Supporting Information

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

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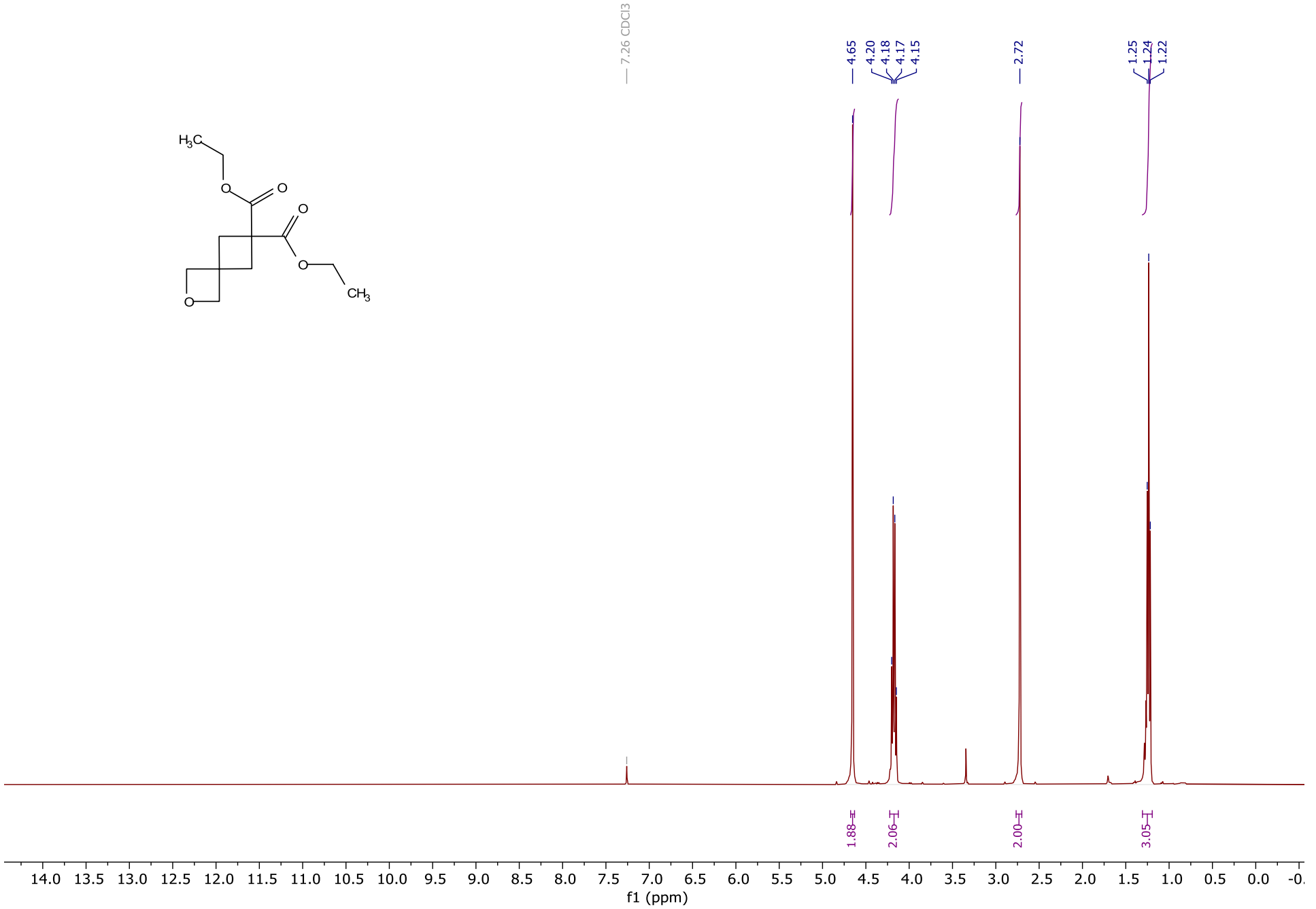


Figure 1. Diethyl 2-oxaspiro[3.3]heptane-6,6-dicarboxylate **13,** ^{1}H NMR (400 MHz, $CDCl_3$).

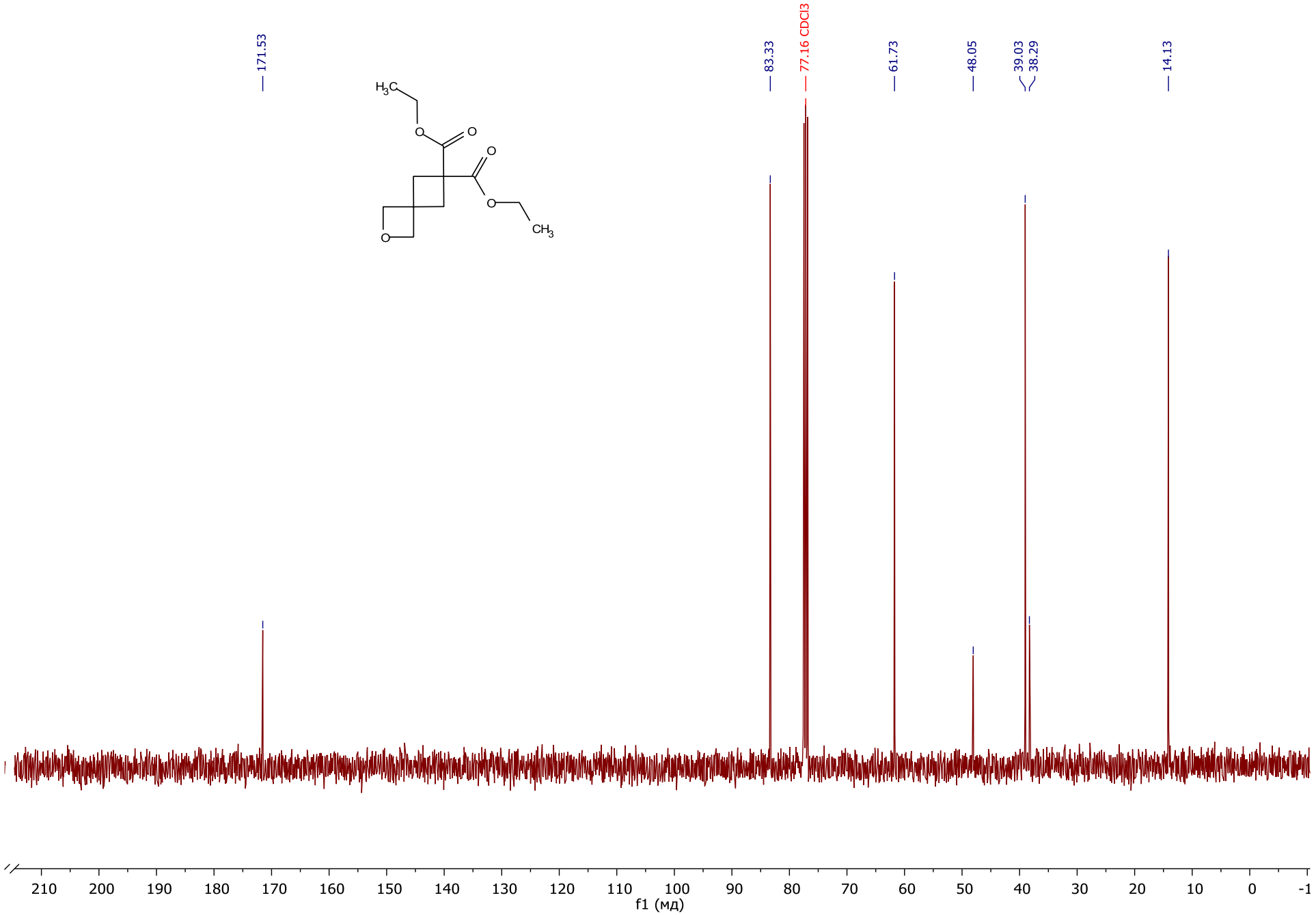


Figure 2. Diethyl 2-oxaspiro[3.3]heptane-6,6-dicarboxylate **13,** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$).

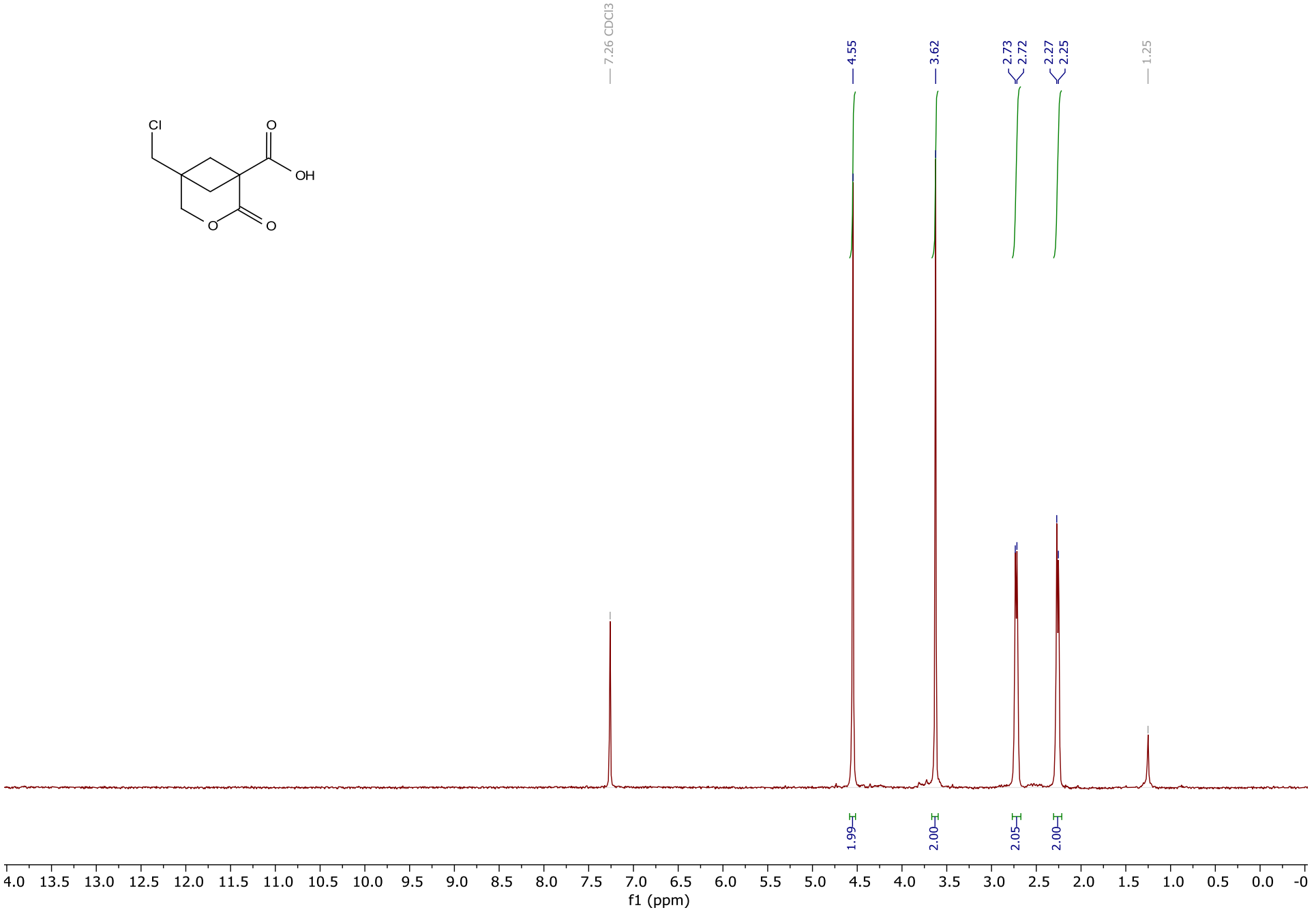


Figure 3. 5-(Chloromethyl)-2-oxo-3-oxabicyclo[3.1.1]heptane-1-carboxylic acid **7,** ^{1}H NMR (400 MHz, $CDCl_3$)

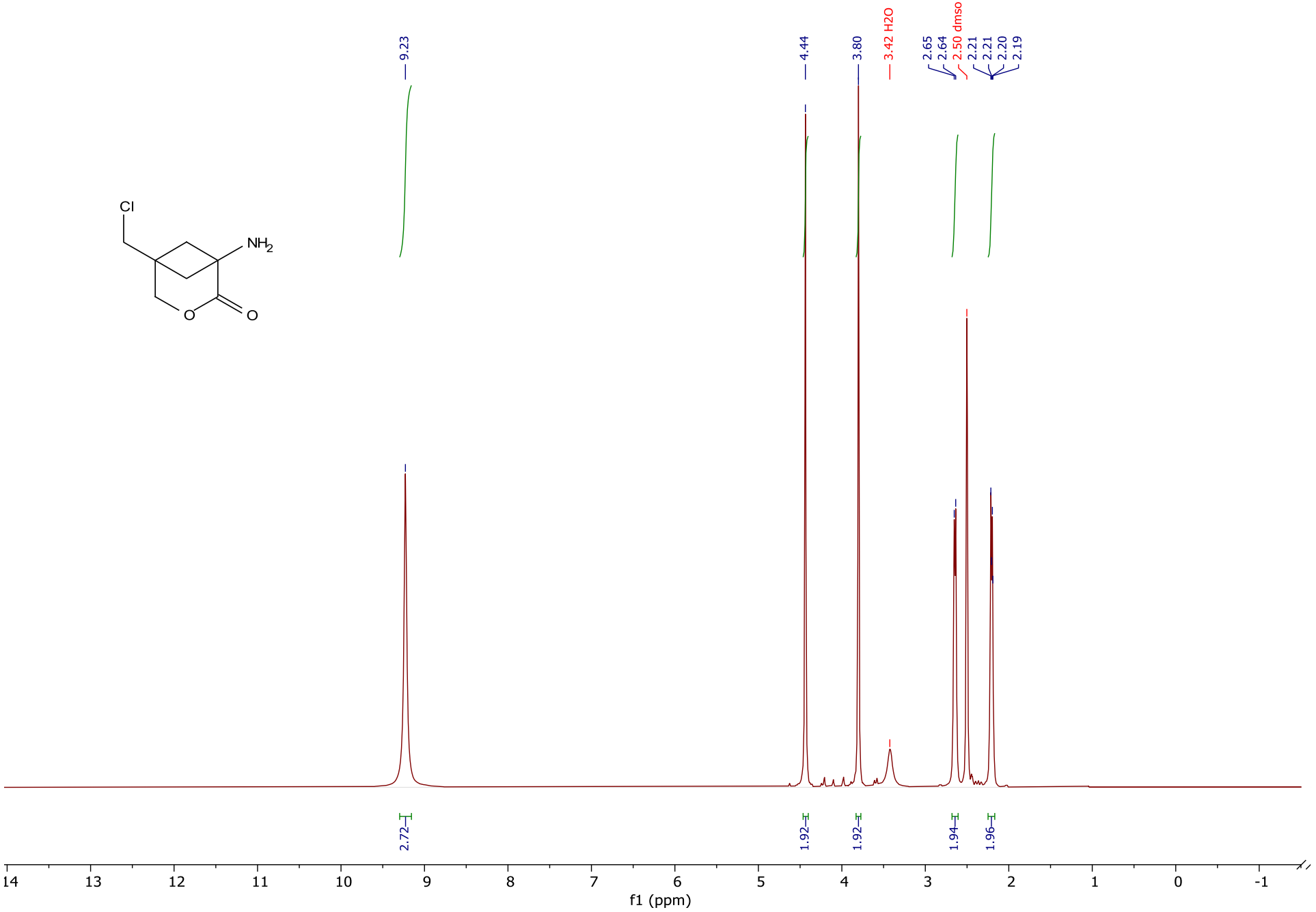


Figure 4. 1-Amino-5-(chloromethyl)-3-oxabicyclo[3.1.1]heptan-2-one hydrochloride **14,** ^{1}H NMR (400 MHz, DMSO-d_6)

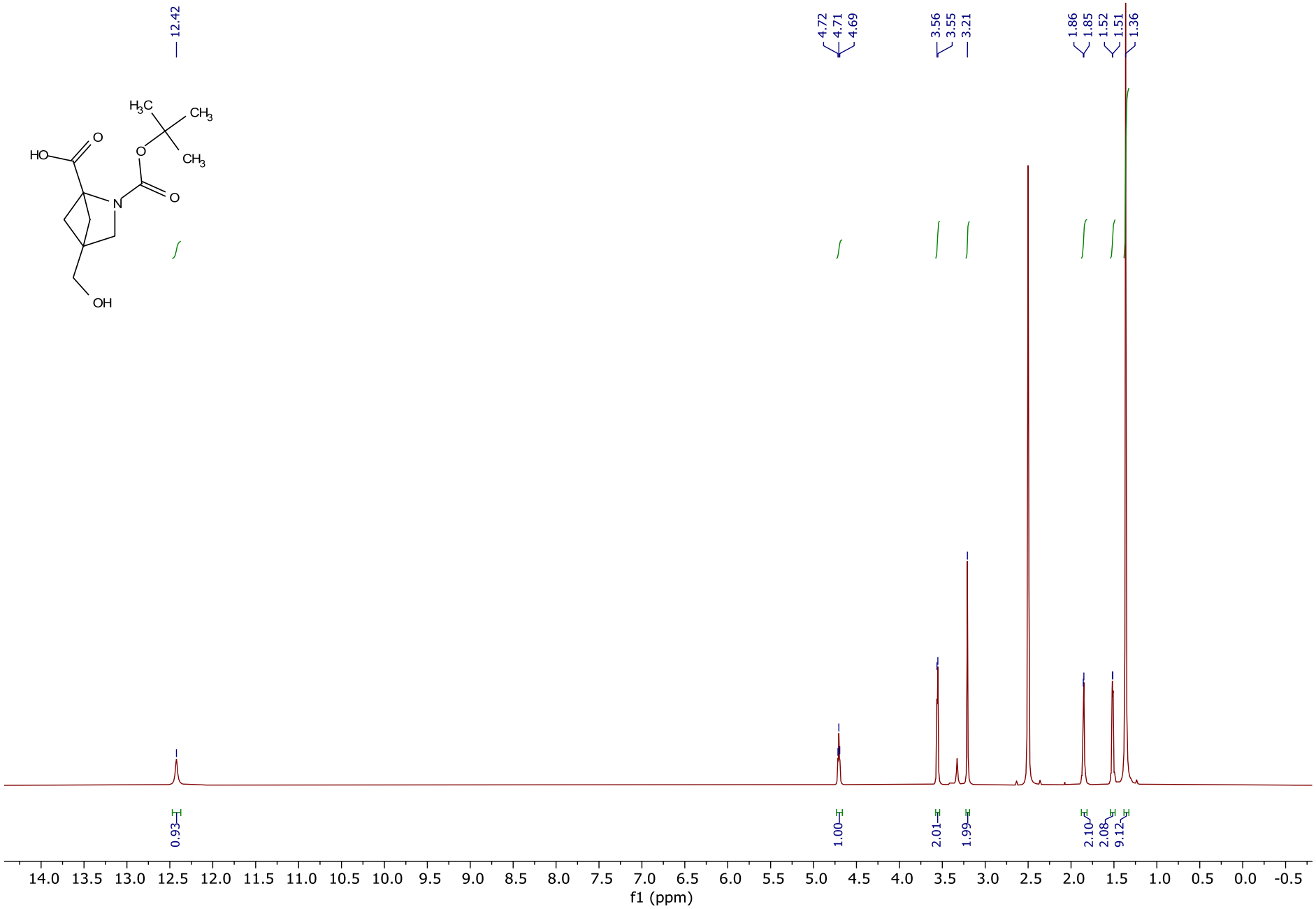


Figure 5. 2-(*tert*-Butoxycarbonyl)-4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **6,** ^{1}H NMR (500 MHz, DMSO-d_6).

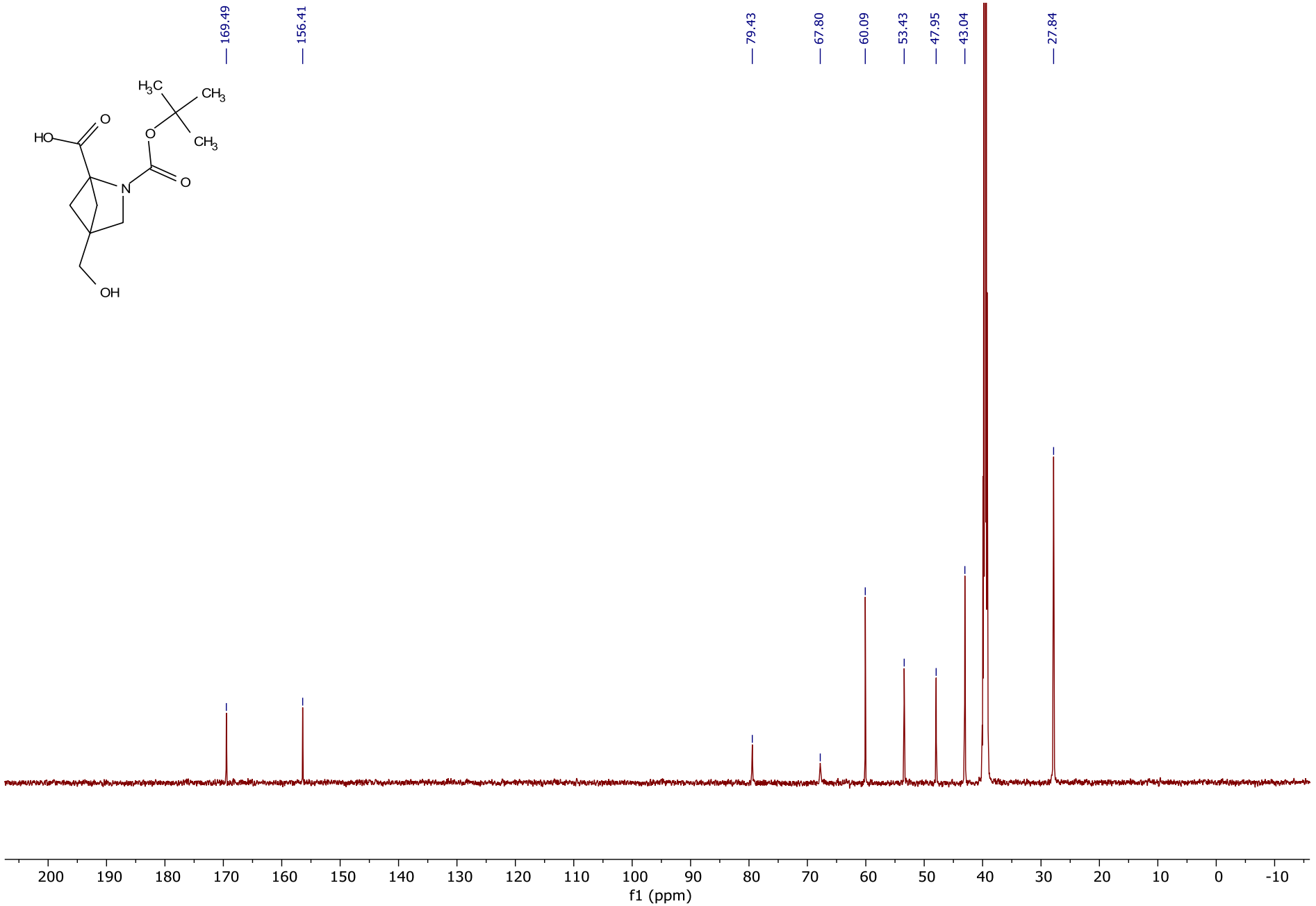
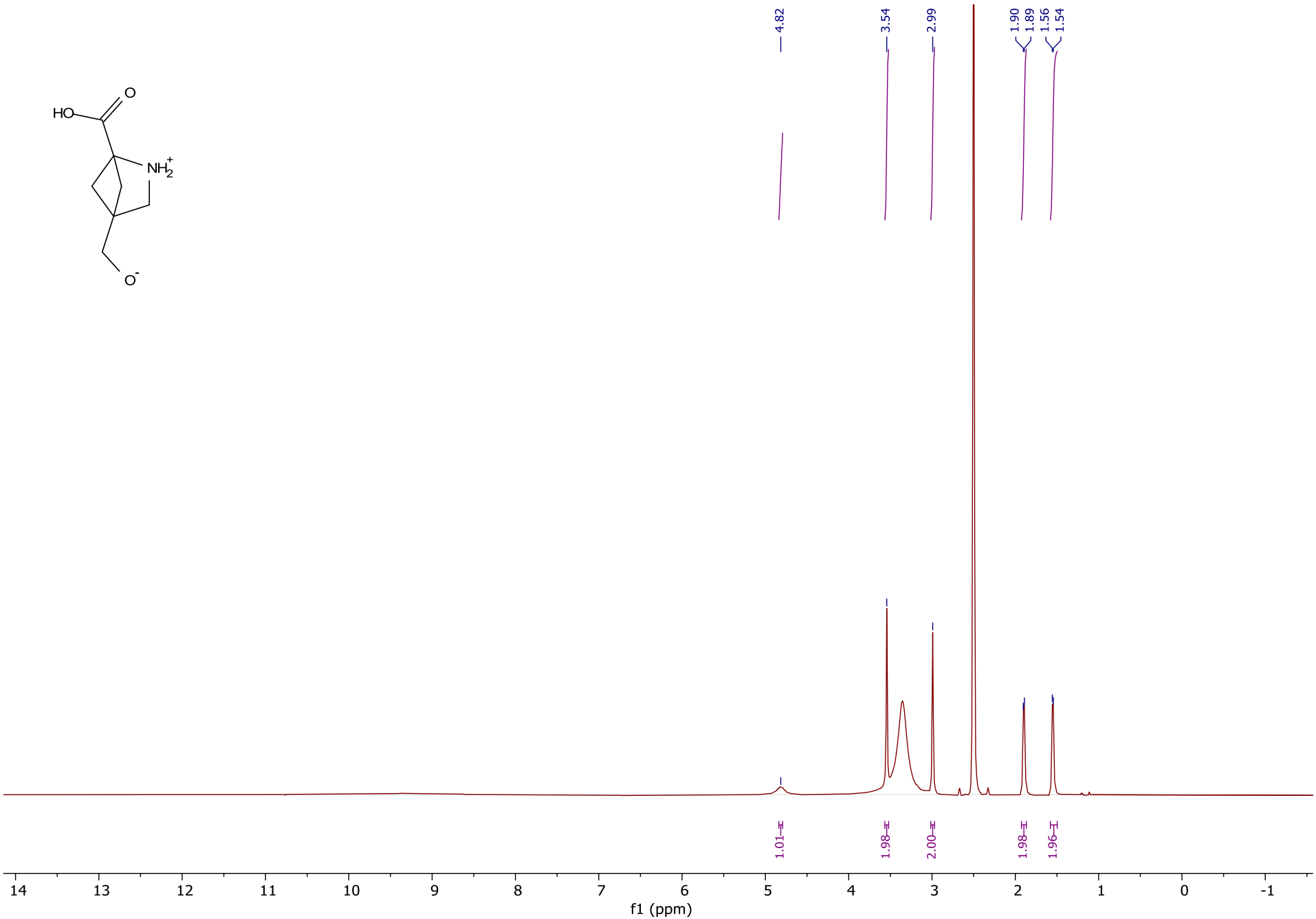


Figure 6. 2-(*tert*-Butoxycarbonyl)-4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **6,** $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6).



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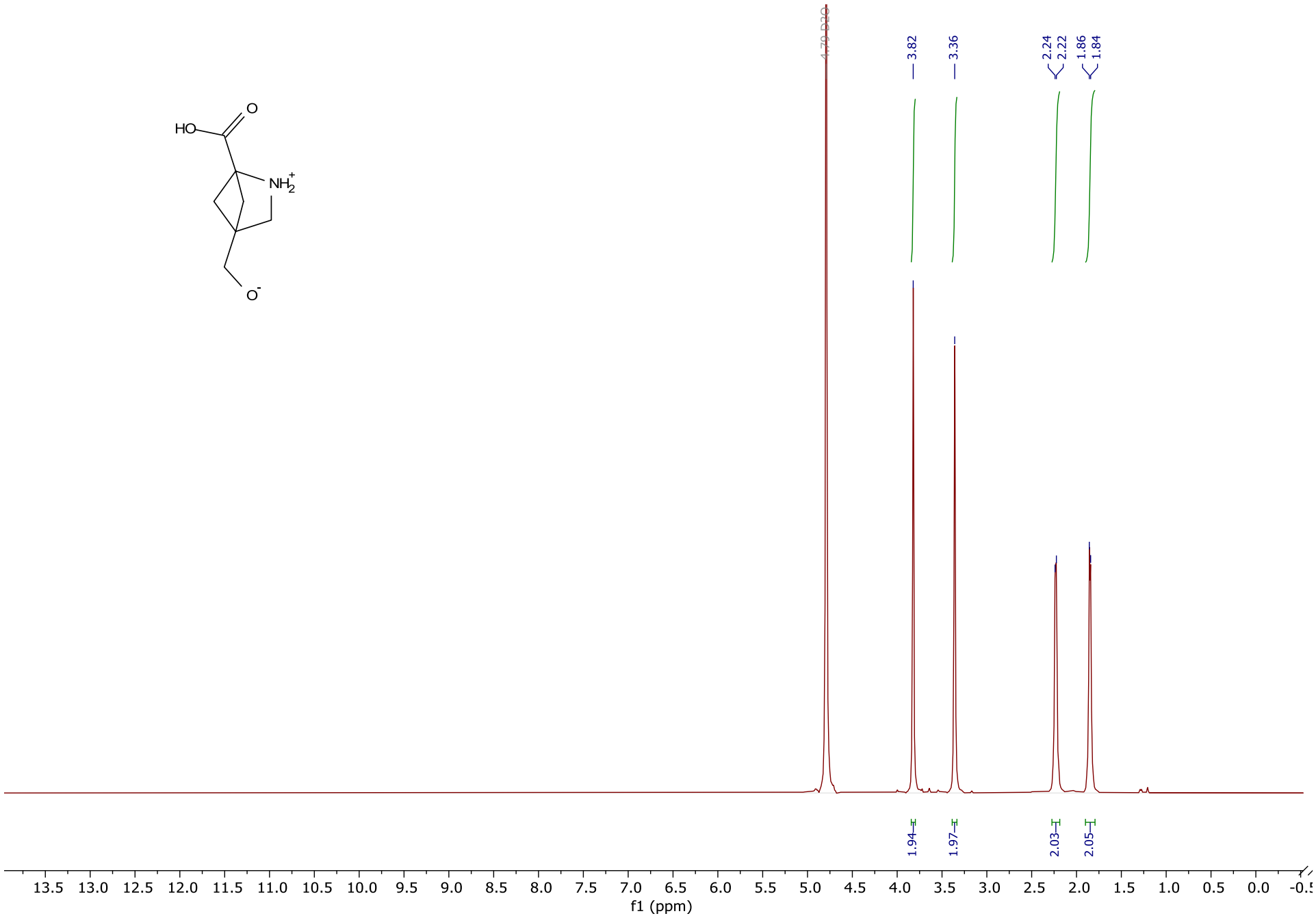


Figure 8. 4-(Hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **16**. ^{1}H NMR (400 MHz, D_2O)

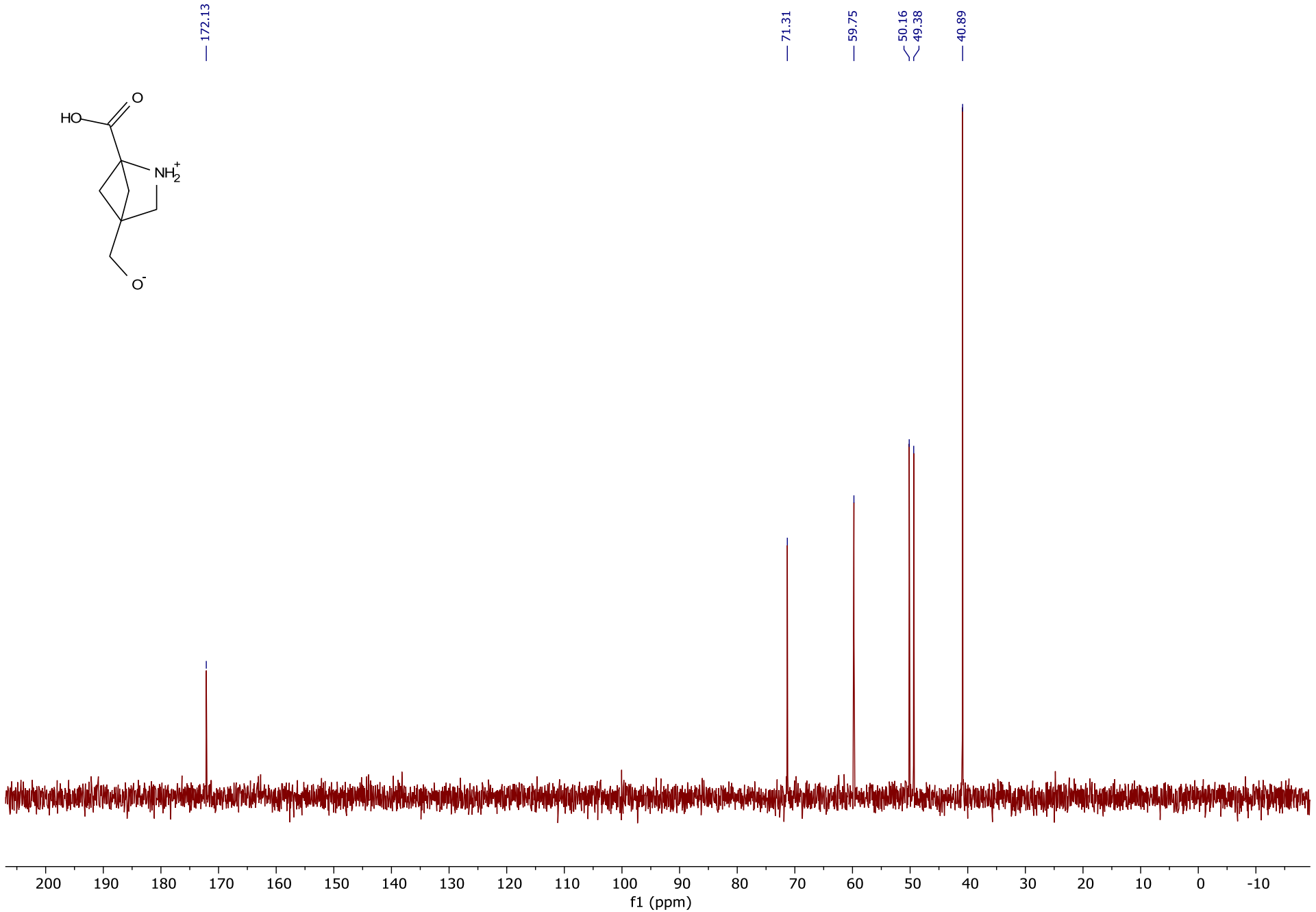


Figure 9. 4-(Hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **16,** $^{13}C\{^{1}H\}$ NMR (101 MHz, D_2O).

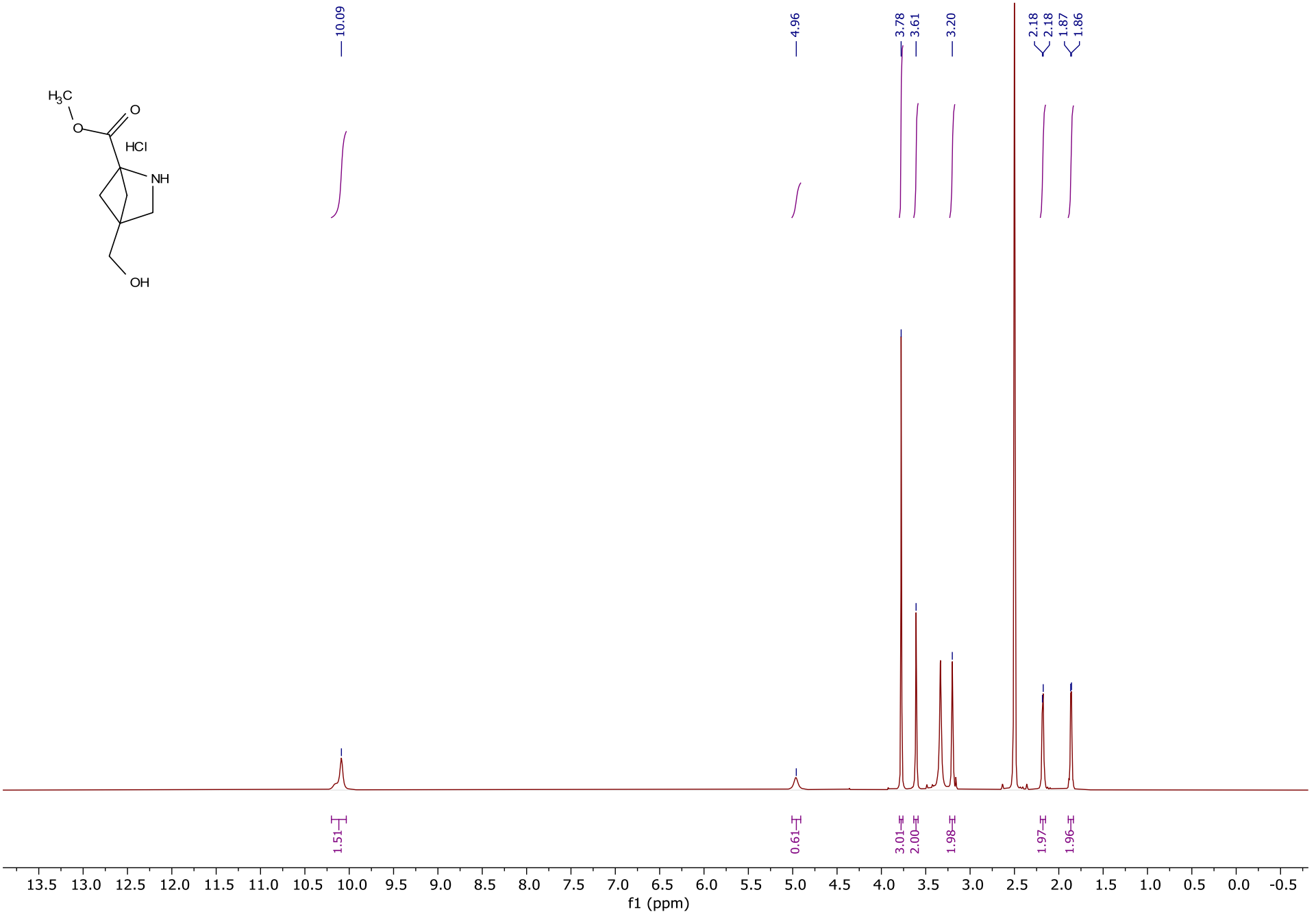


Figure 10. Methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **17,** ^{1}H NMR (500 MHz, DMSO-d_6).

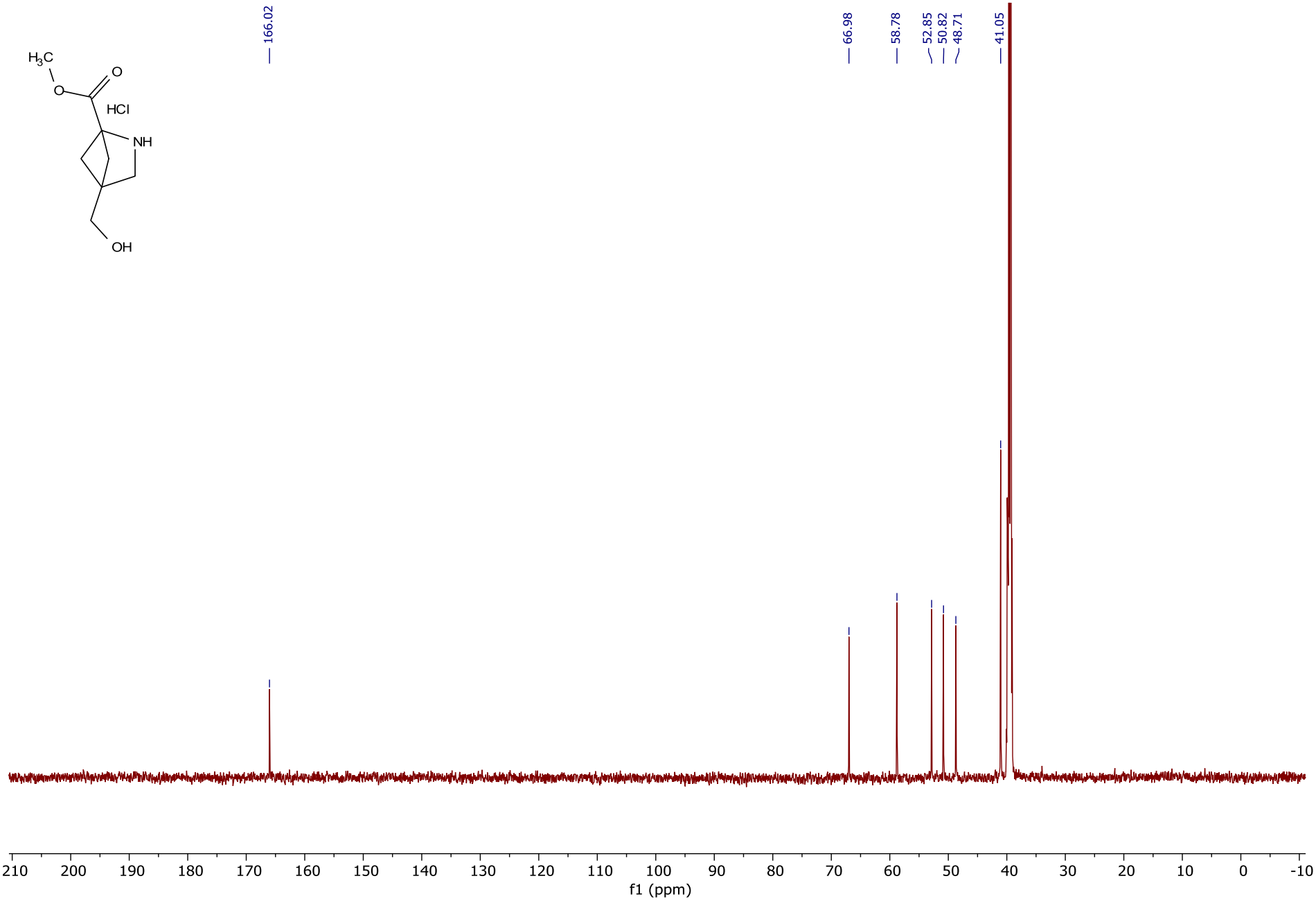


Figure 11. Methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **17,** $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6).

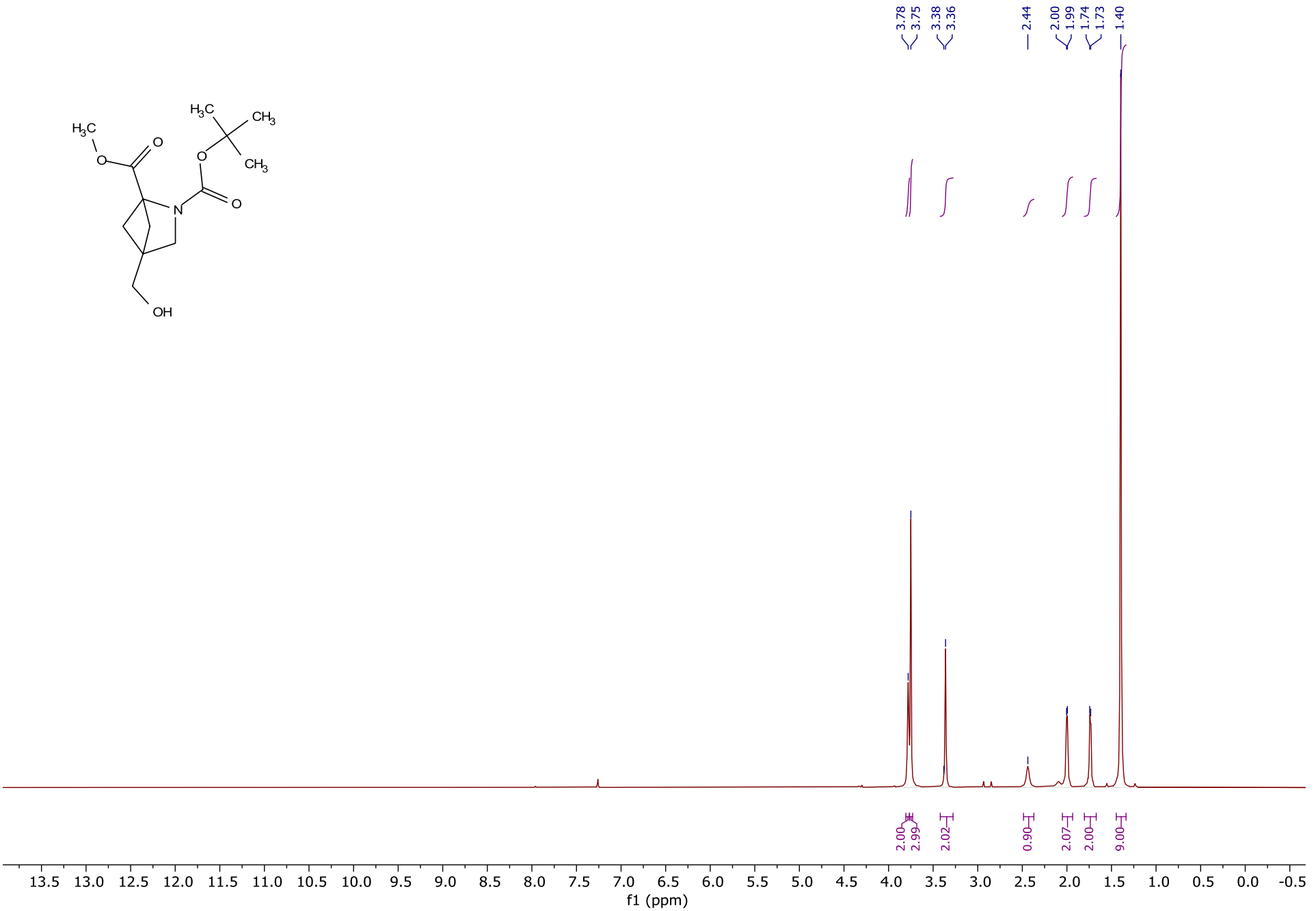
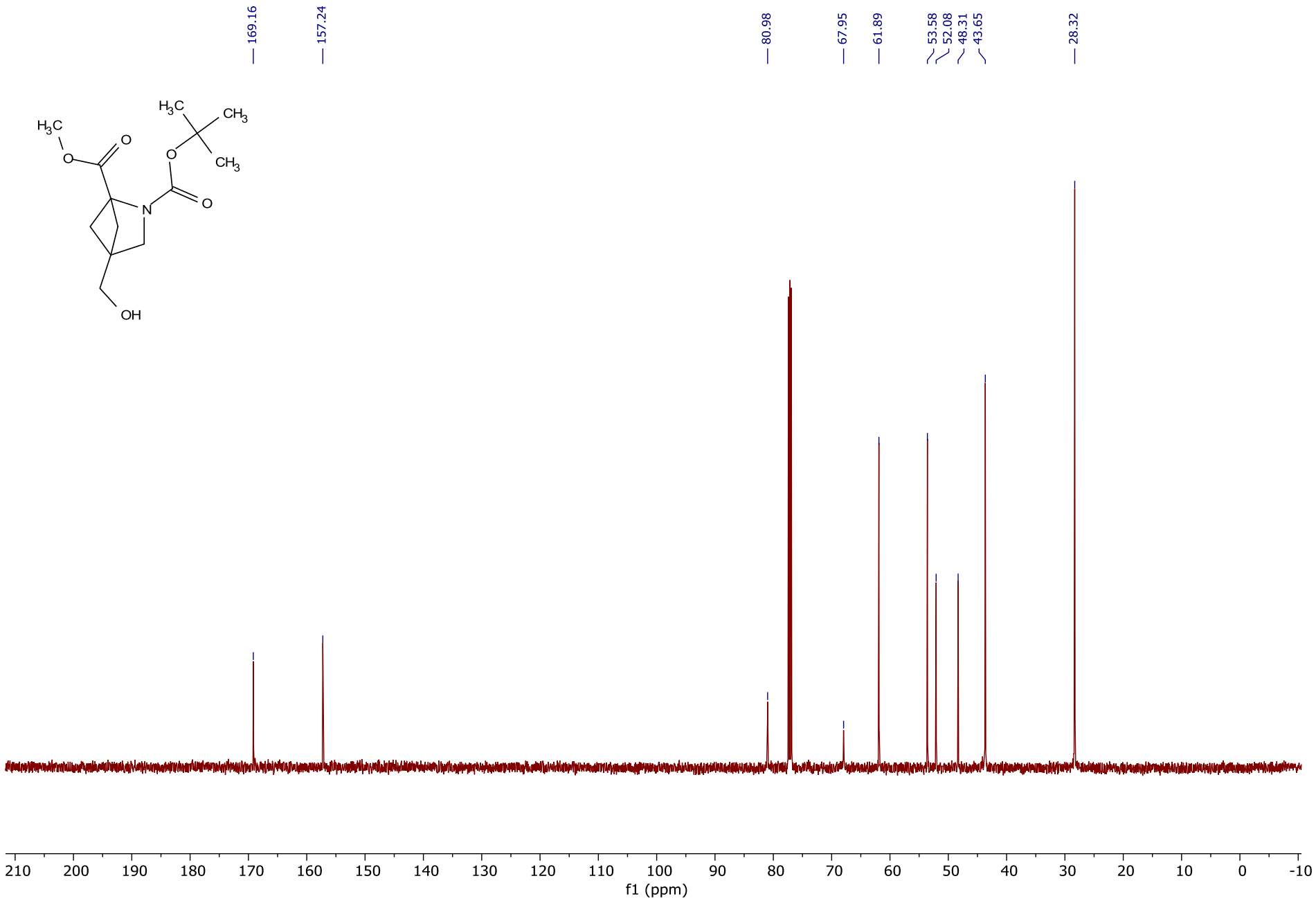


Figure 12. 2-(*tert*-Butyl) 1-methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **18**, ^{1}H NMR (400 MHz, $CDCl_3$).



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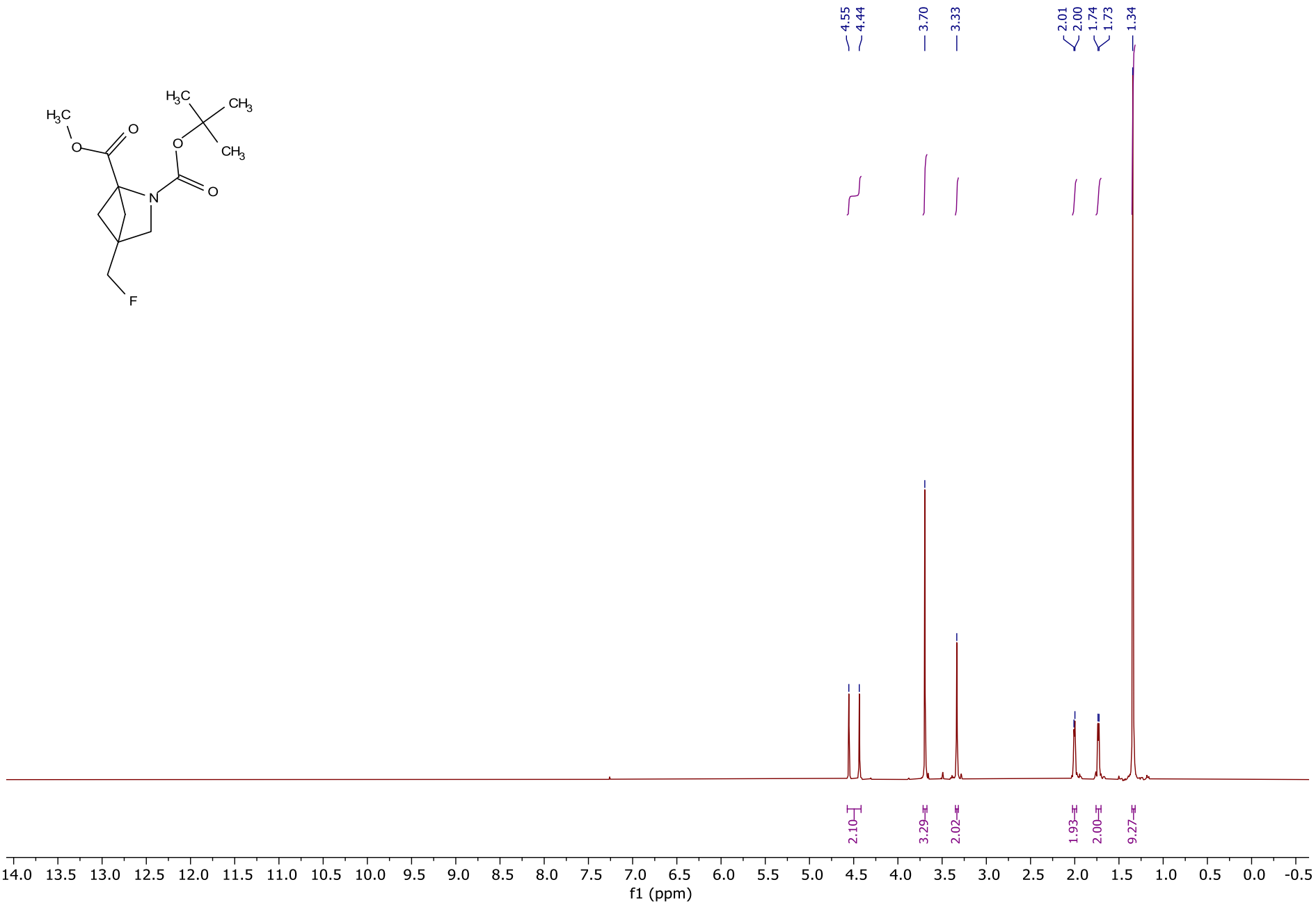
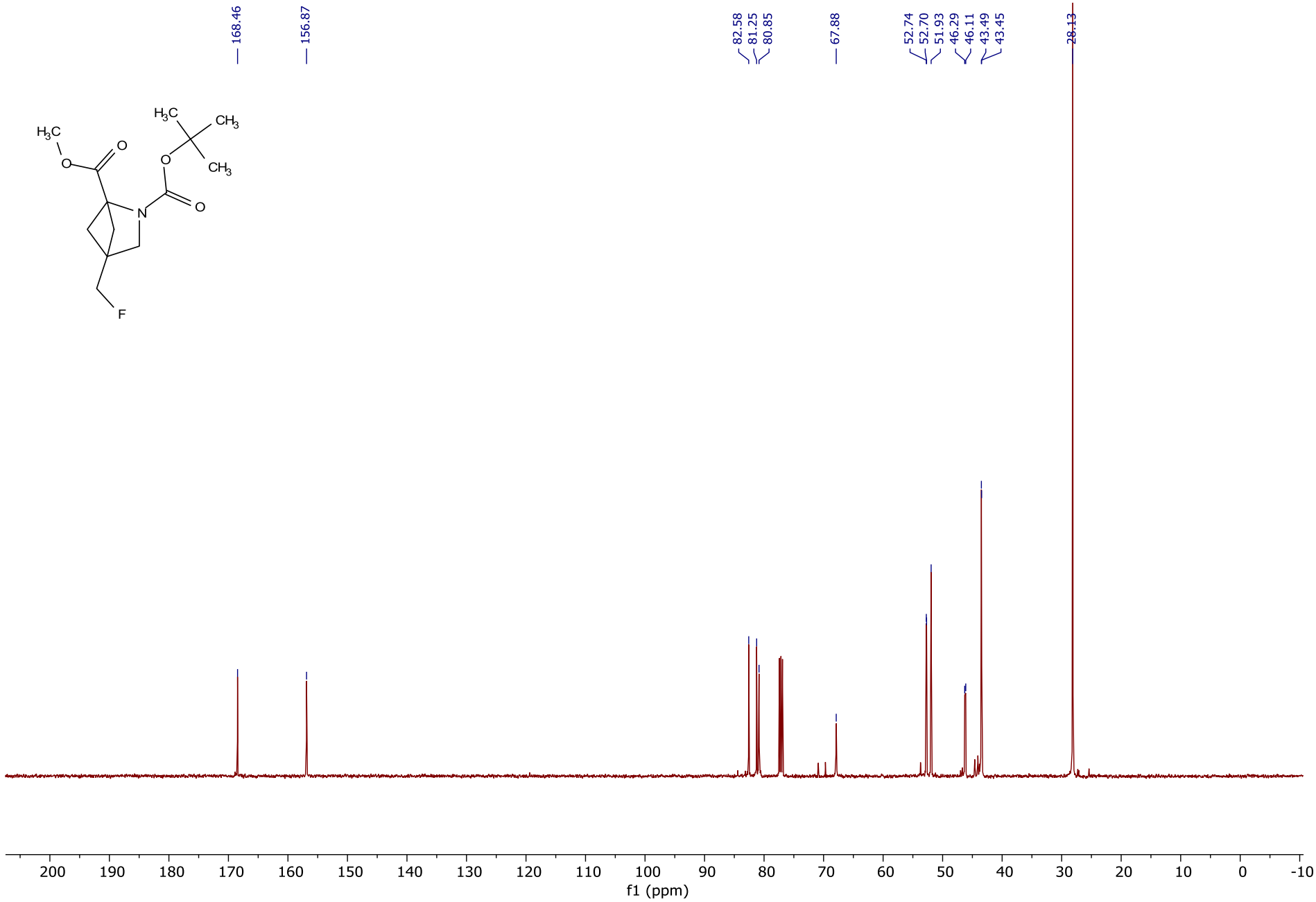


Figure 14. 2-(*tert*-Butyl) 1-methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **19,** ^{1}H NMR (400 MHz, $CDCl_3$).



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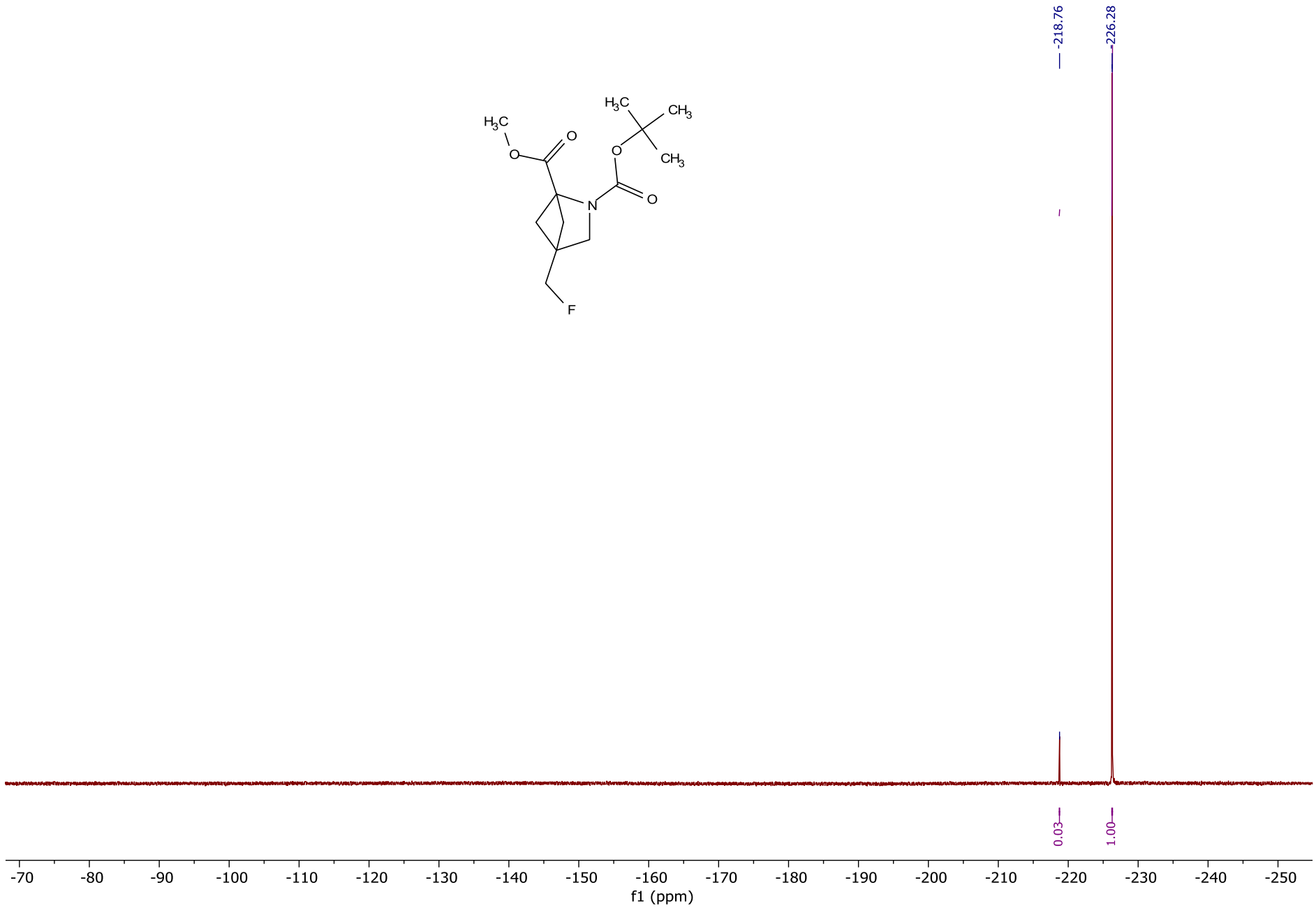

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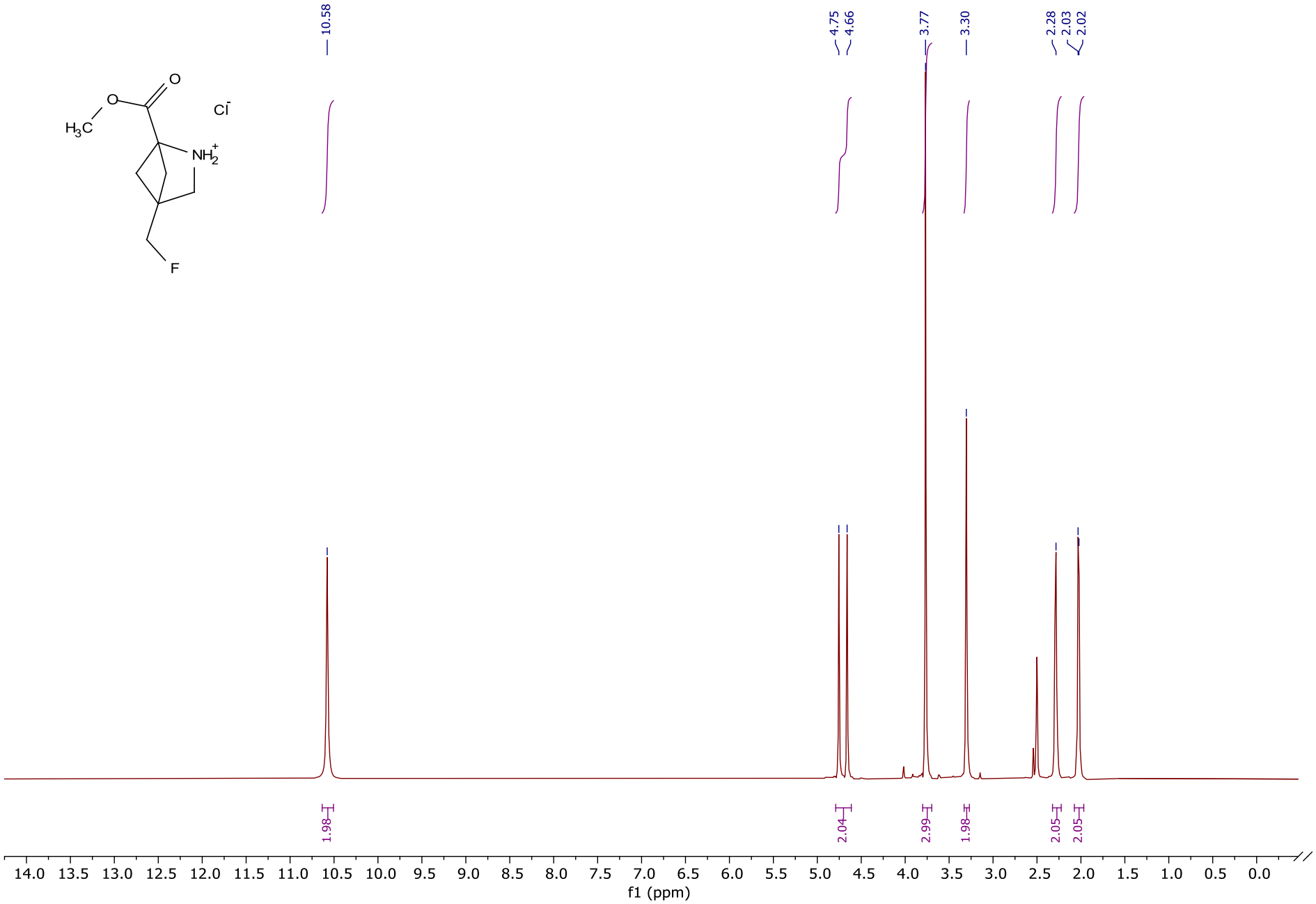


Figure 17. Methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **20,** ^{1}H NMR (500 MHz, DMSO-d_6).

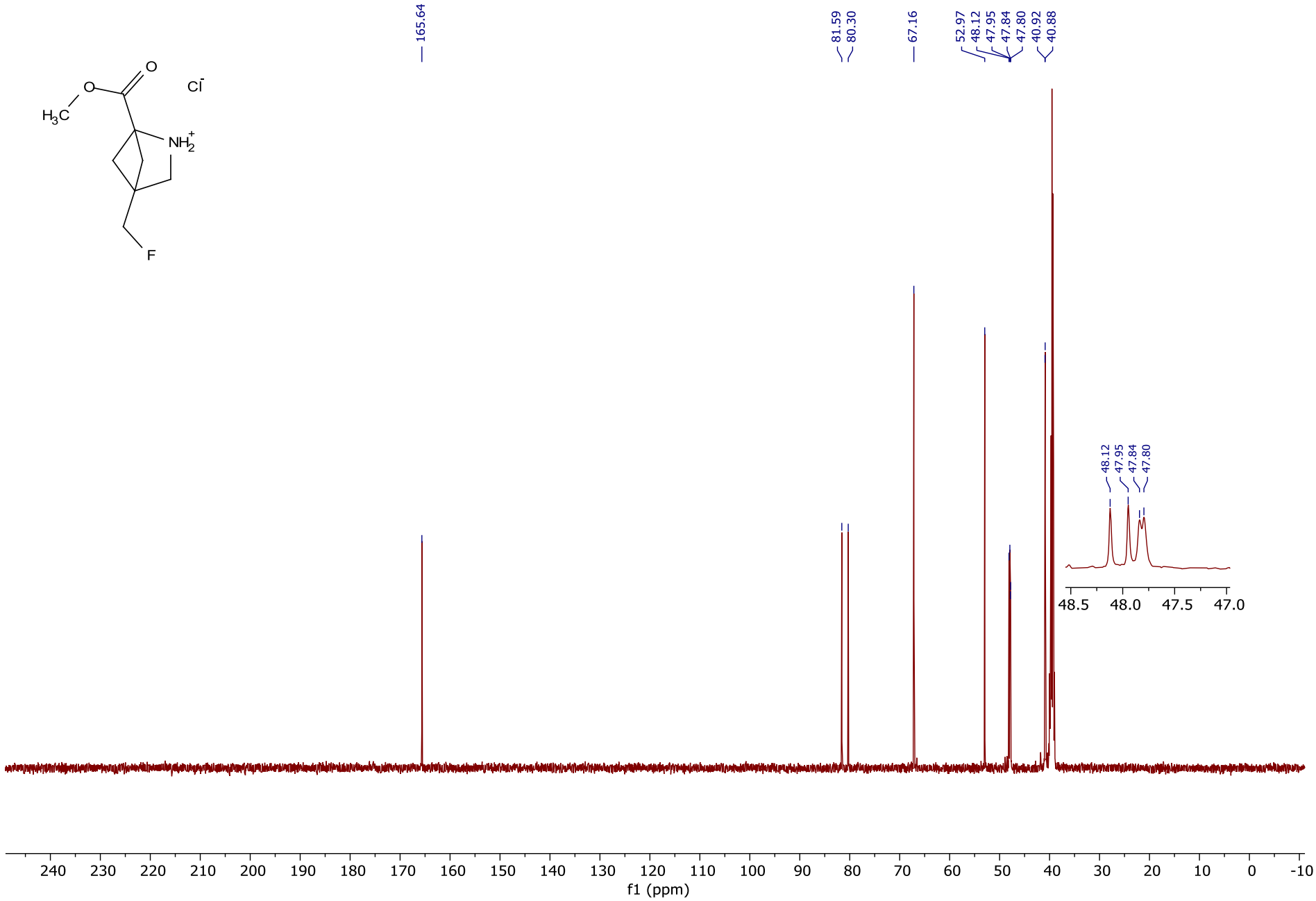


Figure 18. Methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **20,** $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6).

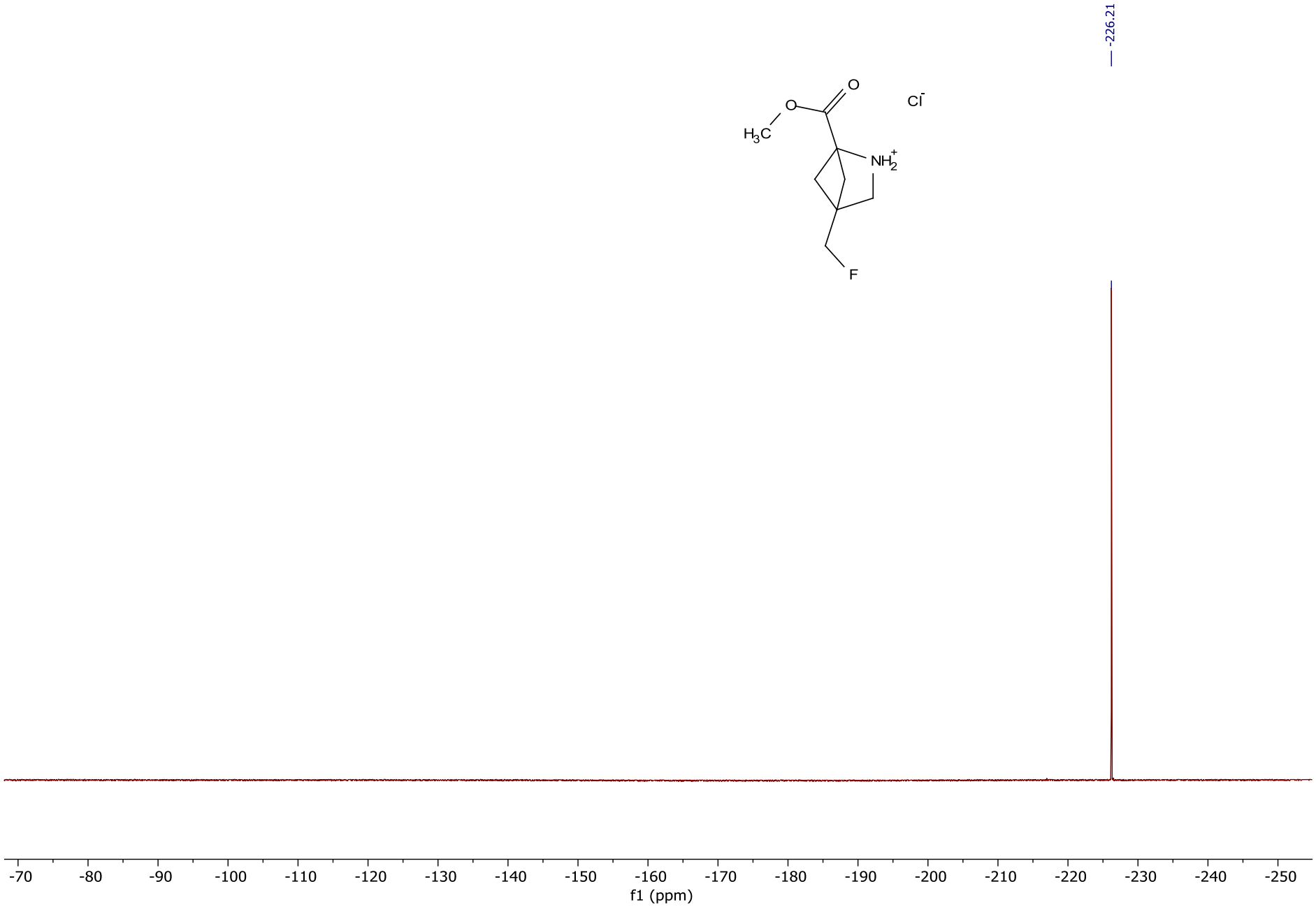


Figure 19. Methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **20,** $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6).

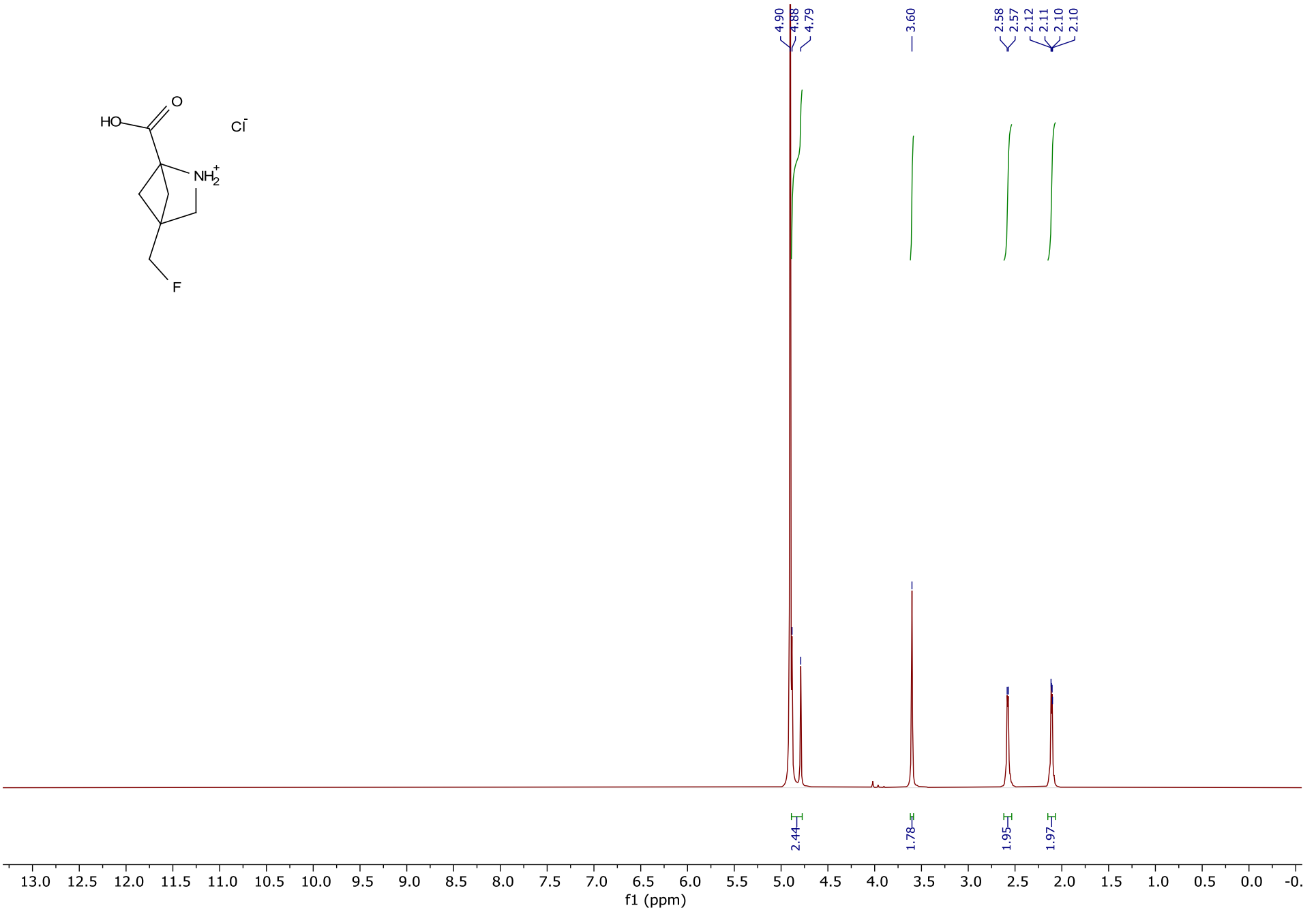
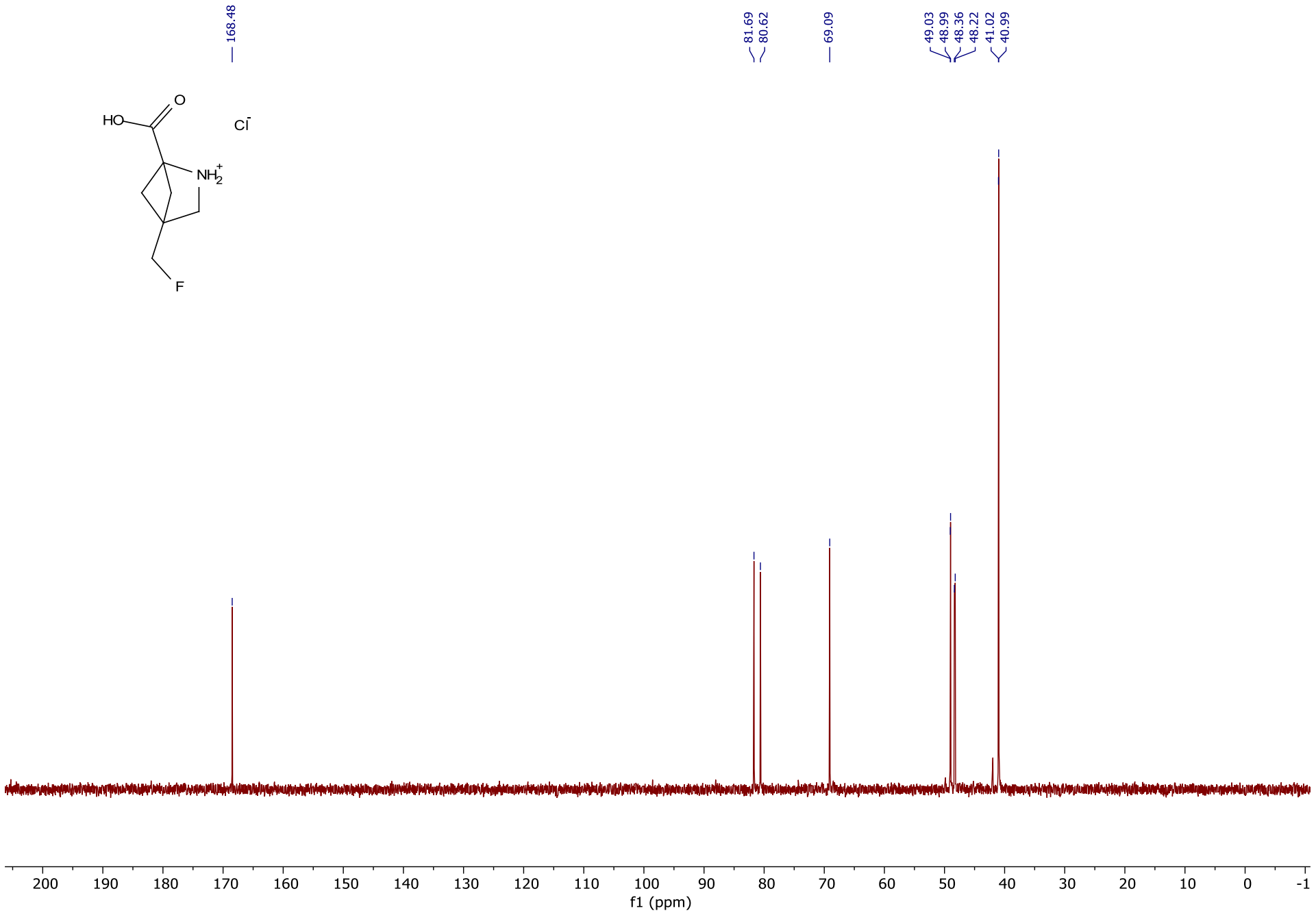


Figure 20. 4-(Fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylate hydrochloride **21,** ^{1}H NMR (500 MHz, D_2O).



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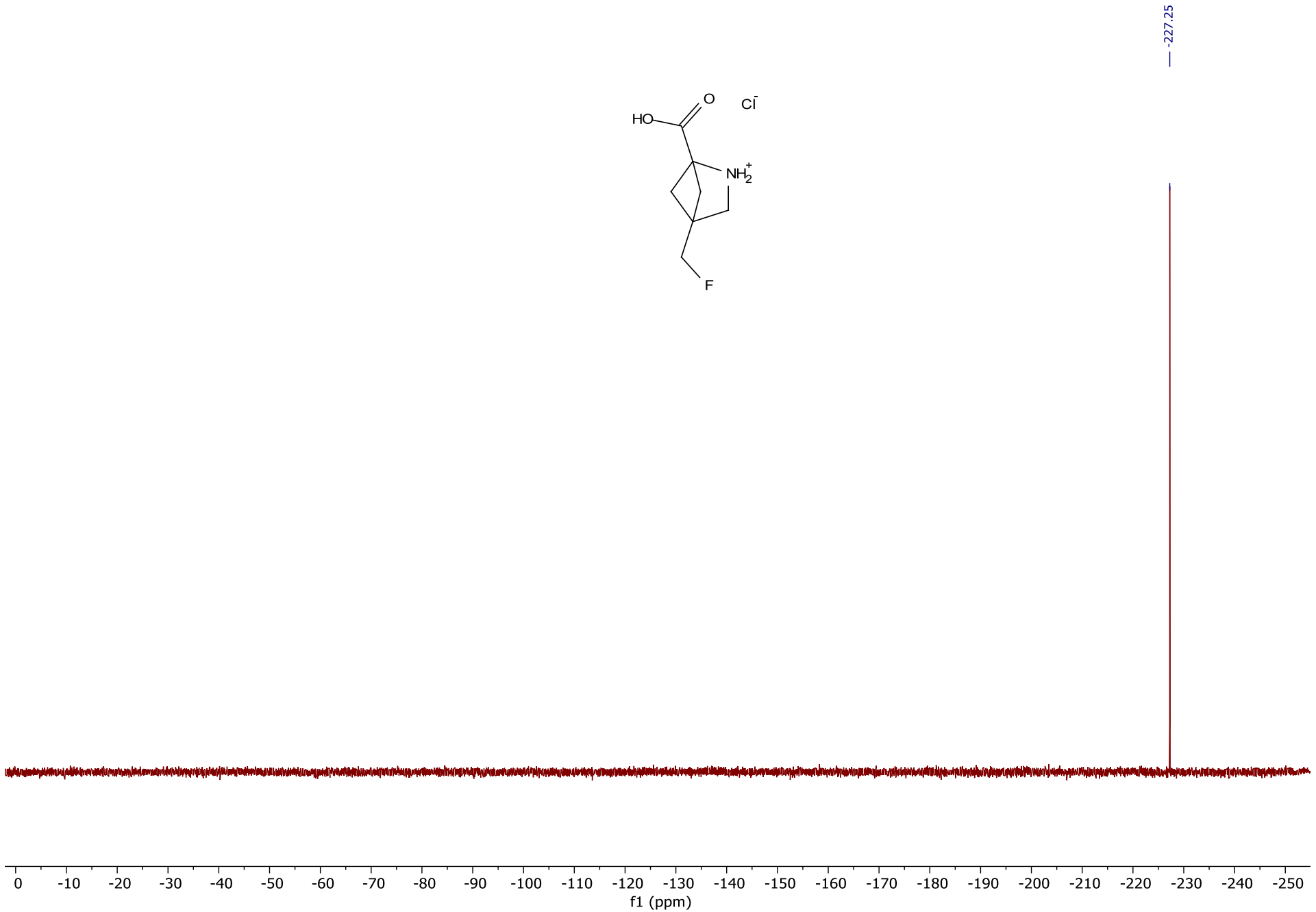

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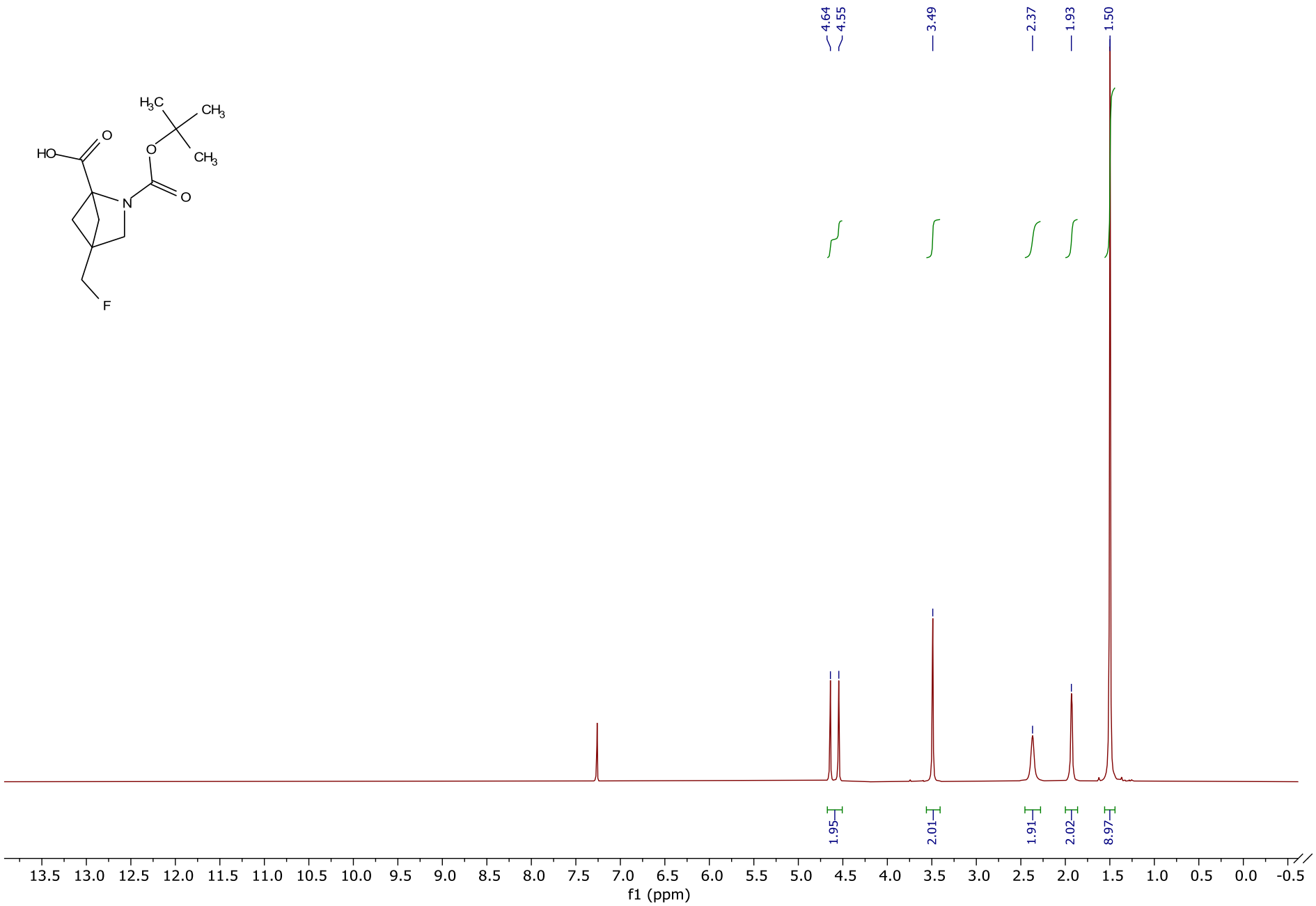

Figure 23. 2-(*tert*-Butoxycarbonyl)-4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **22,** ^{1}H NMR (500 MHz, $CDCl_3$).

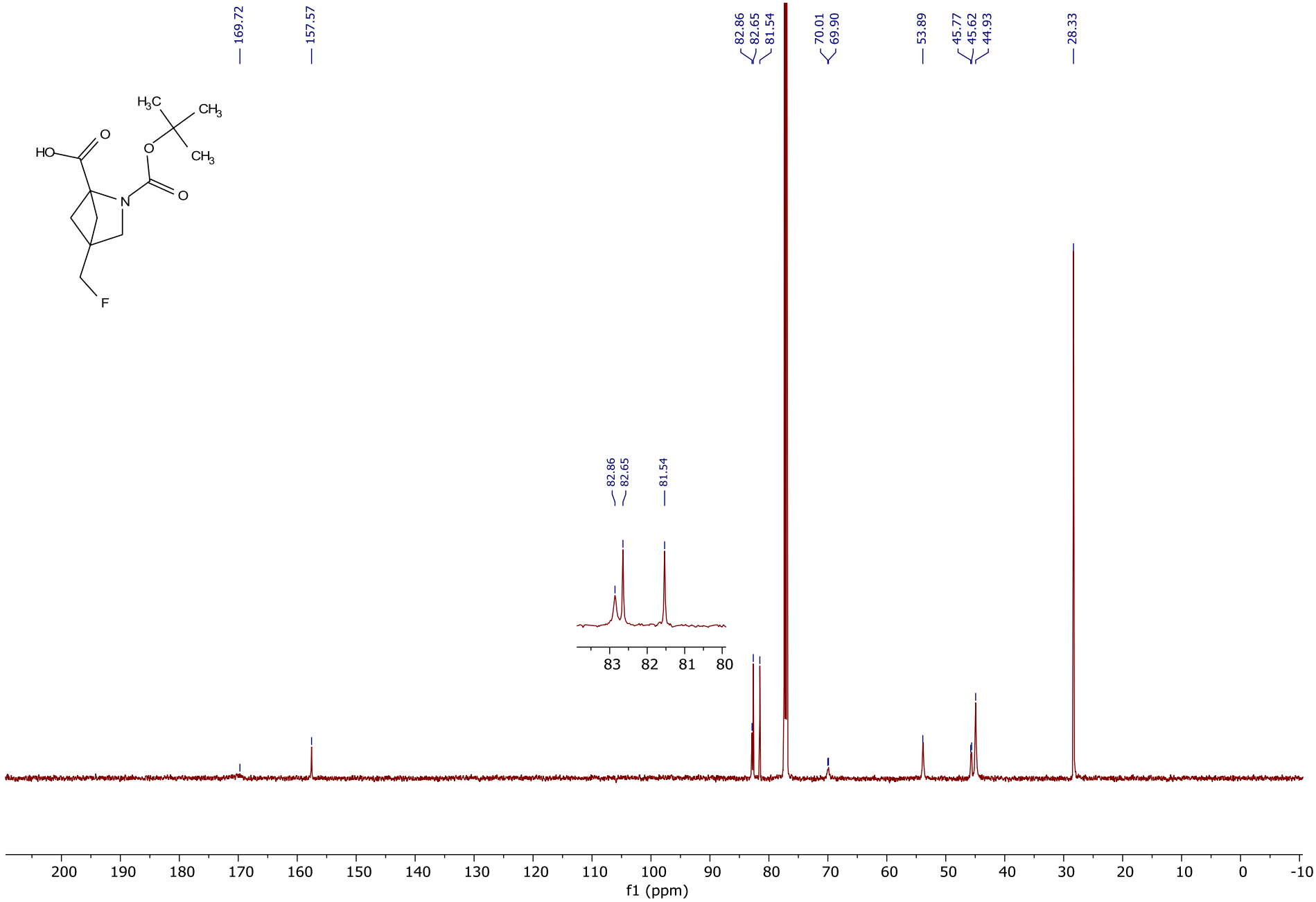

Figure 24. 2-(*tert*-Butoxycarbonyl)-4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **22,** $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$).

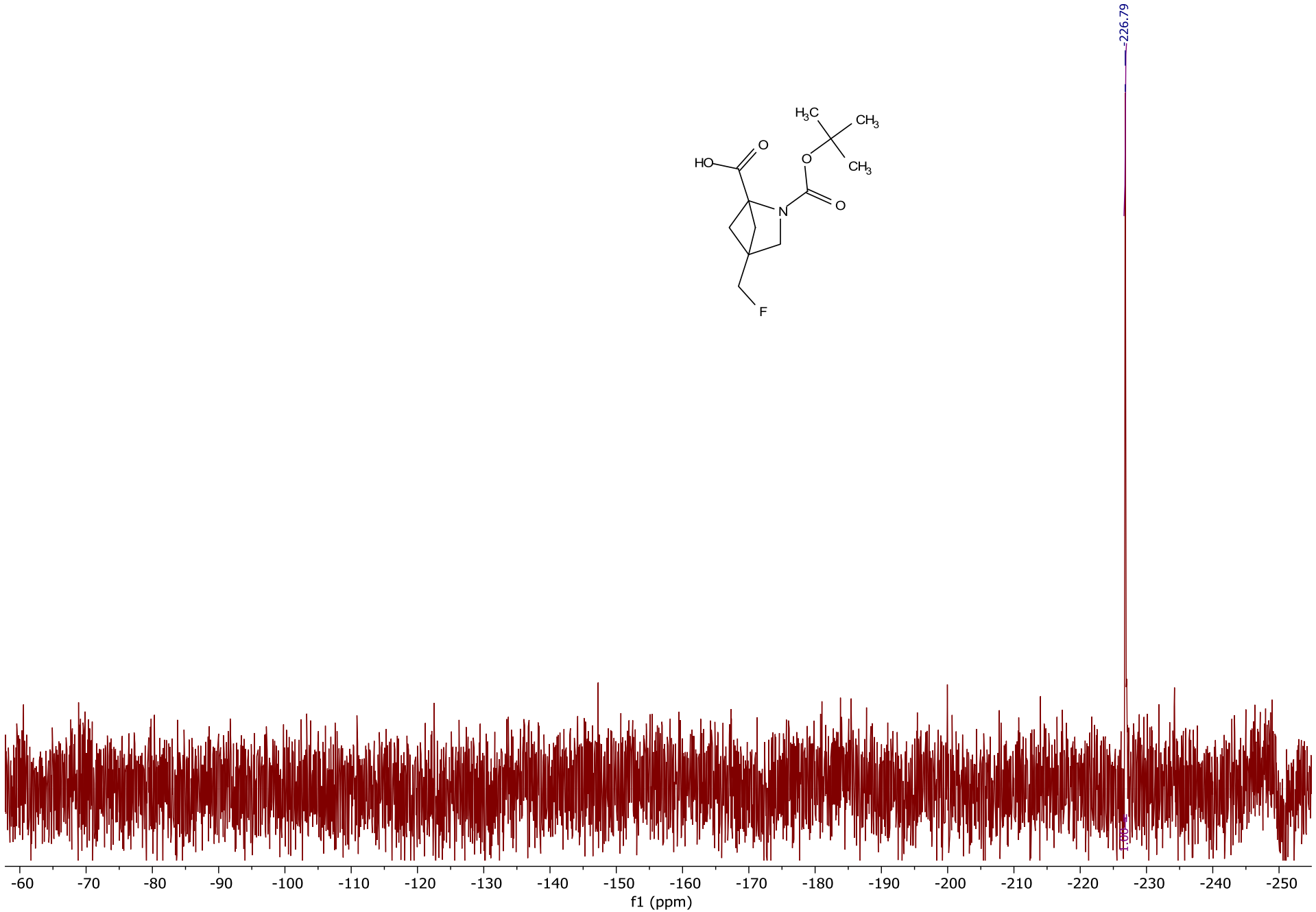

Figure 25. 2-(*tert*-Butoxycarbonyl)-4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid **22,** $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$).

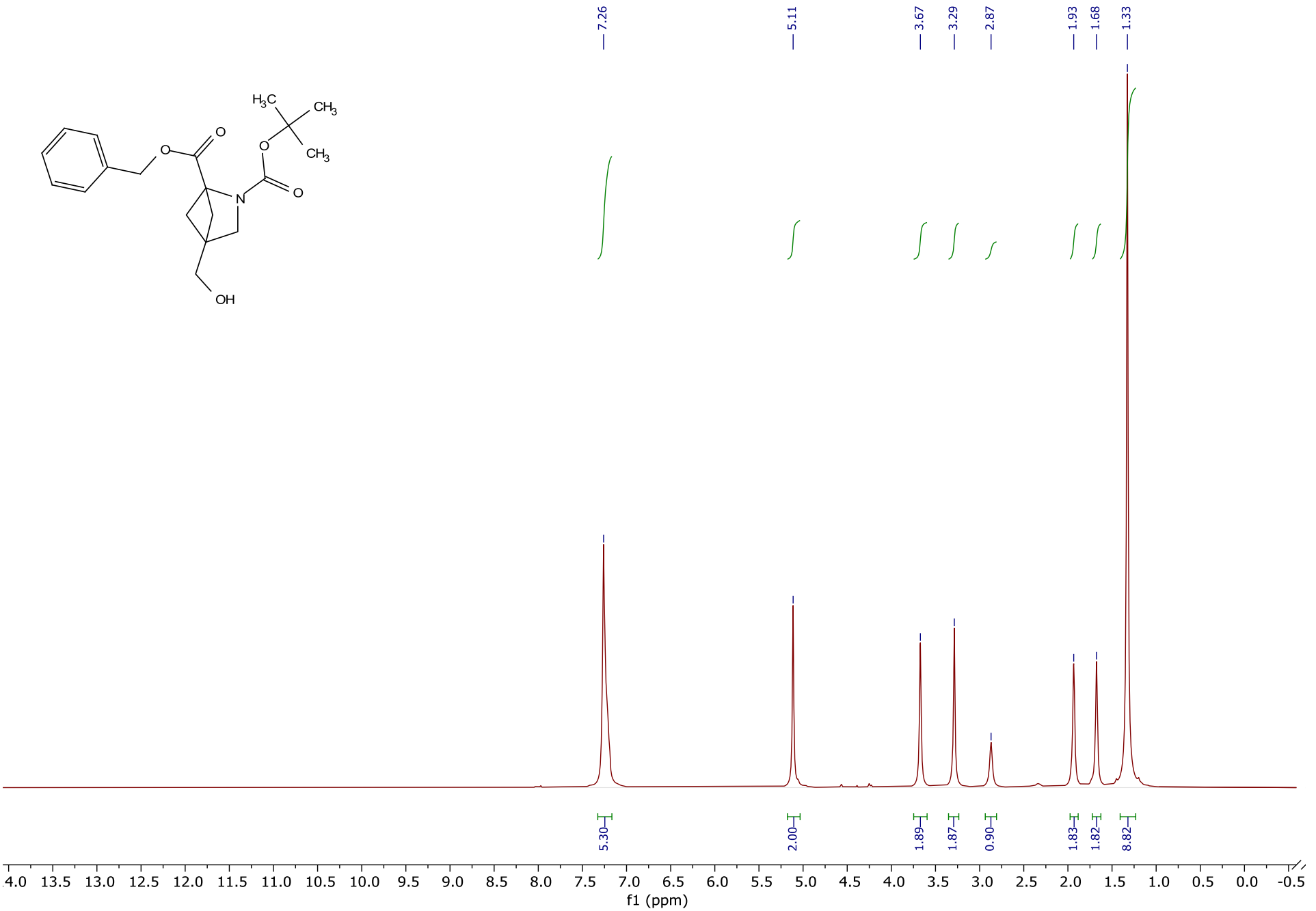

Figure 26. 1-Benzyl 2-(*tert*-butyl) 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **23,** ^{1}H NMR (500 MHz, $CDCl_3$).

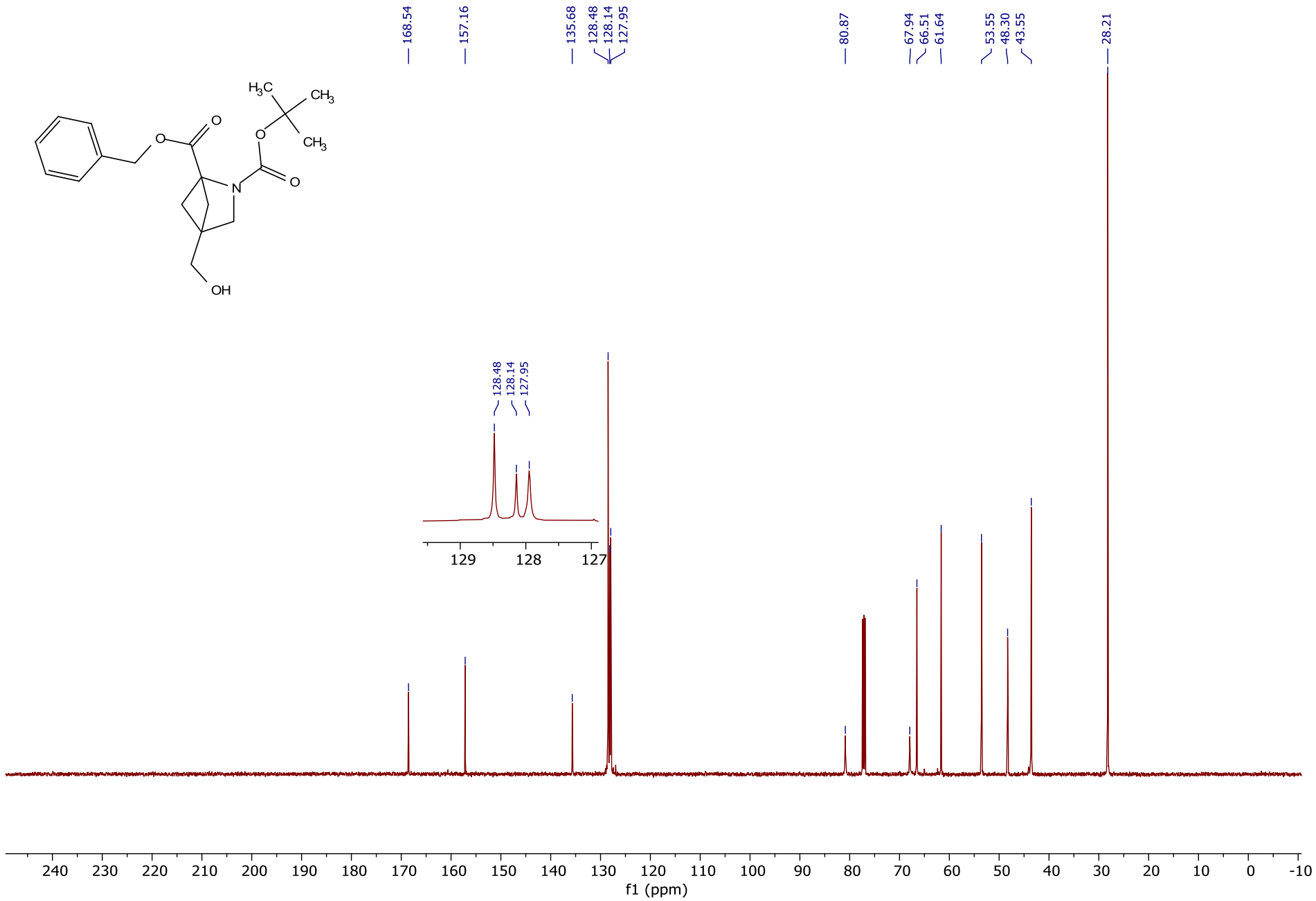

Figure 27. 1-Benzyl 2-(*tert*-butyl) 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **23,** $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$).

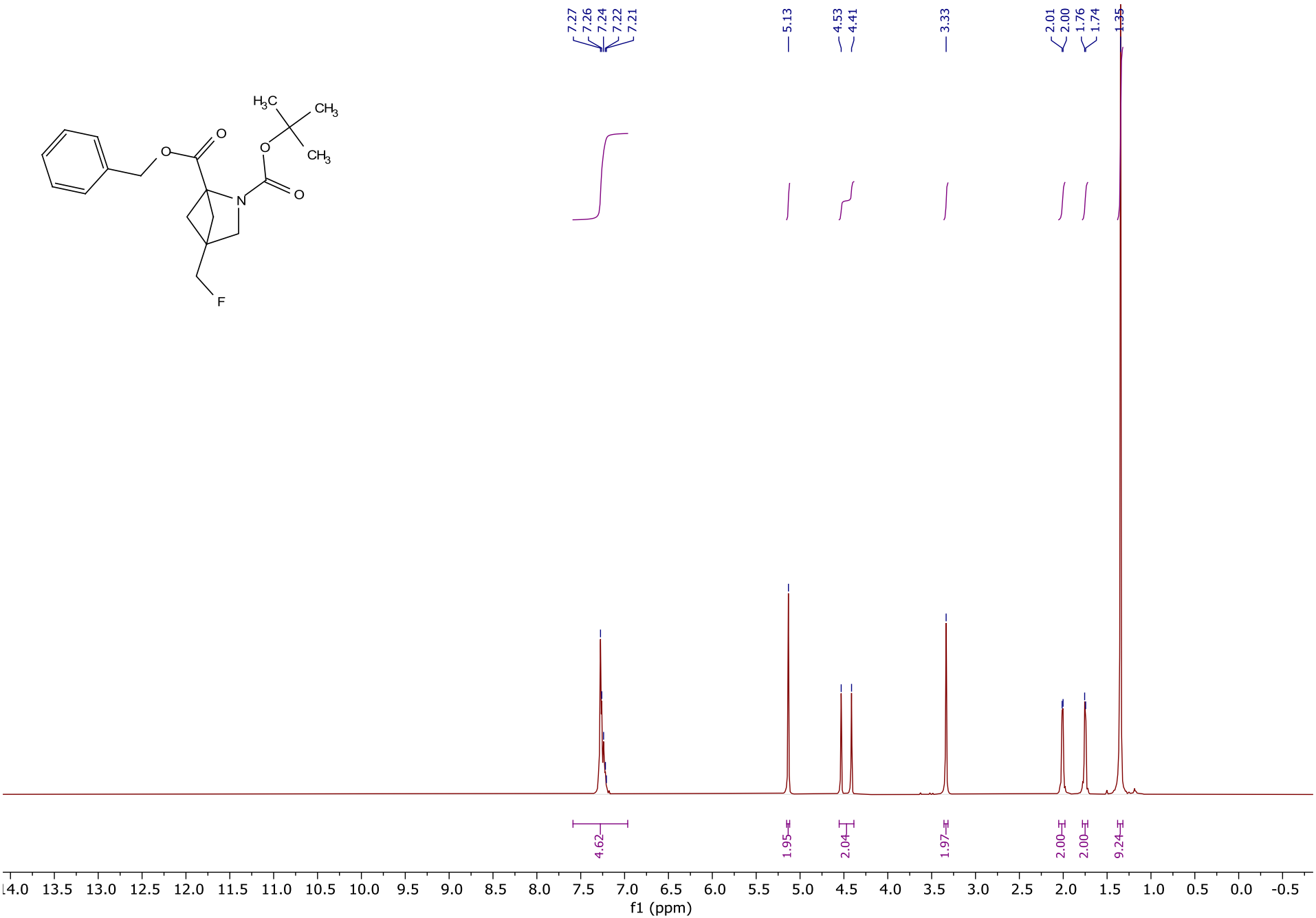

Figure 28. 1-Benzyl 2-(*tert*-butyl) 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **24,** ^{1}H NMR (400 MHz, $CDCl_3$).

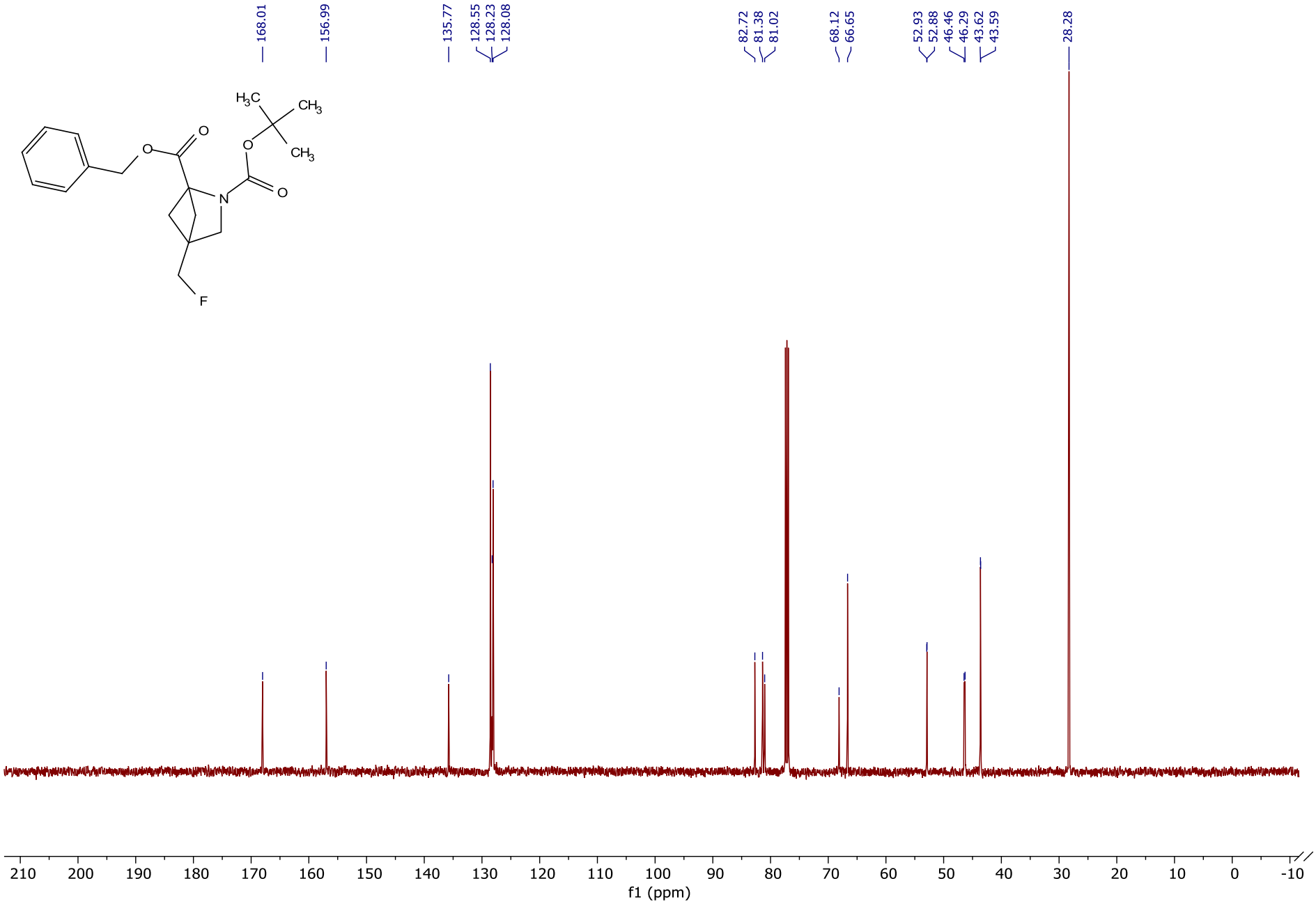

Figure 29. 1-Benzyl 2-(*tert*-butyl) 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **24,** $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$).

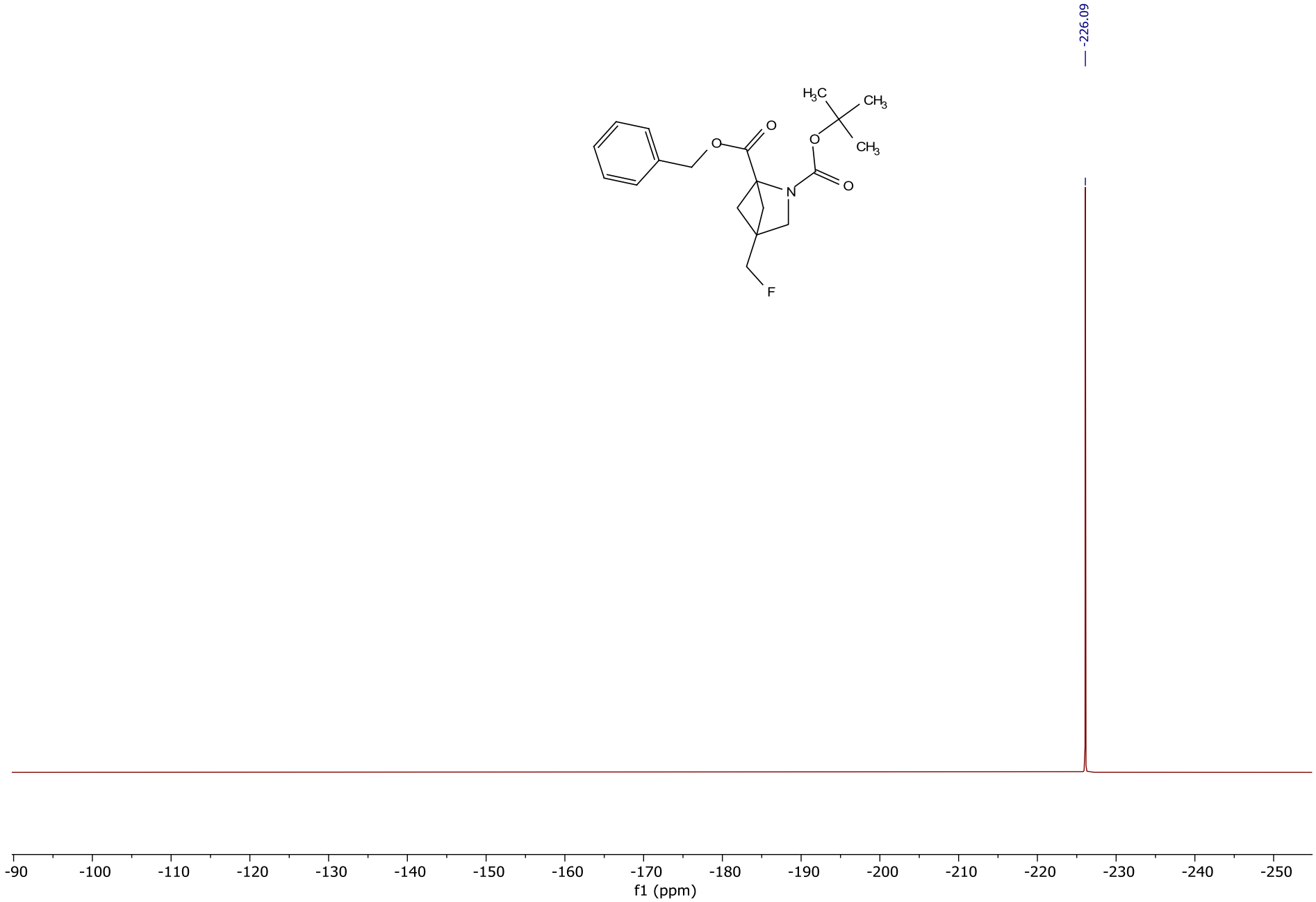

Figure 30. 1-Benzyl 2-(*tert*-butyl) 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **24,** $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$).

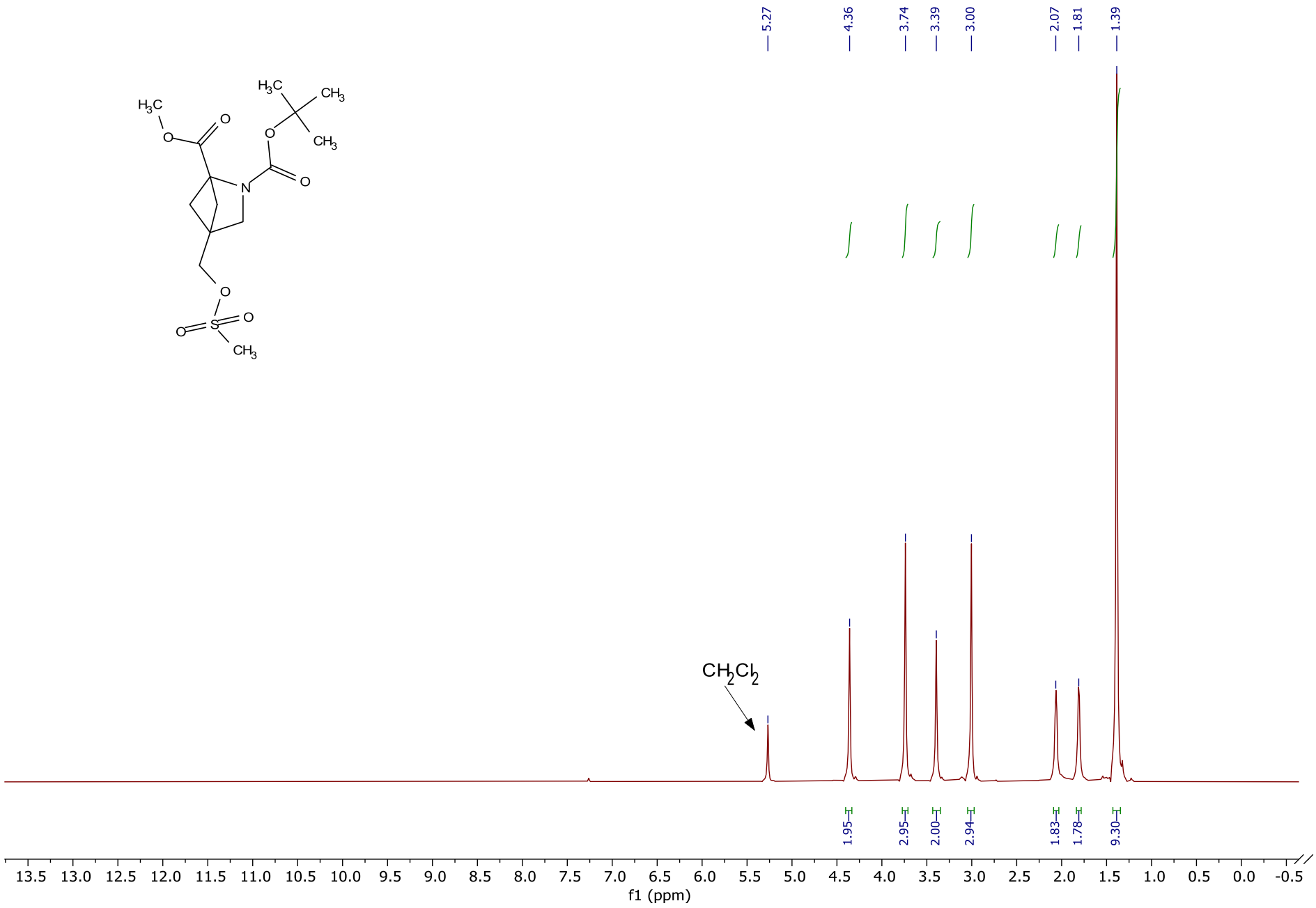

Figure 31. 2-(*tert*-Butyl) 1-methyl 4-(((methylsulfonyl)oxy)methyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **25,** ^{1}H NMR (400 MHz, $CDCl_3$).

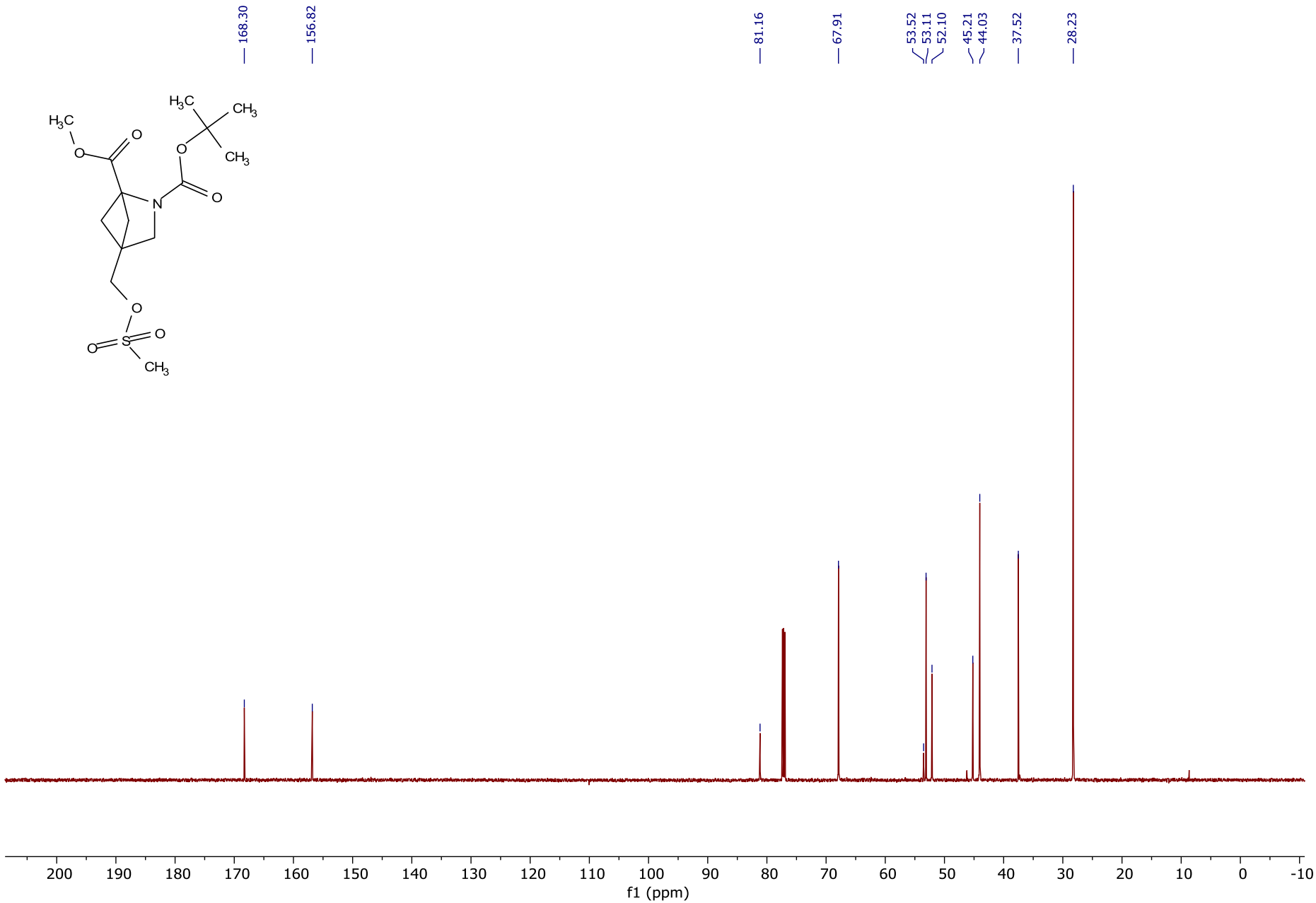

Figure 32. 2-(*tert*-Butyl) 1-methyl 4-(((methylsulfonyl)oxy)methyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **25,** $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$).

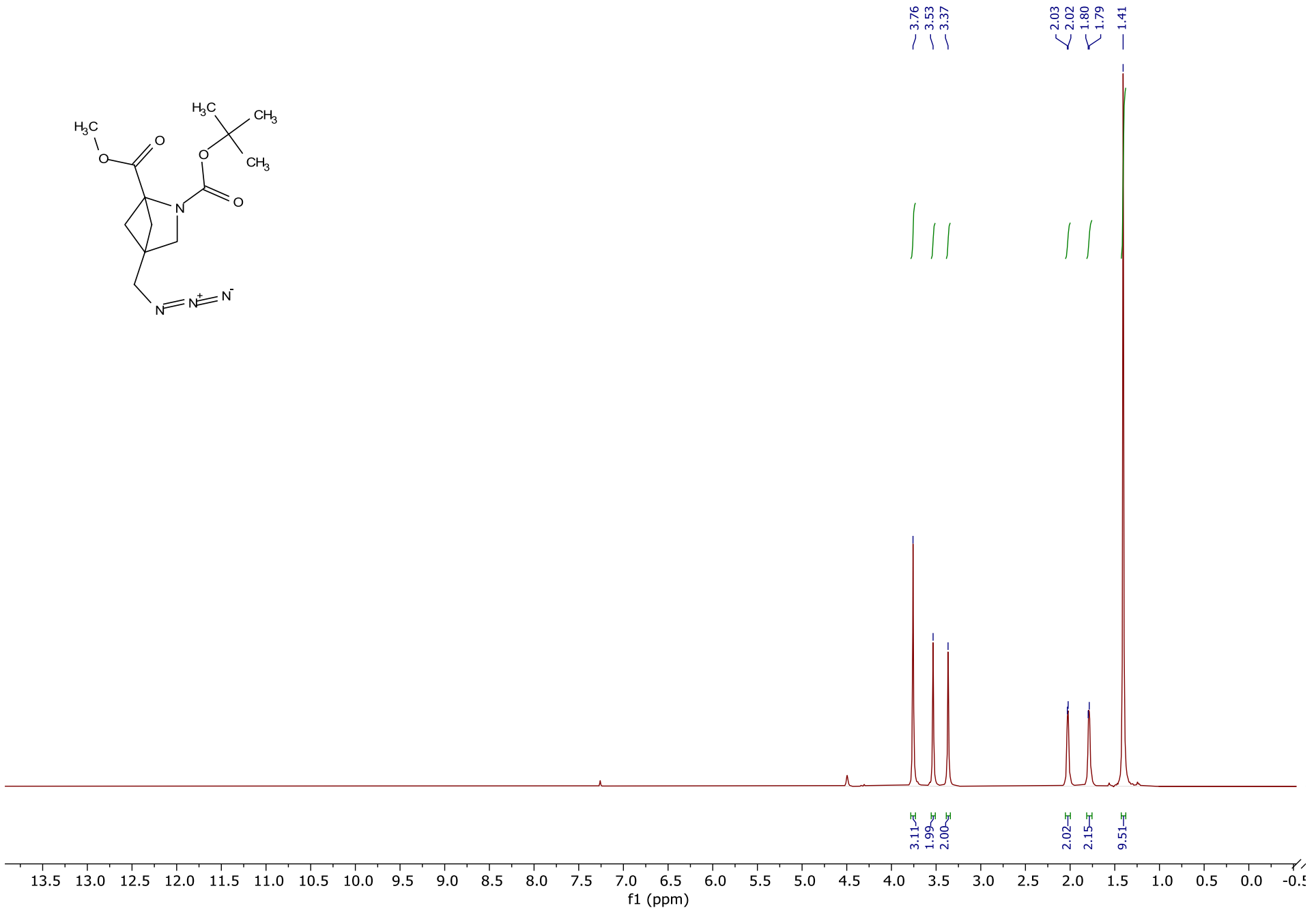

Figure 33. 2-(*tert*-Butyl) 1-methyl 4-(azidomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **26,** ^{1}H NMR (400 MHz, $CDCl_3$).

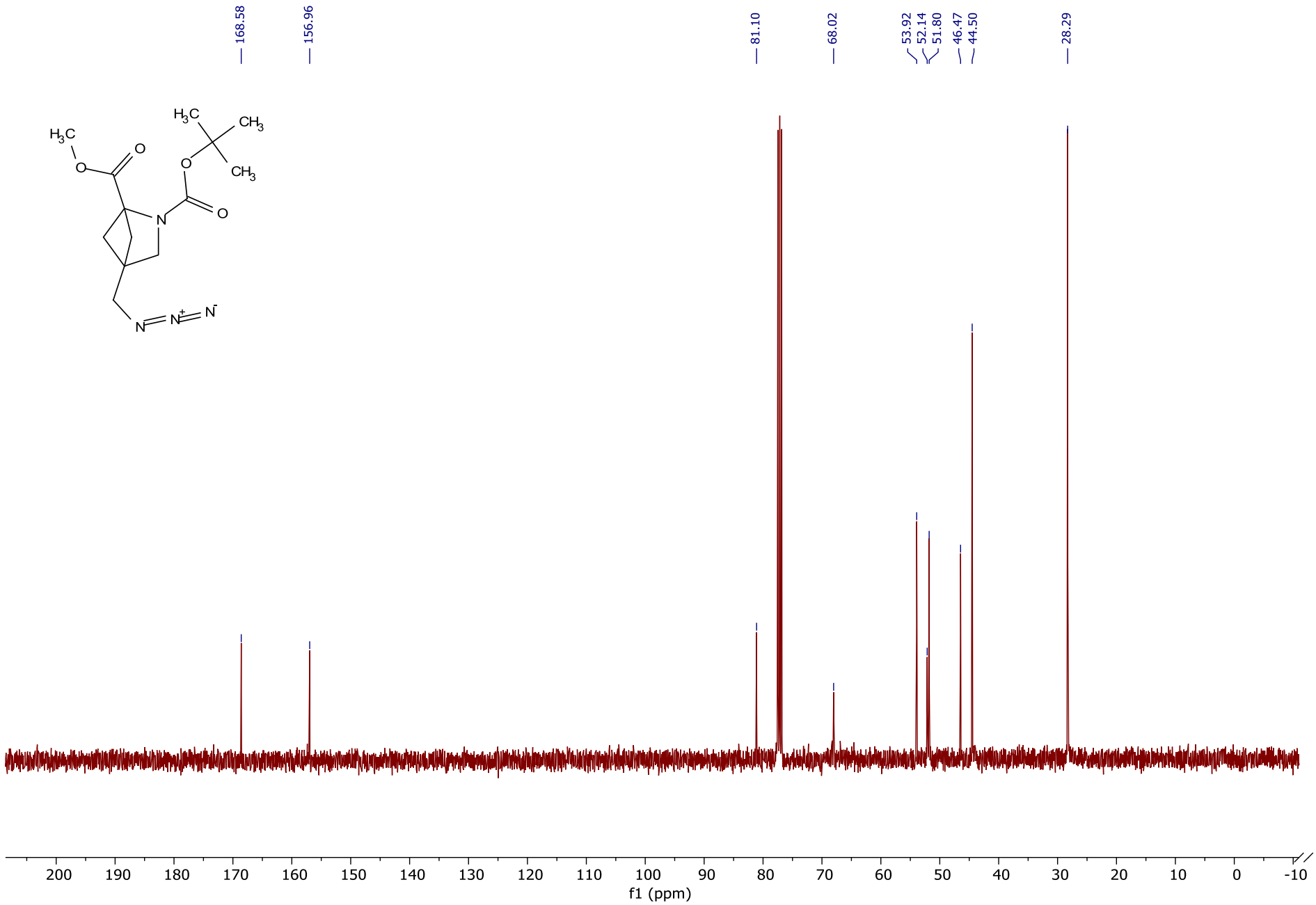

Figure 34. 2-(*tert*-Butyl) 1-methyl 4-(azidomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **26,** $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$).

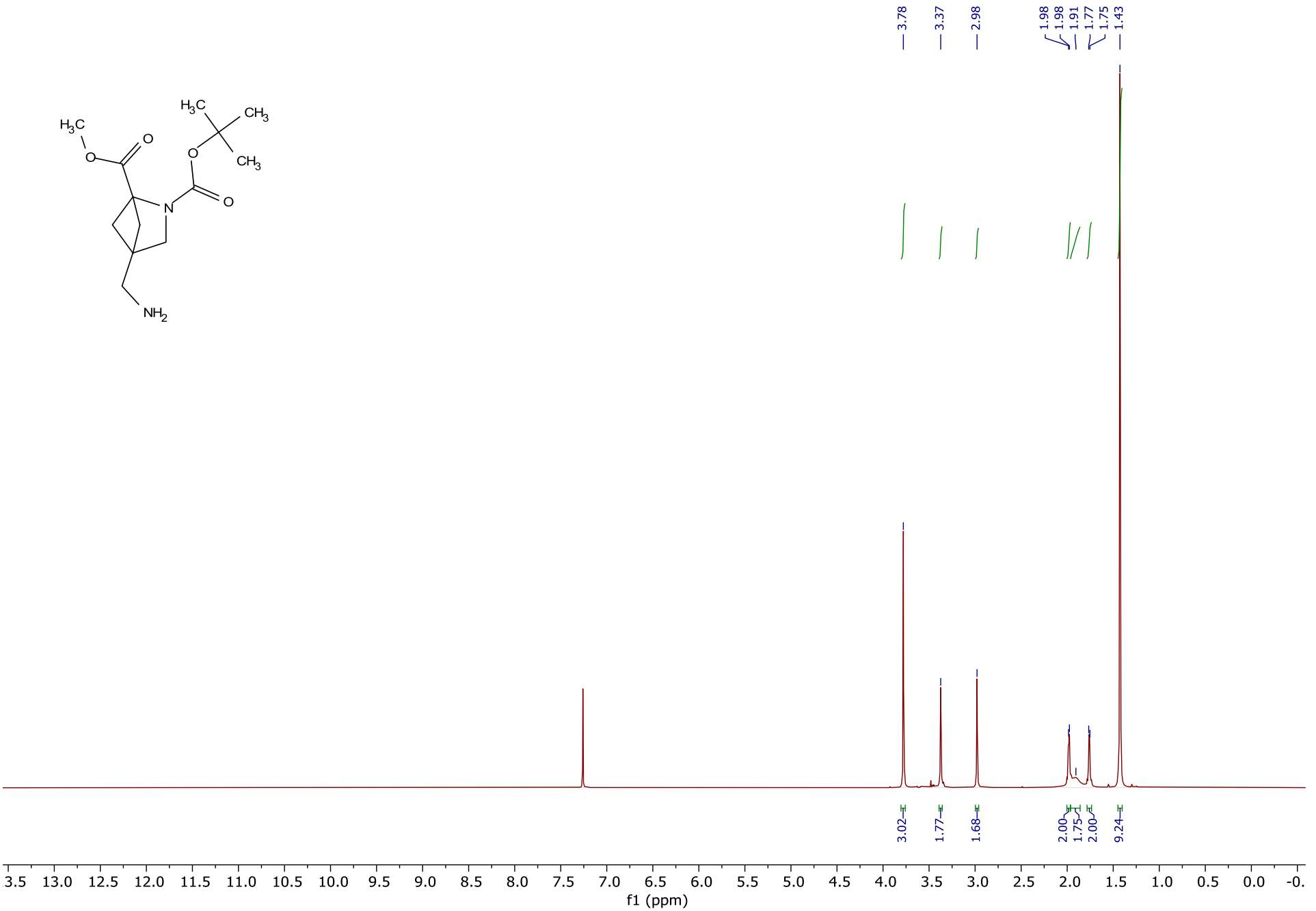

Figure 35. 2-(*tert*-Butyl) 1-methyl 4-(aminomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **27,** ^{1}H NMR (500 MHz, $CDCl_3$).

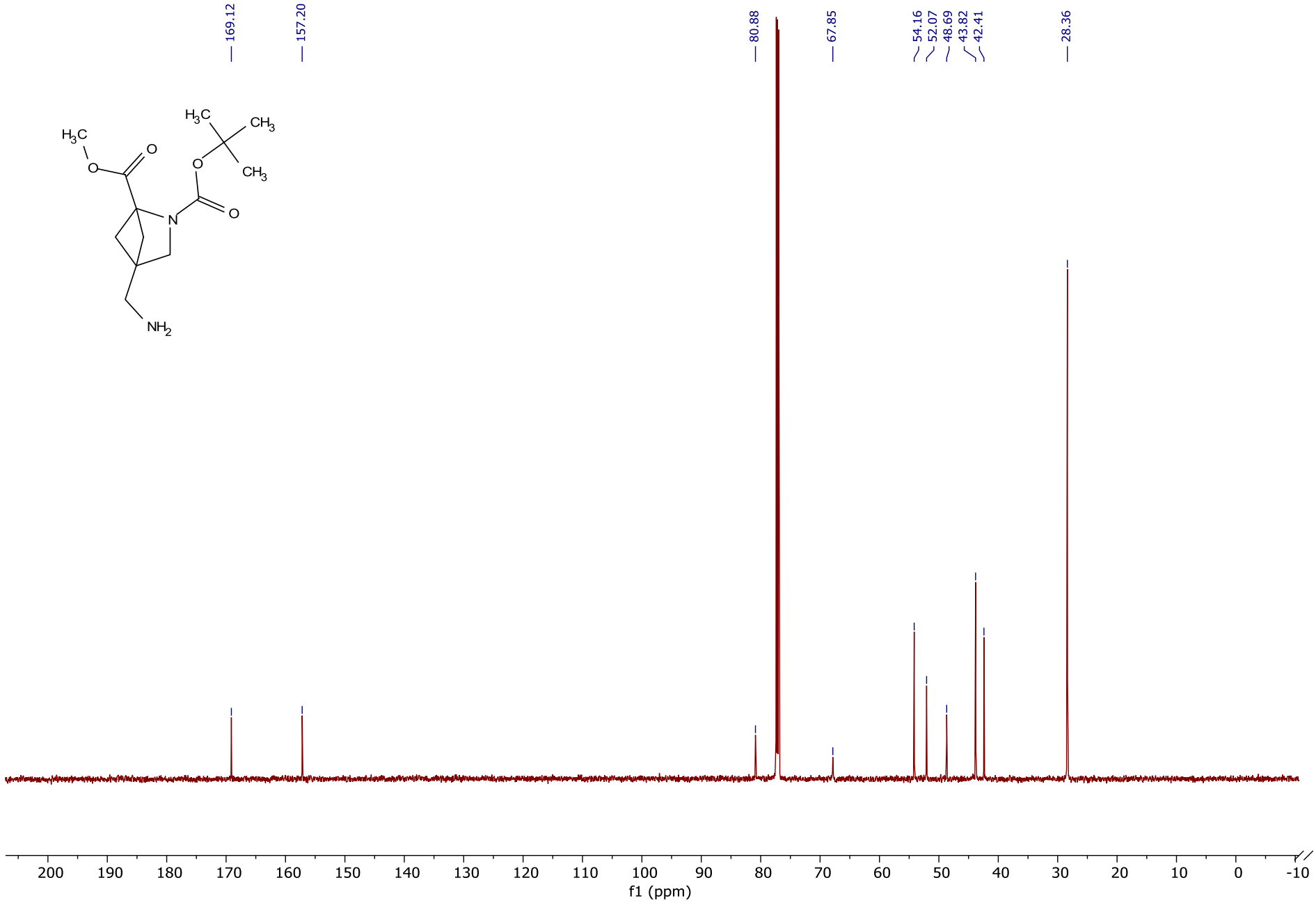

Figure 36. 2-(*tert*-Butyl) 1-methyl 4-(aminomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **27,** $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$).

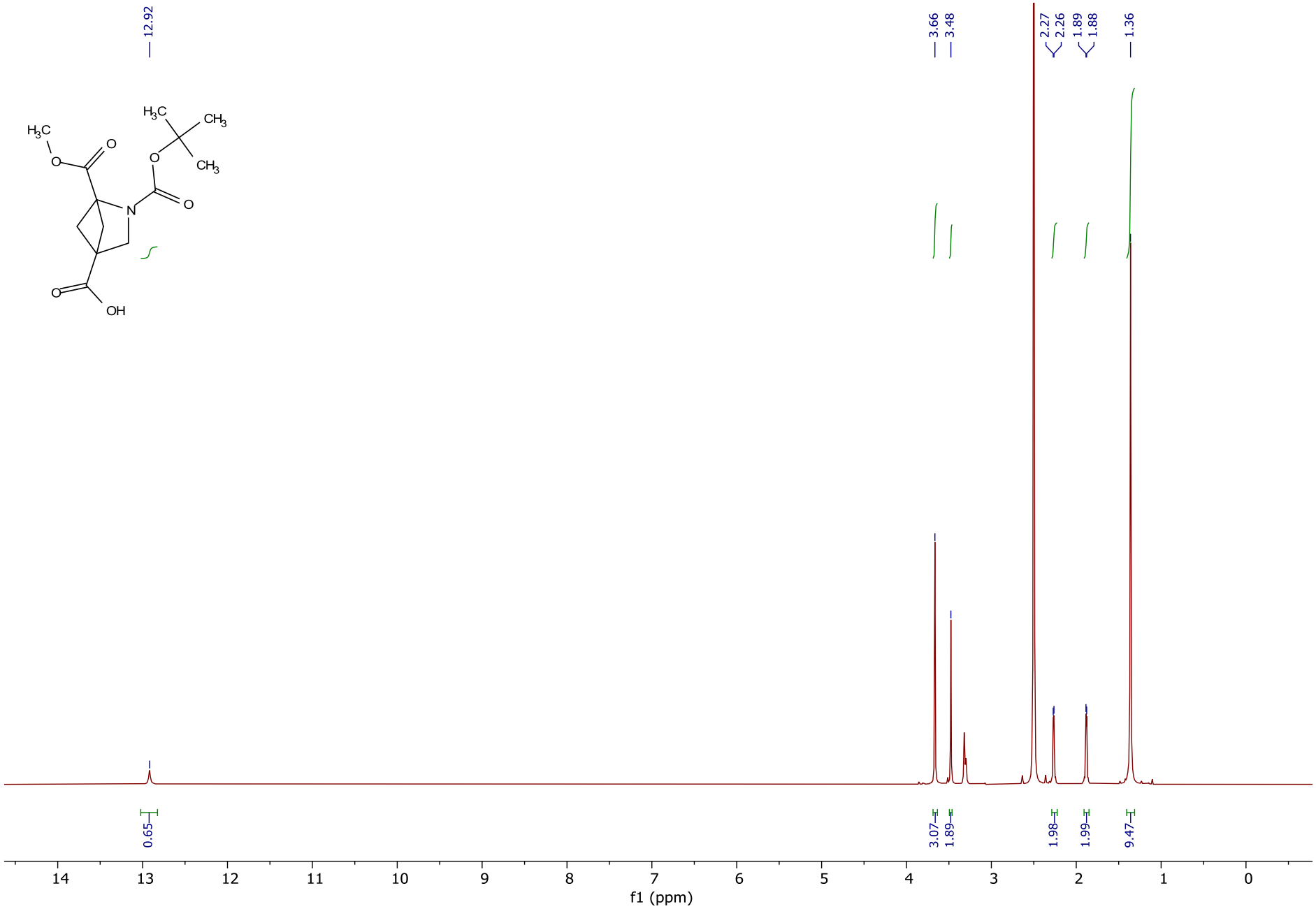

Figure 37. 2-(*tert*-Butoxycarbonyl)-1-(methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **28,** ^{1}H NMR (500 MHz, DMSO-d_6).

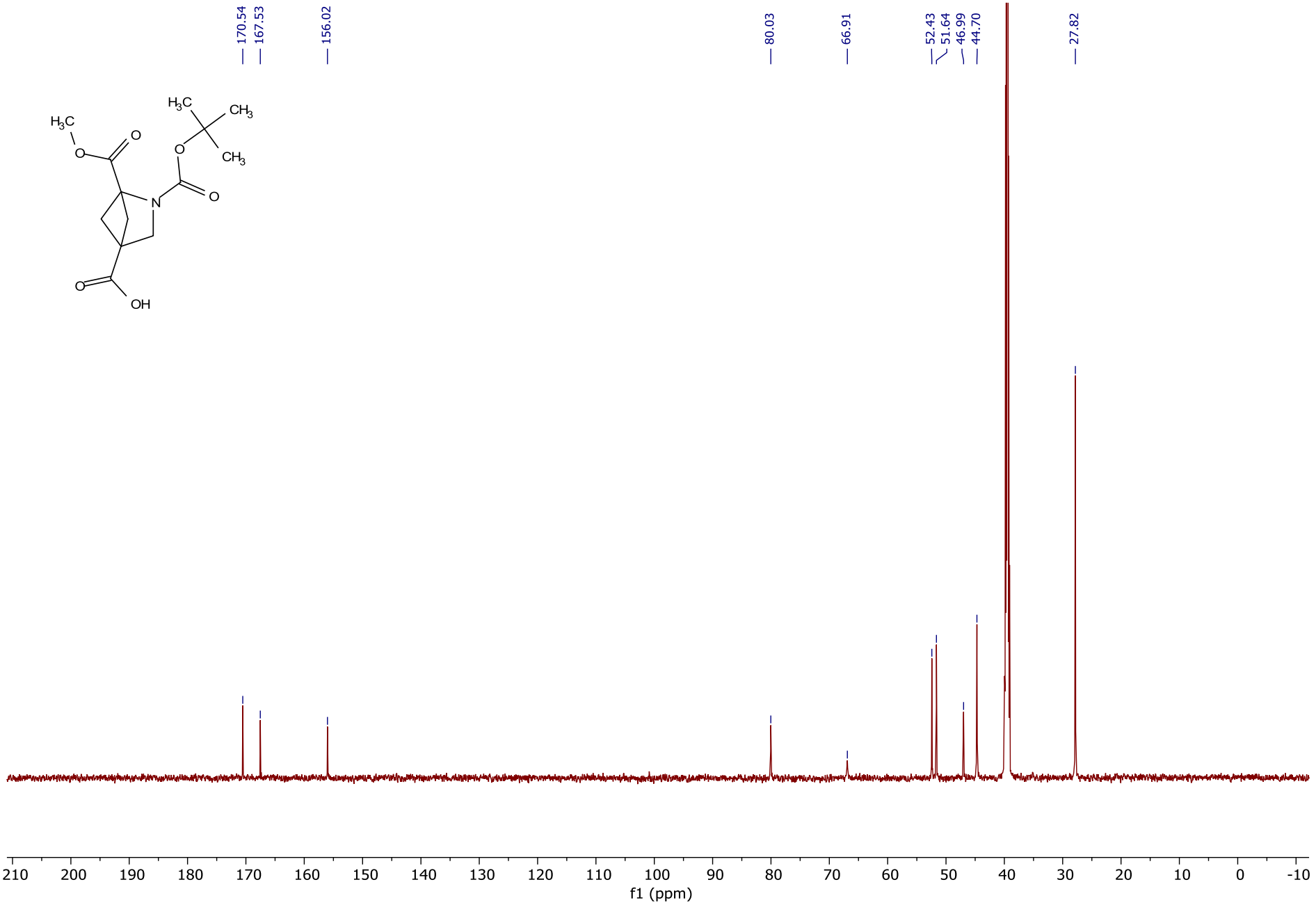

Figure 38. 2-(*tert*-Butoxycarbonyl)-1-(methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **28,** $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6).

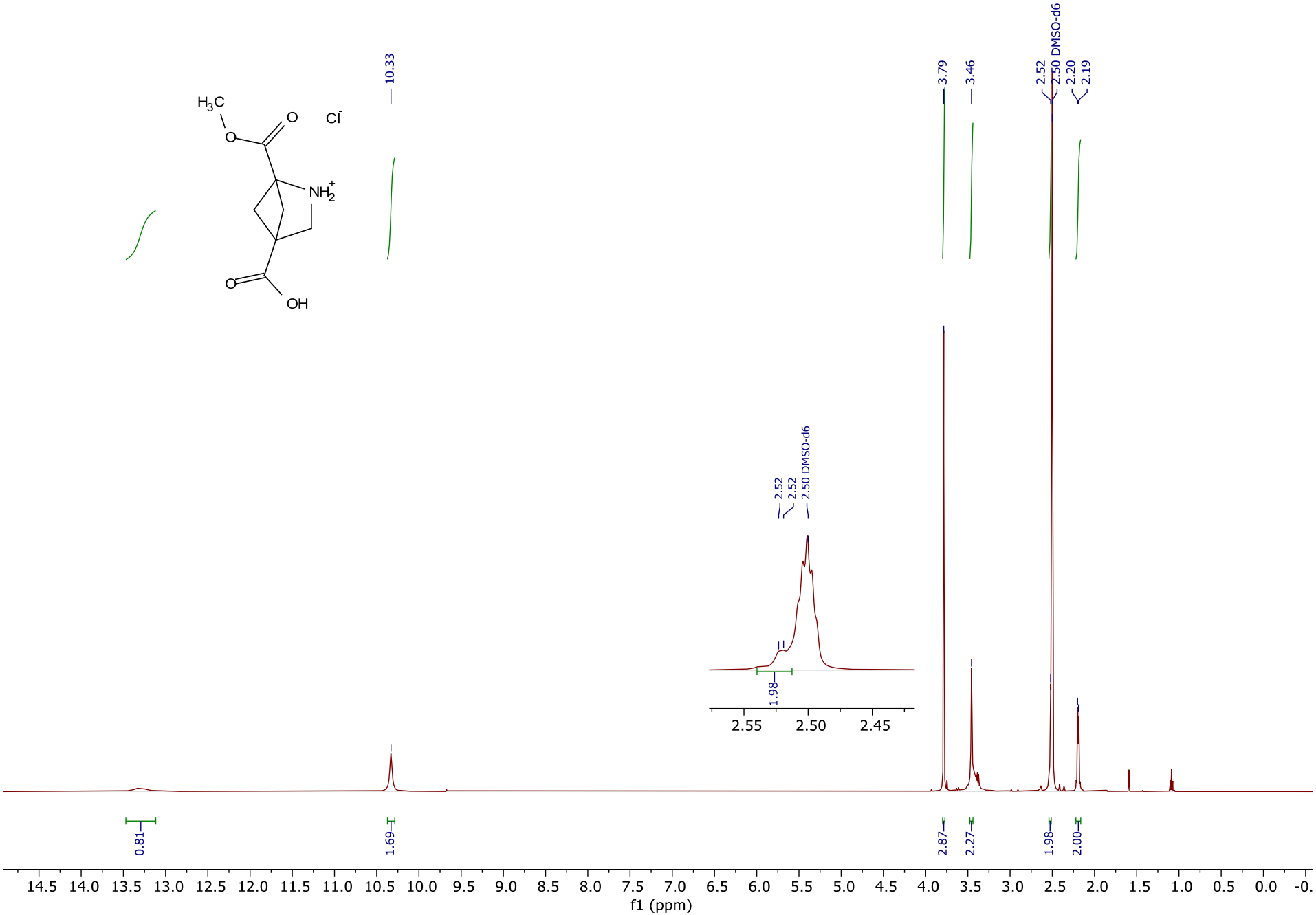

Figure 39. 1-(Methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid hydrochloride **29,** ^{1}H NMR (500 MHz, DMSO-d_6).

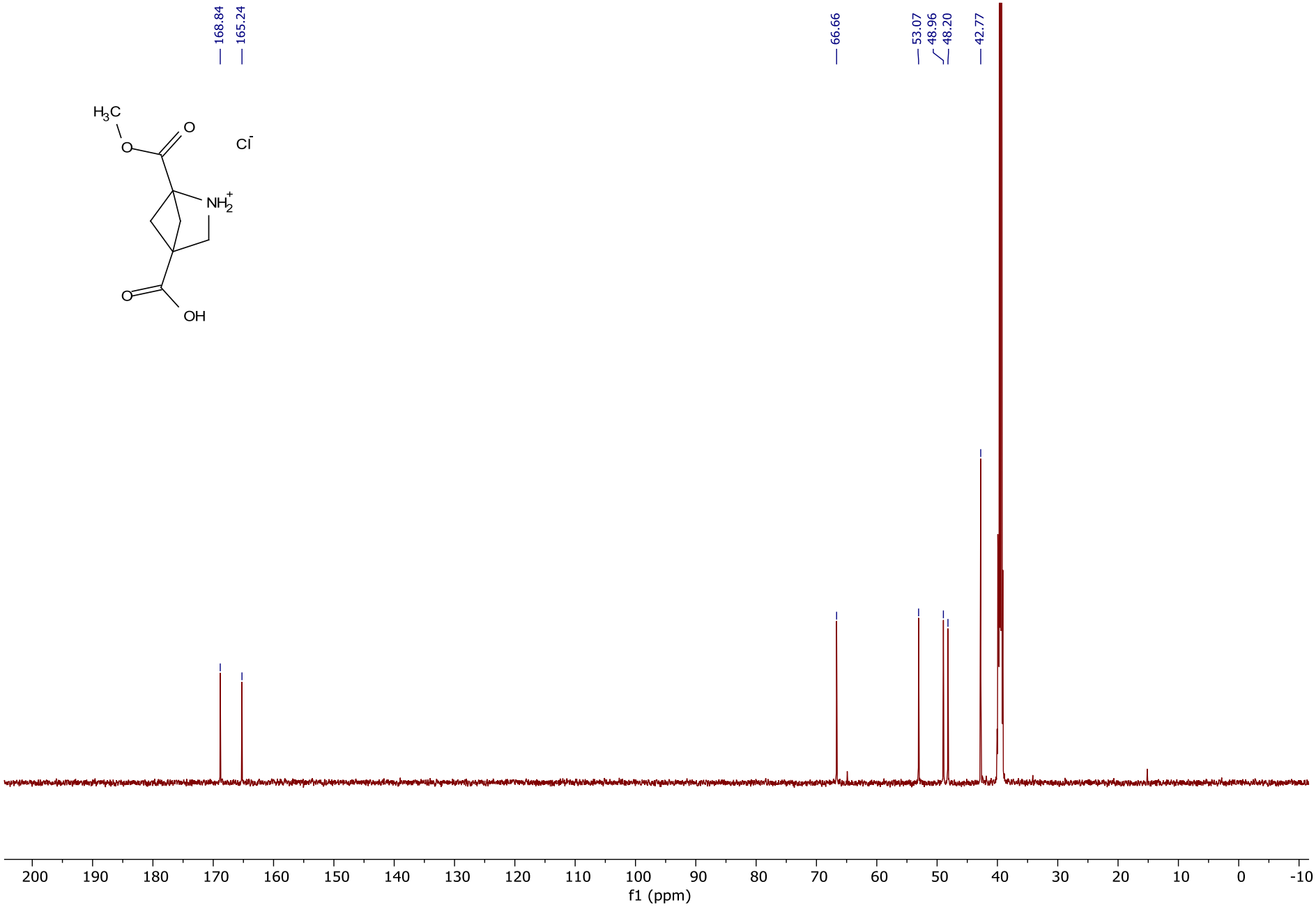

Figure 40. 1-(Methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid hydrochloride **29,** $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6).

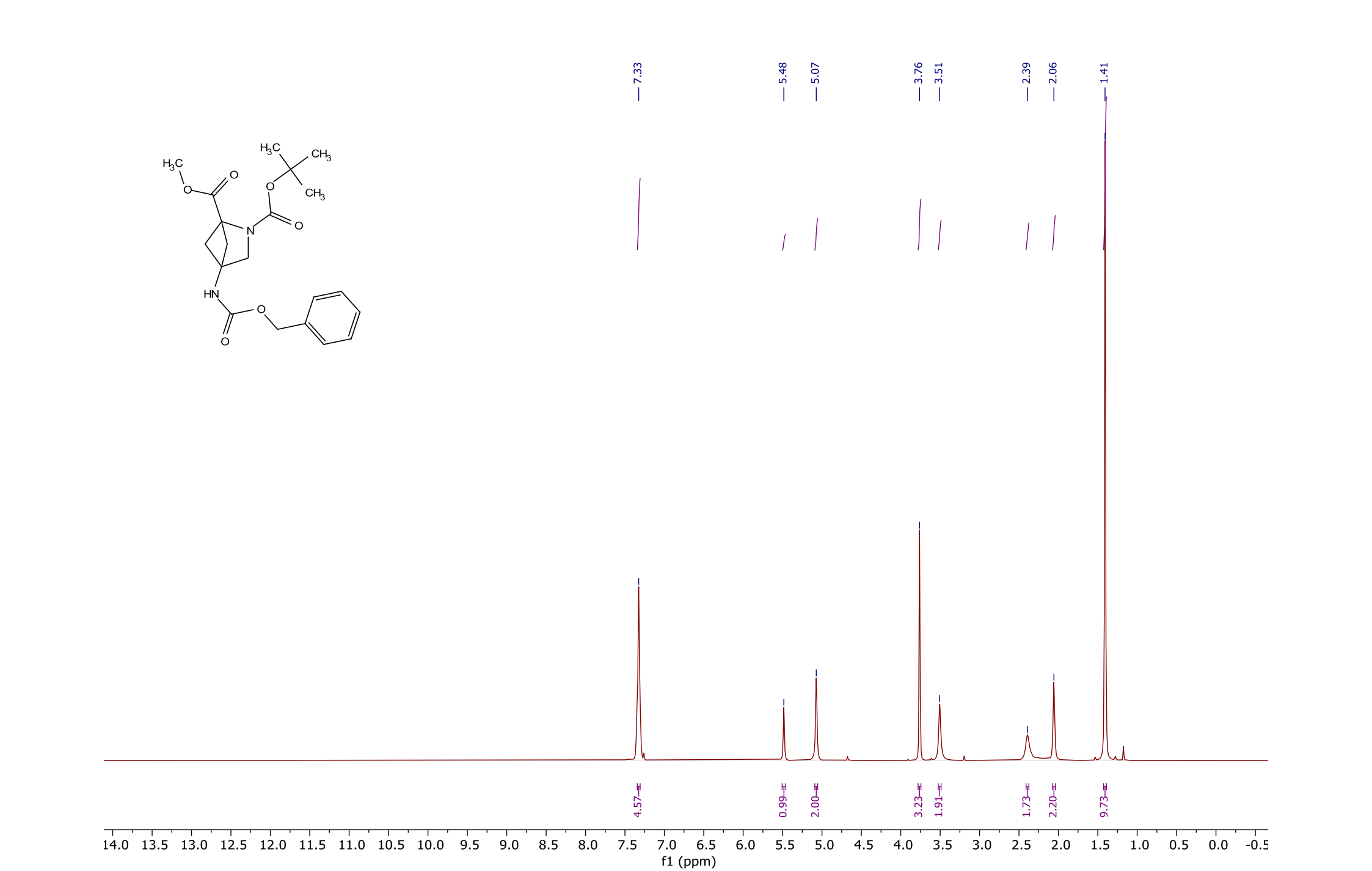

Figure 41. 2-(*tert*-Butyl) 1-methyl 4-(((benzyloxy)carbonyl)amino)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **30,** ^{1}H NMR (400 MHz, $CDCl_3$).

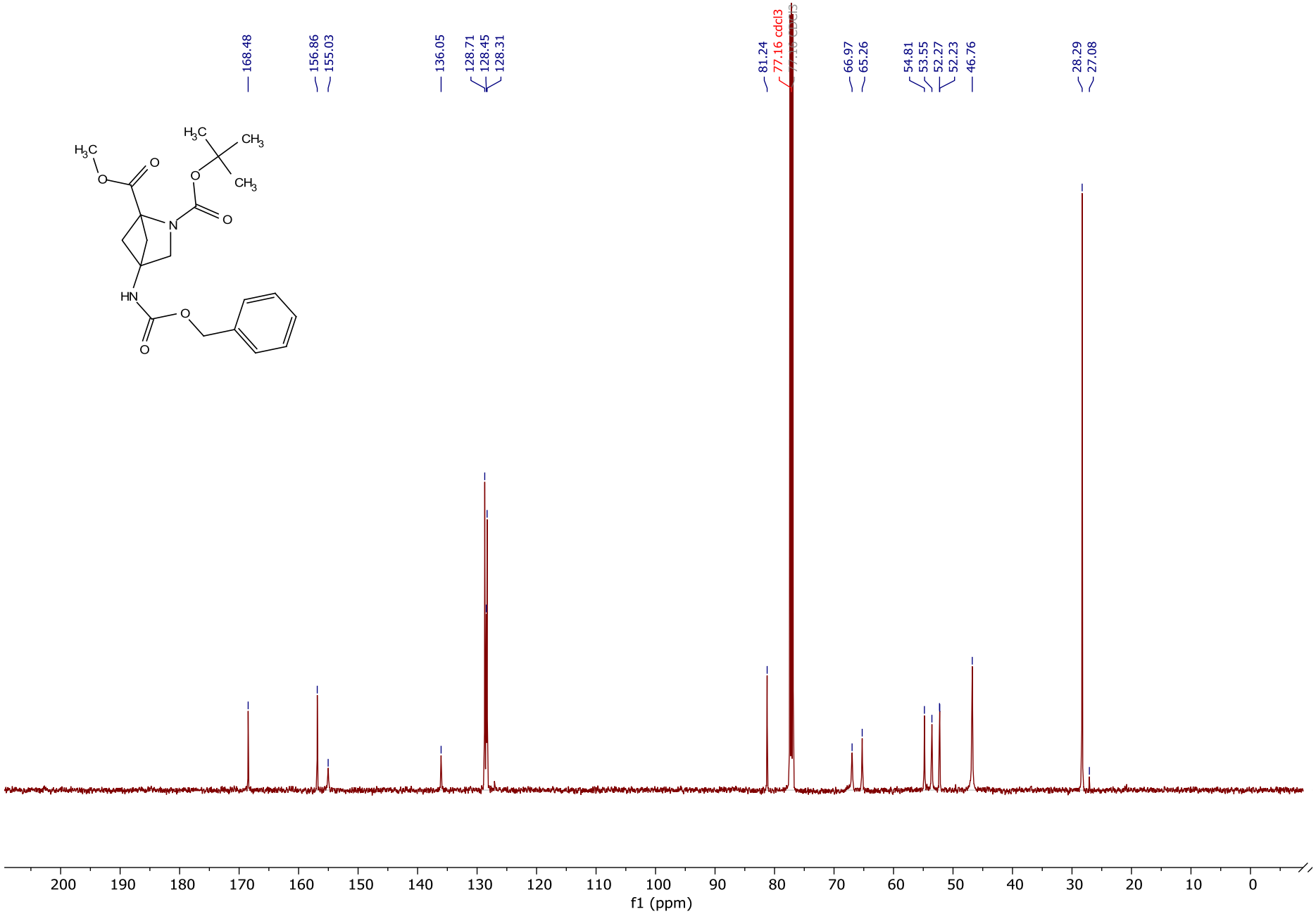

Figure 42. 2-(*tert*-Butyl) 1-methyl 4-(((benzyloxy)carbonyl)amino)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **30,** $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$).

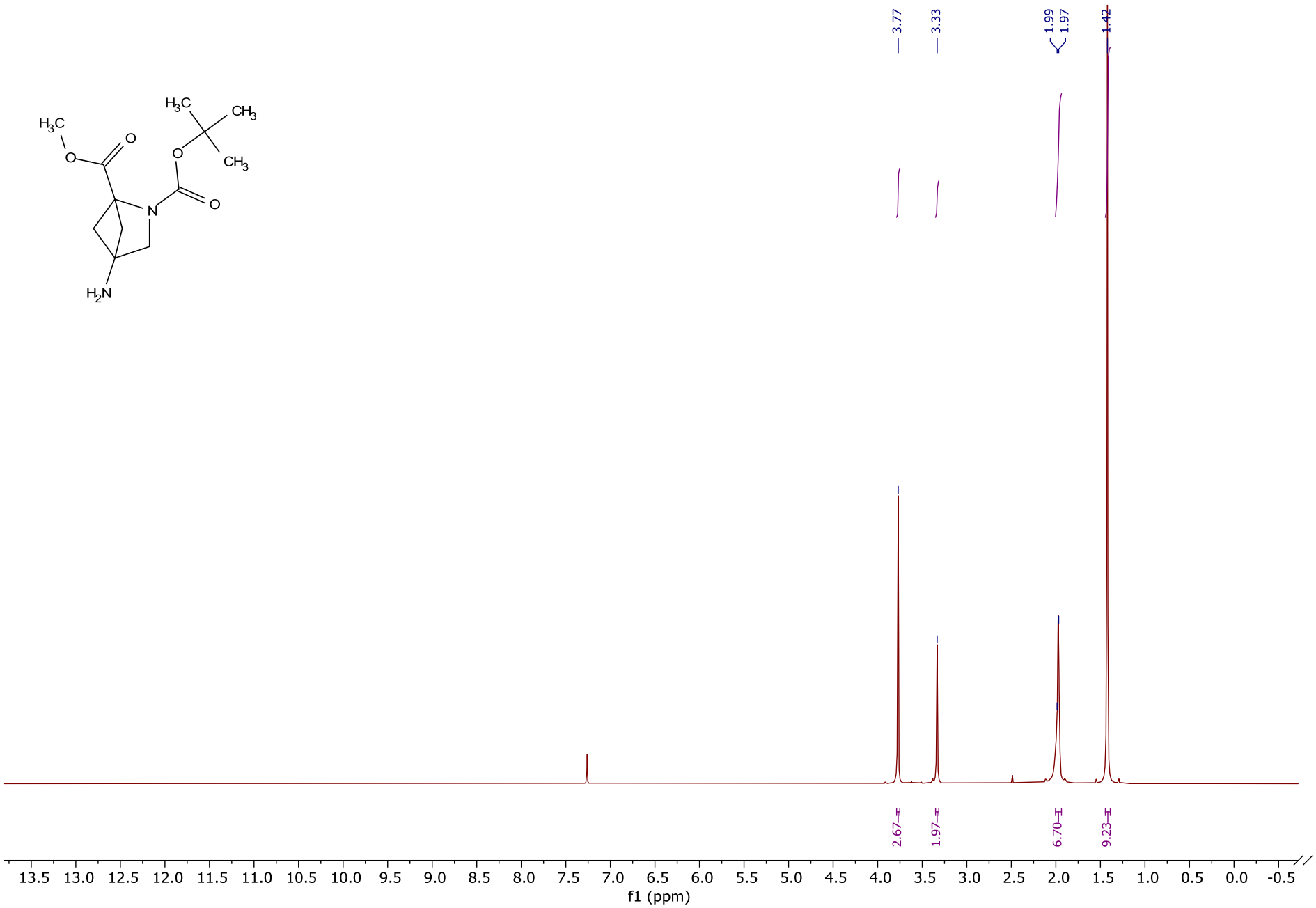

Figure 43. 2-(*tert*-Butyl) 1-methyl 4-amino-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **31,** ^{1}H NMR (500 MHz, $CDCl_3$).

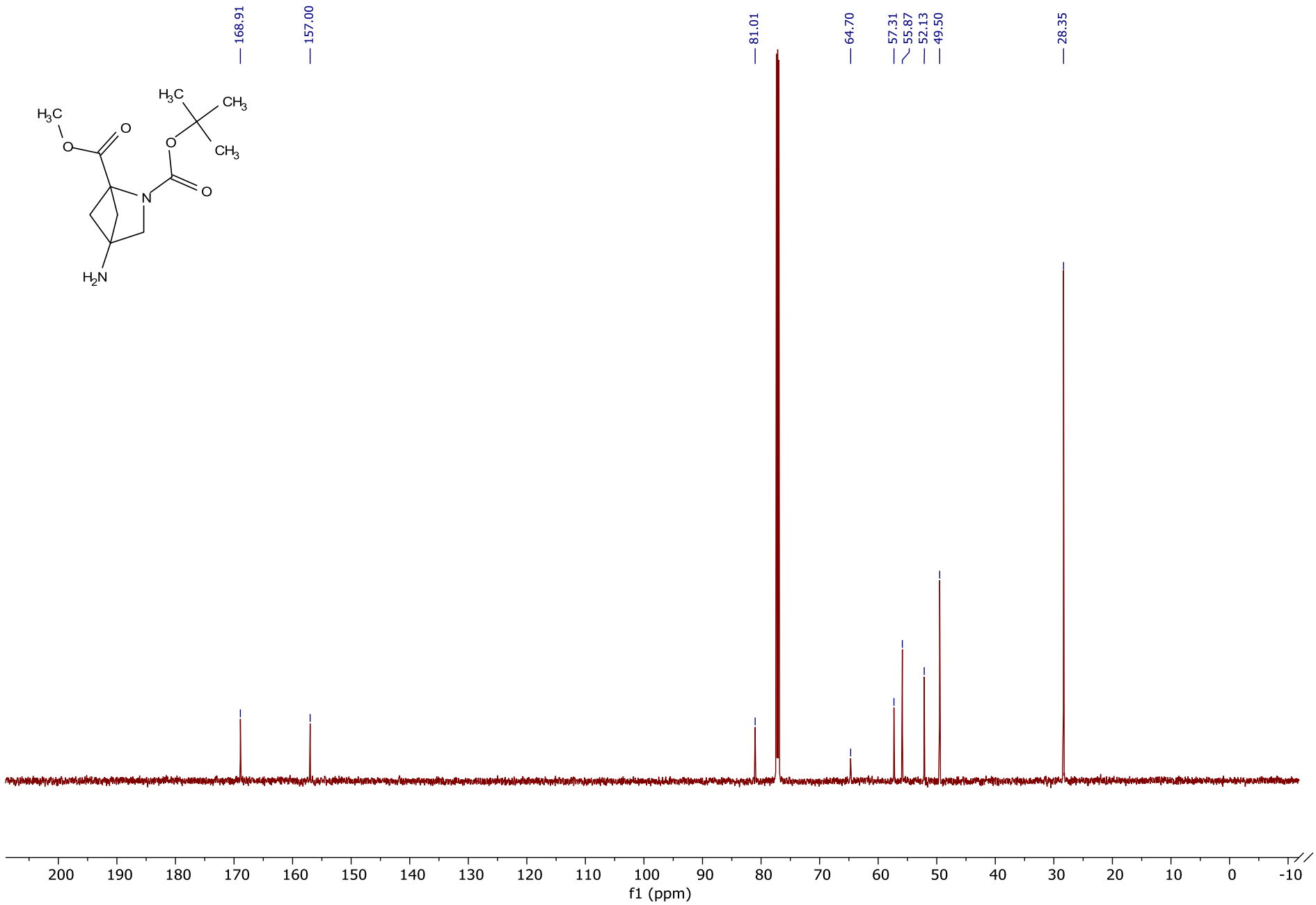

Figure 44. 2-(*tert*-Butyl) 1-methyl 4-amino-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate **31,** $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$).