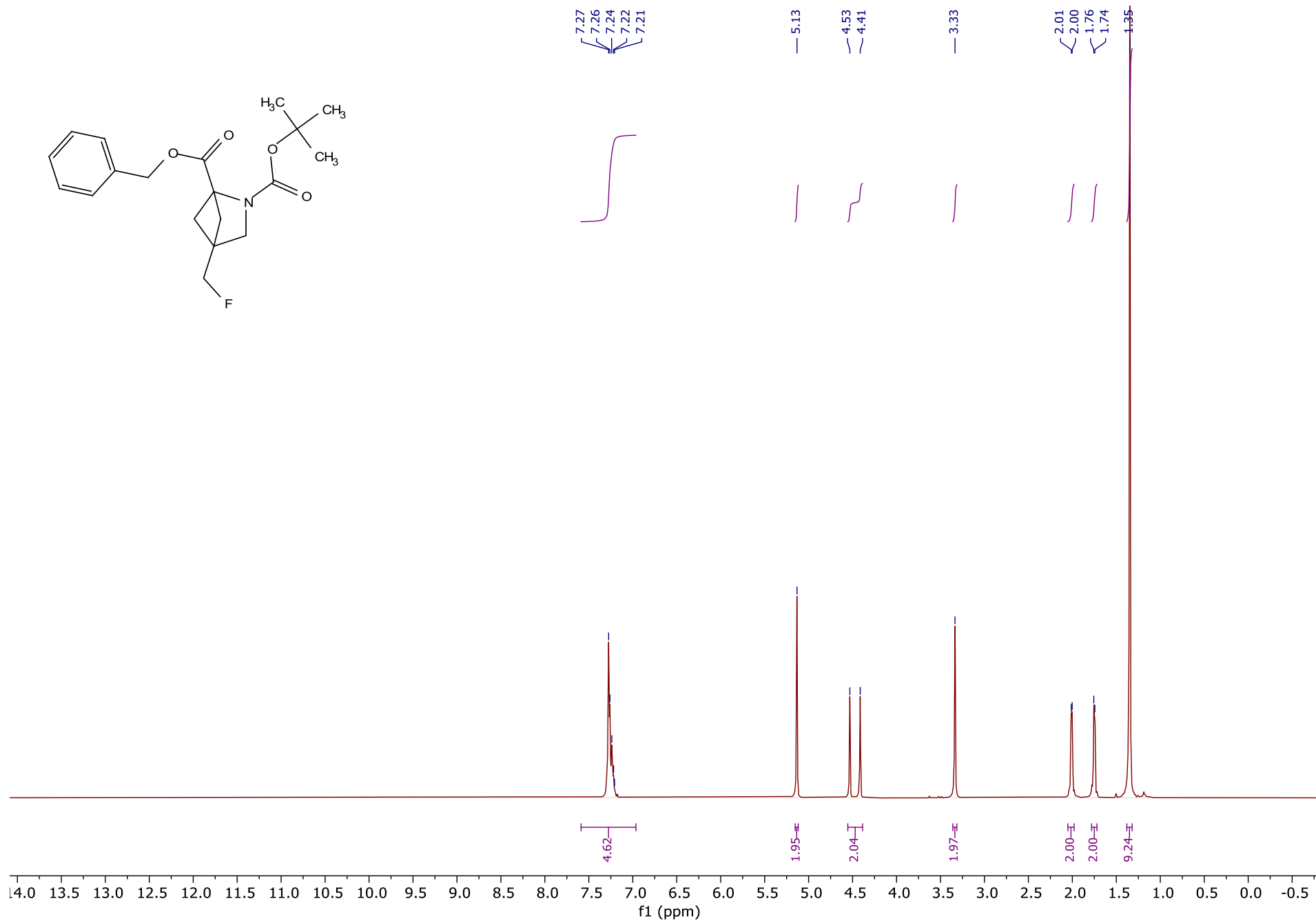


Figure 28. 1-Benzyl 2-(*tert*-butyl) 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **24**,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ).



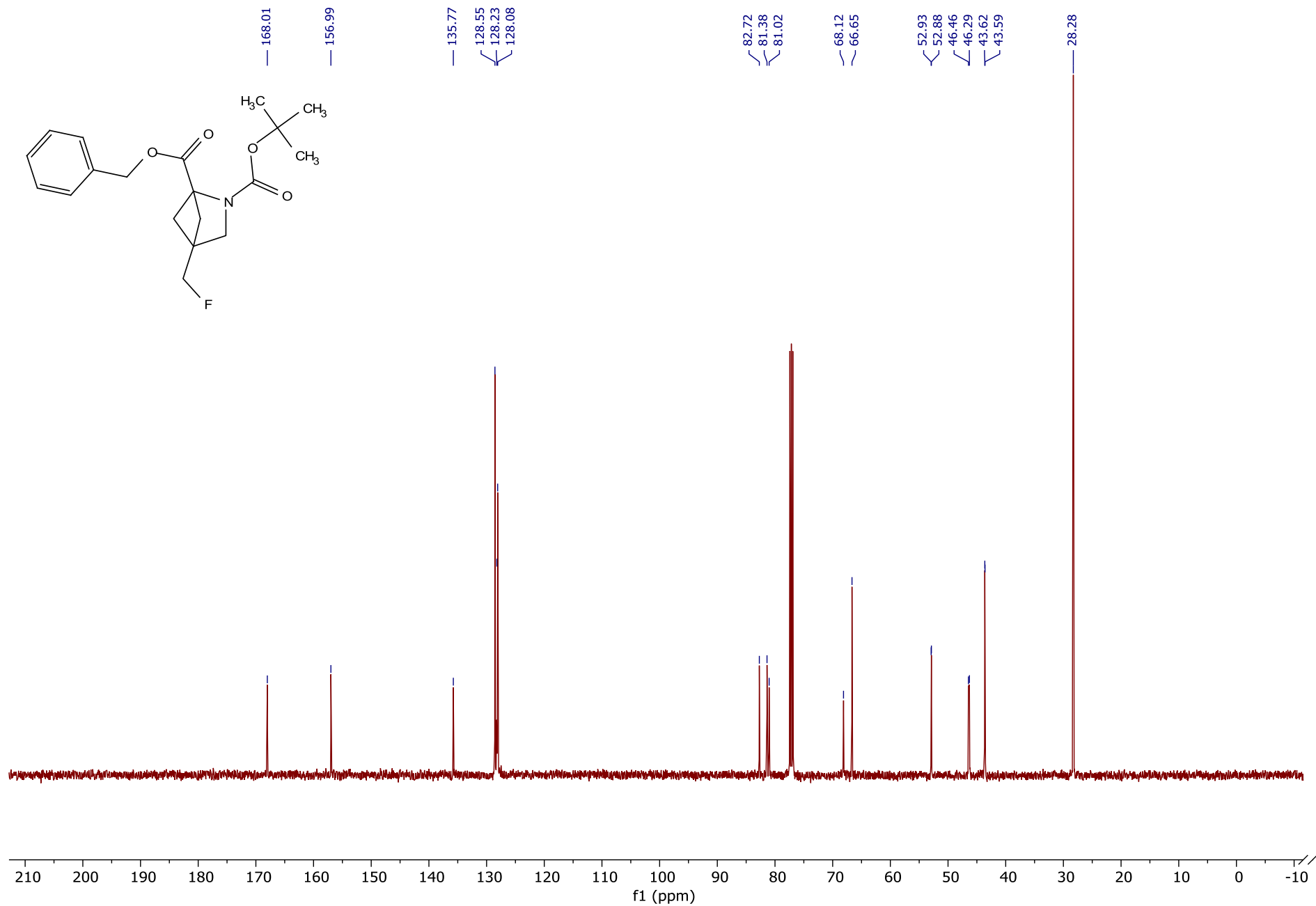


Figure 29. 1-Benzyl 2-(*tert*-butyl) 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **24**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ ).

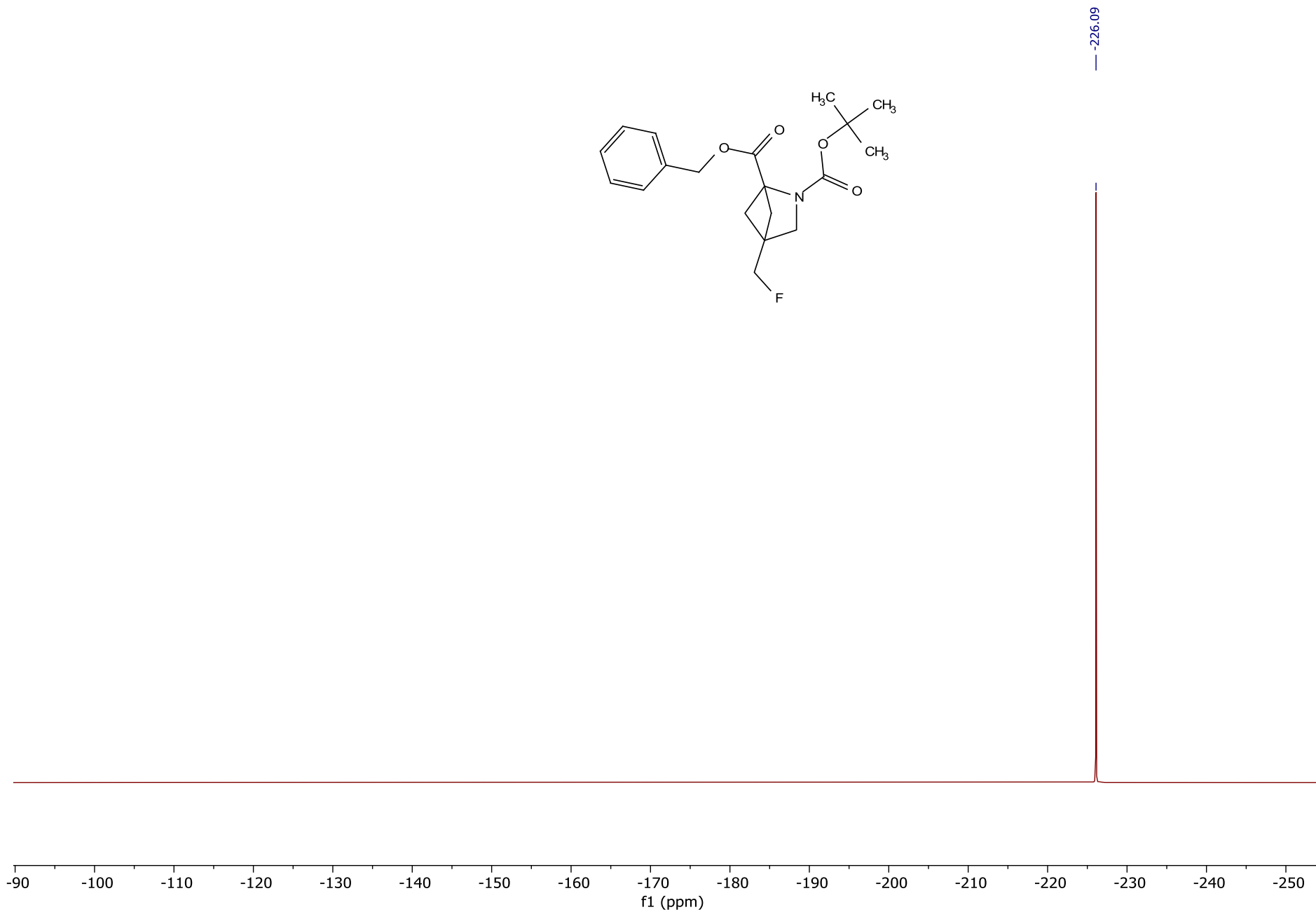


Figure 30. 1-Benzyl 2-(*tert*-butyl) 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **24**,  $^{19}\text{F}\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ ).

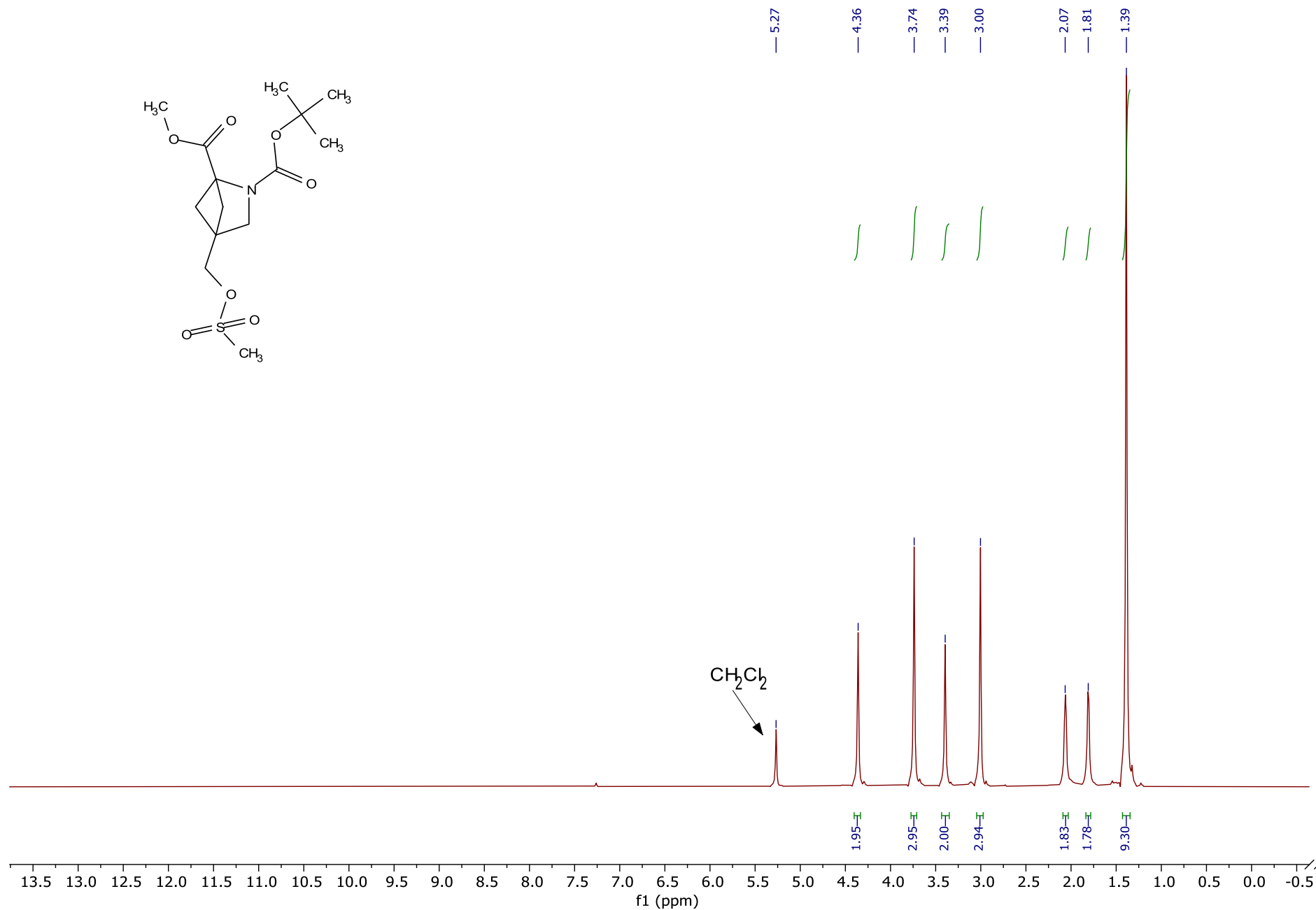


Figure 31. 2-(*tert*-Butyl) 1-methyl 4-(((methylsulfonyl)oxy)methyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **25**, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

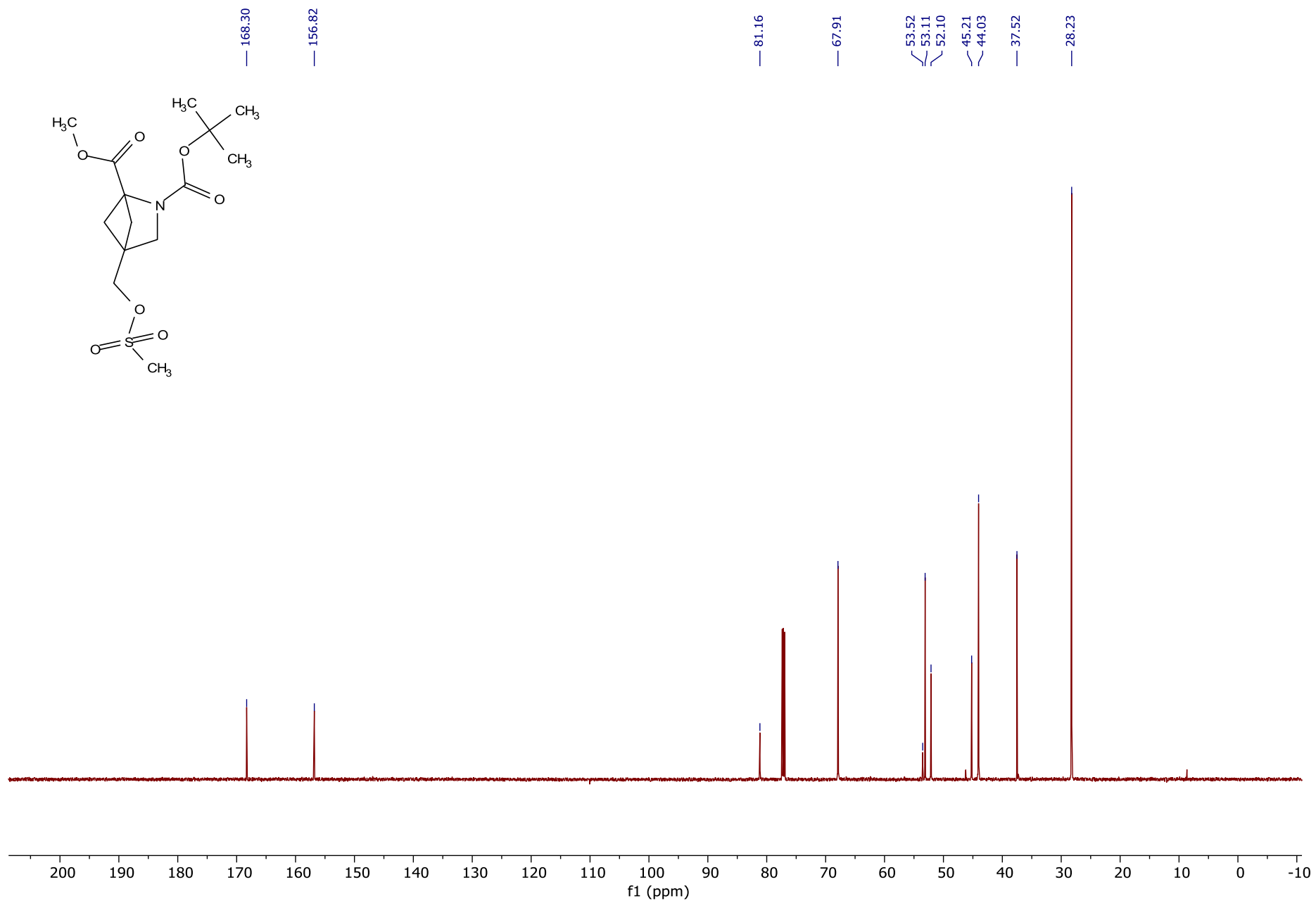


Figure 32. 2-(*tert*-Butyl) 1-methyl 4-(((methylsulfonyl)oxy)methyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **25**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{CDCl}_3$ ).

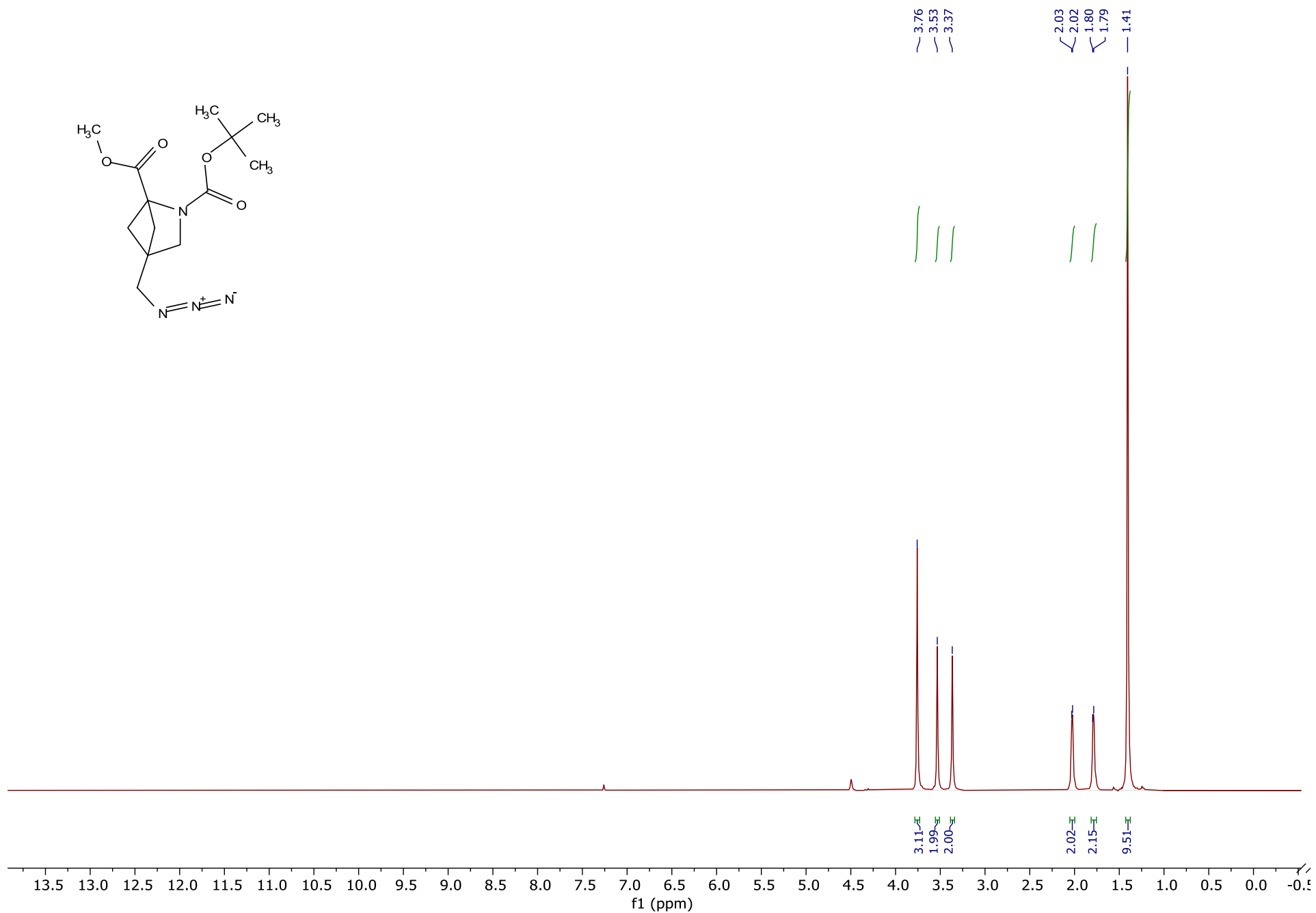


Figure 33. 2-(*tert*-Butyl) 1-methyl 4-(azidomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **26**, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

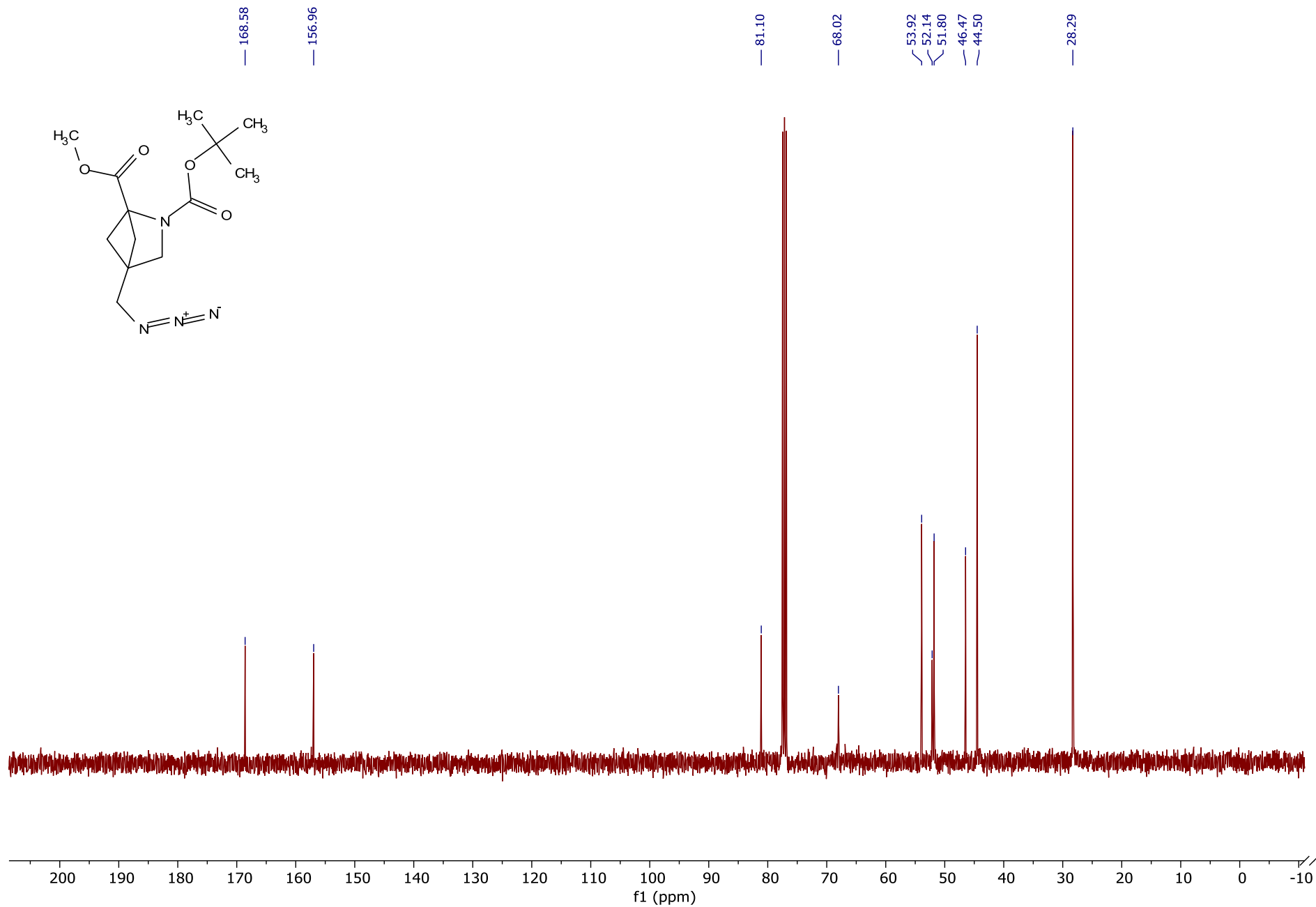


Figure 34. 2-(*tert*-Butyl) 1-methyl 4-(azidomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **26**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ).

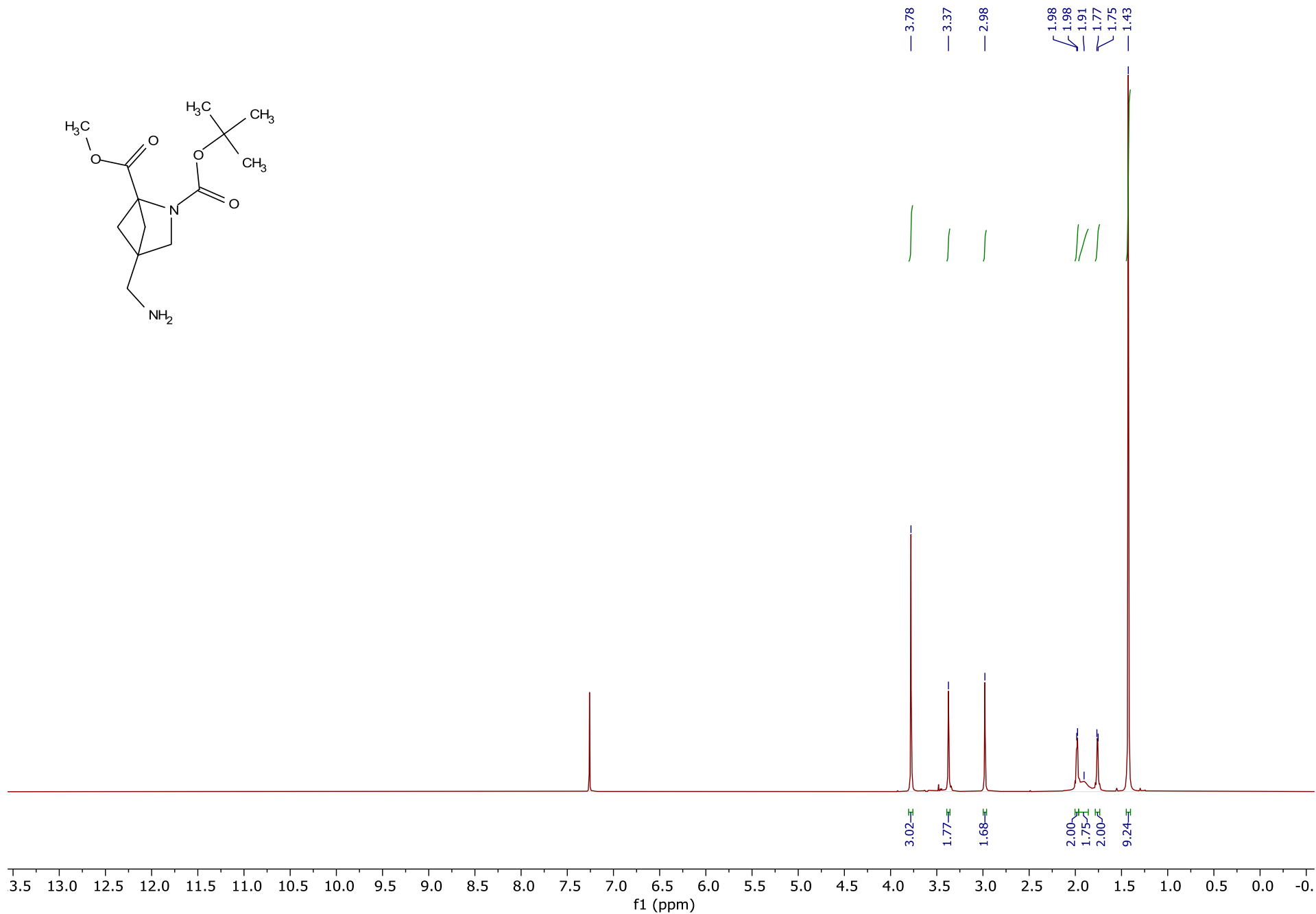


Figure 35. 2-(*tert*-Butyl) 1-methyl 4-(aminomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **27**, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>).

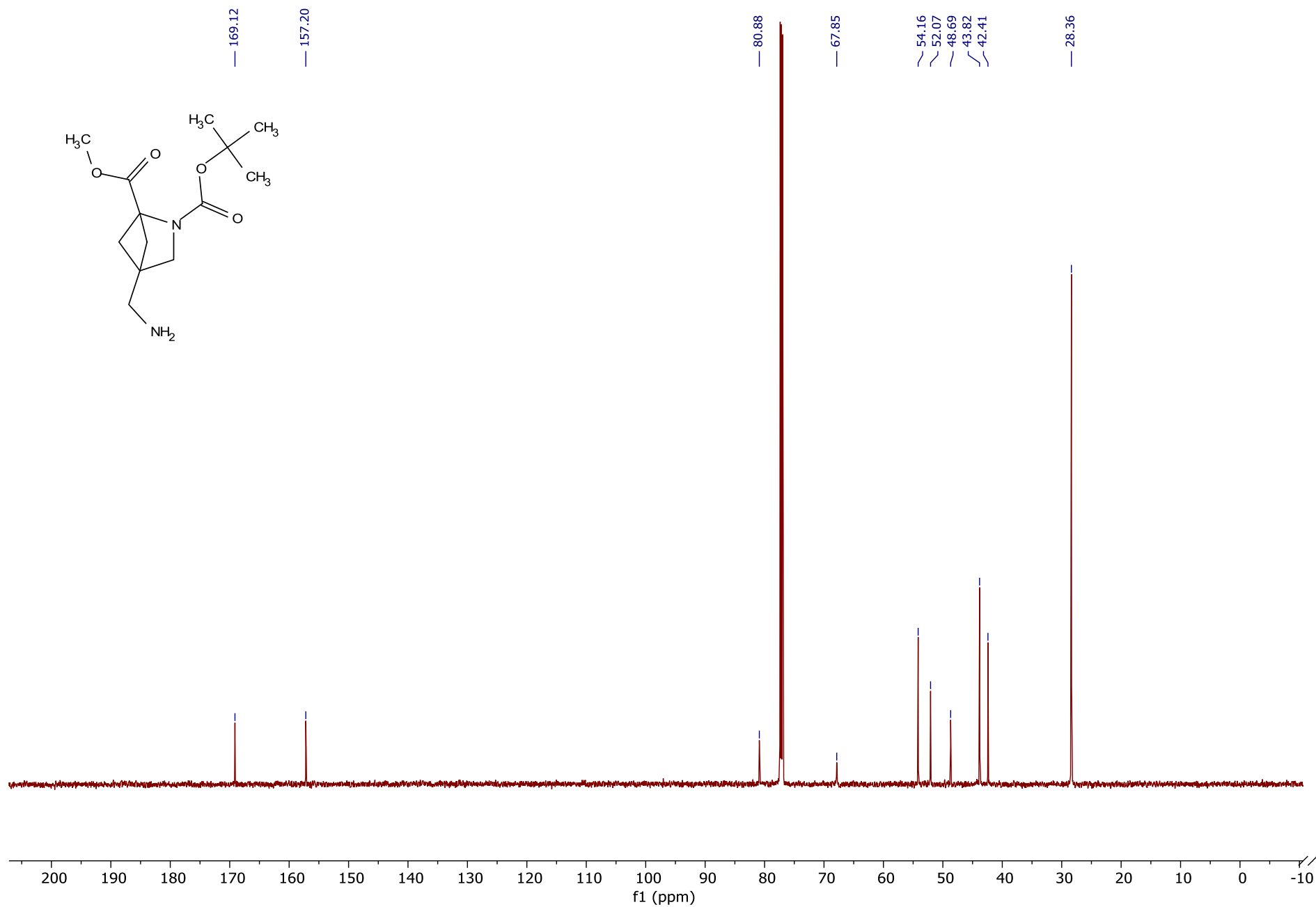


Figure 36. 2-(*tert*-Butyl) 1-methyl 4-(aminomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **27**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{CDCl}_3$ ).



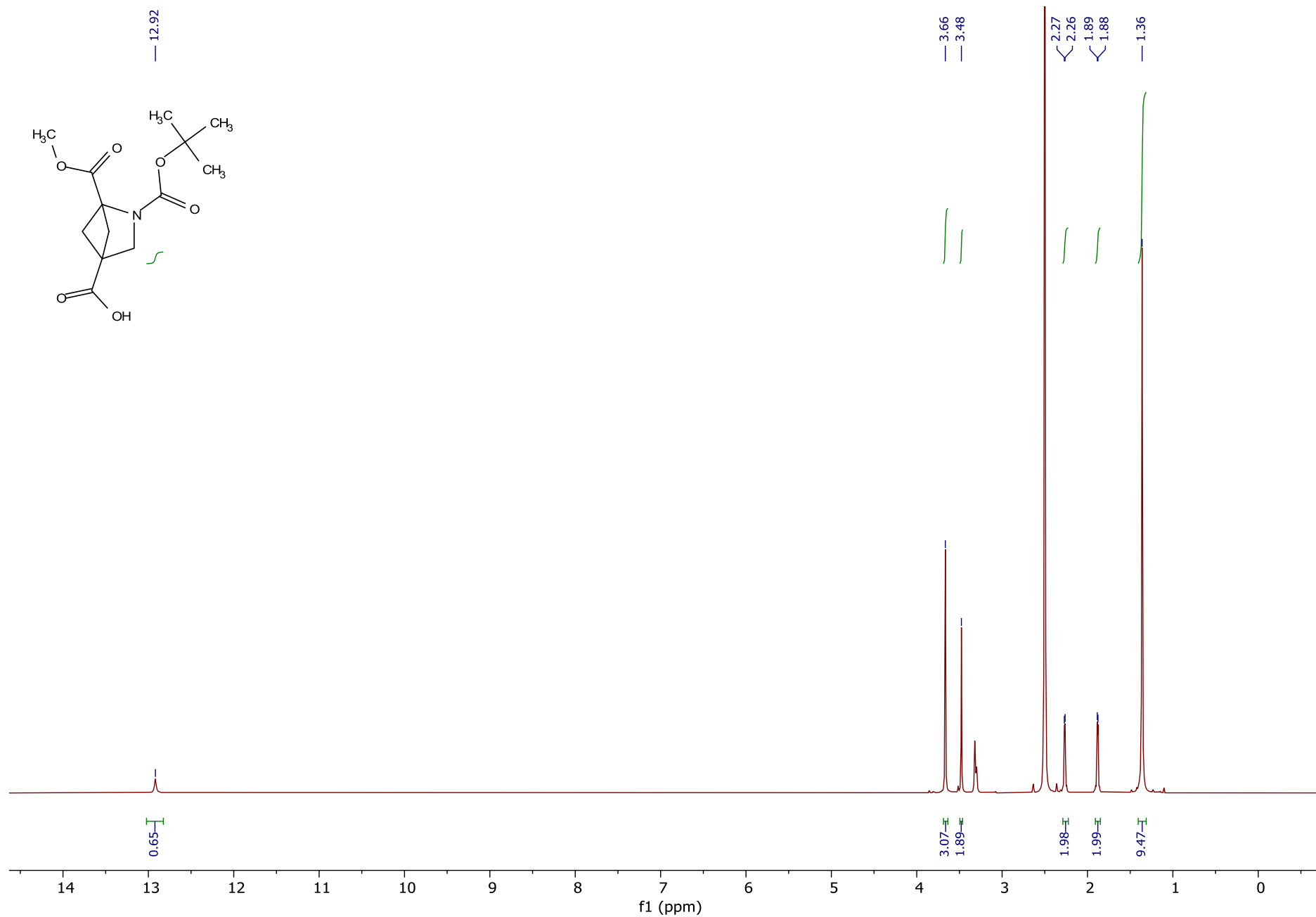


Figure 37. 2-(*tert*-Butoxycarbonyl)-1-(methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **28**, <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>).

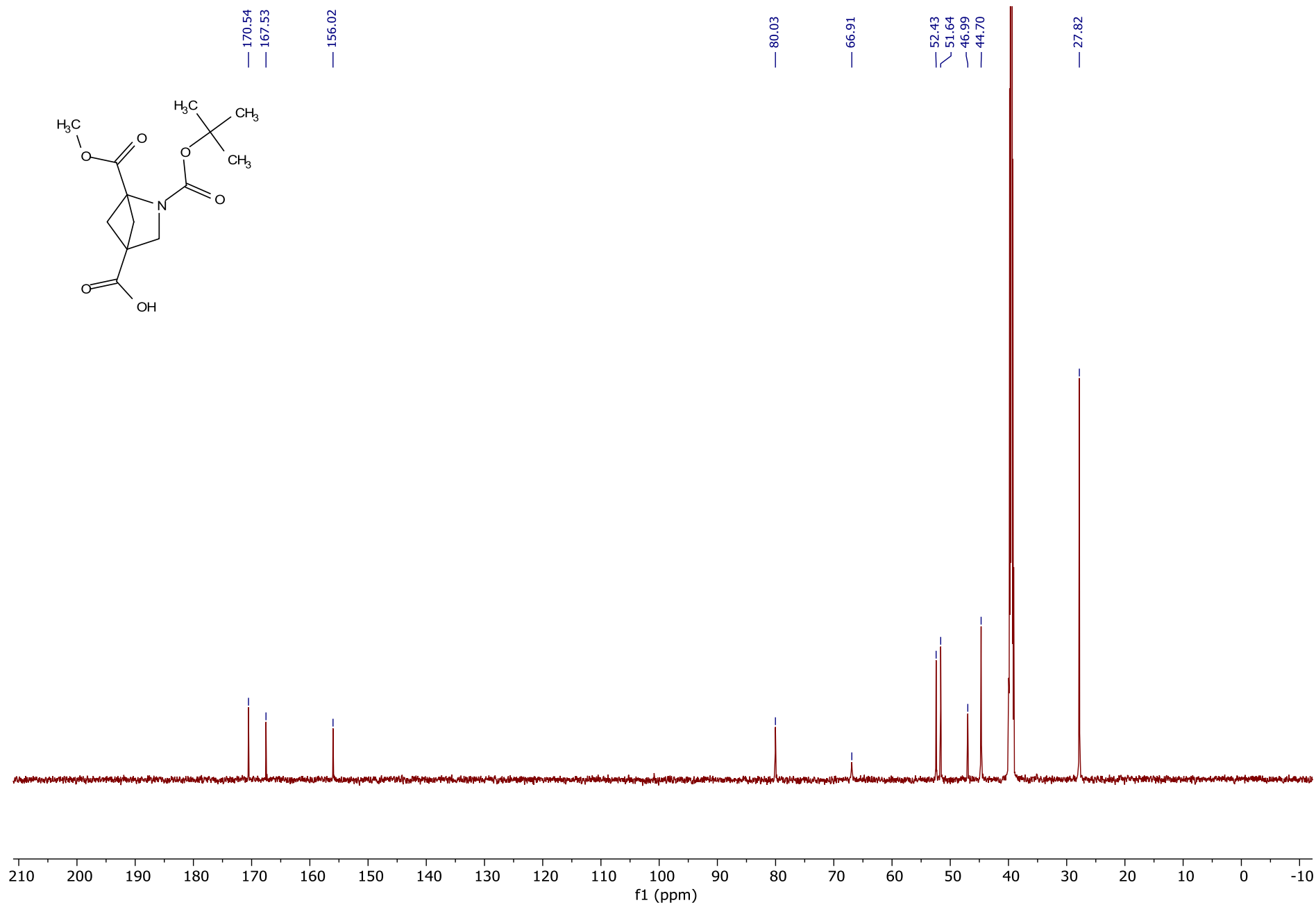


Figure 38. 2-(*tert*-Butoxycarbonyl)-1-(methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **28**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{DMSO-}d_6$ ).

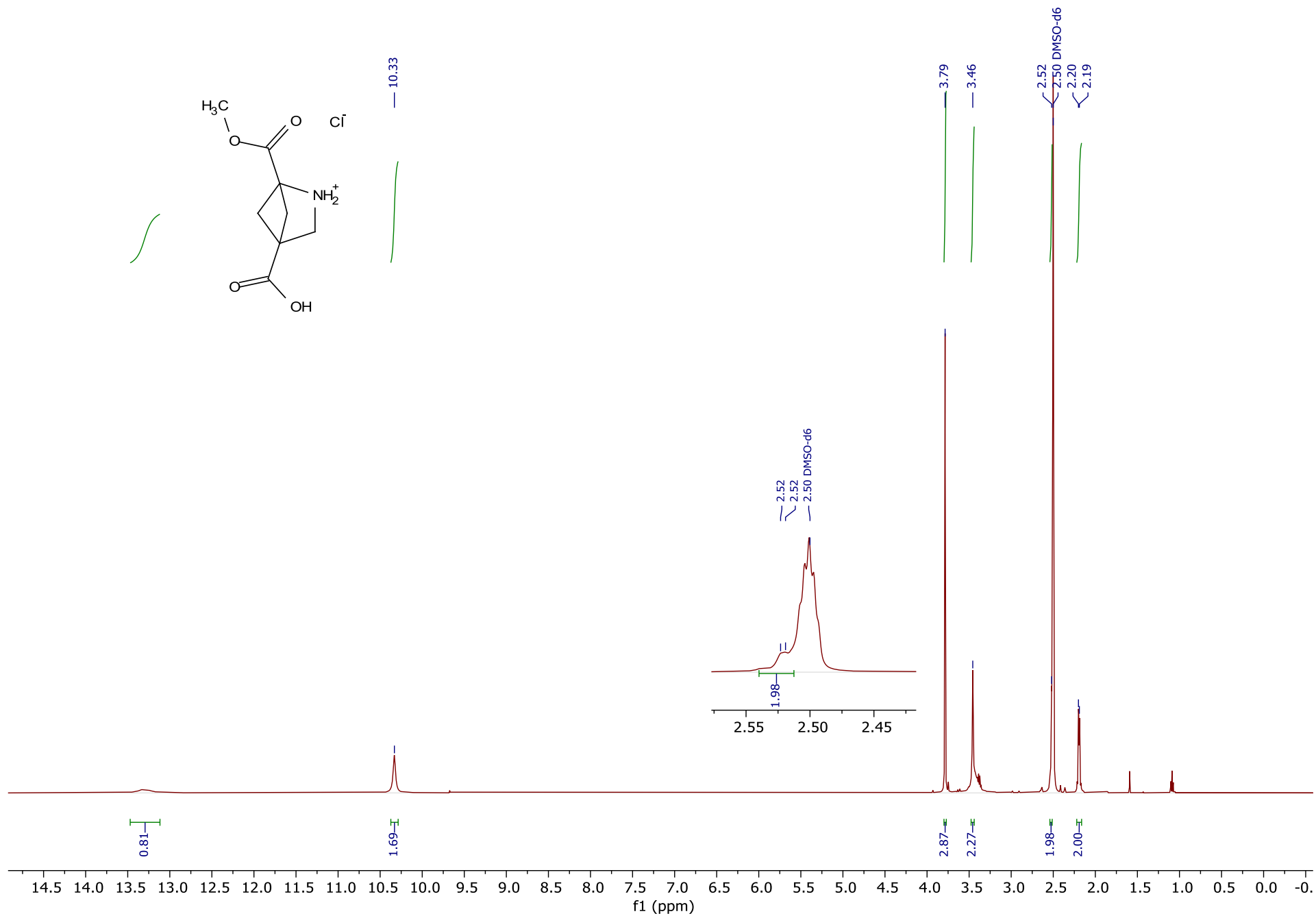


Figure 39. 1-(Methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid hydrochloride **29**,  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ ).

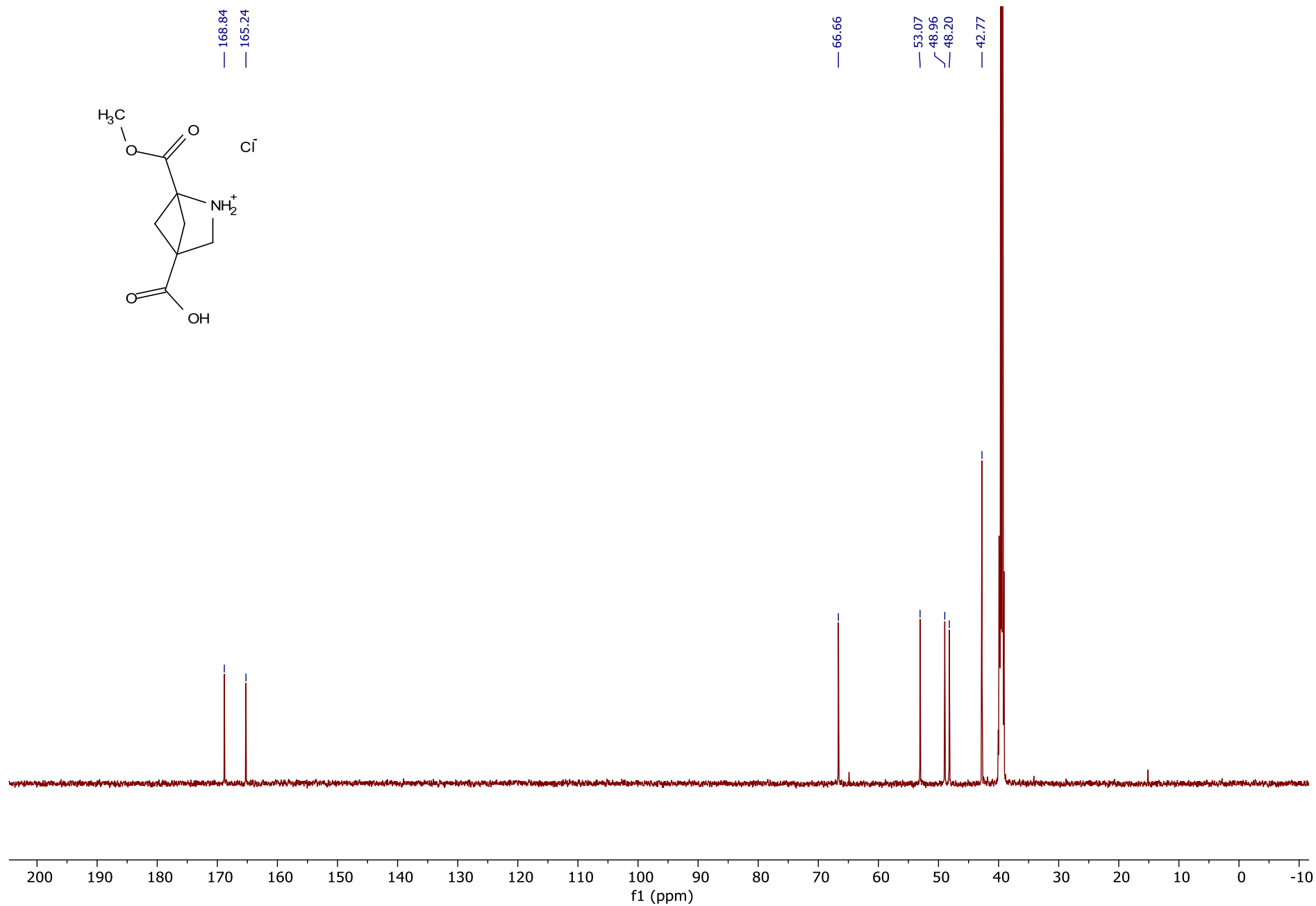


Figure 40. 1-(Methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid hydrochloride **29**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{DMSO}-d_6$ ).

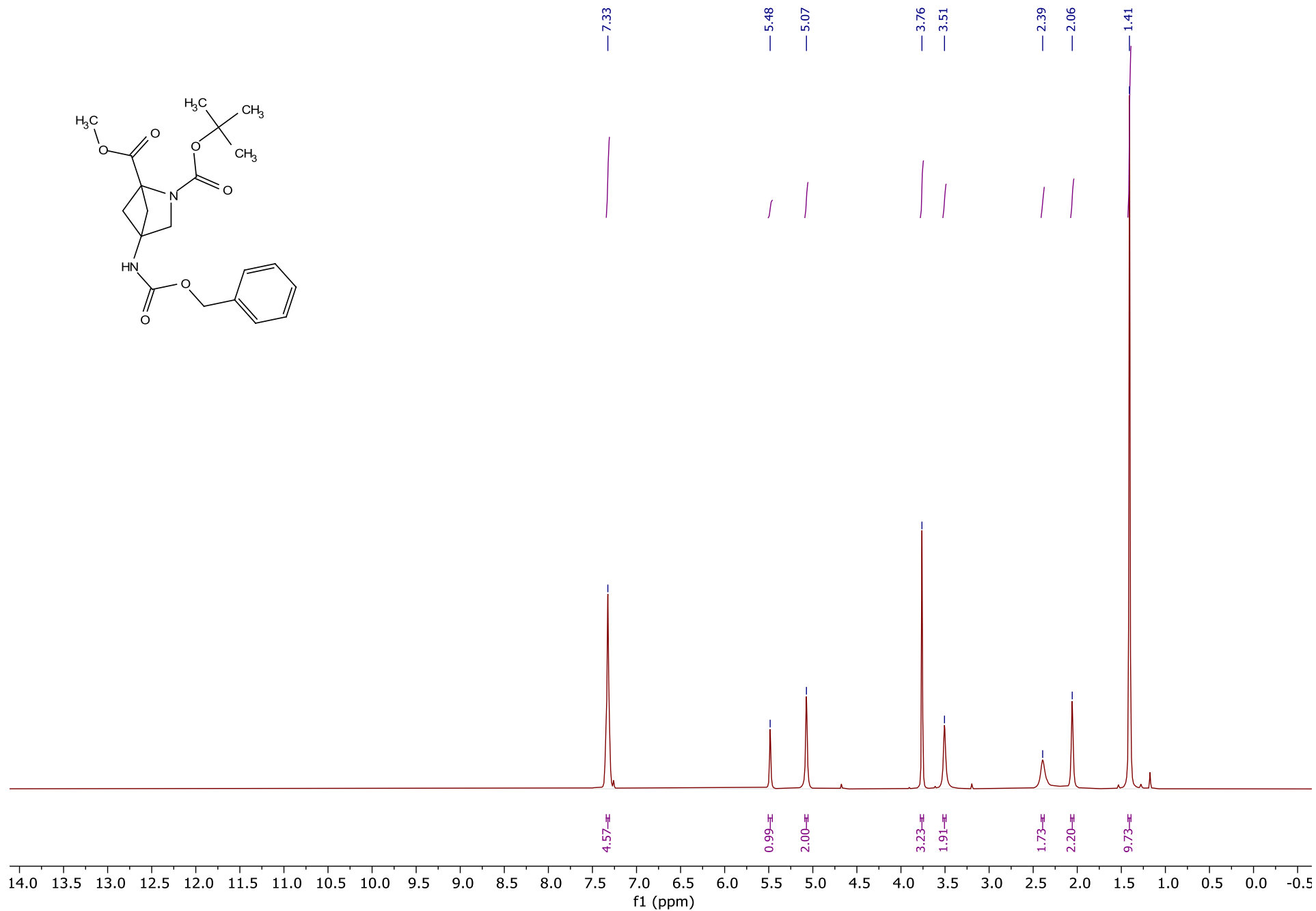


Figure 41. 2-(*tert*-Butyl) 1-methyl 4-(((benzyloxy)carbonyl)amino)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **30**, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>).

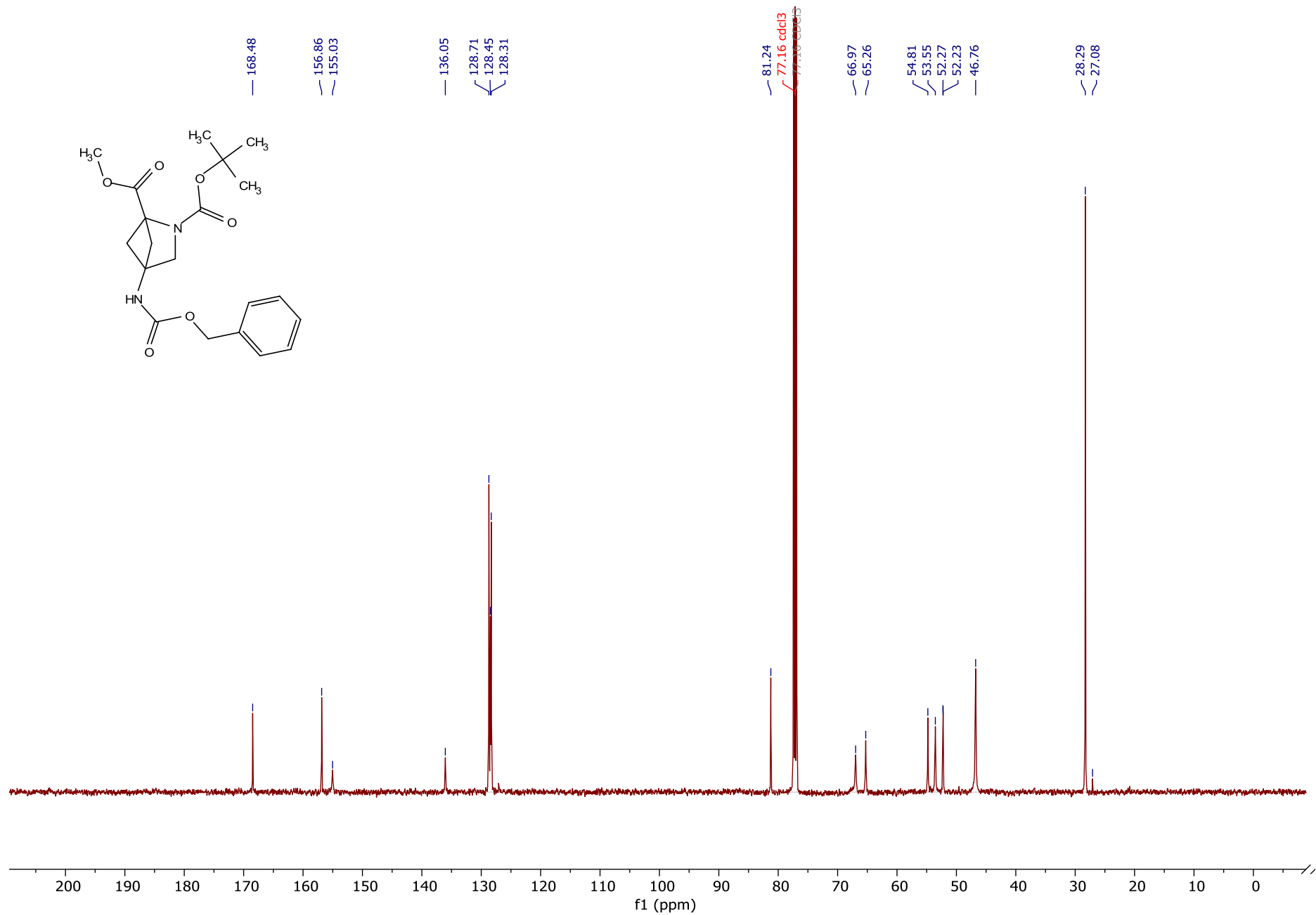


Figure 42. 2-(*tert*-Butyl) 1-methyl 4-(((benzyloxy)carbonyl)amino)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **30**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (126 MHz,  $\text{CDCl}_3$ ).

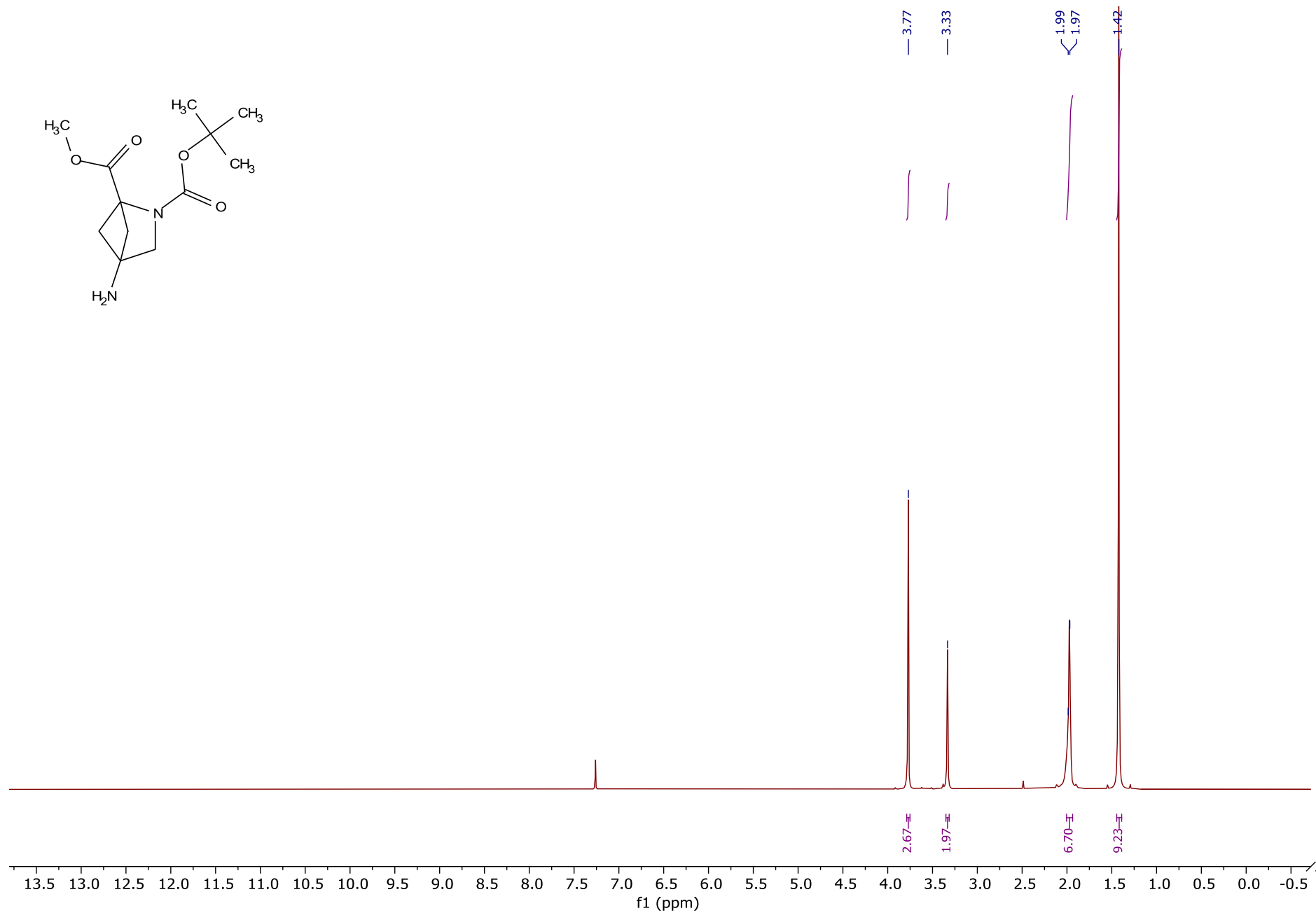


Figure 43. 2-(*tert*-Butyl) 1-methyl 4-amino-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **31**, <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>).

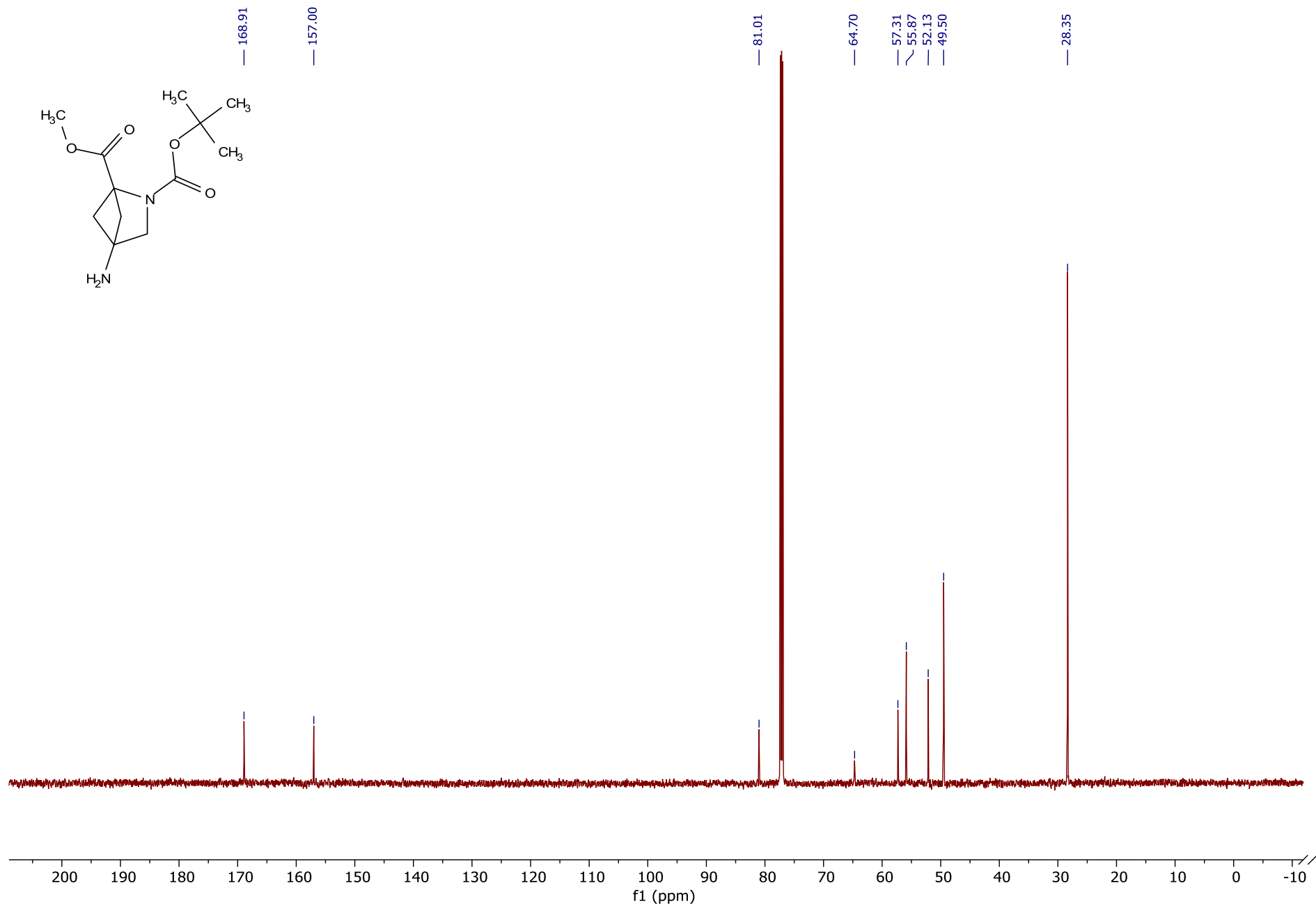


Figure 44. 2-(*tert*-Butyl) 1-methyl 4-amino-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **31**,  $^{13}\text{C}\{^1\text{H}\}$  NMR (151 MHz,  $\text{CDCl}_3$ ).