

Supporting Information for:

Squaric Acid-Based Peptidic Inhibitors of Matrix Metalloprotease-1 (MMP-1)

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General Methods. NMR spectra were recorded on 300 or 400 MHz instruments. Spectra were calibrated using TMS ($\delta = 0.00$ ppm) for ^1H -NMR, methanol- d_4 ($\delta = 49.2$ ppm) or DMSO- d_6 ($\delta = 39.5$ ppm) for ^{13}C -NMR. Mass spectra were recorded using fast atom bombardment or electrospray ionization methods. Methylene chloride and methanol were used from a dry solvent dispensing system. All other reagents were used as received. Full characterization for compounds **3b**, **3c**, **3e**¹ and **10e**,² as well as ^1H NMR spectra for compounds **10c** and **10f**³ have been reported previously. ^{13}C NMR spectra for compounds **18** and **19** (Figures S86 and S88, respectively) were recorded using an MRM/Protasis CapNMRTM flow probe. These spectra have two regions that contain additional resonances caused by the fluorocarbon background from the susceptibility matching fluid. Multiple ^{13}C - ^{19}F couplings result in broad carbon peaks at δ 113.1, 110.3, 107.6, 104.8, 90.2, 87.9, 86.1, 84.0 ppm.

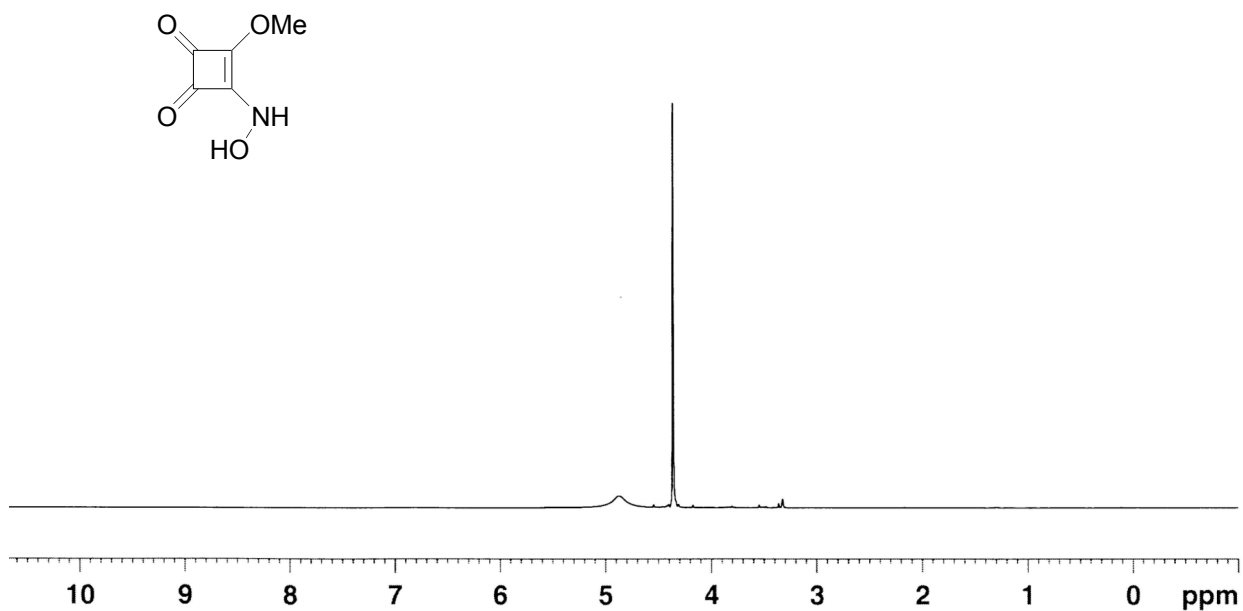


Figure S1. ^1H -NMR spectrum of compound **3a**.

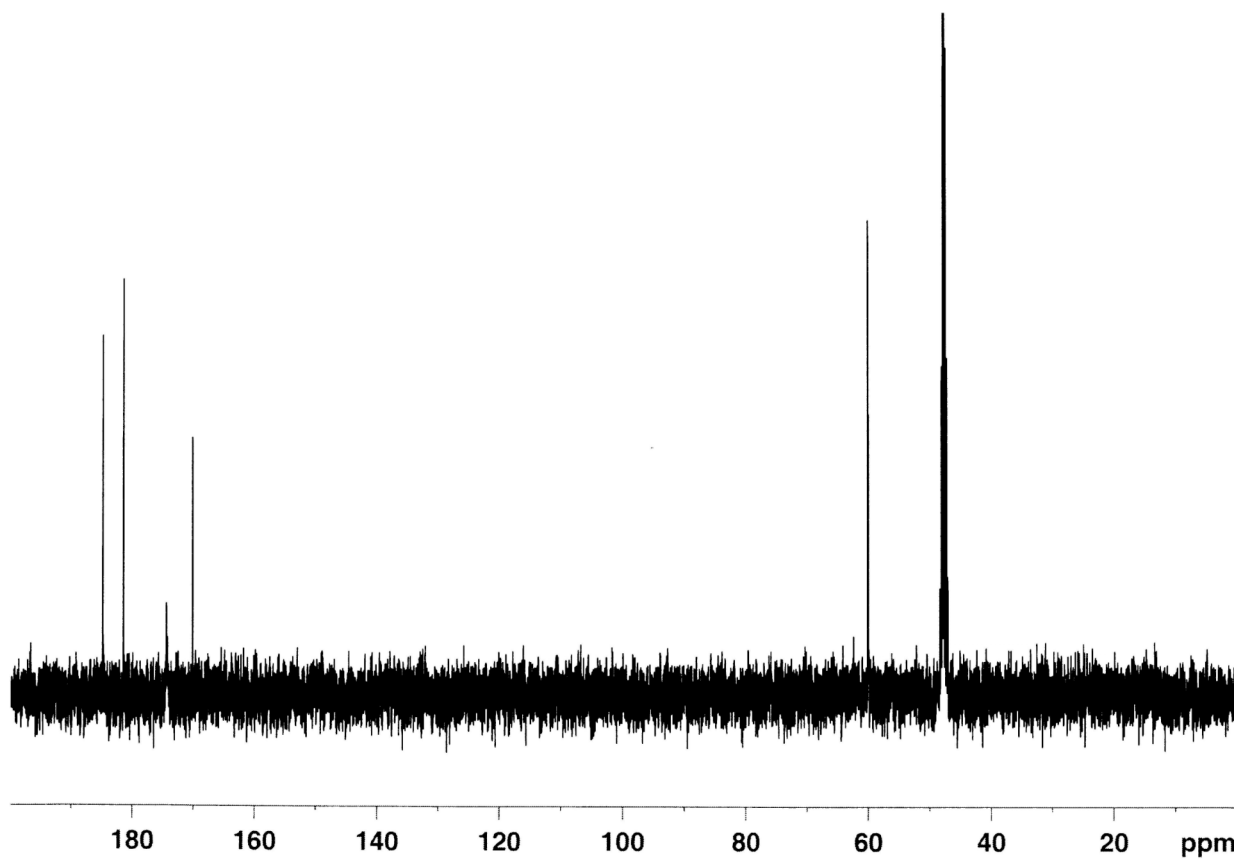


Figure S2. ^{13}C -NMR spectrum of compound **3a**.

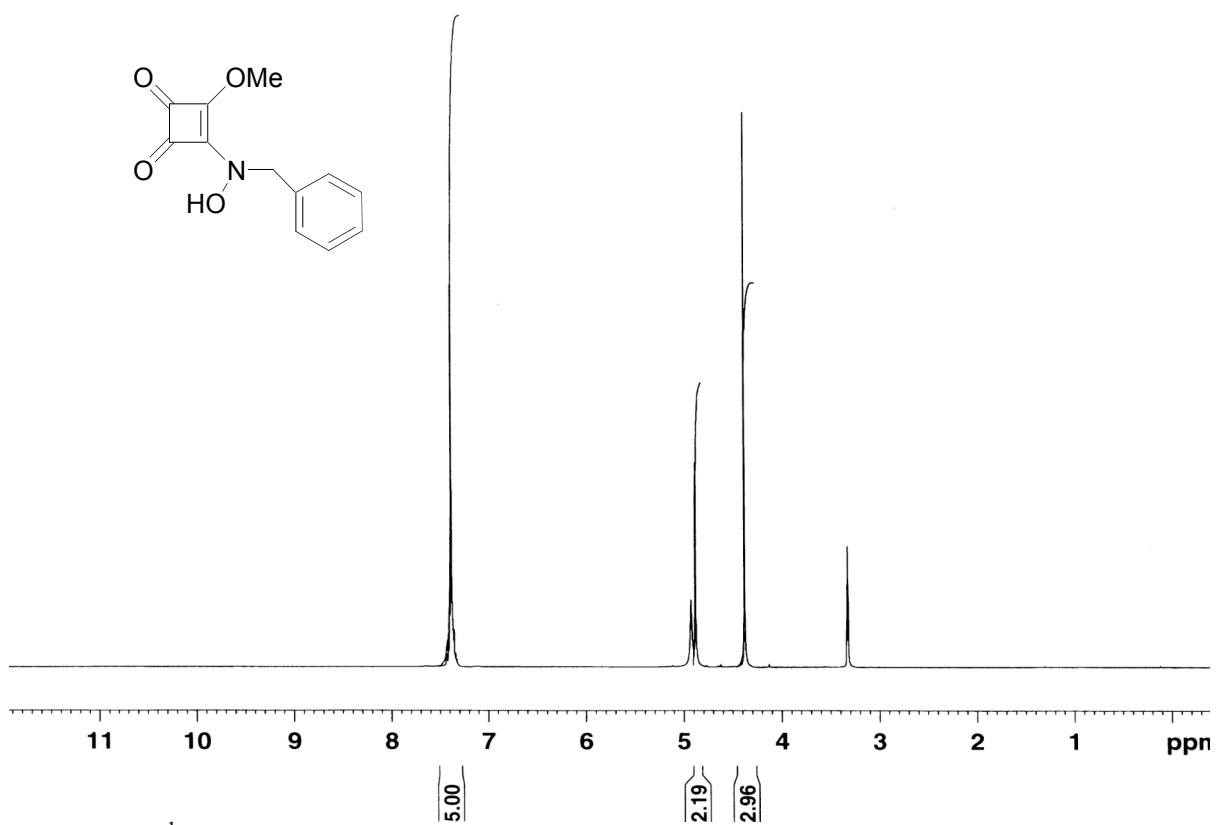


Figure S3. ¹H-NMR spectrum of compound 3d.

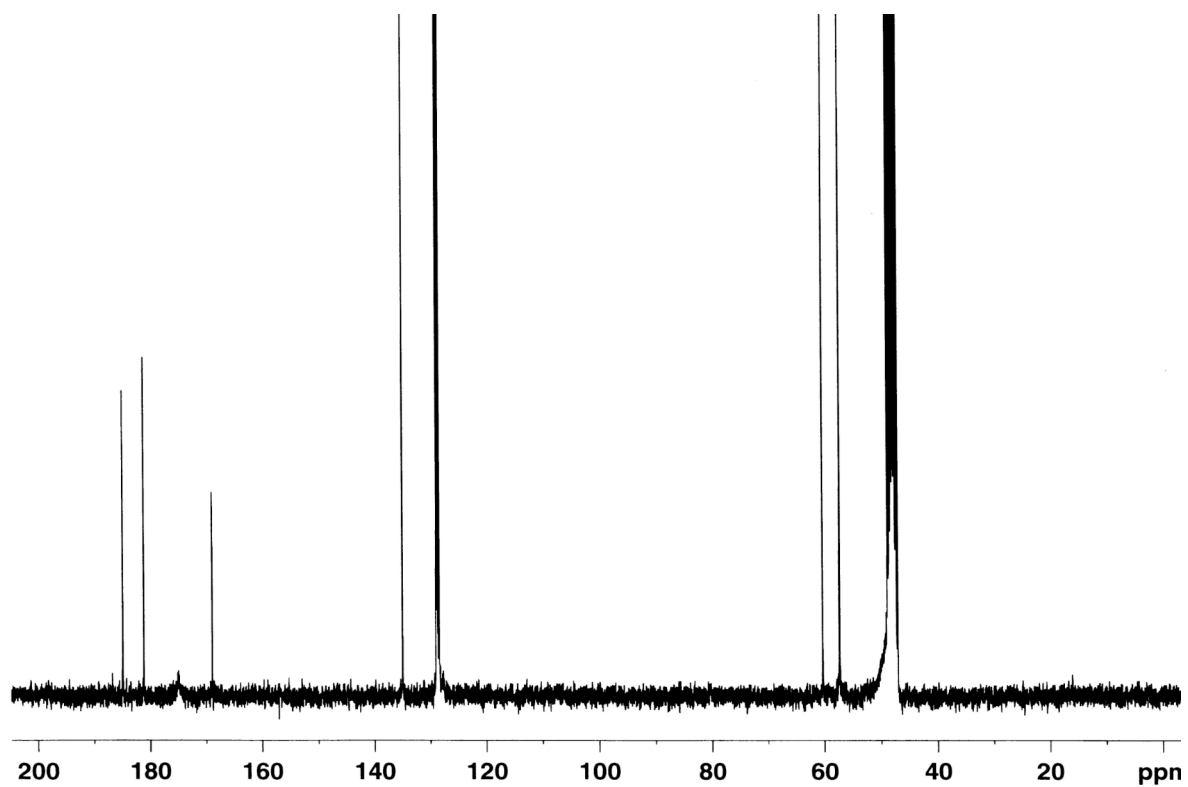


Figure S4. ¹³C-NMR spectrum of compound 3d.

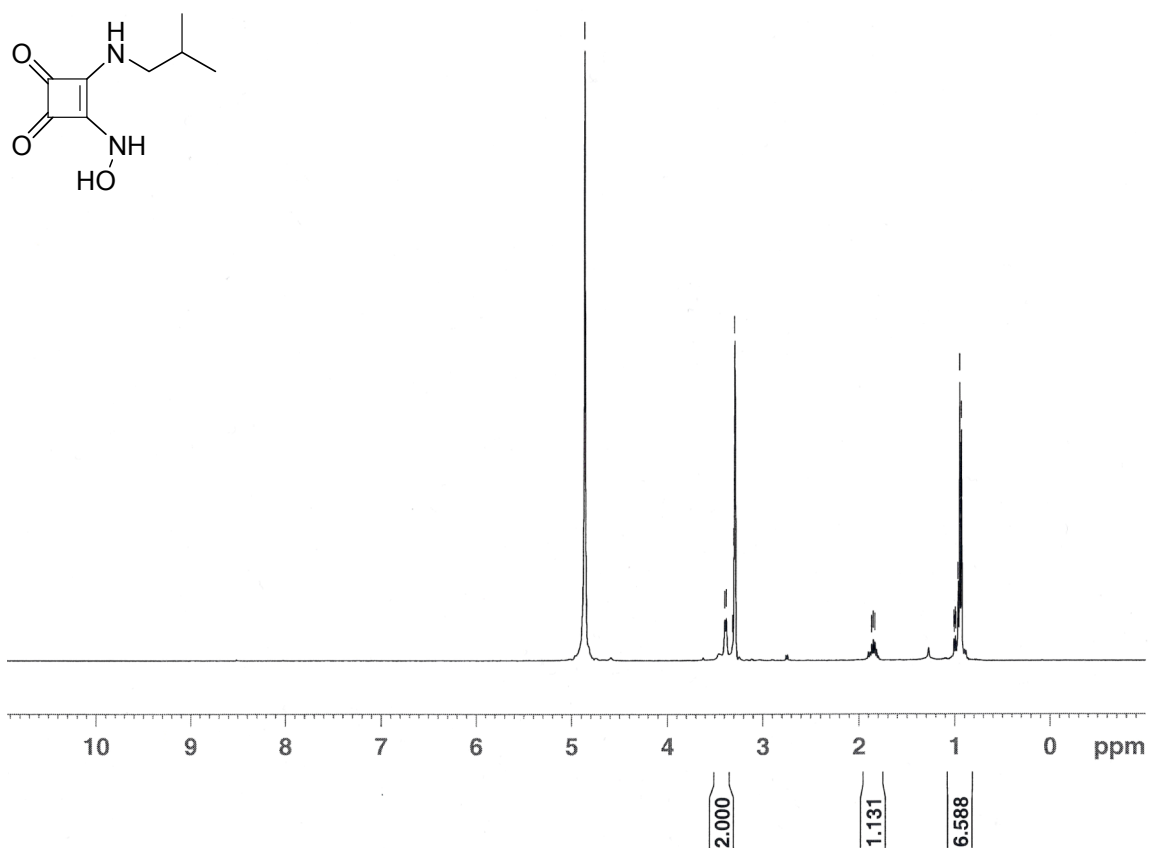


Figure S5. ¹H NMR spectrum of compound **4a**.

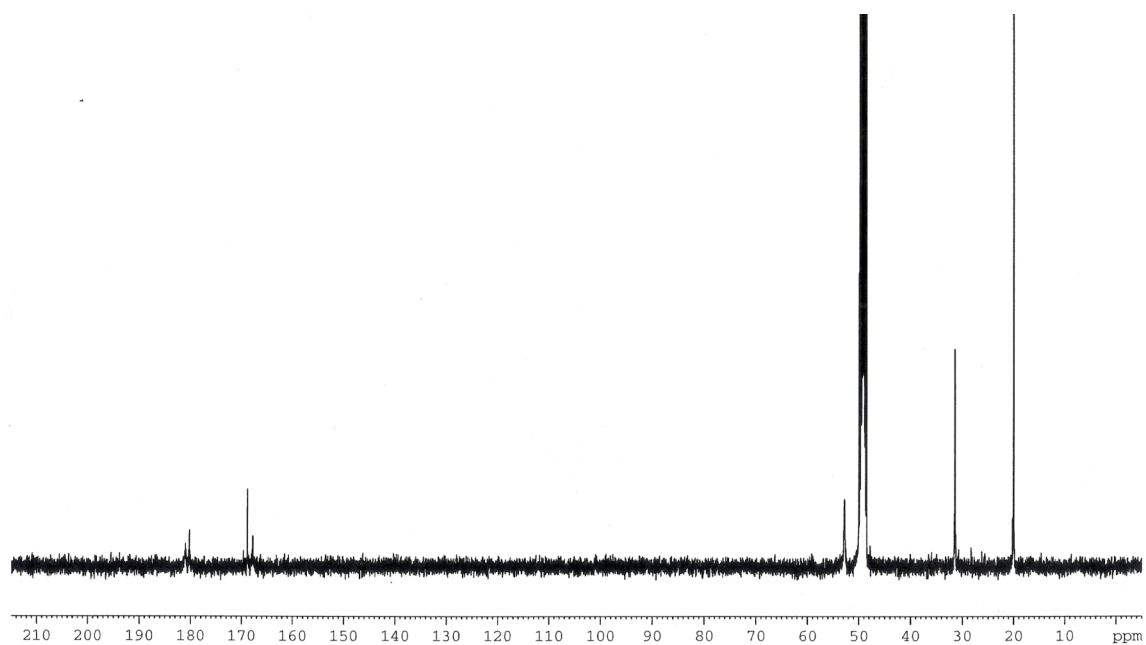


Figure S6. ¹³C NMR spectrum of compound **4a**.

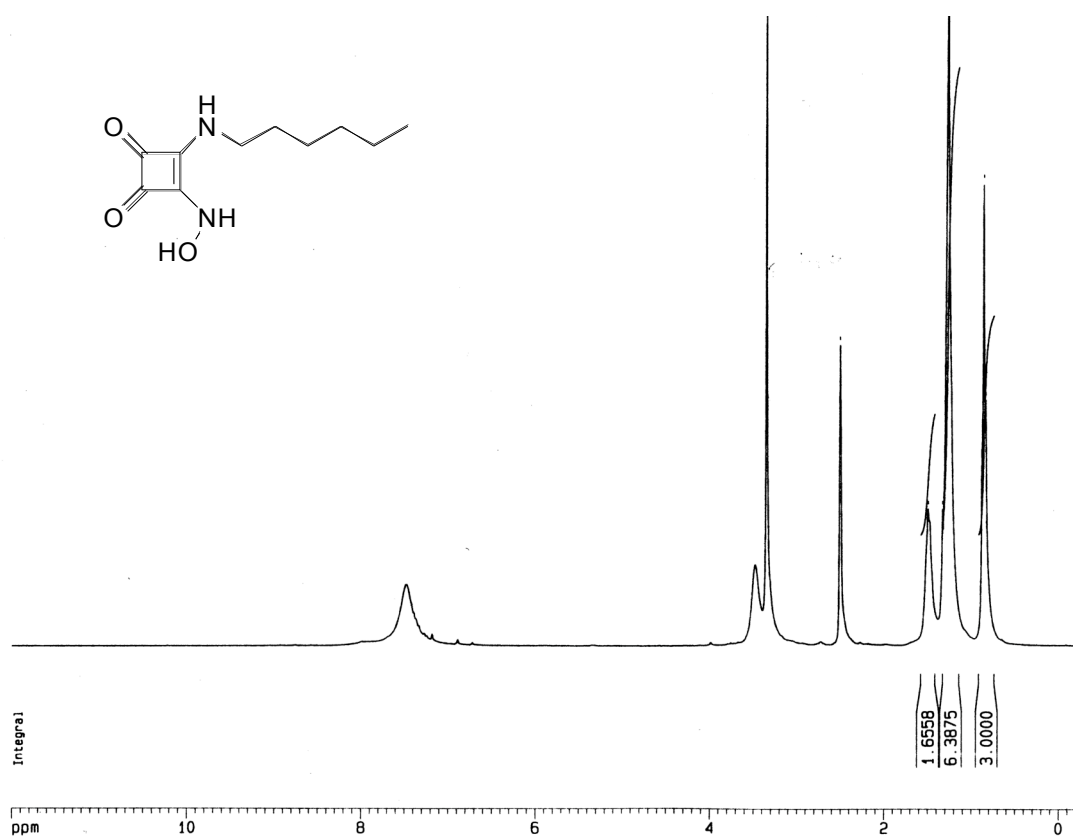


Figure S7. ¹H-NMR spectrum of compound **4b**.

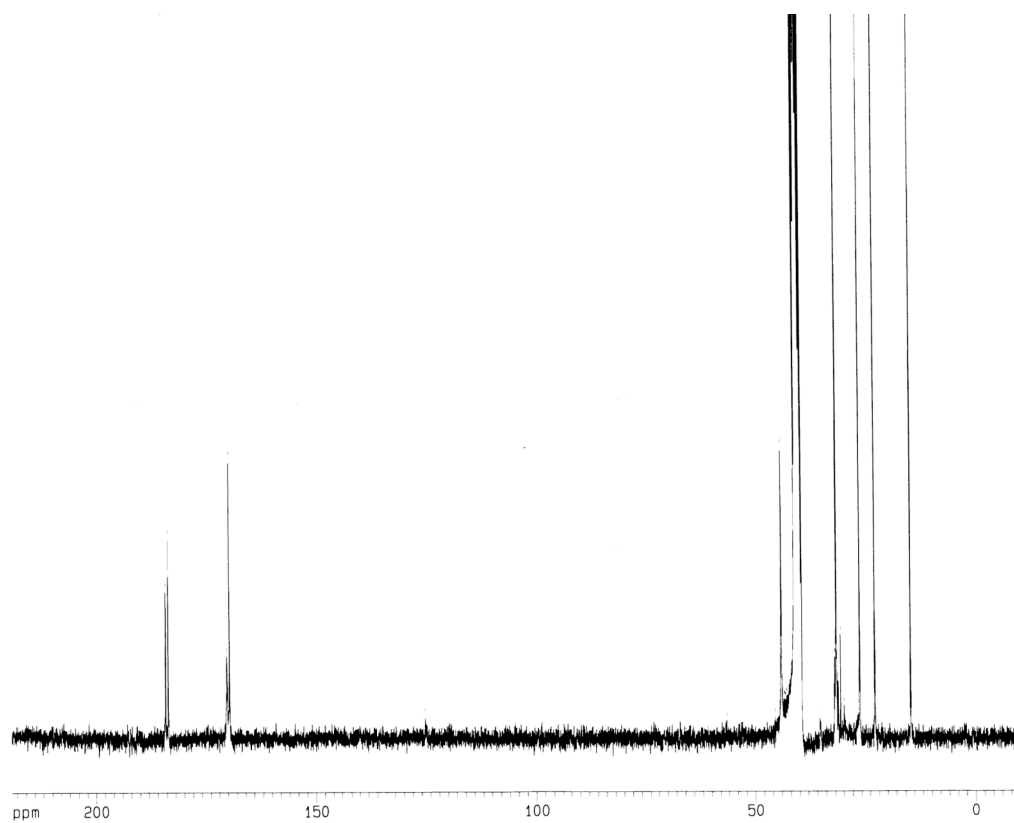


Figure S8. ¹³C-NMR spectrum of compound **4b**.

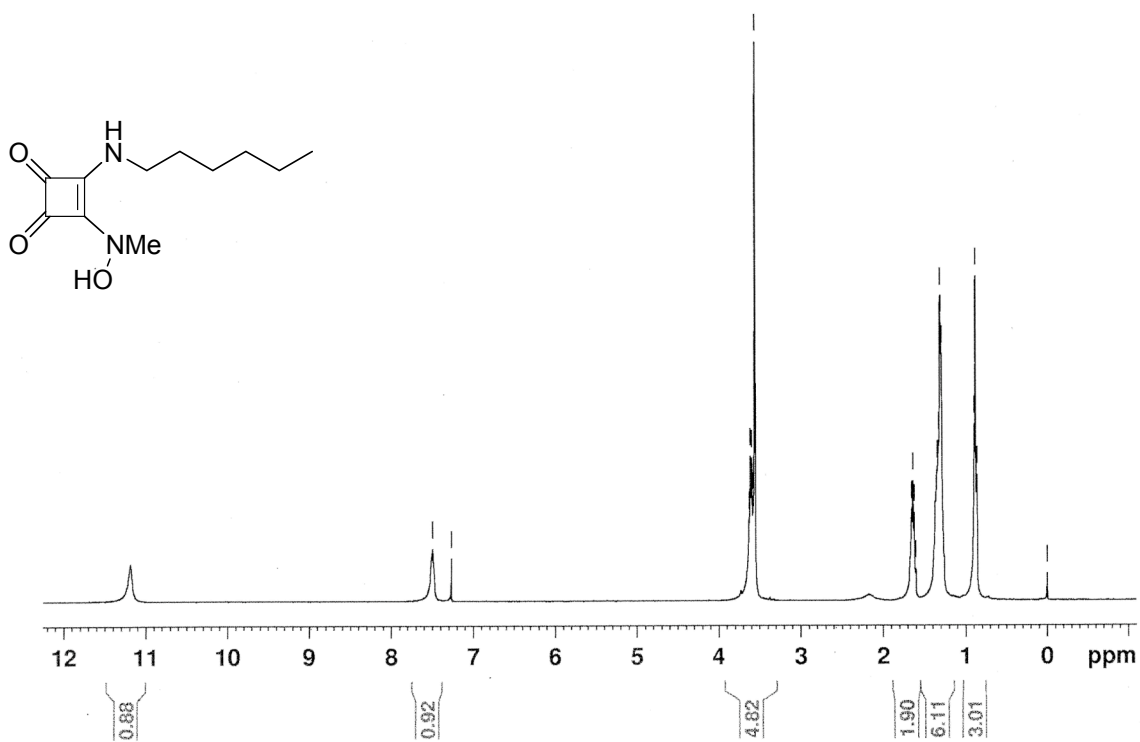


Figure S9. ^1H NMR spectrum of compound 4c.

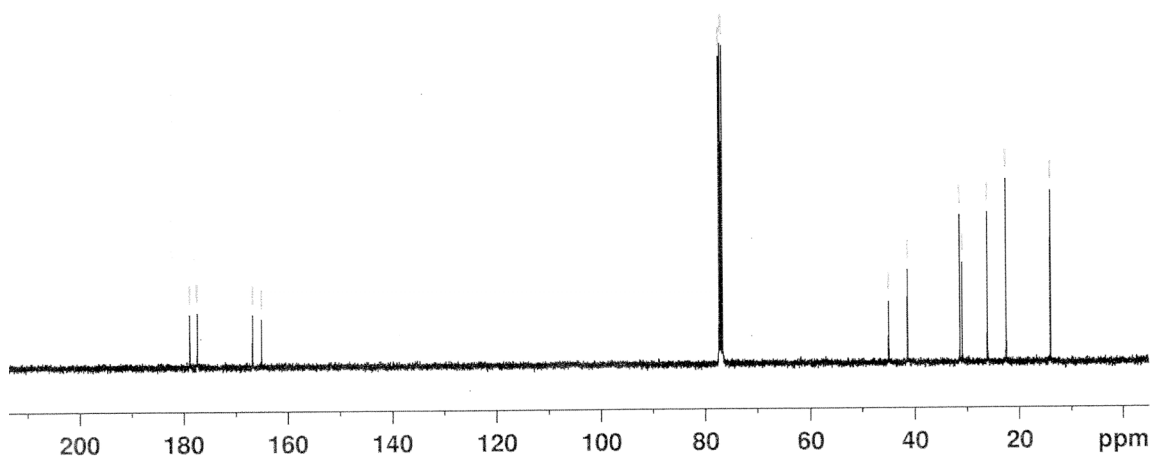


Figure S10. ^{13}C NMR spectrum of compound 4c.

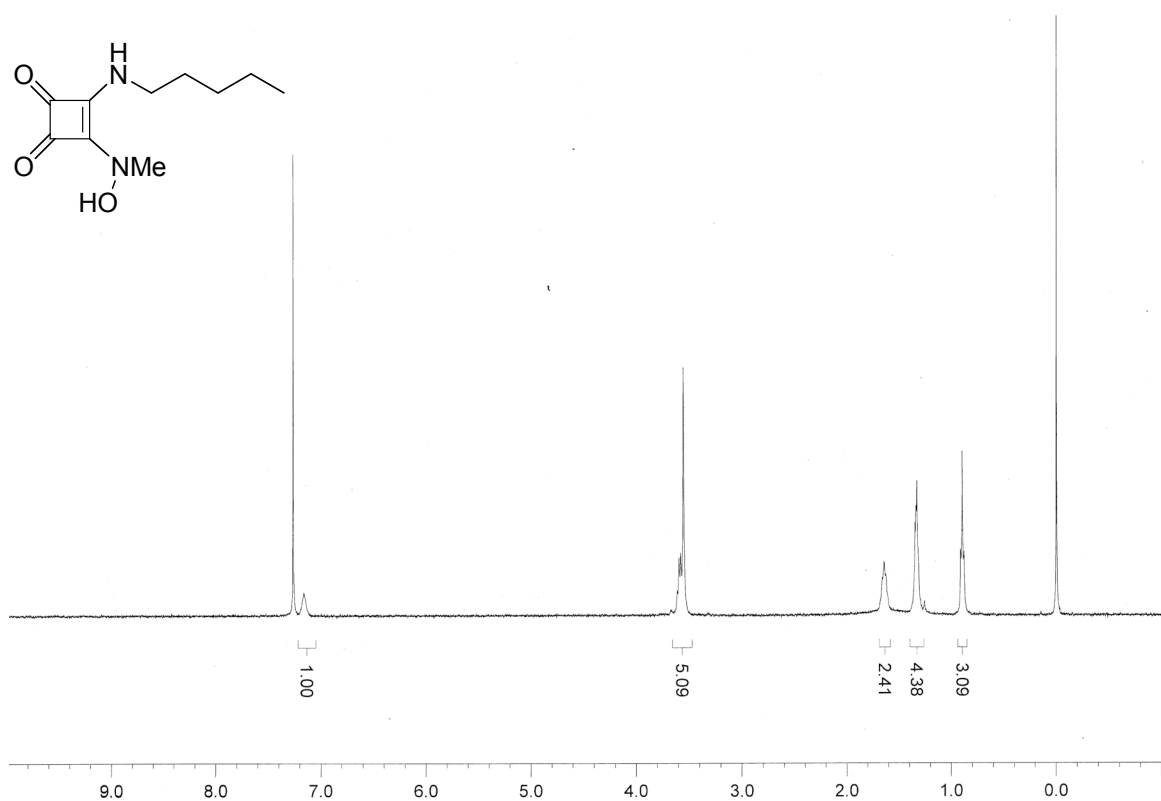


Figure S11. ¹H NMR spectrum of compound **4d**.

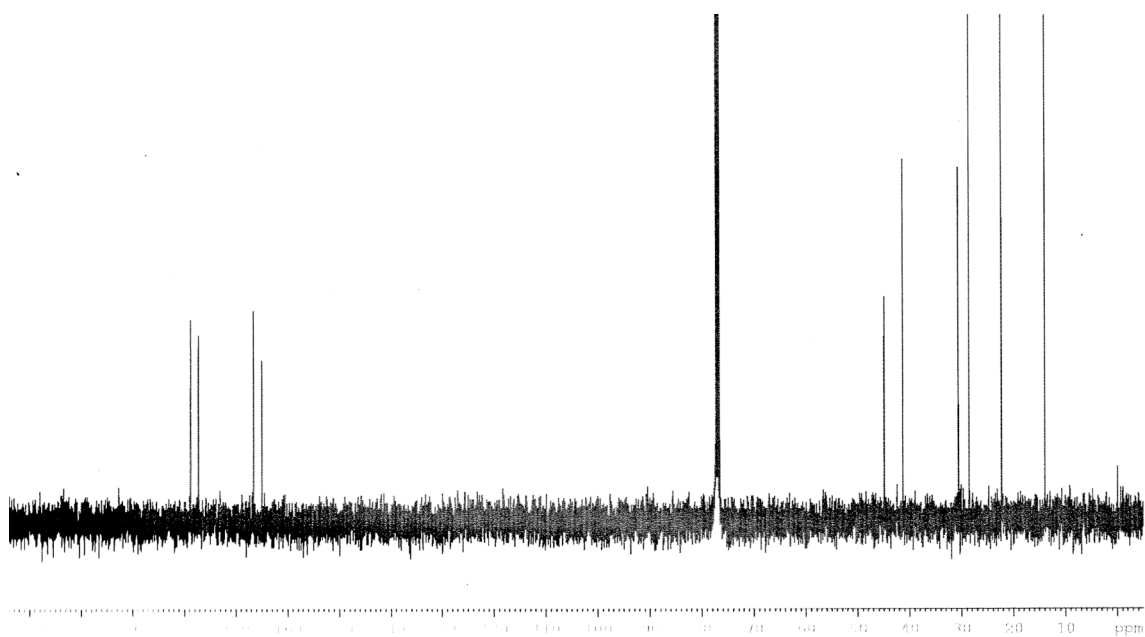


Figure S12. ¹³C NMR spectrum of compound **4d**.

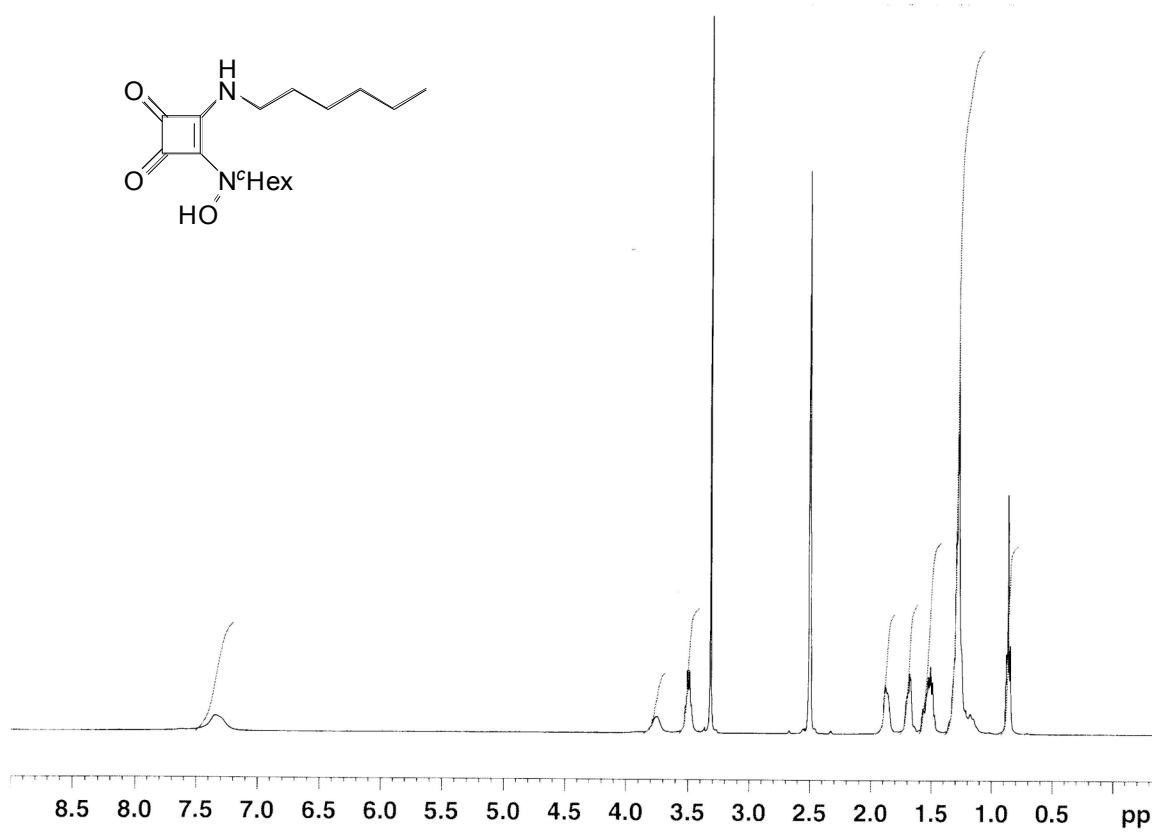


Figure S13. ^1H NMR spectrum of compound **4e**.

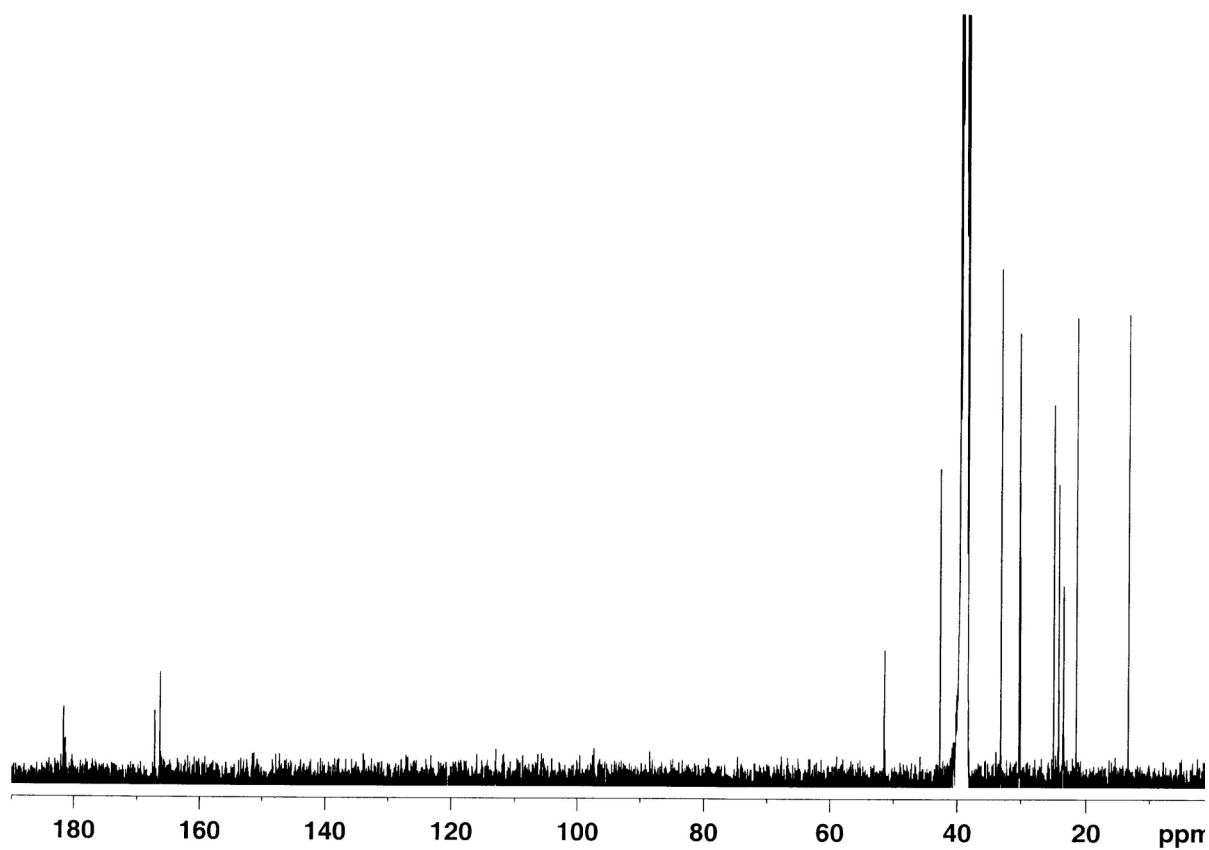


Figure S14. ^{13}C NMR spectrum of compound **4e**.

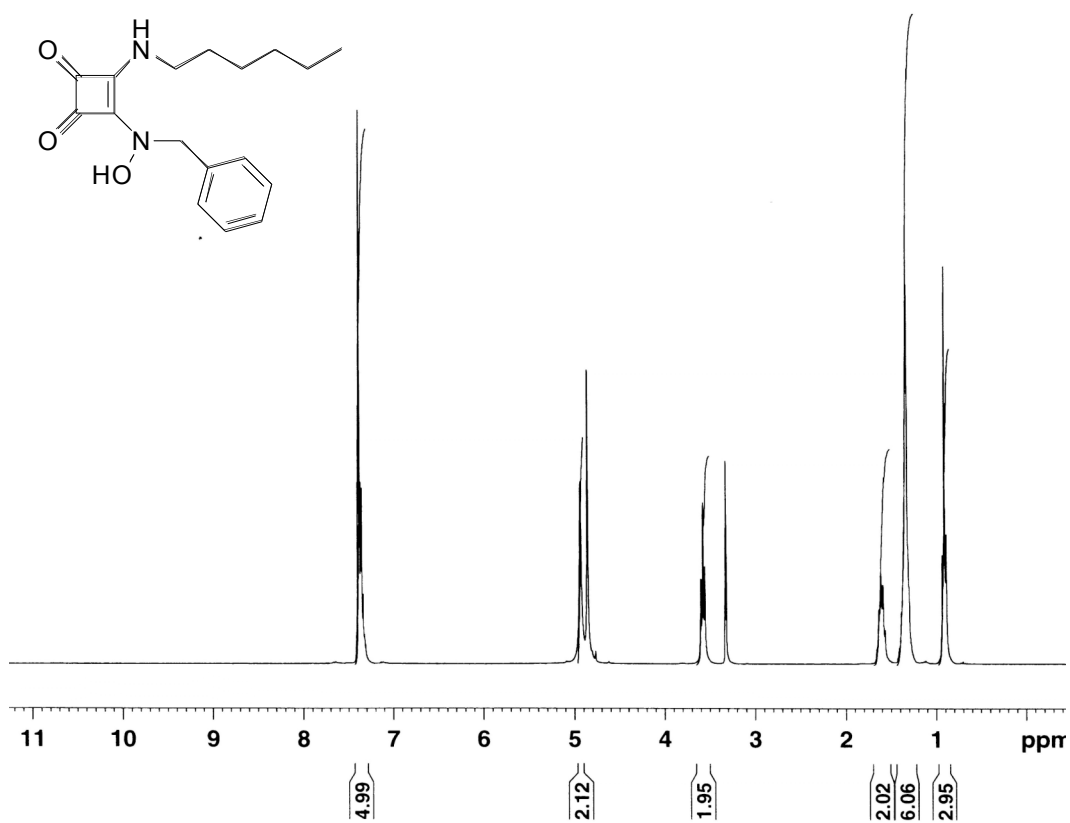


Figure S15. ¹H-NMR spectrum of compound **4f**.

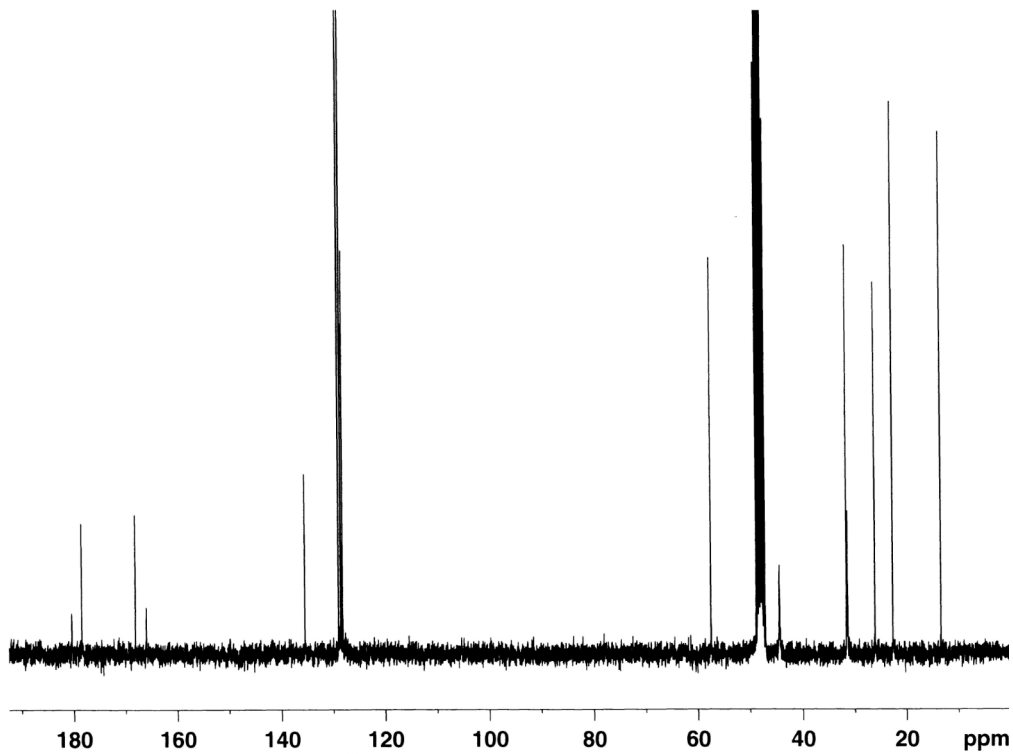


Figure S16. ¹³C-NMR spectrum of compound **4f**.

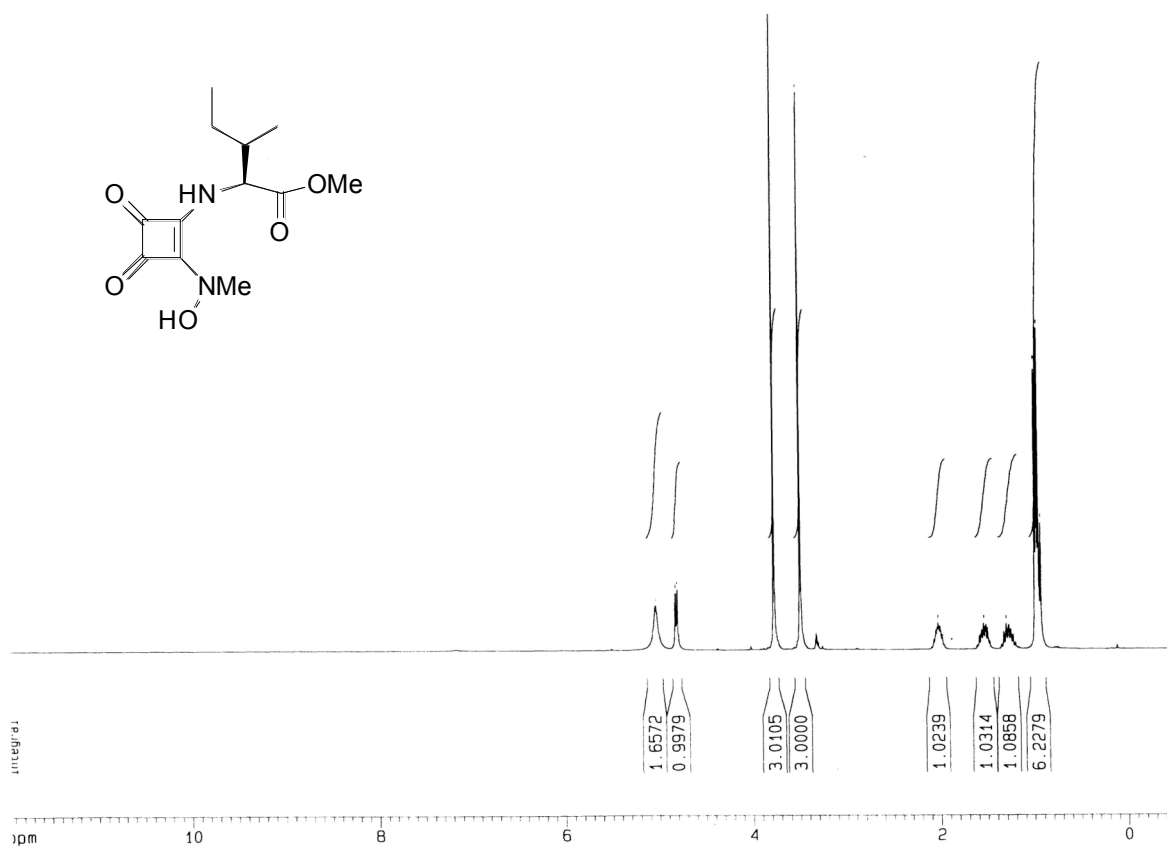


Figure S17. ¹H-NMR spectrum of compound **6a**.

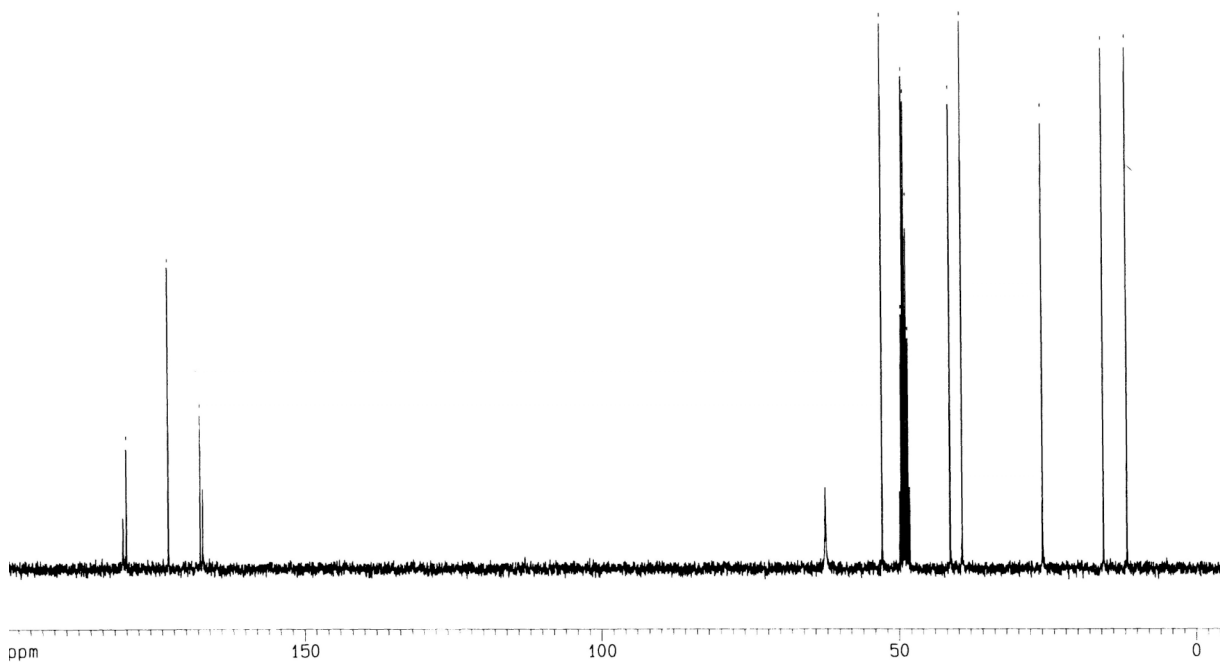


Figure S18. ¹³C-NMR spectrum of compound **6a**.

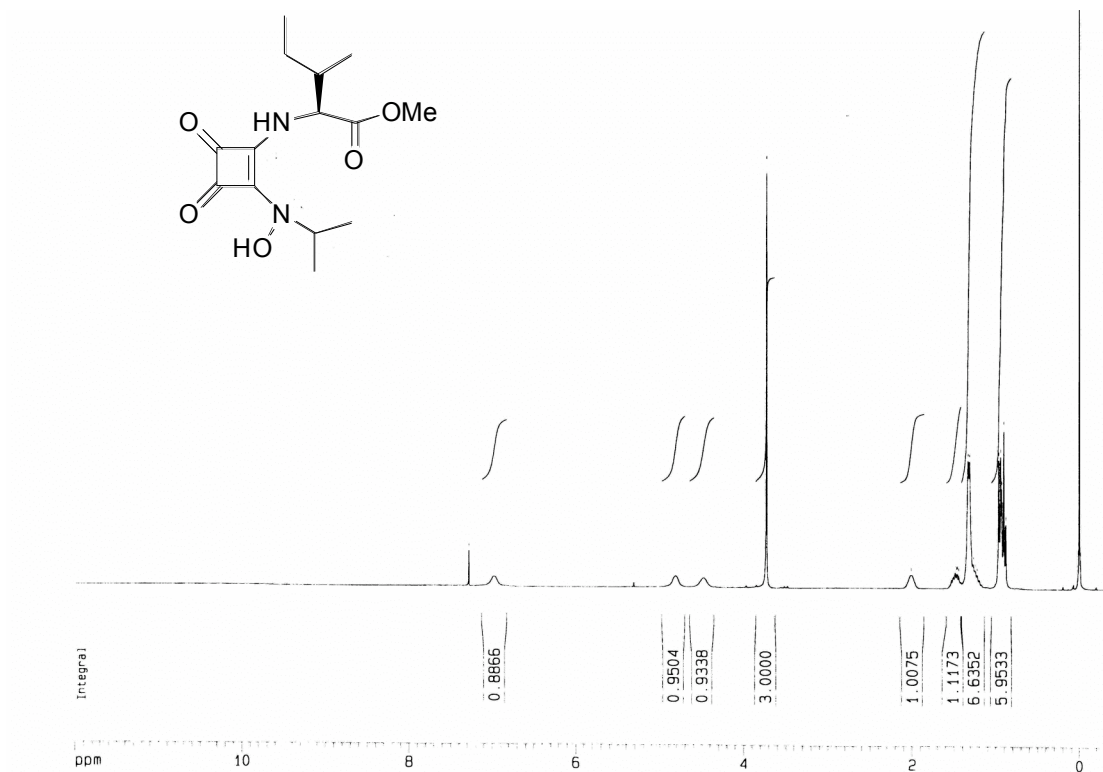


Figure S19. ¹H-NMR spectrum of compound **6b**.

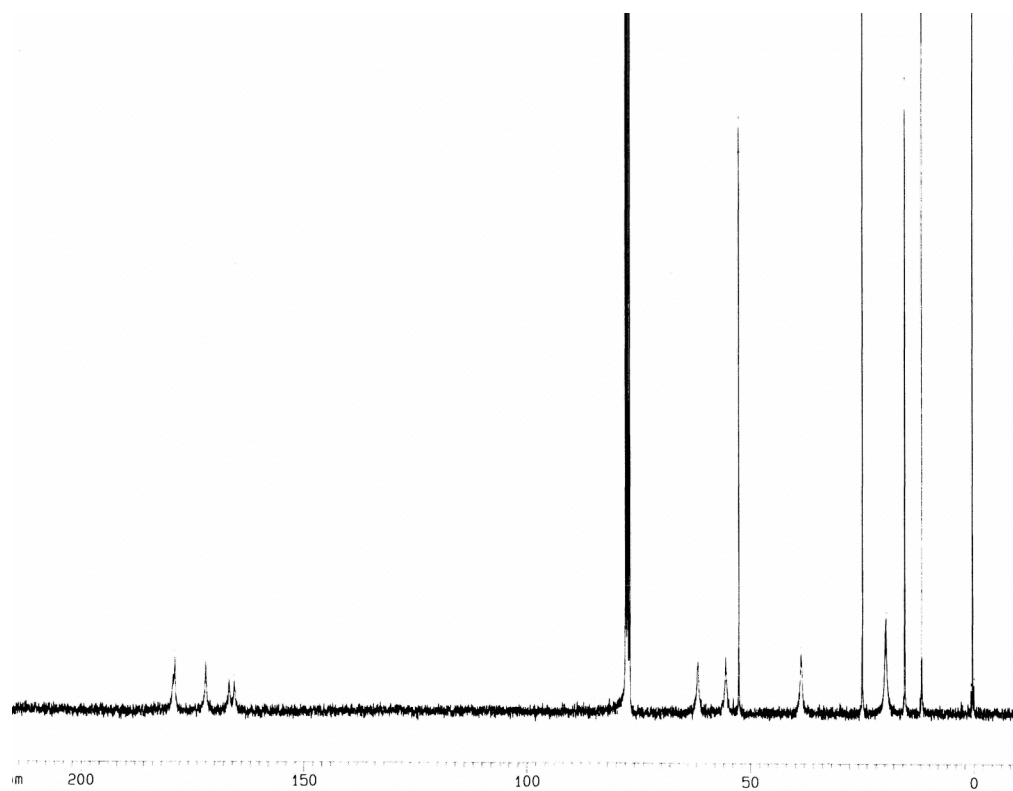


Figure S20. ¹³C-NMR spectrum of compound **6b**.

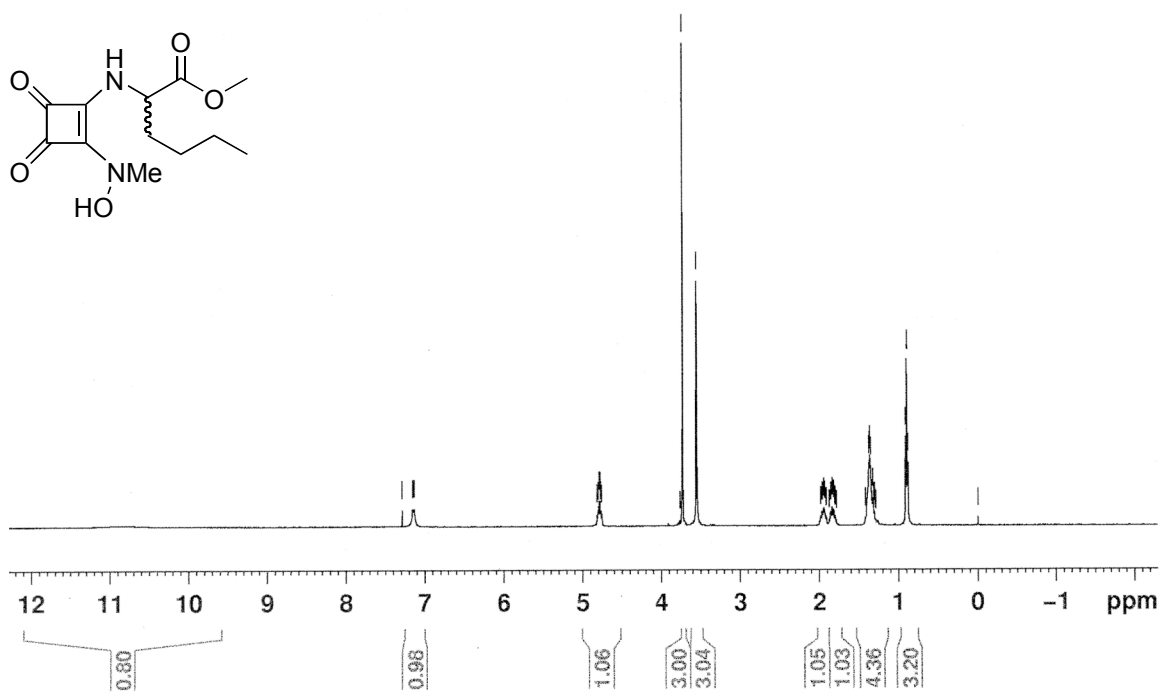


Figure S21. ¹H NMR spectrum of compound 6c.

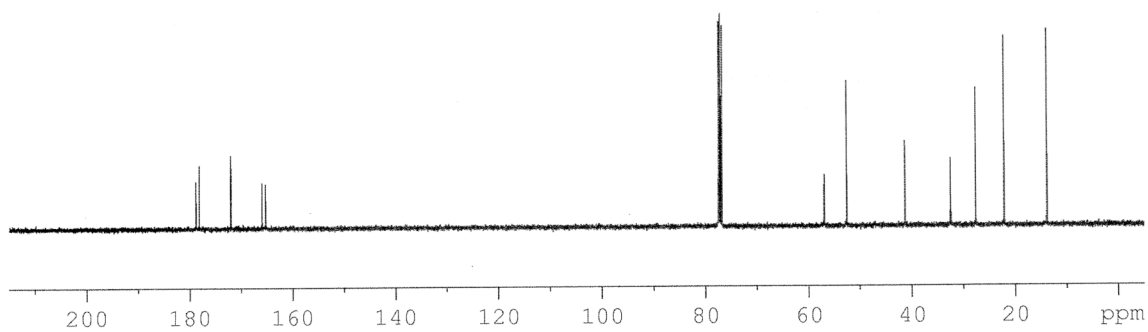


Figure S22. ¹³C NMR spectrum of compound 6c.

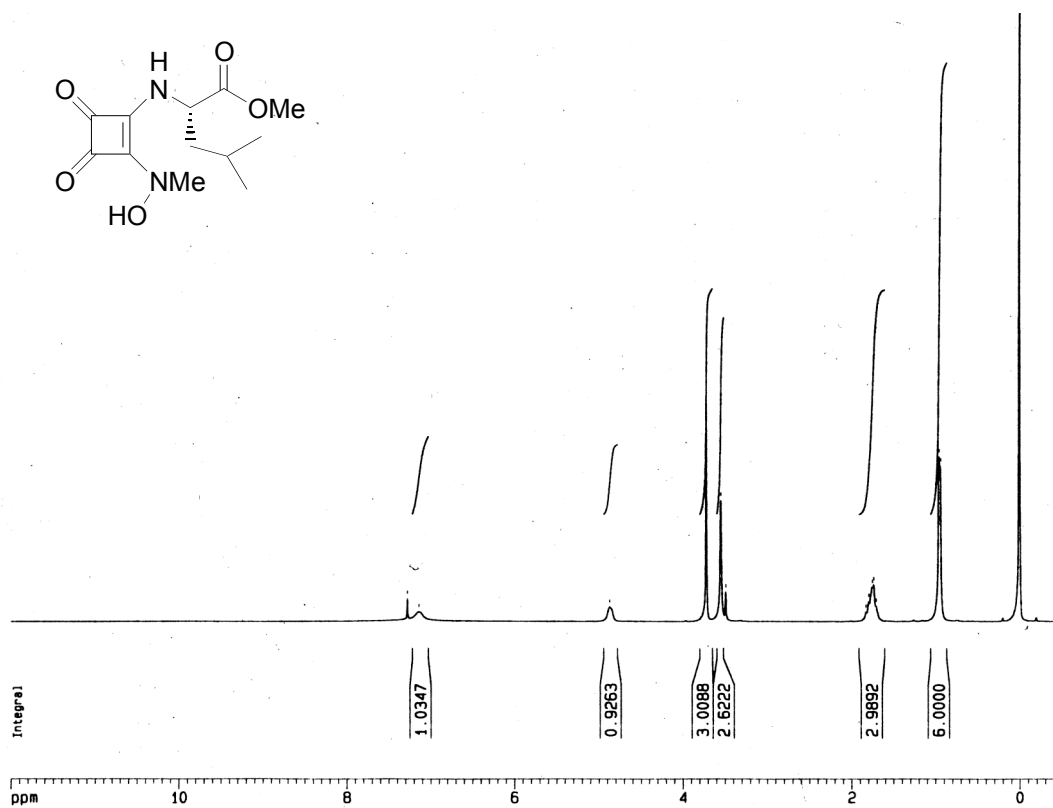


Figure S23. ¹H NMR spectrum of compound **6d**.

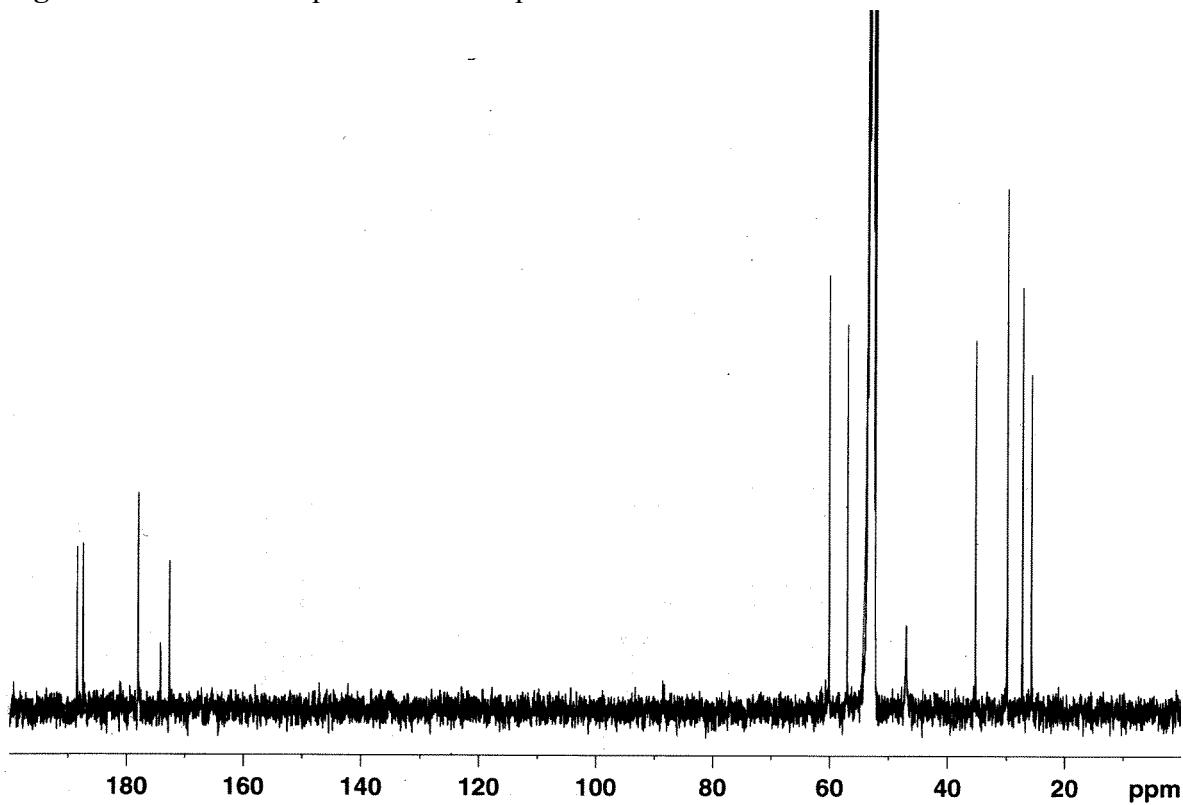


Figure S24. ¹³C NMR spectrum of compound **6d**.

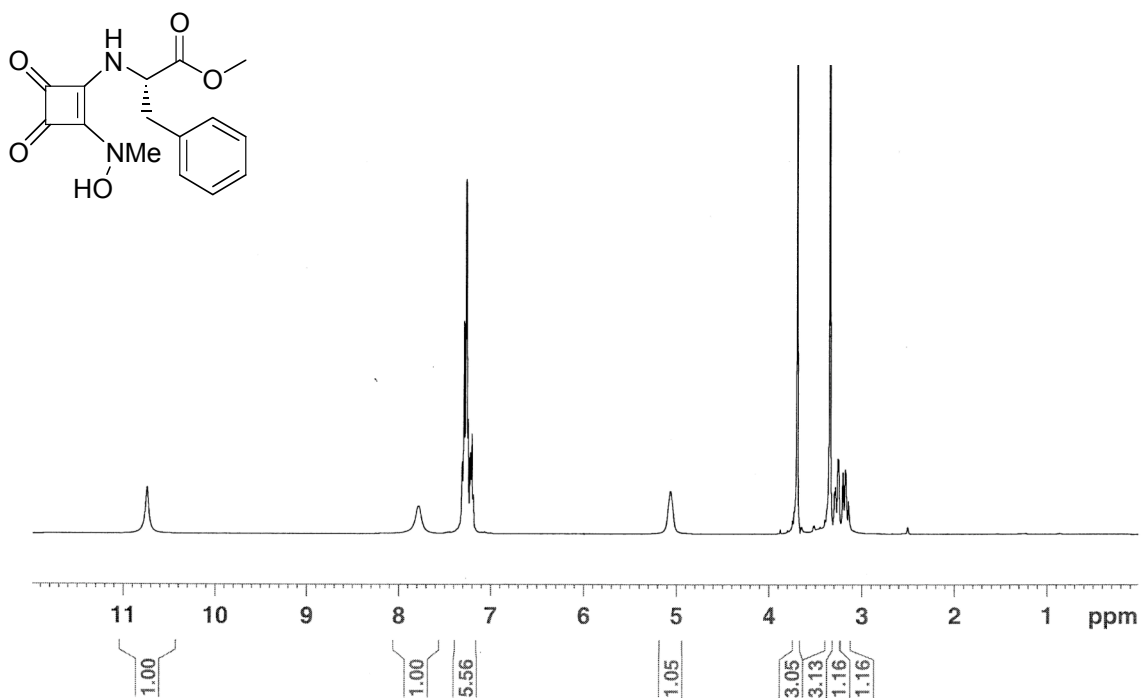


Figure S25. ¹H NMR spectrum of compound **6e**.

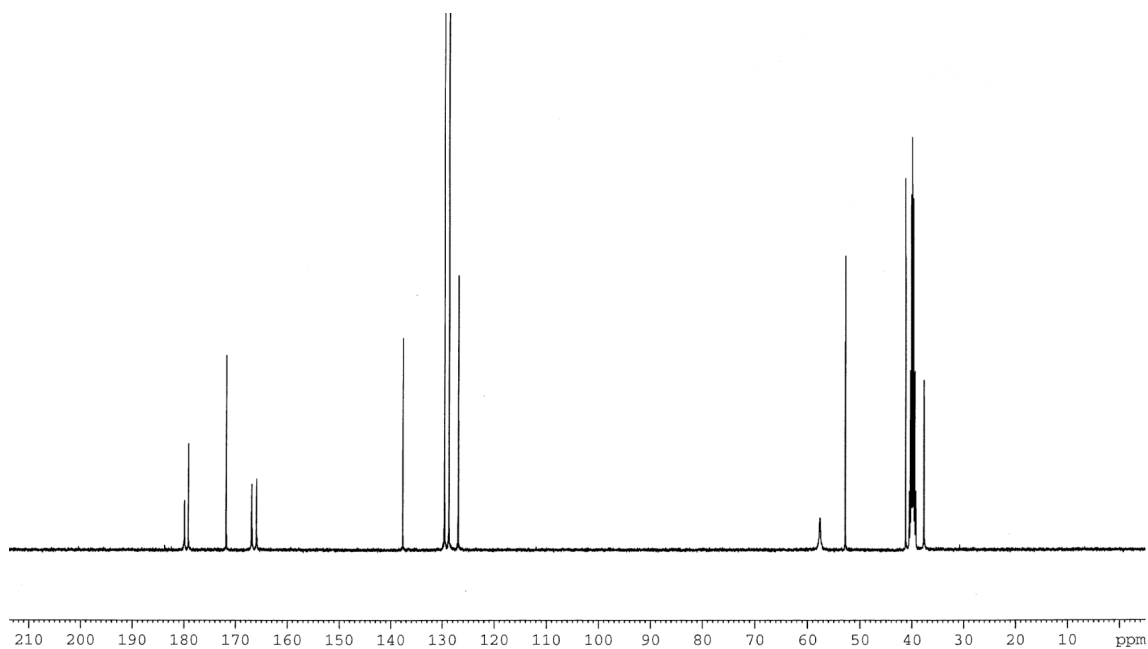


Figure S26. ¹³C NMR spectrum of compound **6e**.

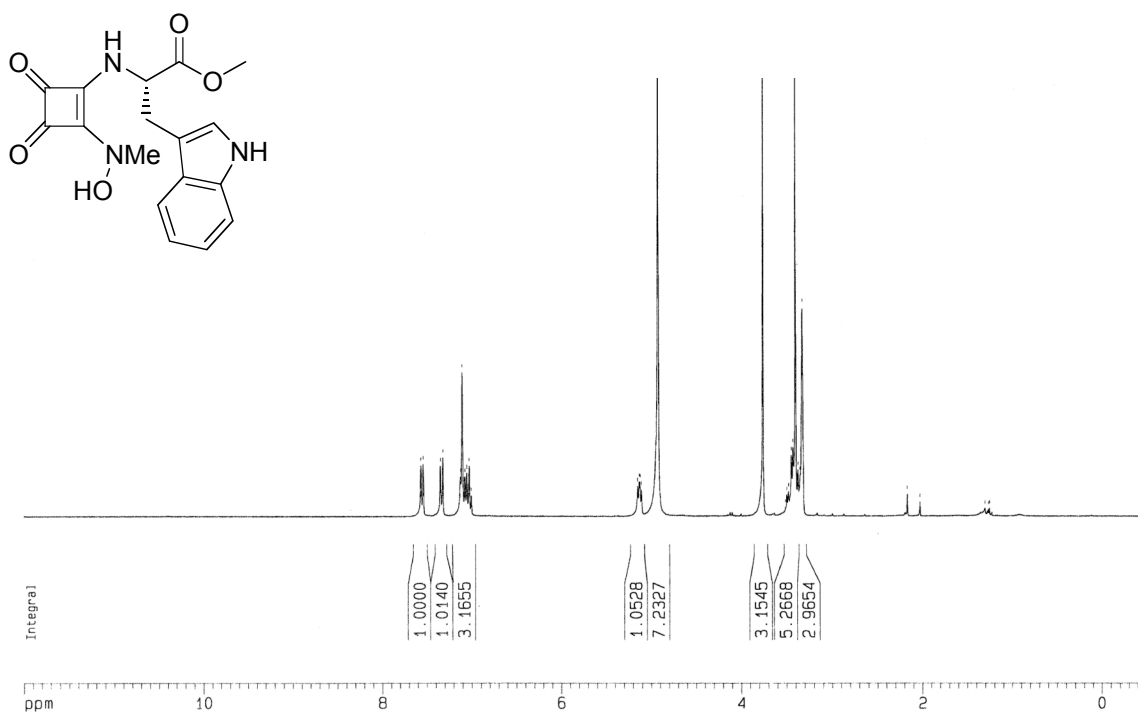


Figure S27. ¹H NMR spectrum of compound **6f**.

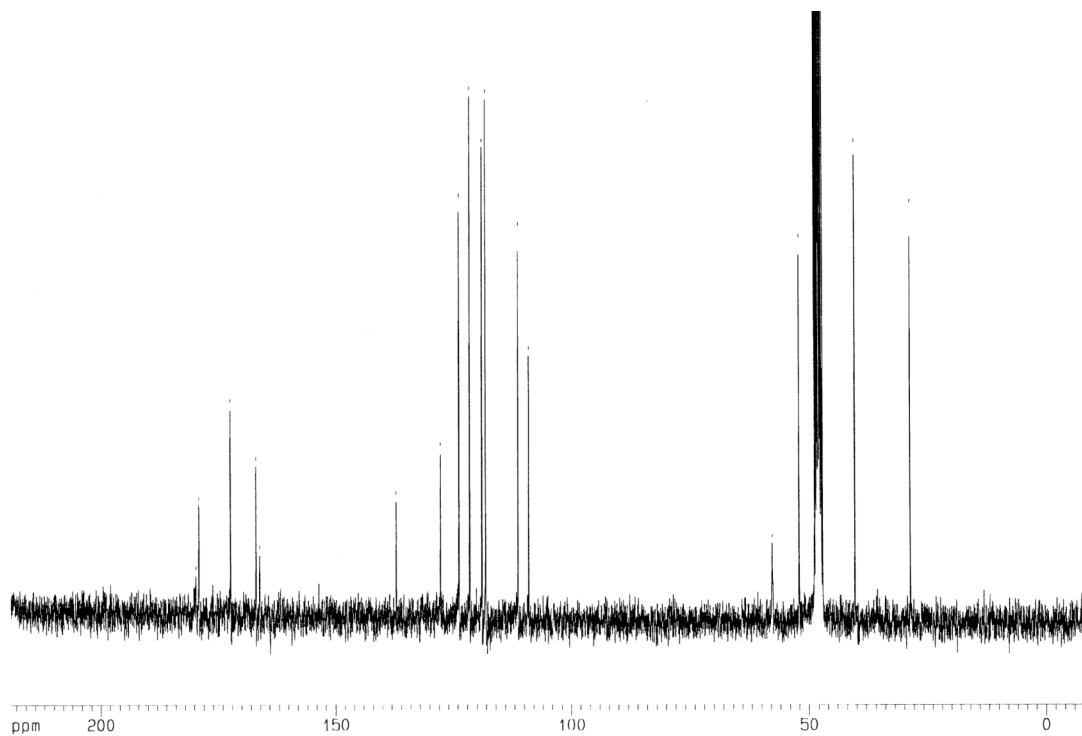


Figure S28. ¹³C NMR spectrum of compound **6f**.

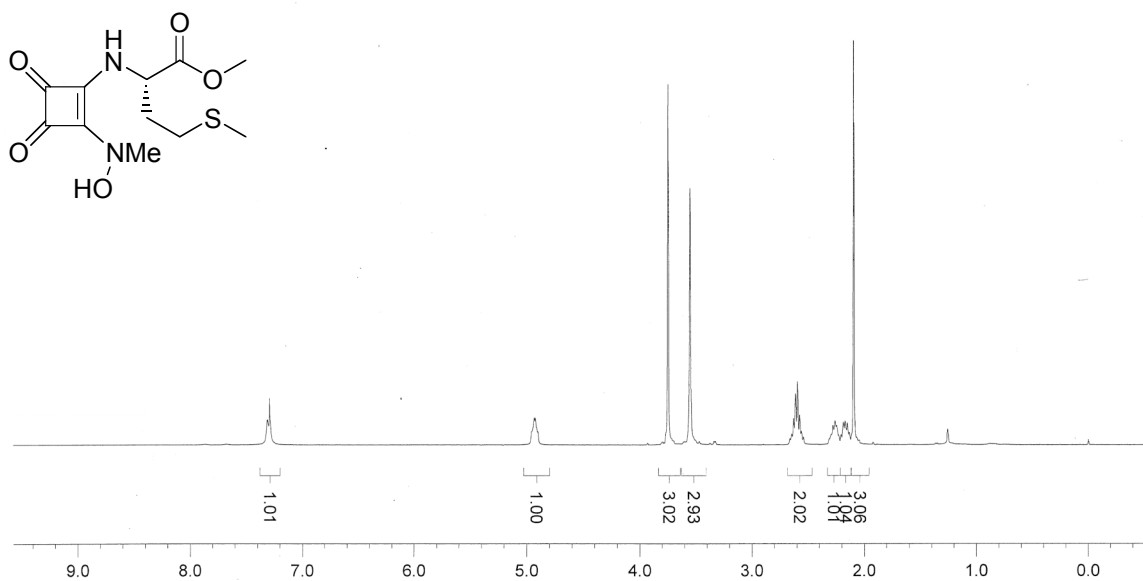


Figure S29. ¹H NMR spectrum of compound **6g**.

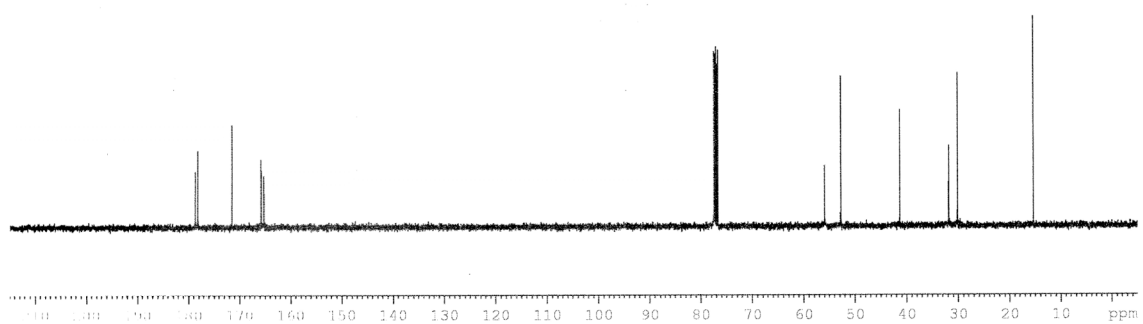


Figure S30. ¹³C NMR spectrum of compound **6g**.

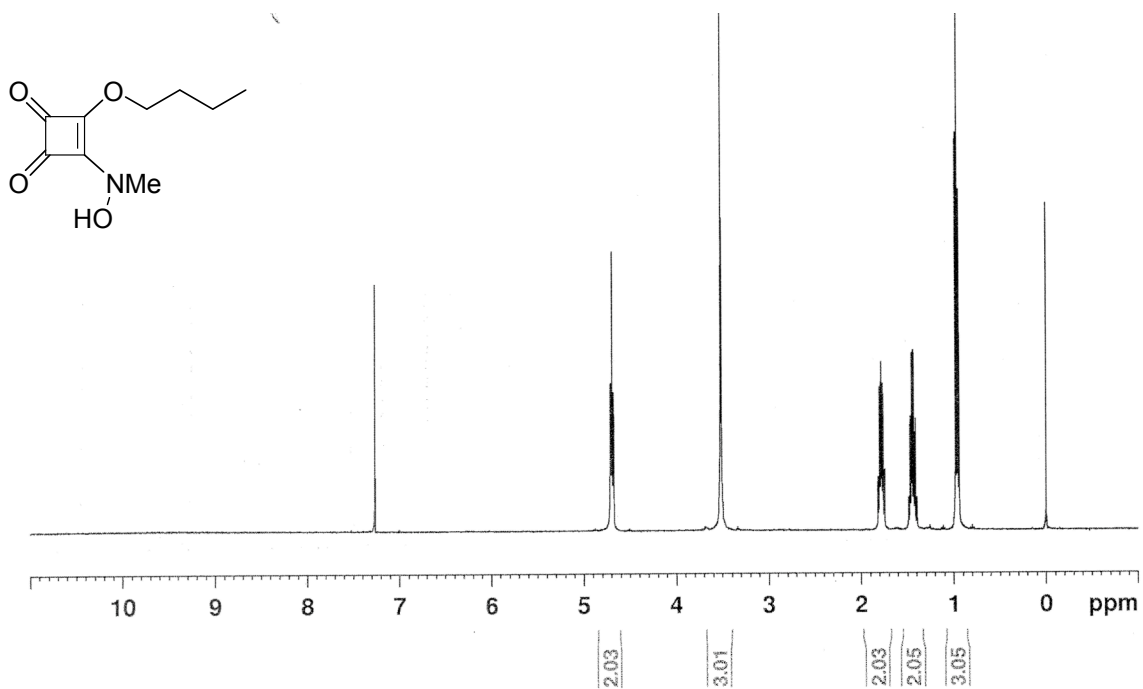


Figure S31. ^1H NMR spectrum of compound 8.

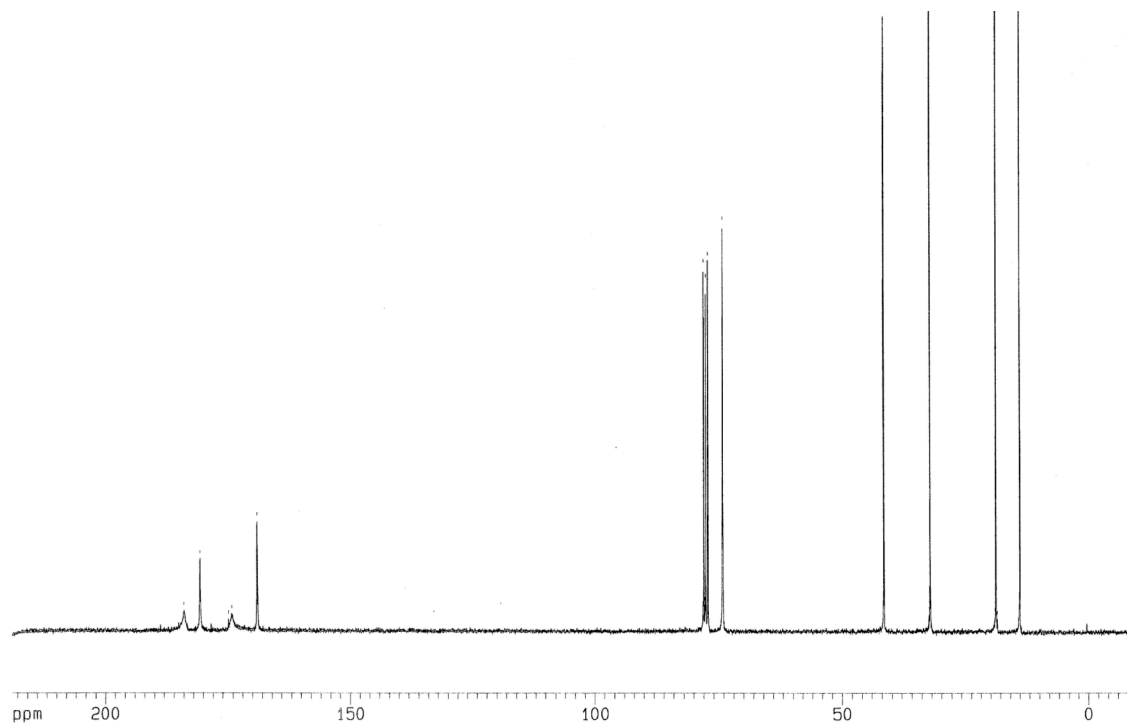


Figure S32. ^{13}C NMR spectrum of compound 8.

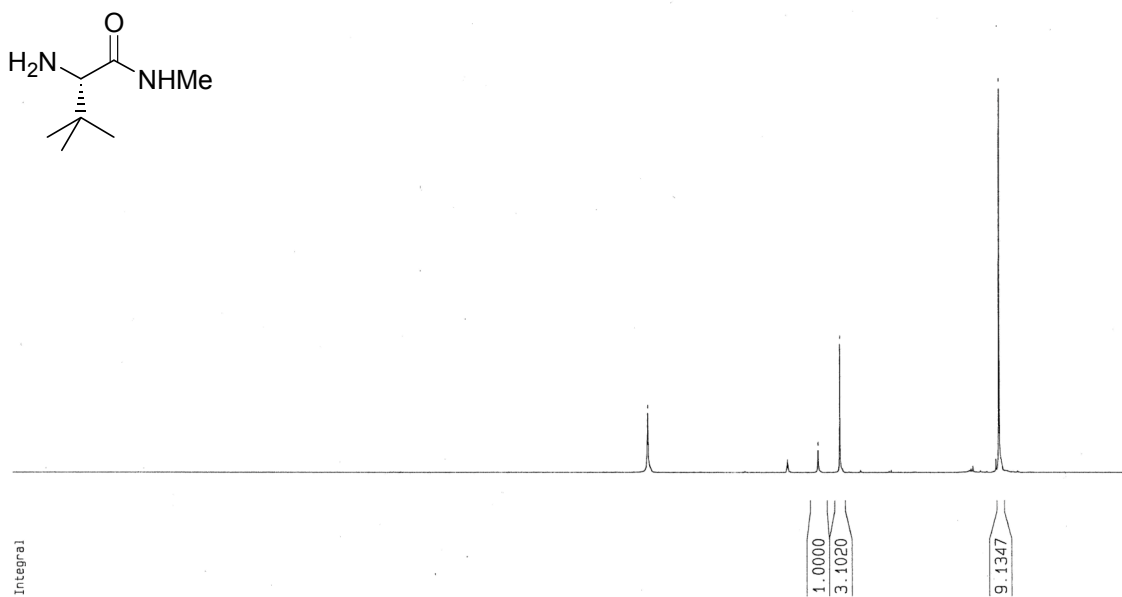


Figure S33. ¹H NMR spectrum of compound 10a.

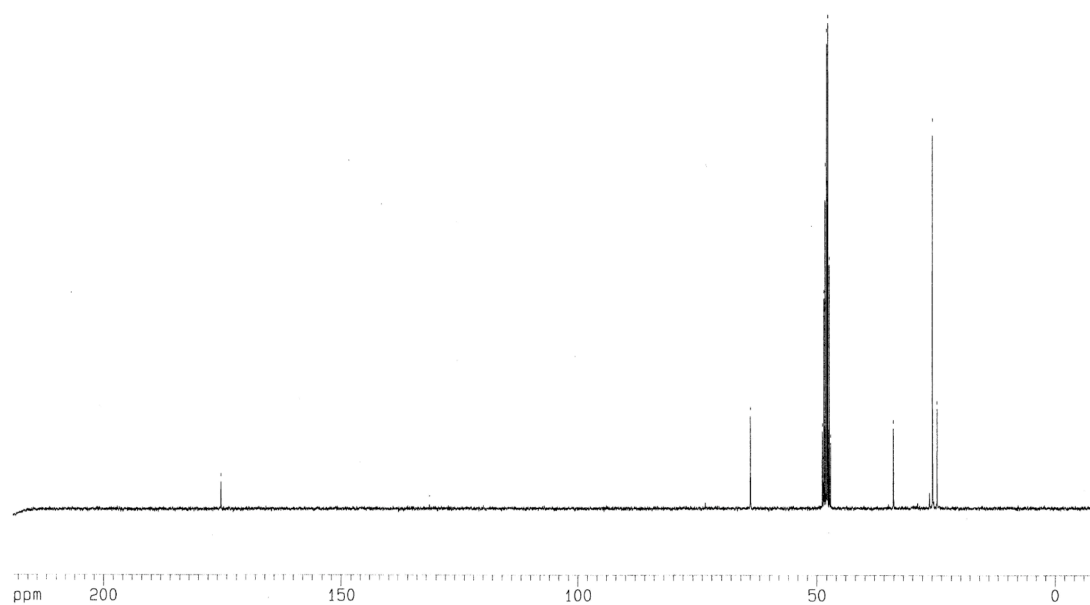


Figure S34. ¹³C NMR spectrum of compound 10a.

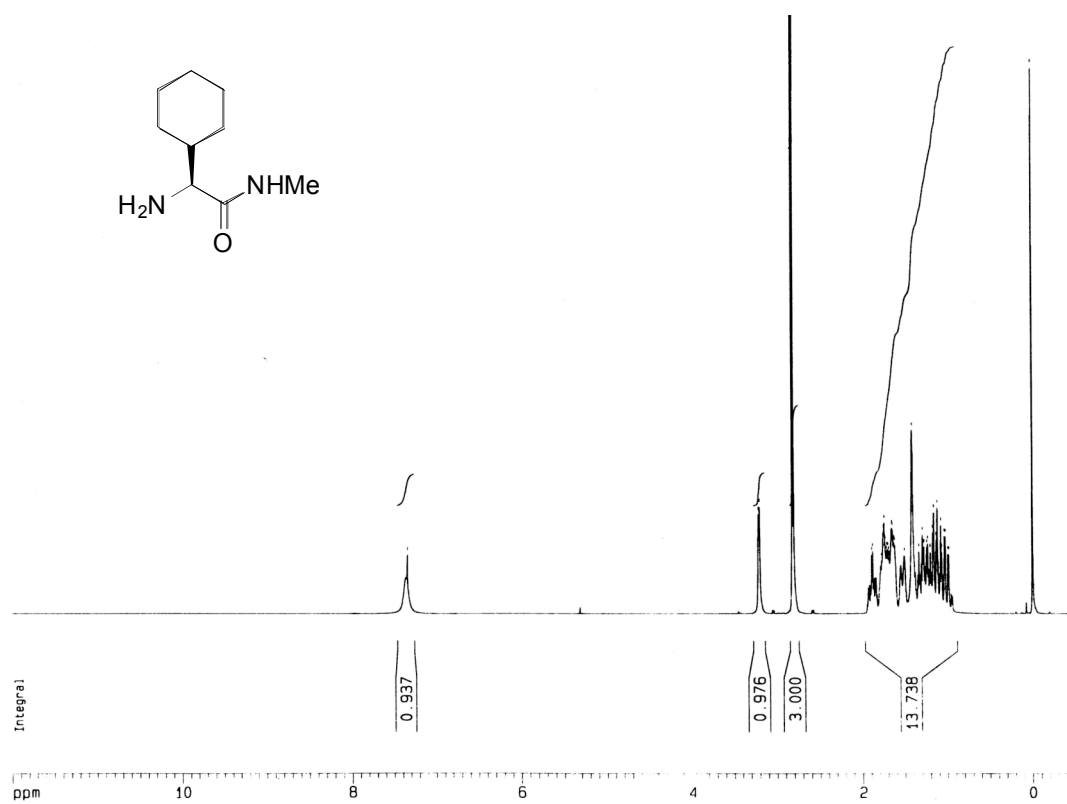


Figure S35. ¹H-NMR spectrum of compound **10b**.

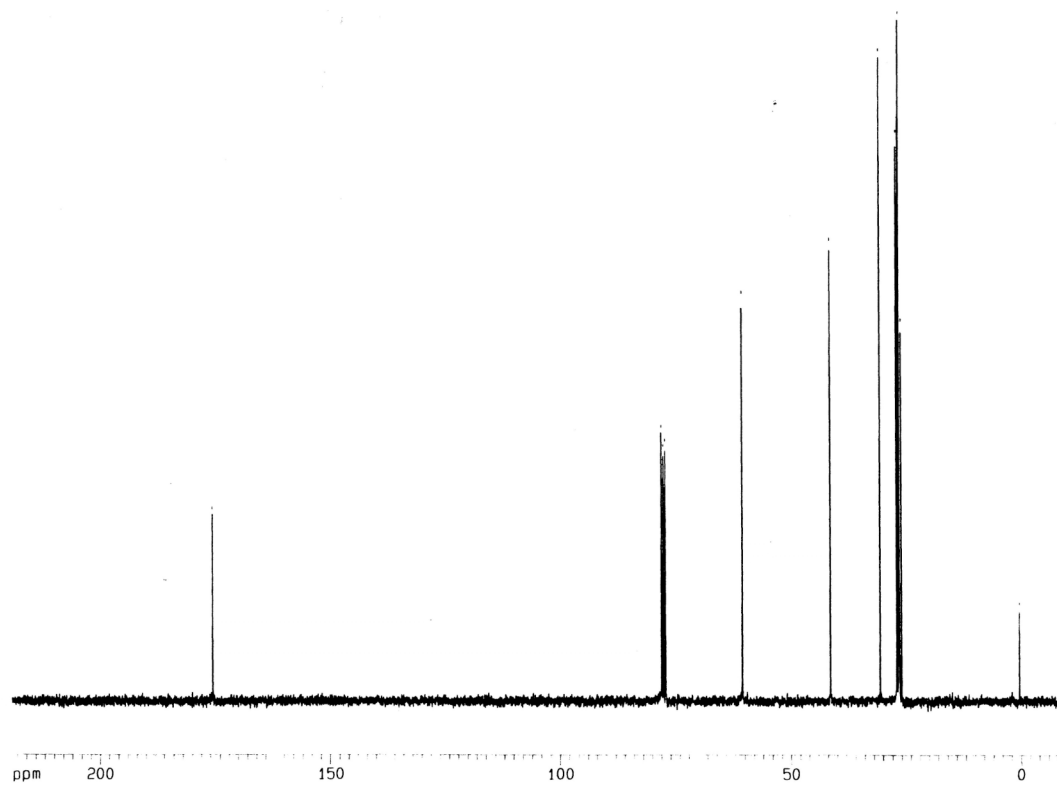


Figure S36. ¹³C-NMR spectrum of compound **10b**.

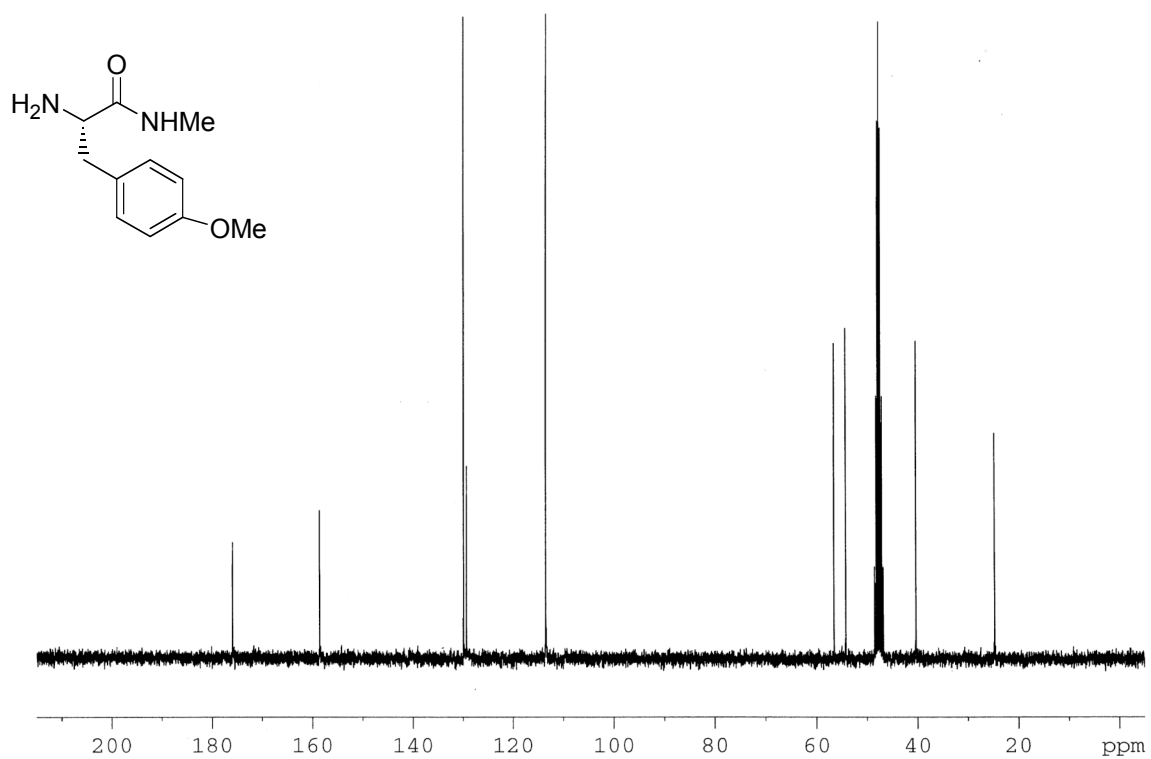


Figure S37. ^{13}C NMR spectrum of compound **10c**.

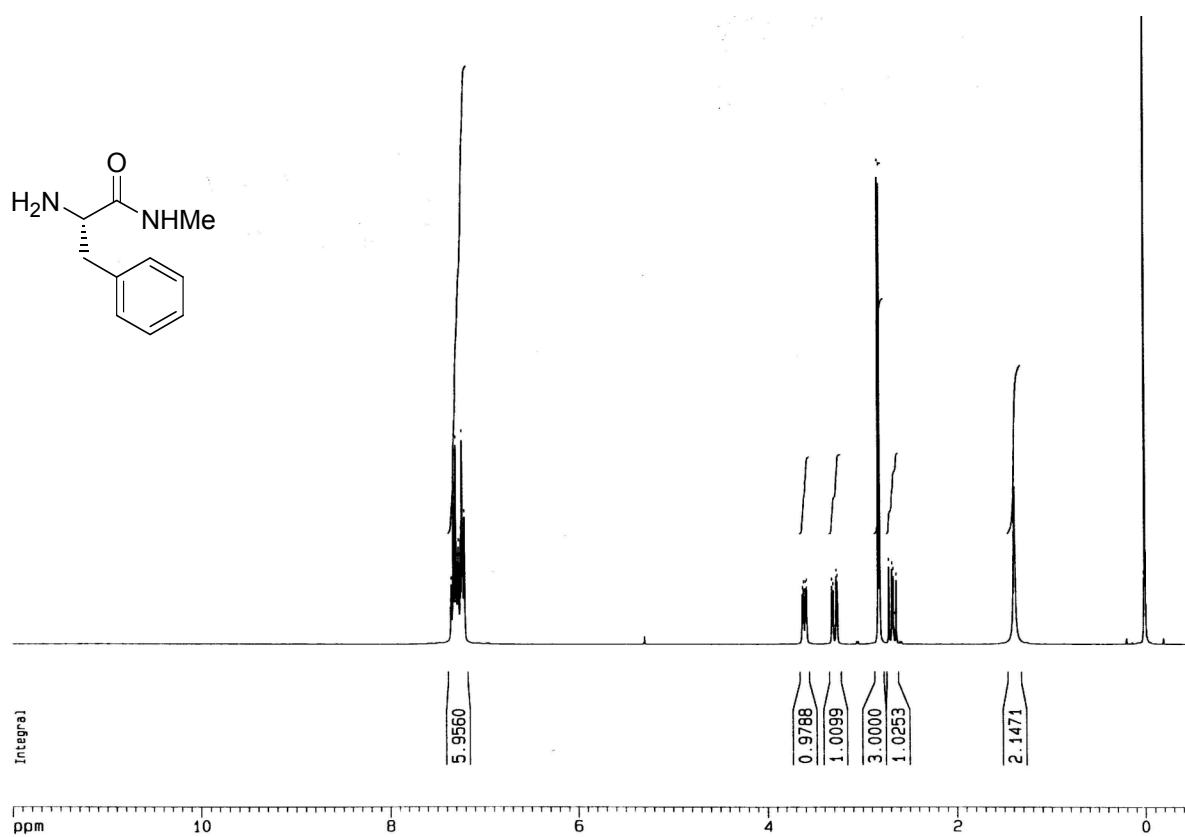


Figure S38. ¹H-NMR spectrum of compound **10d**.

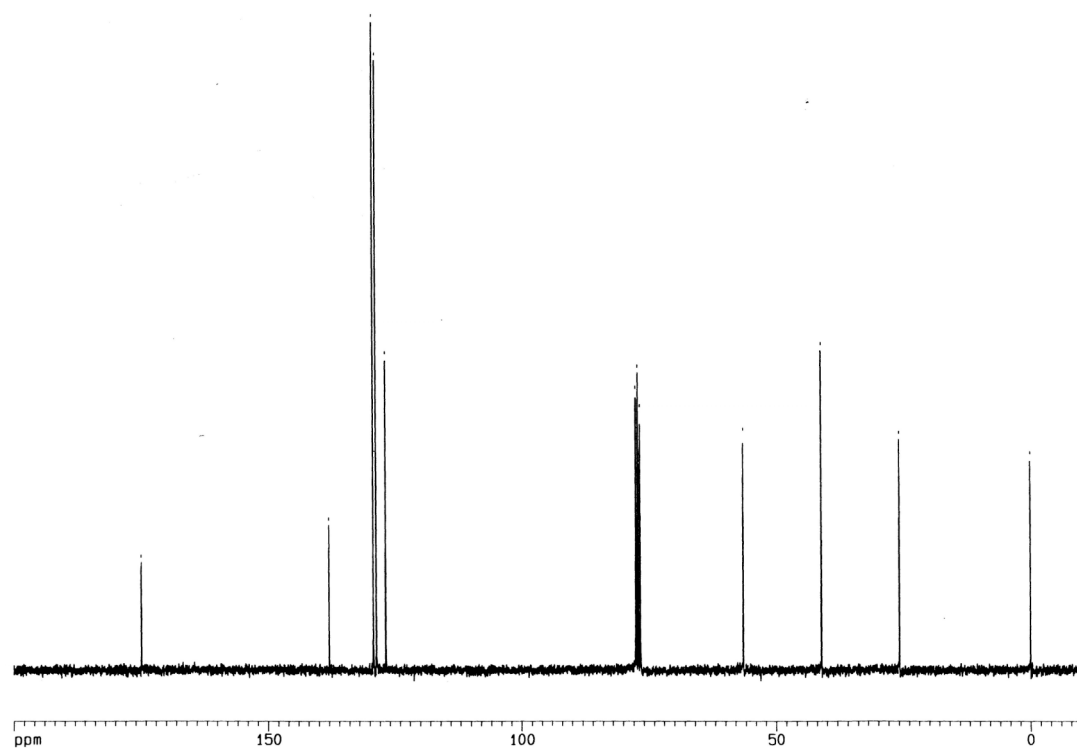


Figure S39. ¹³C-NMR spectrum of compound **10d**.

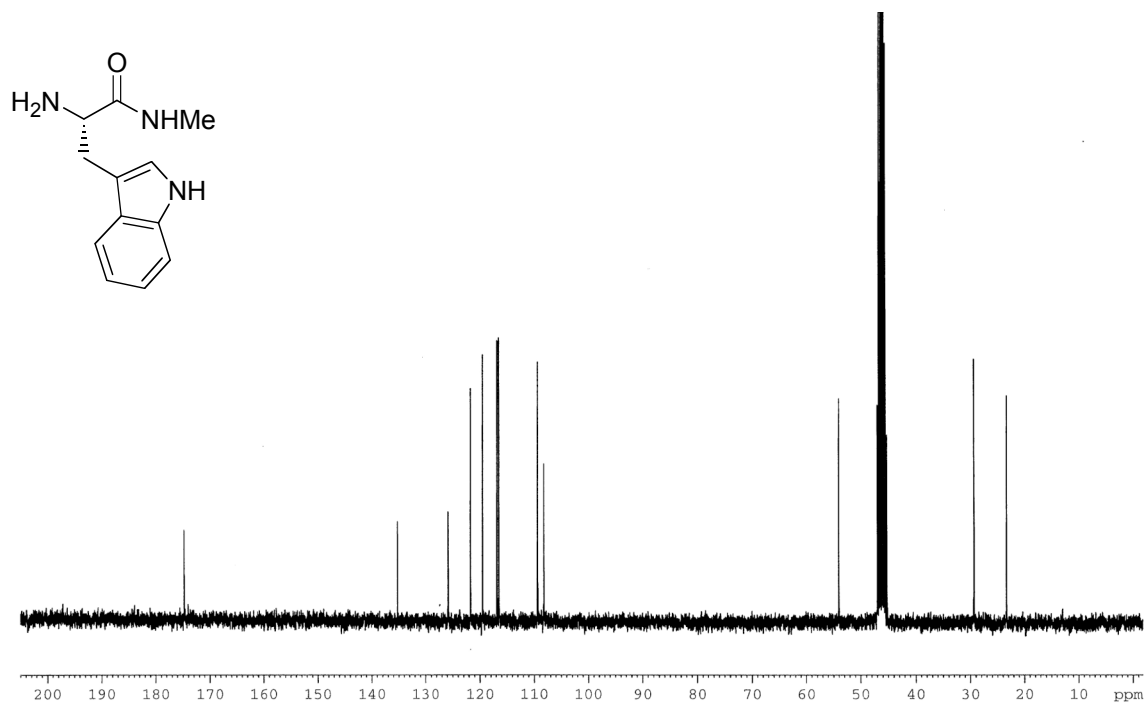


Figure S40. ^{13}C NMR spectrum of compound **10f**.

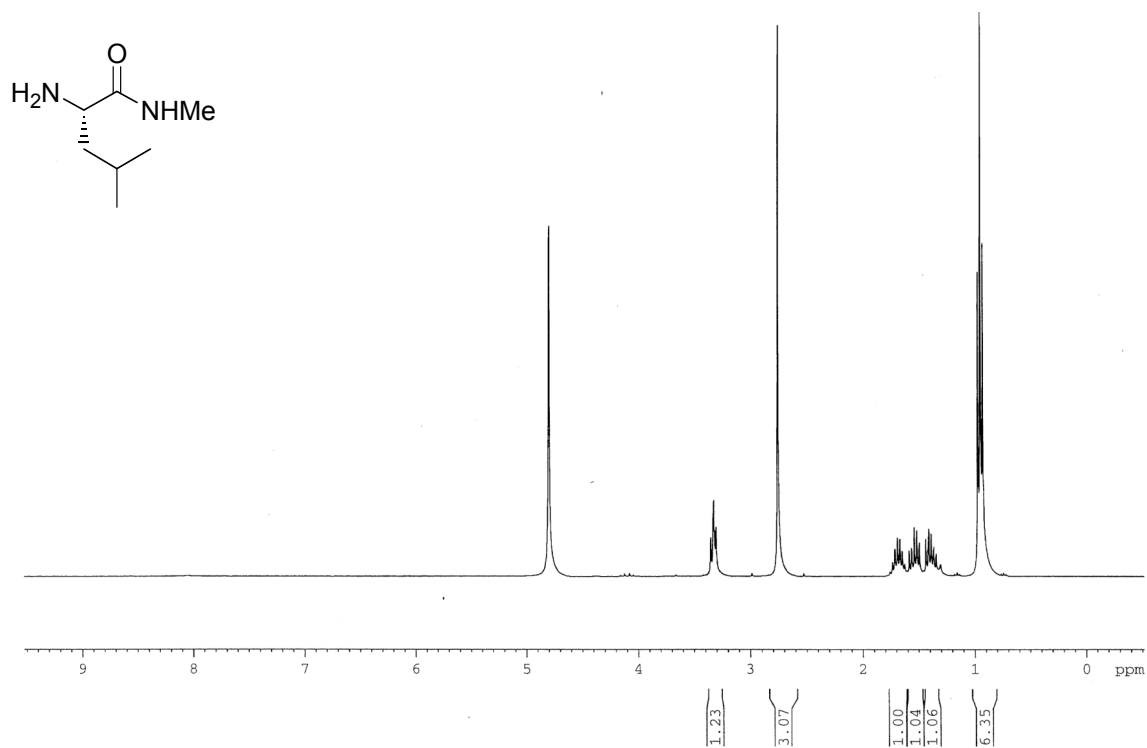


Figure S41. ^1H NMR spectrum of compound **10g**.

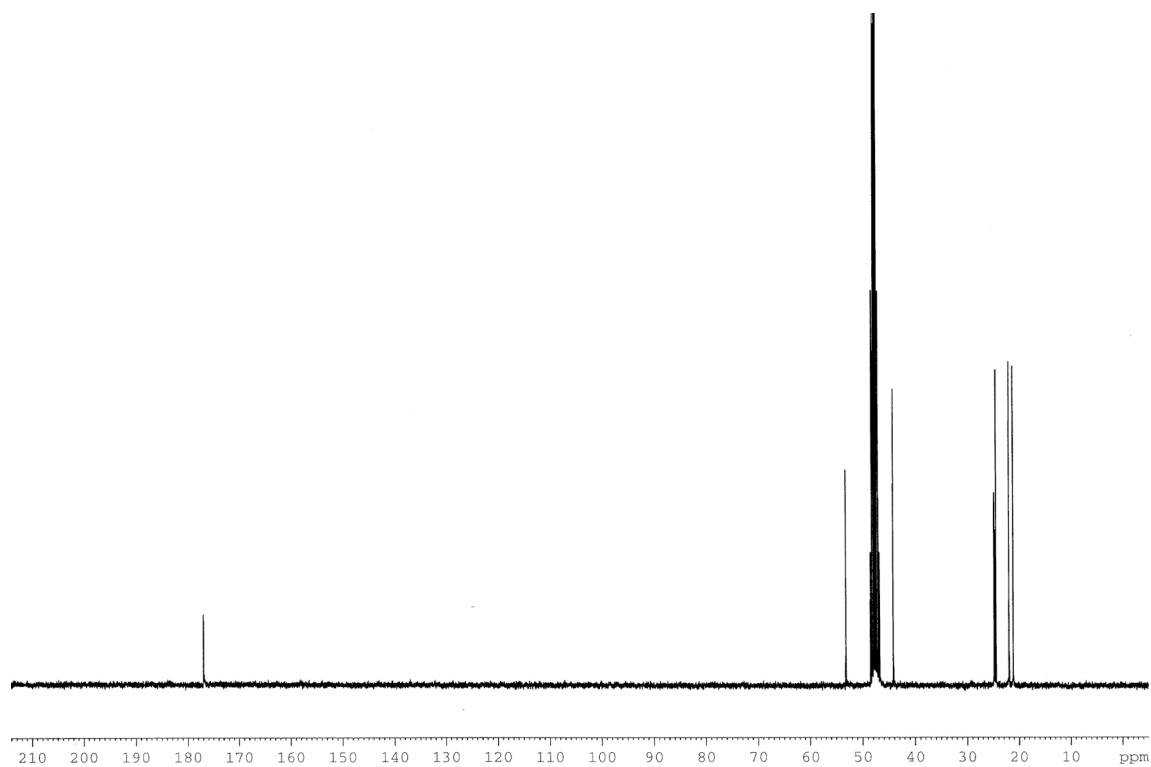


Figure S42. ^{13}C NMR spectrum of compound **10g**.

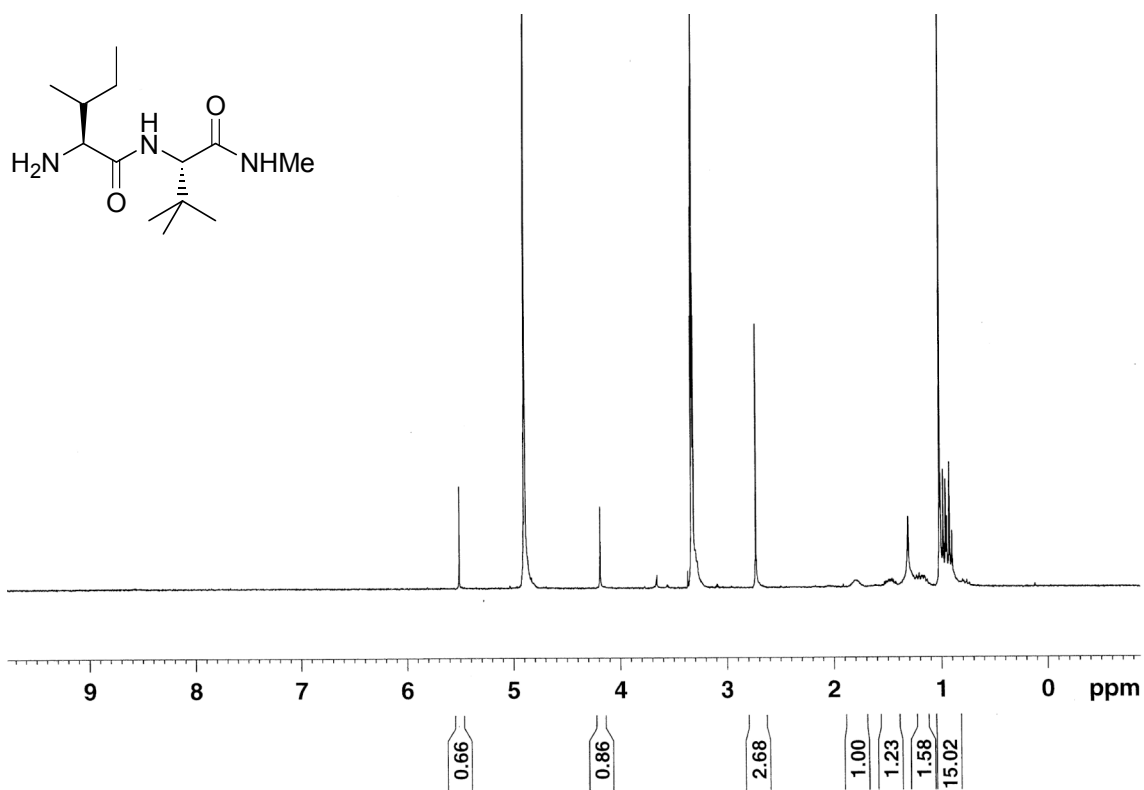


Figure S43. ¹H NMR spectrum of compound 11a.

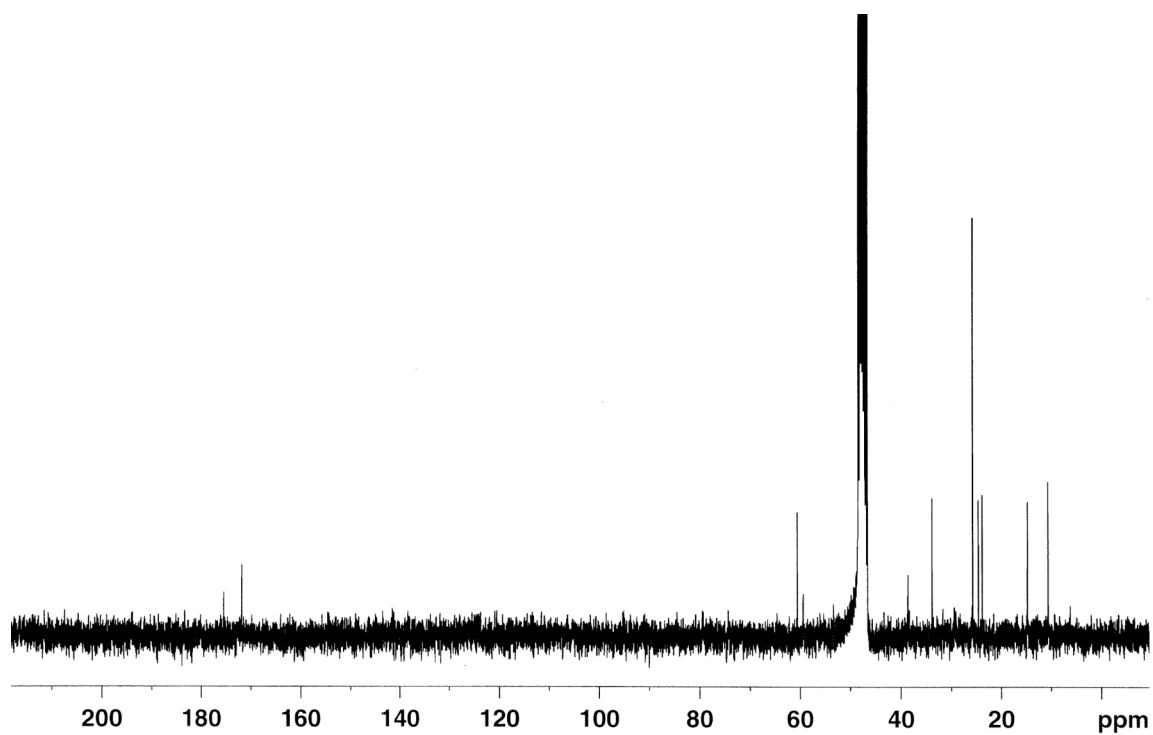


Figure S44. ¹³C NMR spectrum of compound 11a.

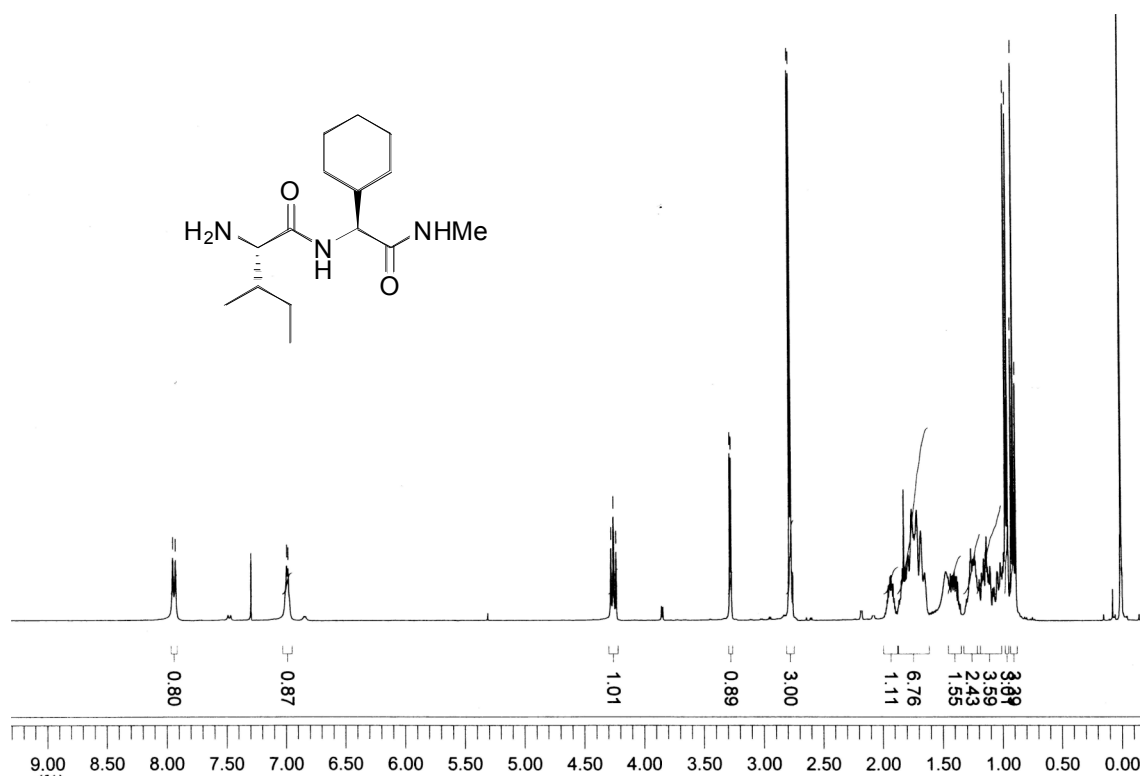


Figure S45. ¹H-NMR spectrum of compound **11b**.

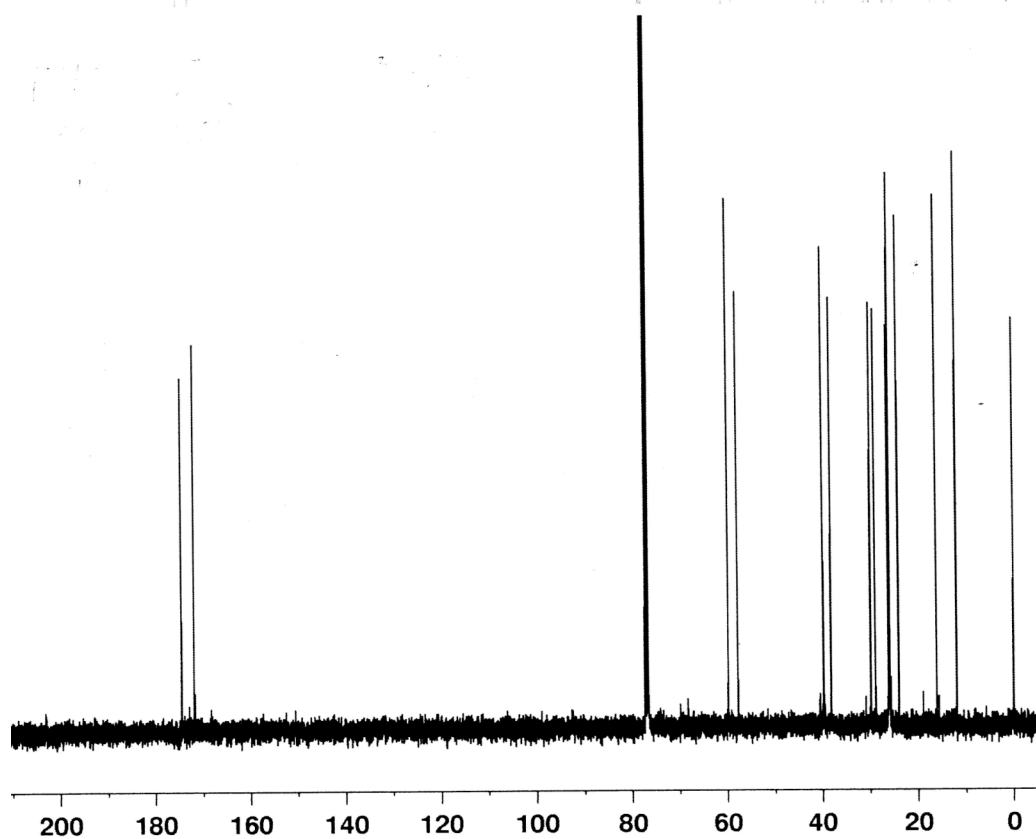


Figure S46. ¹³C-NMR spectrum of compound **11b**.

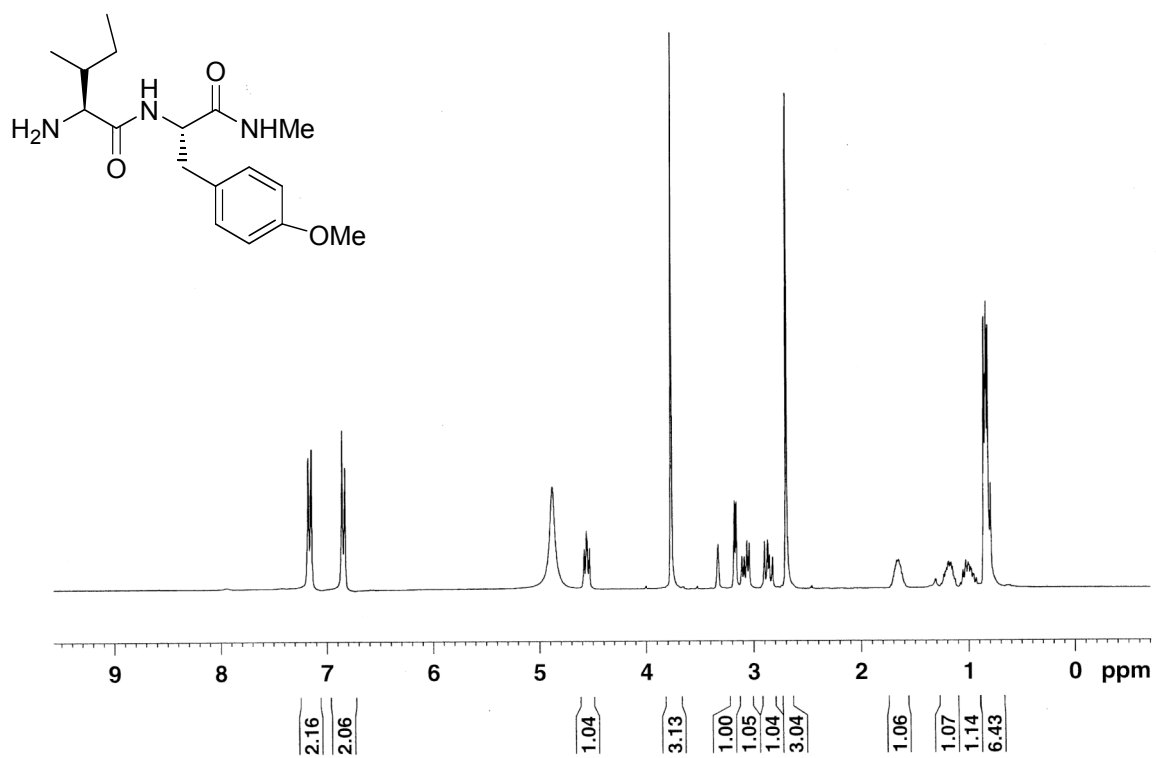


Figure S47. ¹H NMR spectrum of compound **11c**.

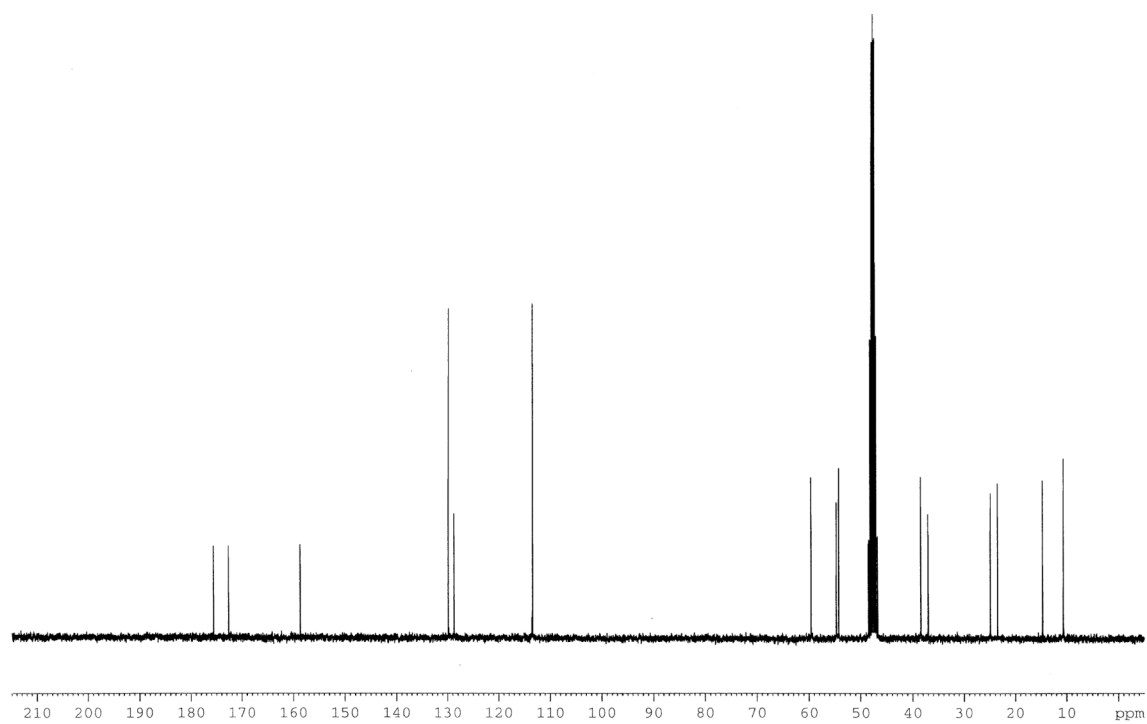


Figure S48. ¹³C NMR spectrum of compound **11c**.

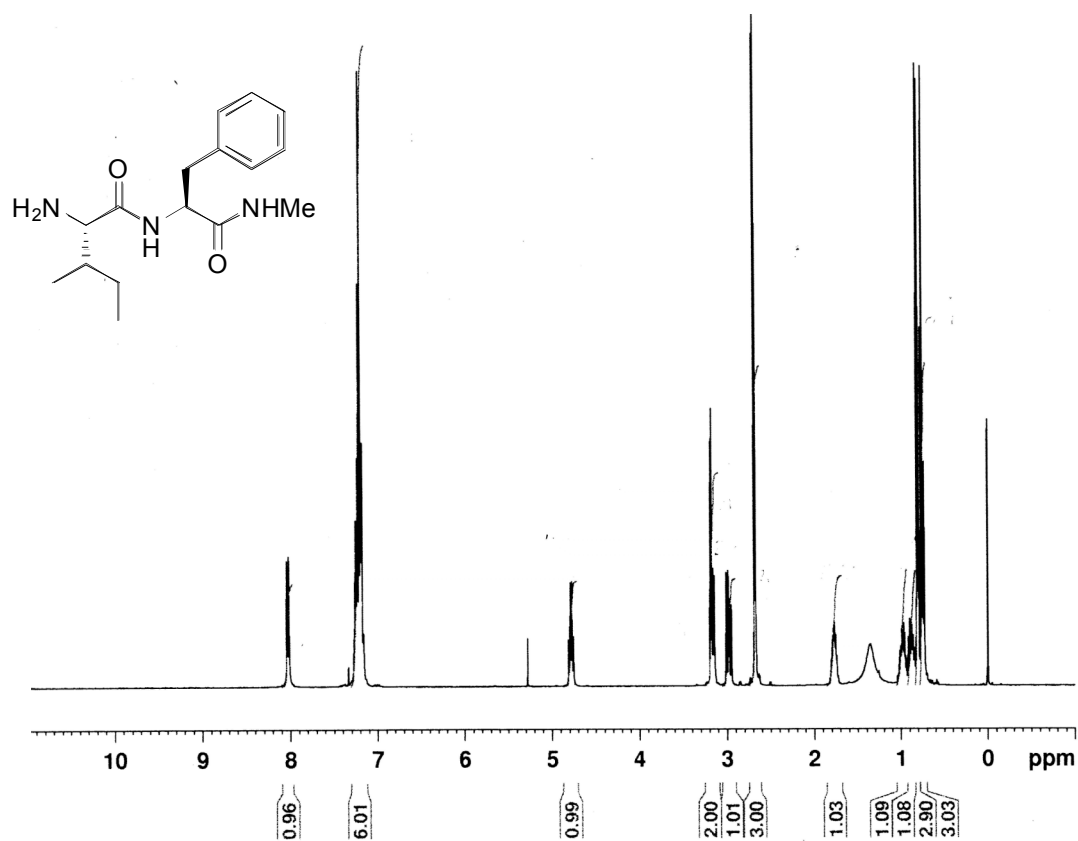


Figure S49. ¹H-NMR spectrum of compound **11d**.

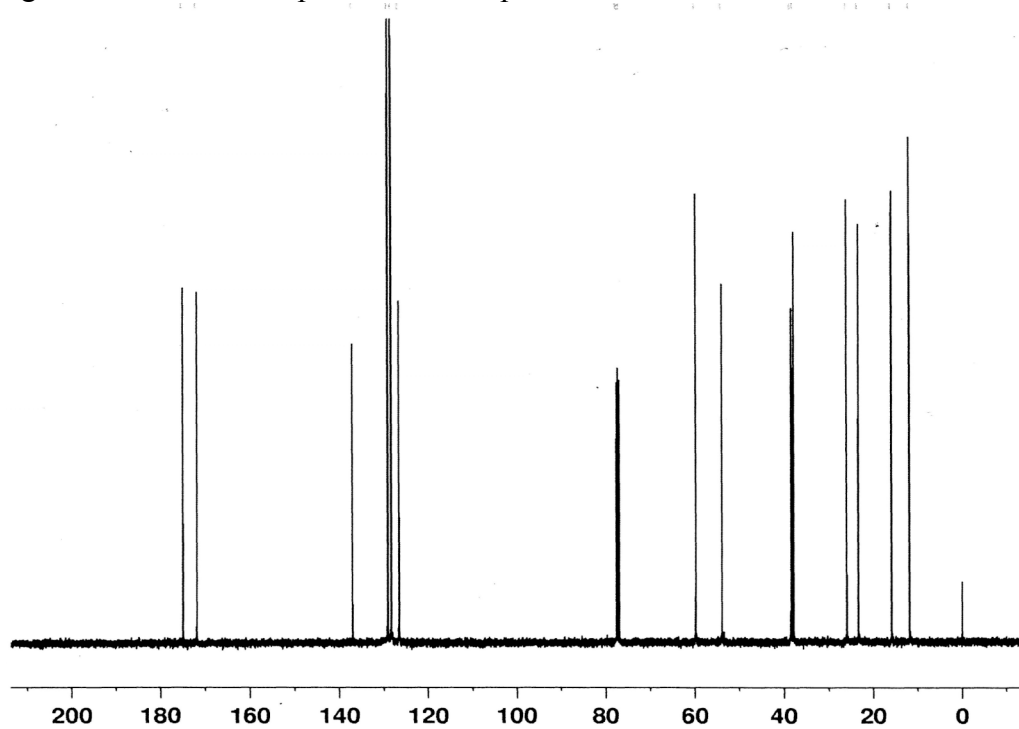


Figure S50. ¹³C-NMR spectrum of compound **11d**.

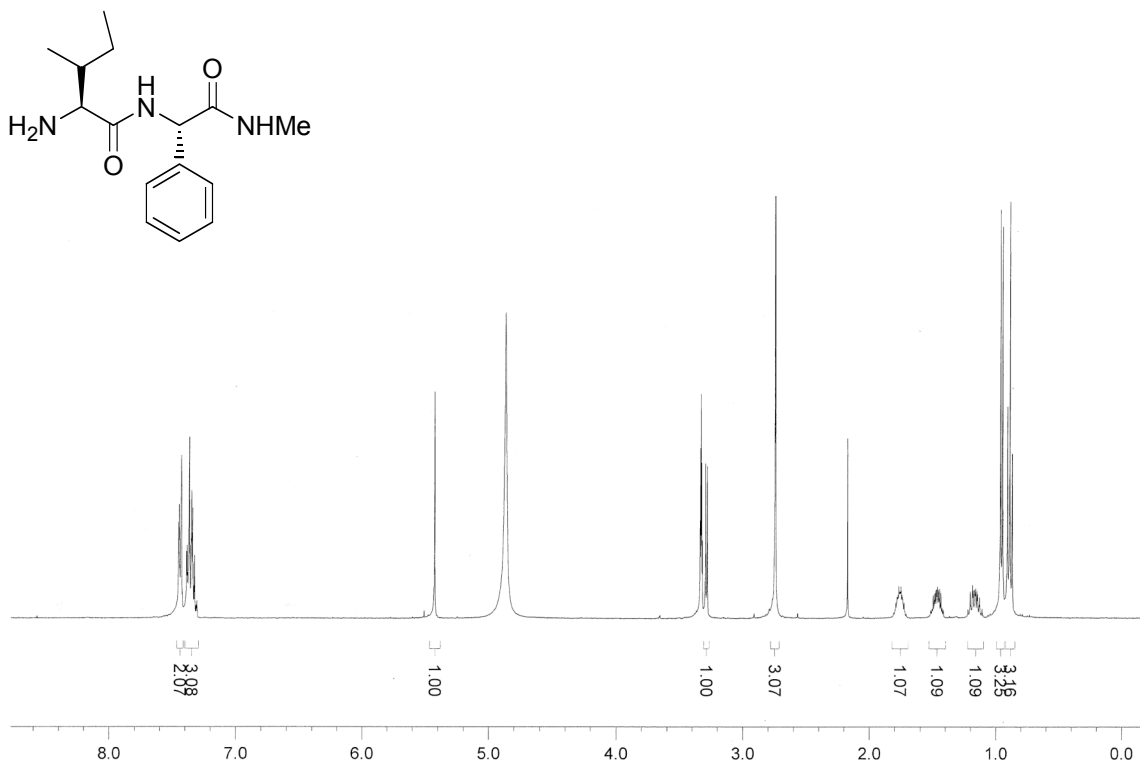


Figure S51. ¹H NMR spectrum of compound **11e**.

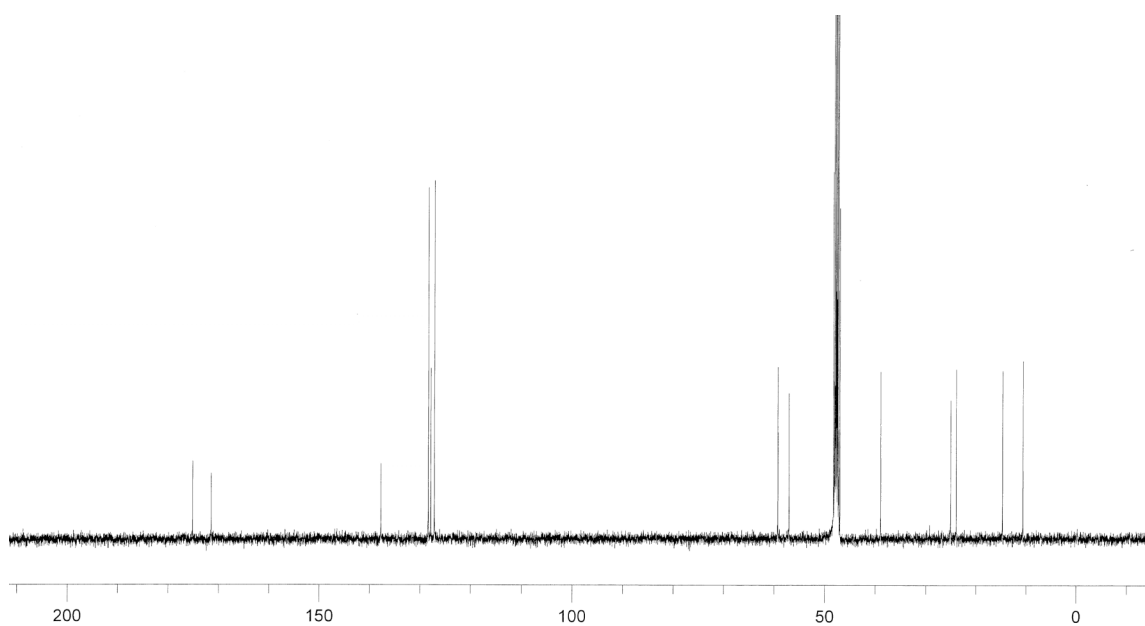


Figure S52. ¹³C NMR spectrum of compound **11e**.

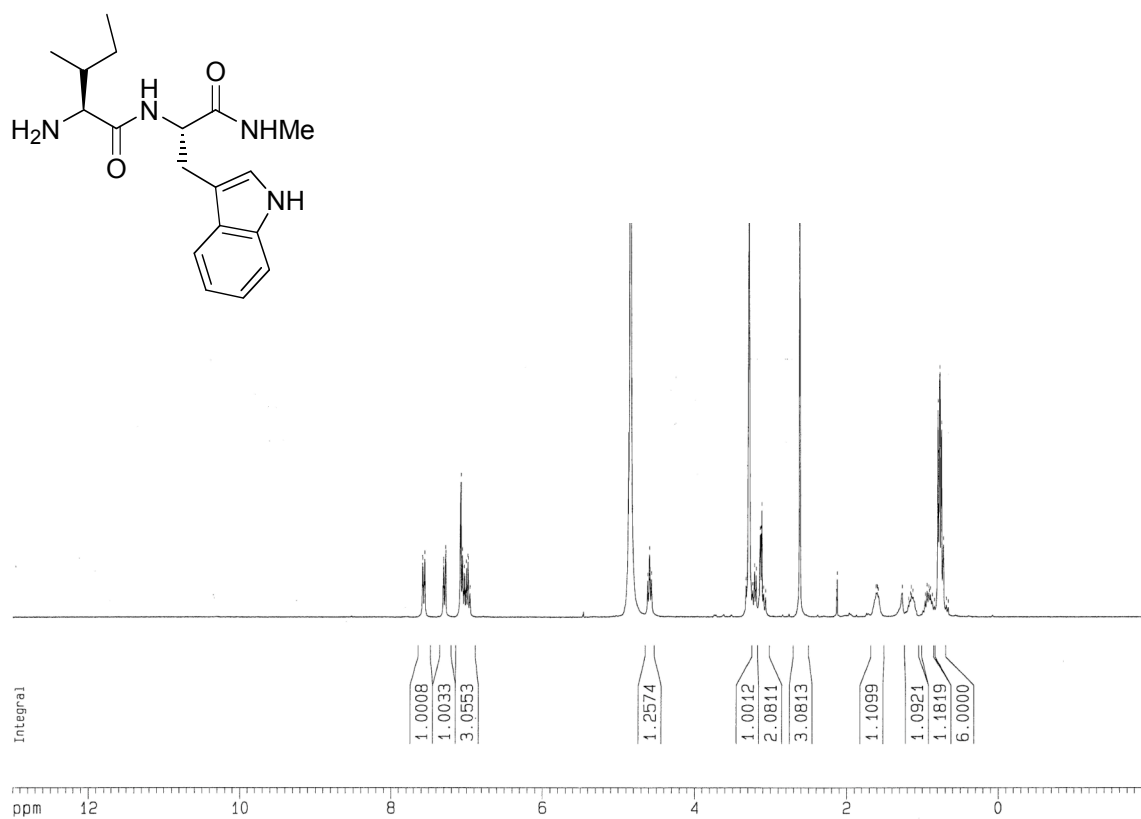


Figure S53. ¹H NMR spectrum of compound **11f**.

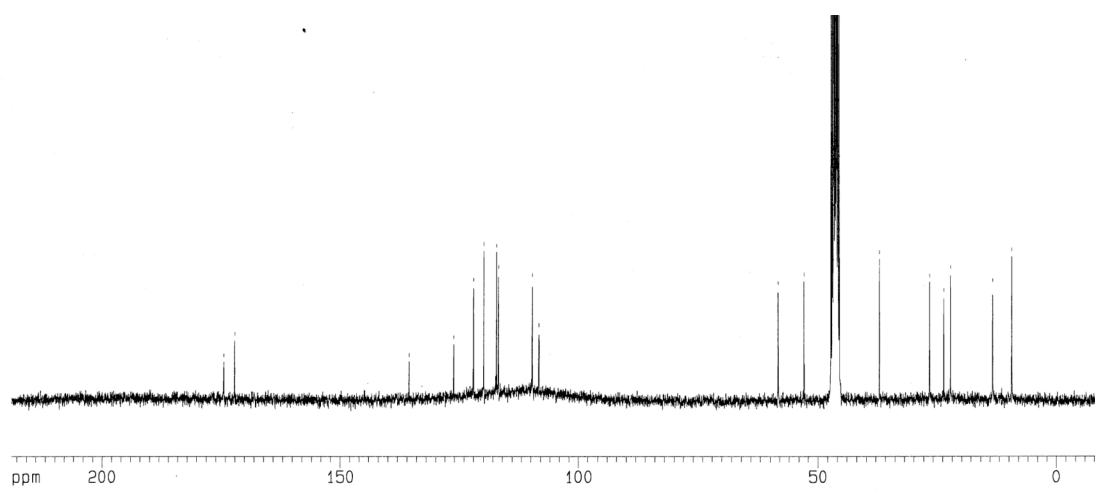


Figure S54. ¹³C NMR spectrum of compound **11f**.

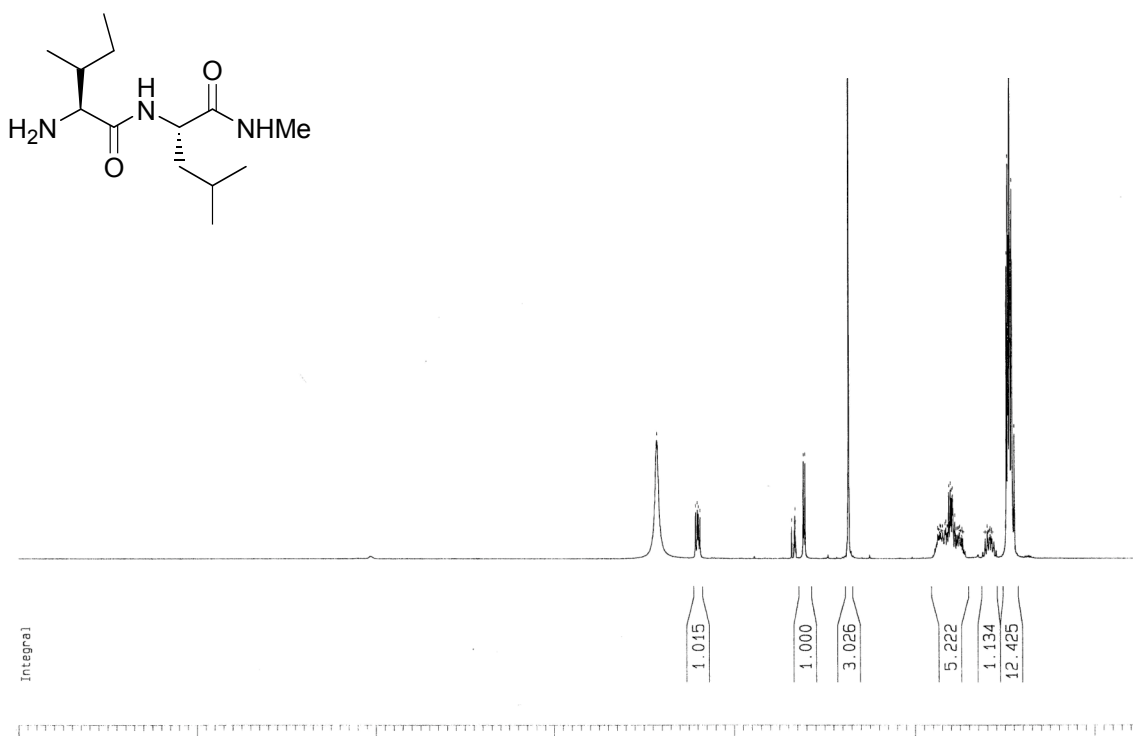


Figure S55. ^1H NMR spectrum of compound **11g**.

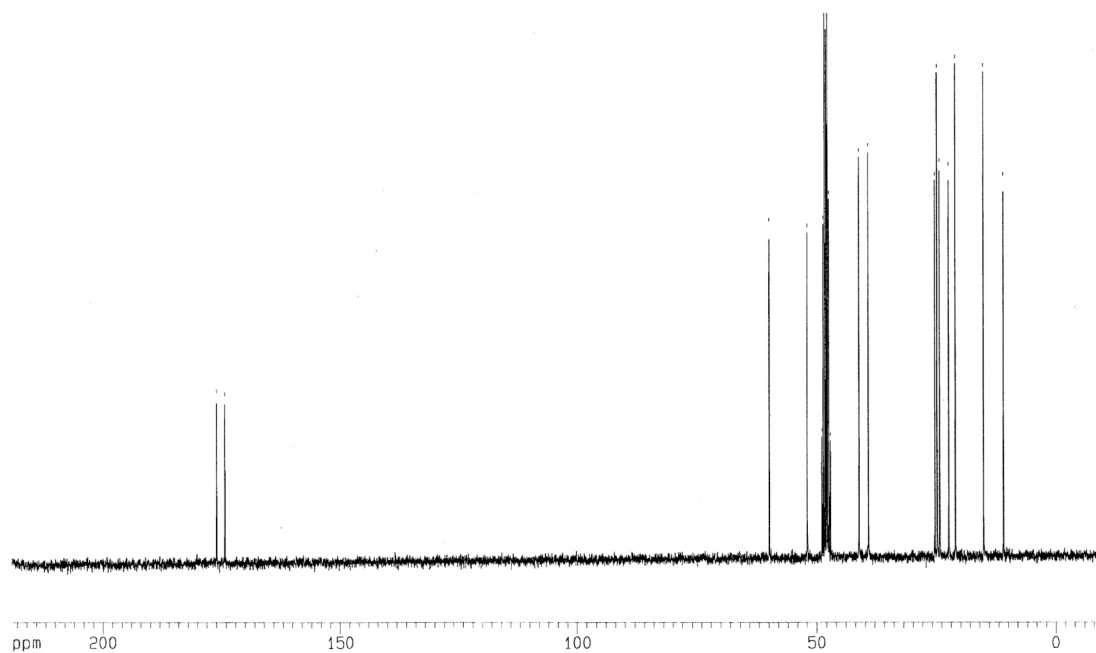


Figure S56. ^{13}C NMR spectrum of compound **11g**.

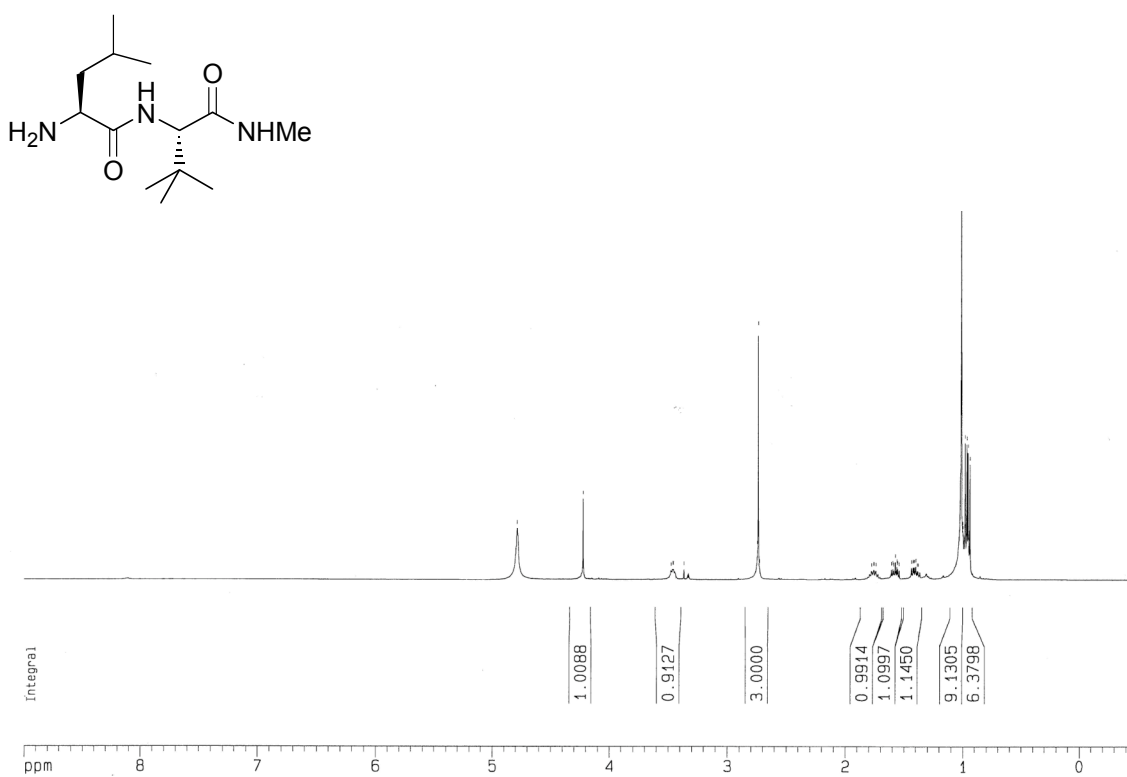


Figure S57. ¹H NMR spectrum of compound **11h**.

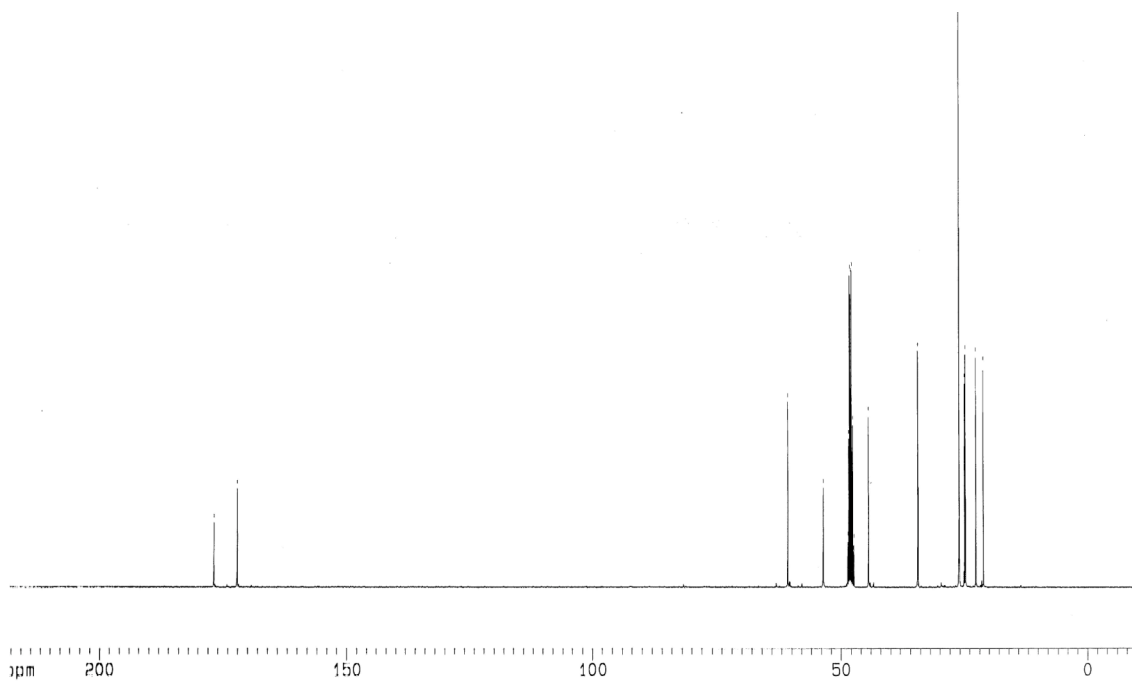


Figure S58. ¹³C NMR spectrum of compound **11h**.

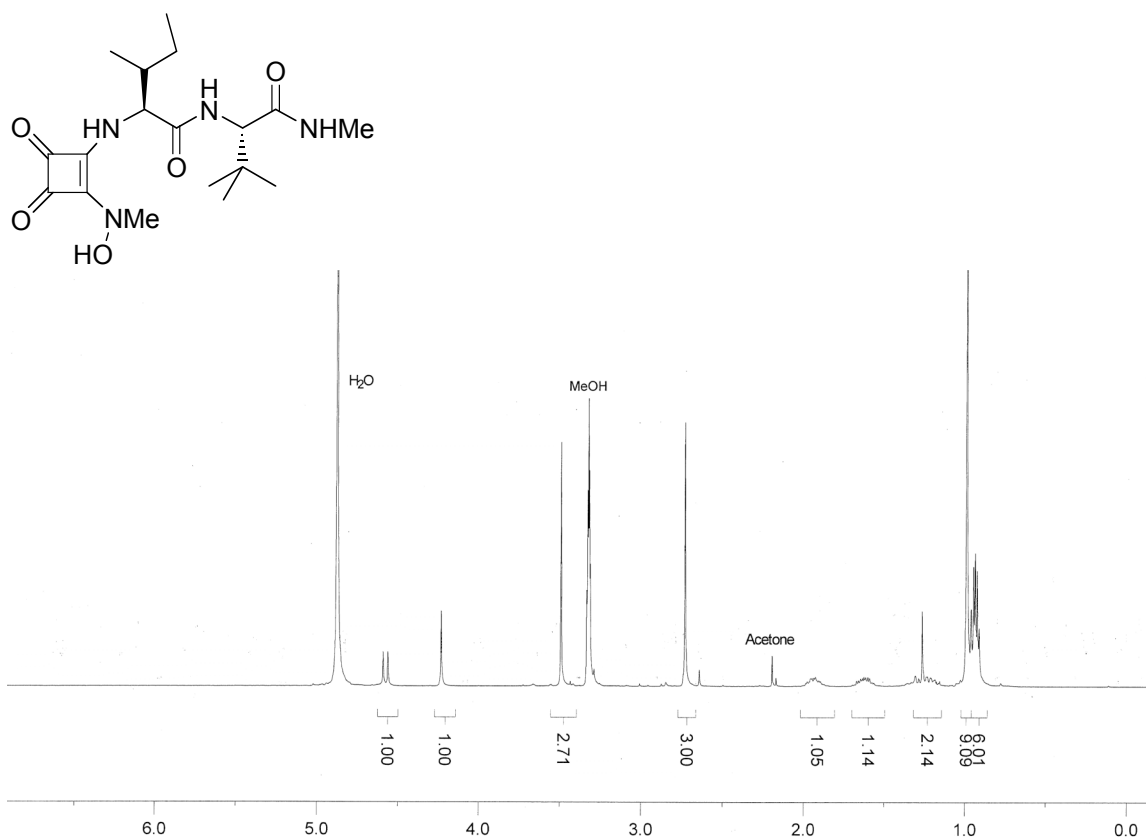


Figure S59. ¹H NMR spectrum of compound **12a**.

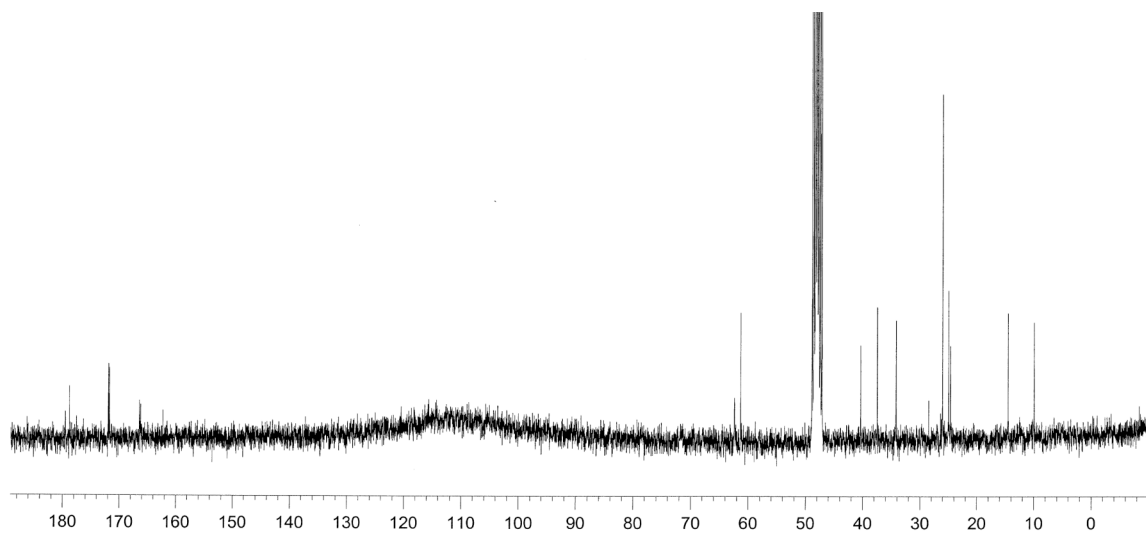


Figure S60. ¹³C NMR spectrum of compound **12a**.

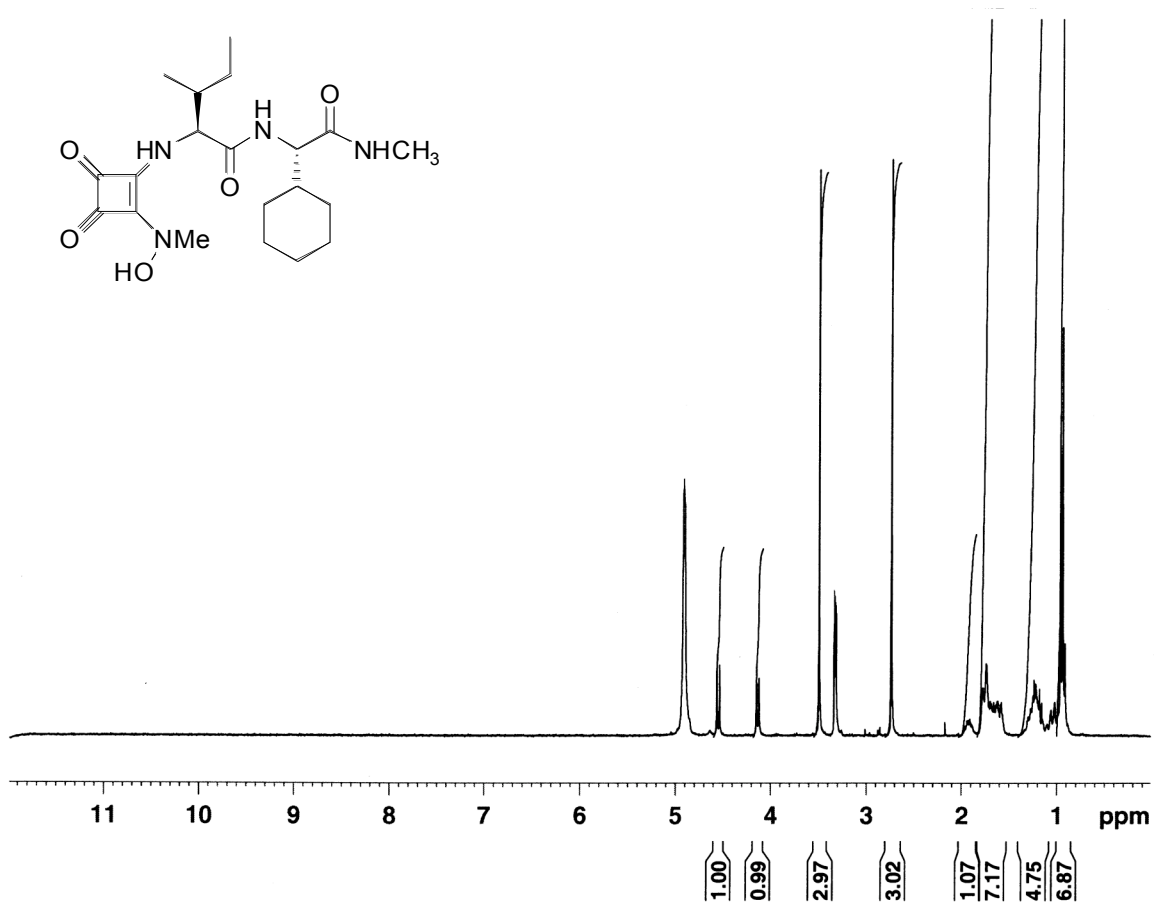


Figure S61. ^1H NMR spectrum of compound **12b**.

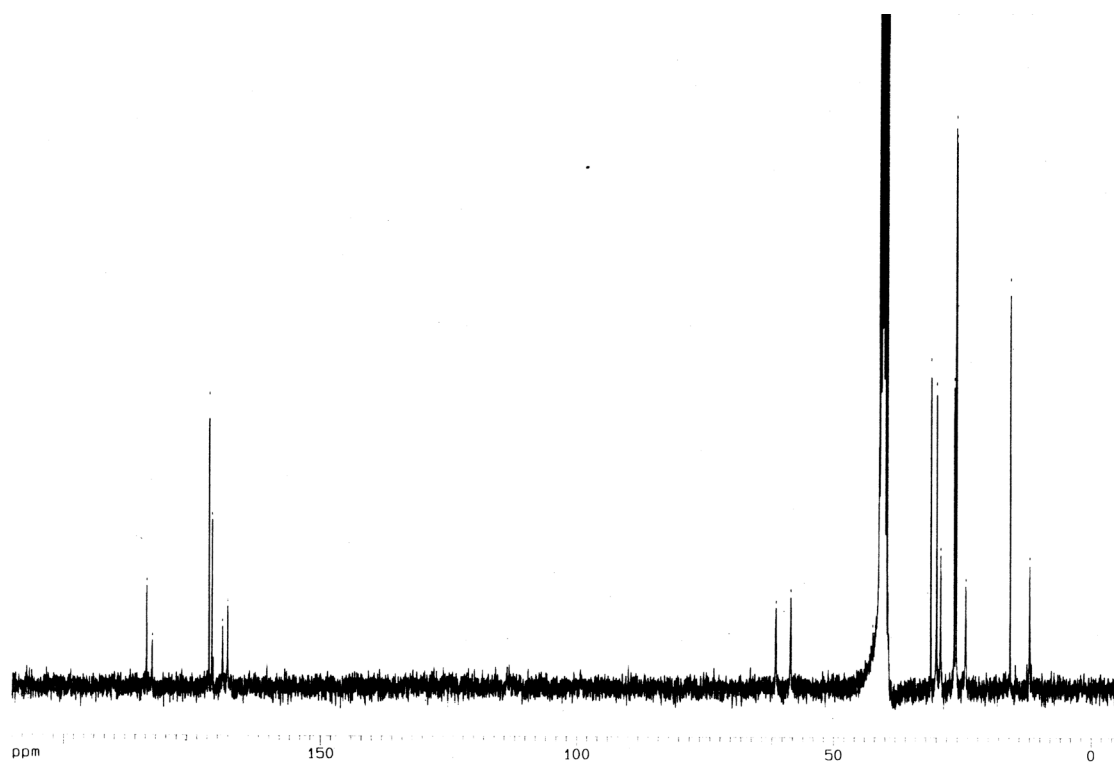


Figure S62. ^{13}C NMR spectrum of compound **12b**.

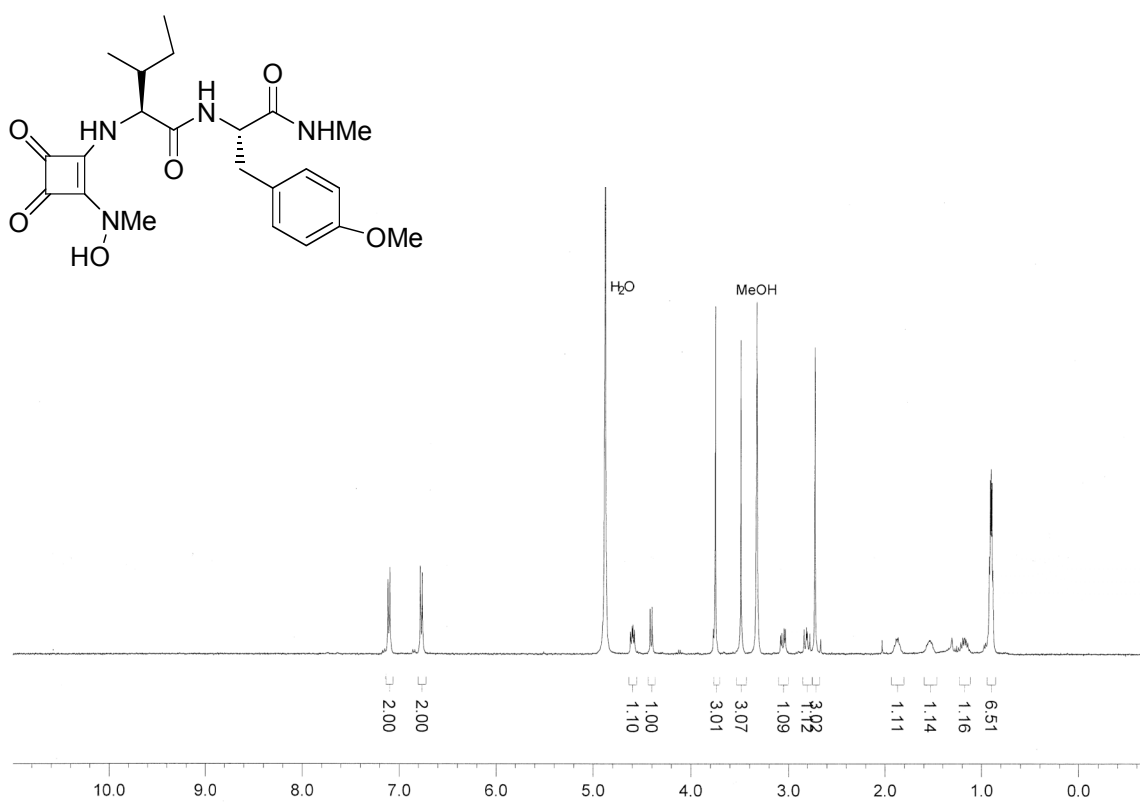


Figure S63. ¹H NMR spectrum of compound 12c.

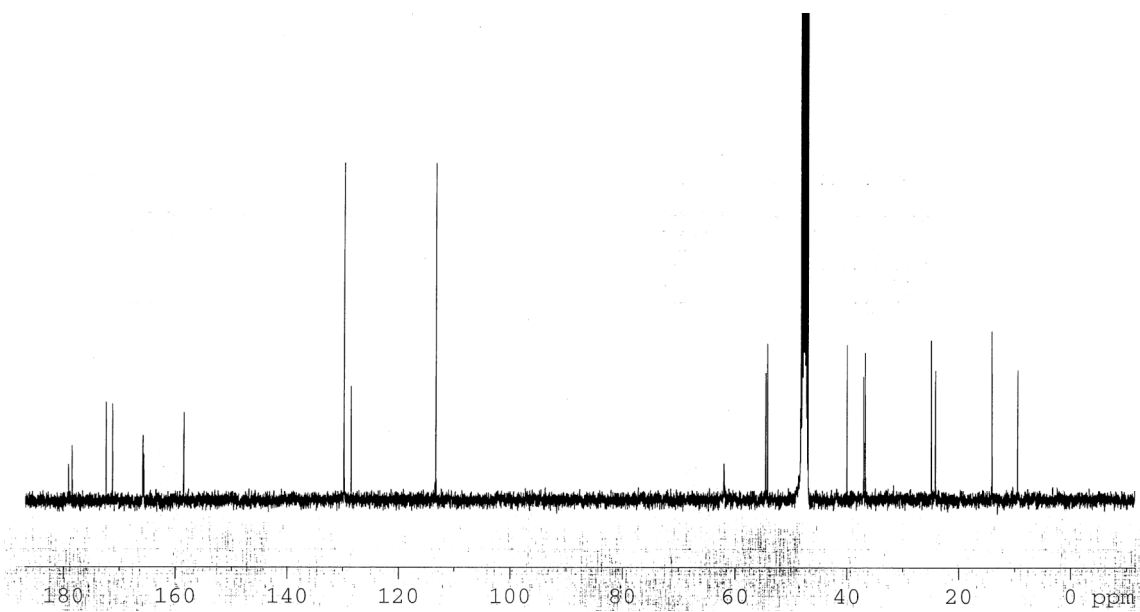


Figure S64. ¹³C NMR spectrum of compound 12c.



Figure S65. ¹H NMR spectrum of compound 12d.

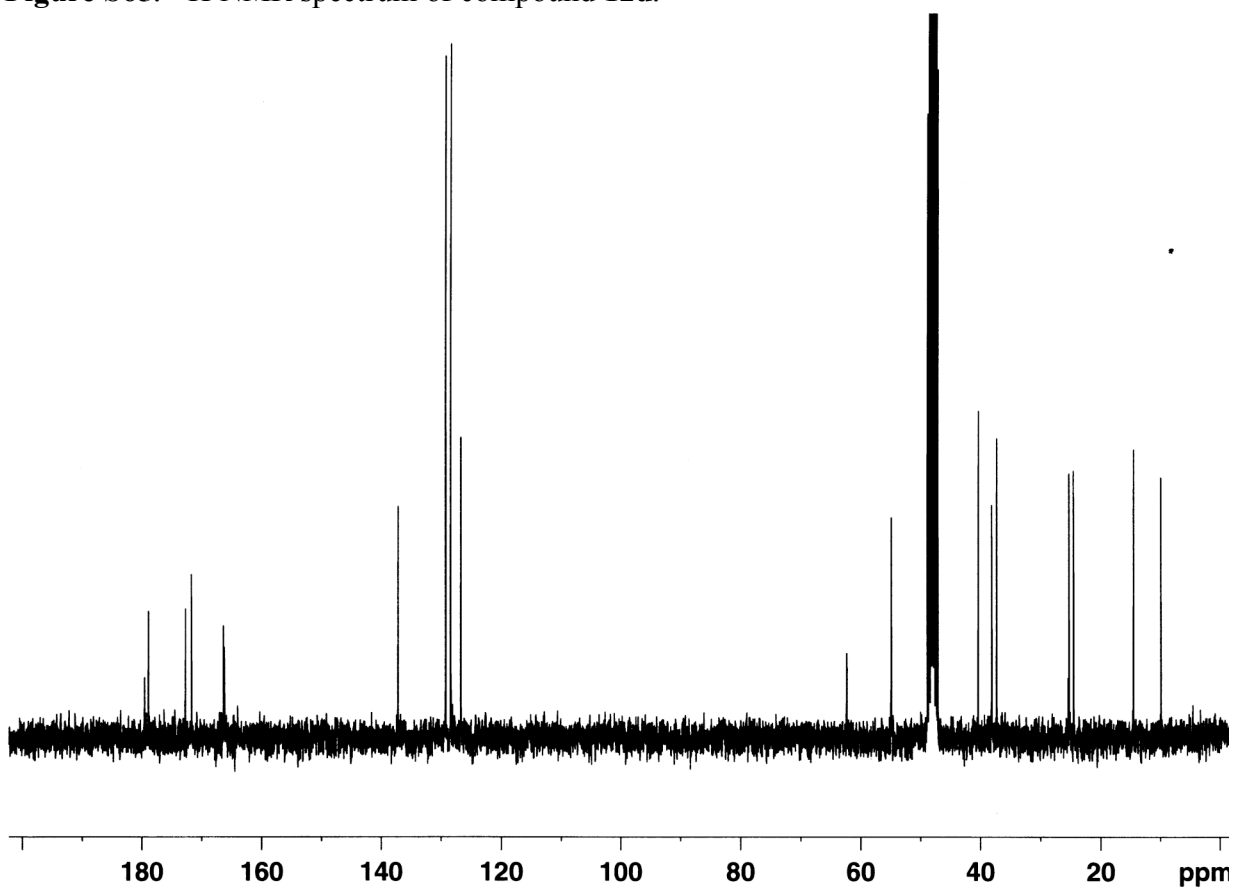


Figure S66. ¹³C NMR spectrum of compound 12d.

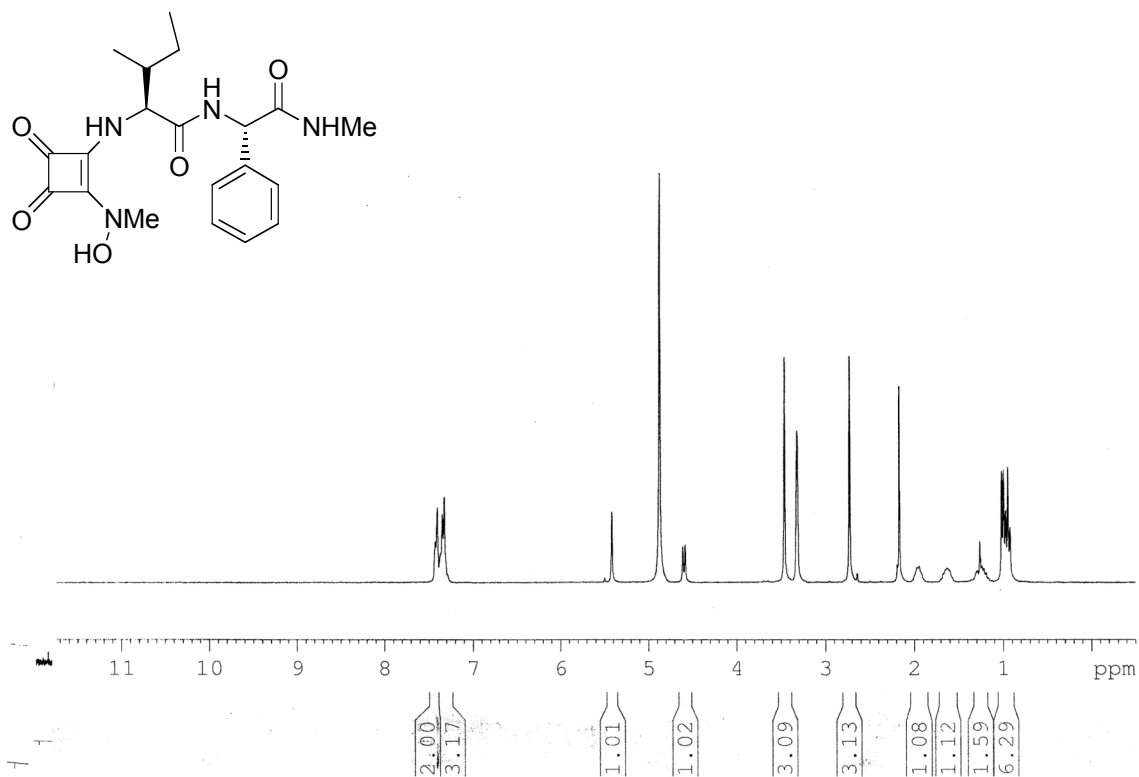


Figure S67. ¹H NMR spectrum of compound 12e.

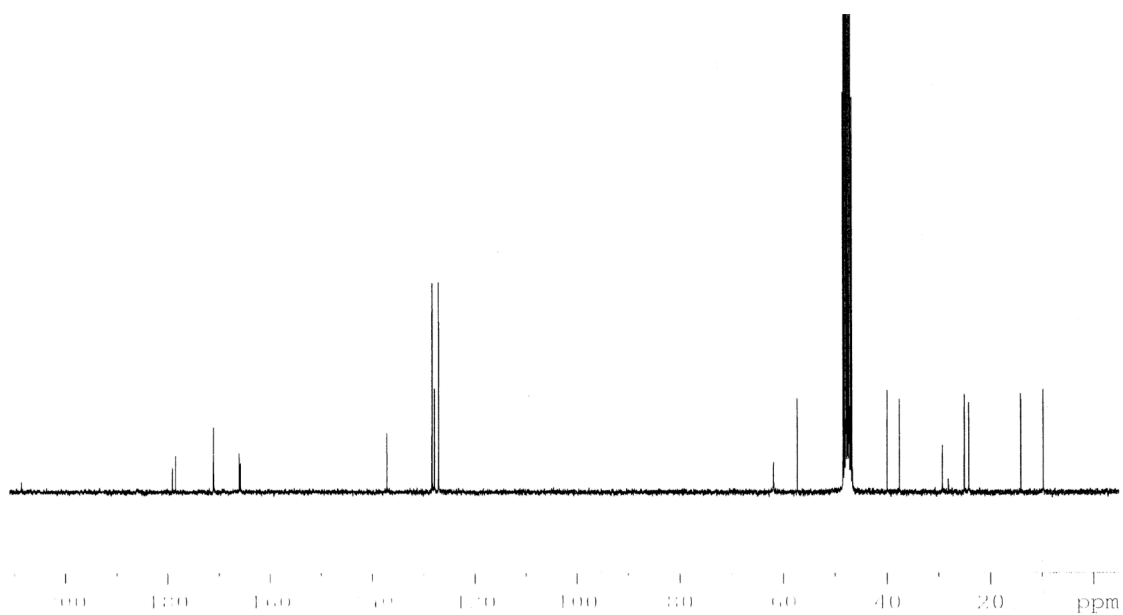


Figure S68. ¹³C NMR spectrum of compound 12e.



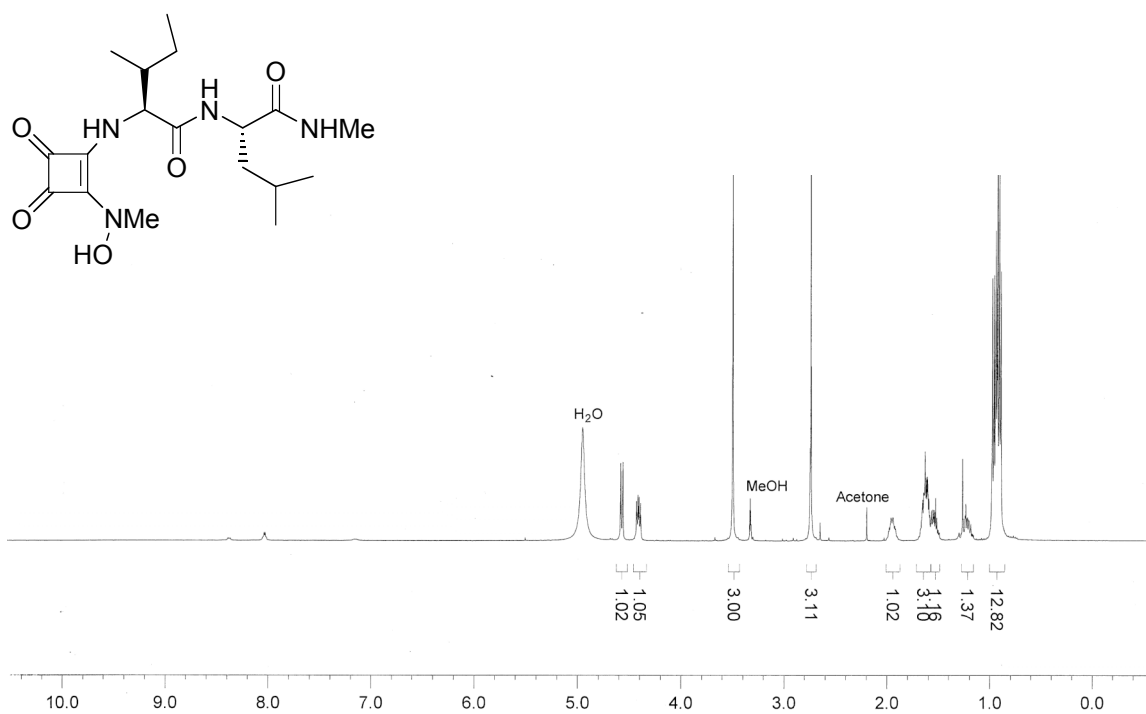


Figure S71. ^1H NMR spectrum of compound **12g**.

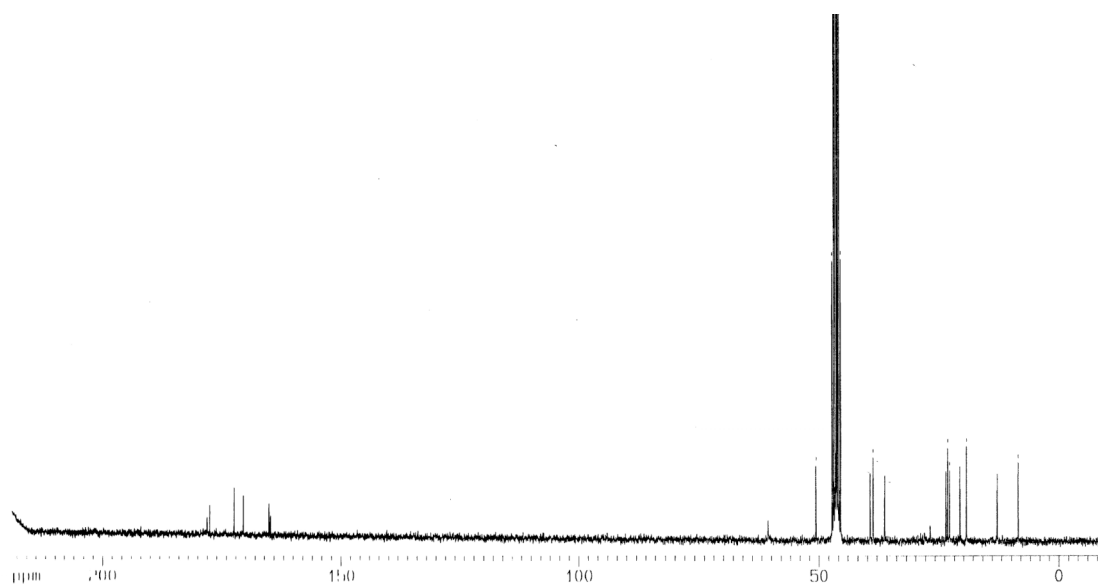


Figure S72. ^{13}C NMR spectrum of compound **12g**.

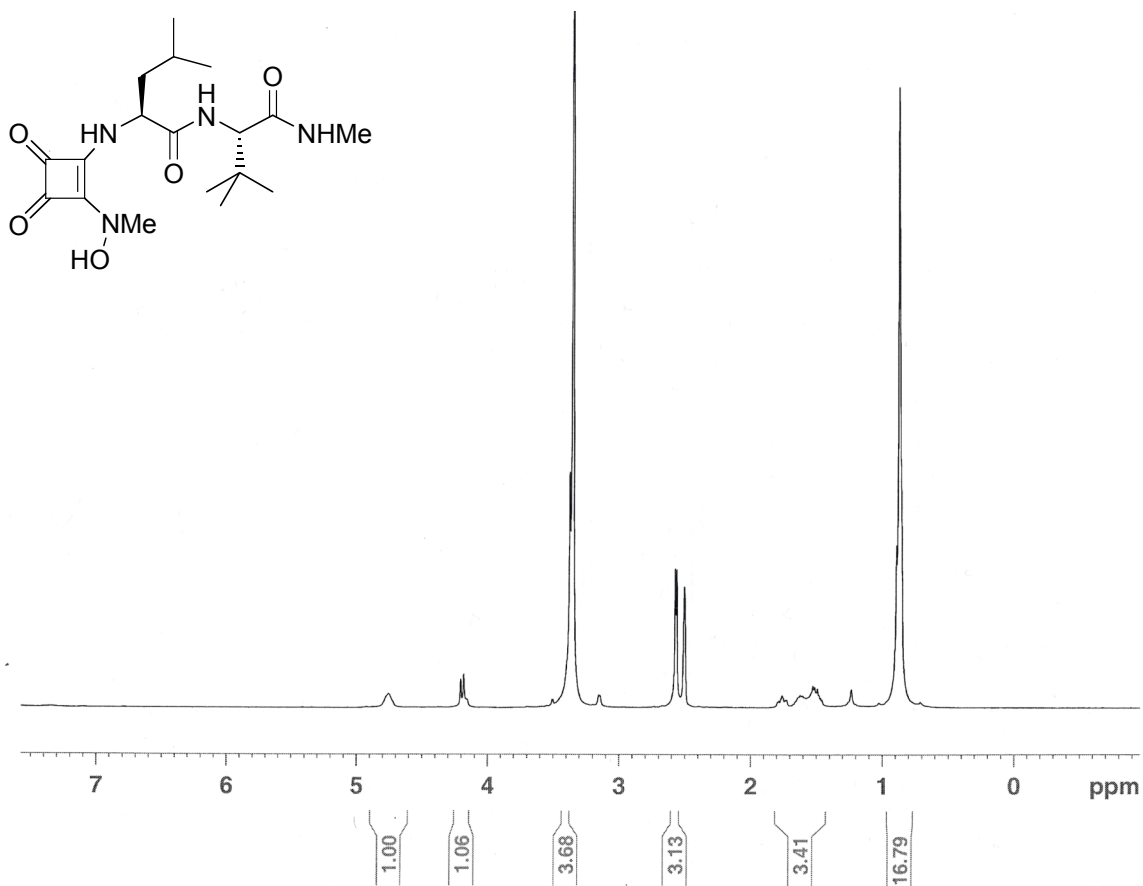


Figure S73. ^1H NMR spectrum of compound **12h**.

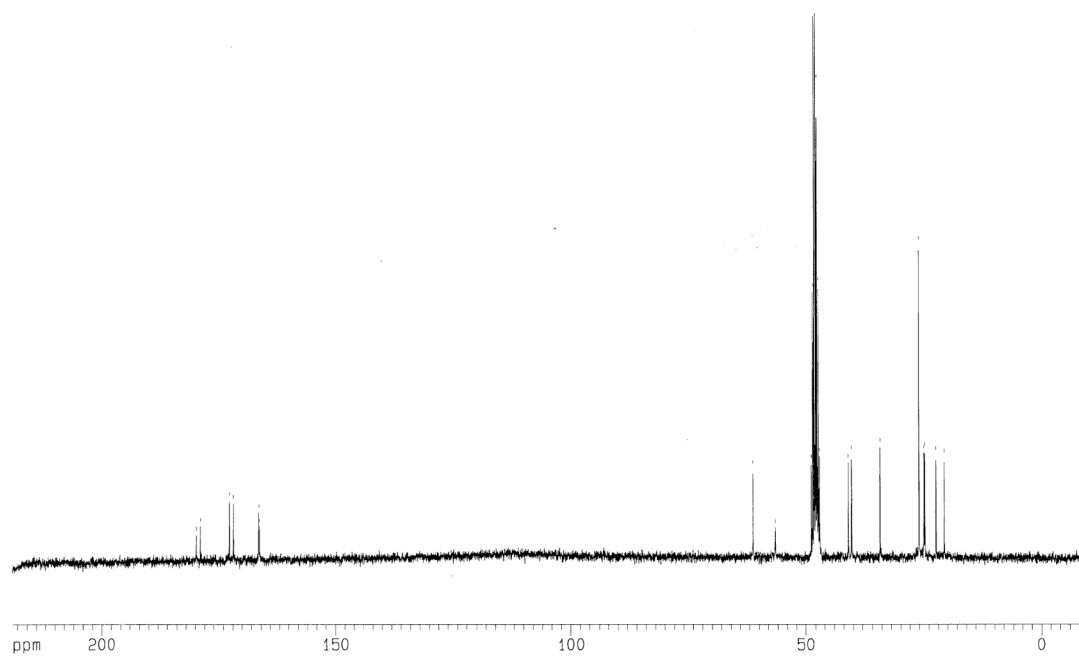


Figure S74. ^{13}C NMR spectrum of compound **12h**.

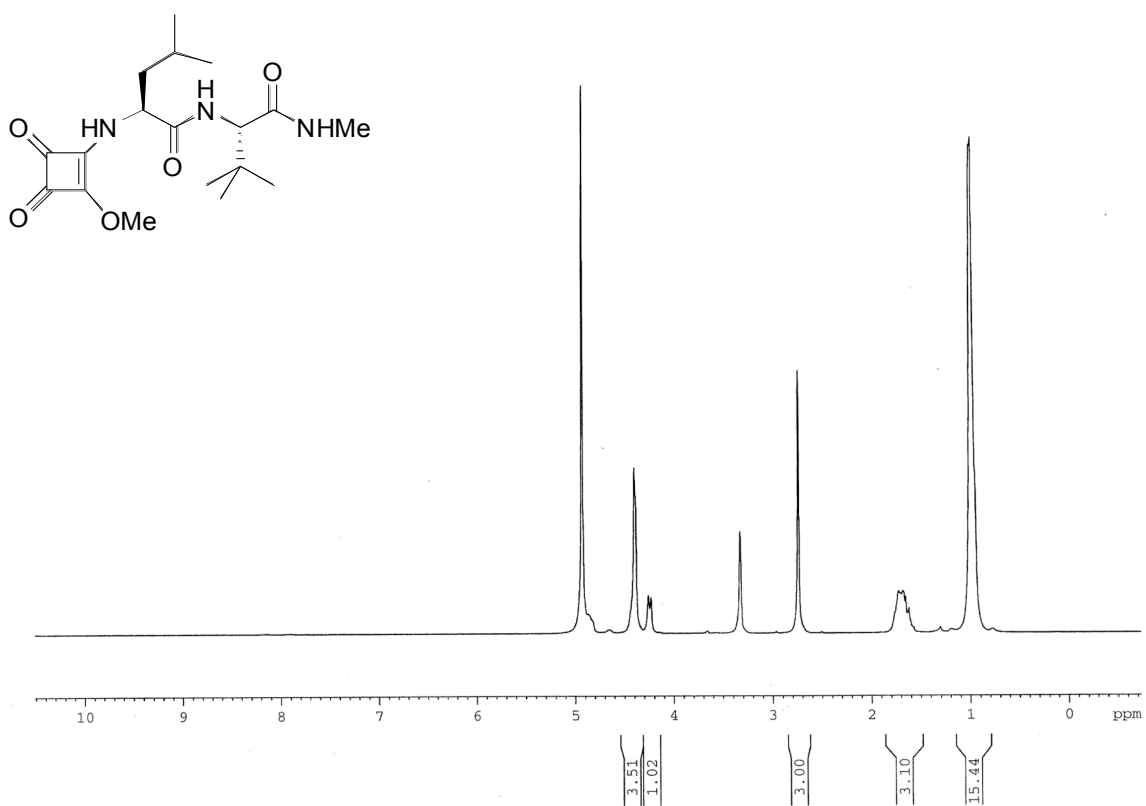


Figure S75. ¹H NMR spectrum of compound **13**.

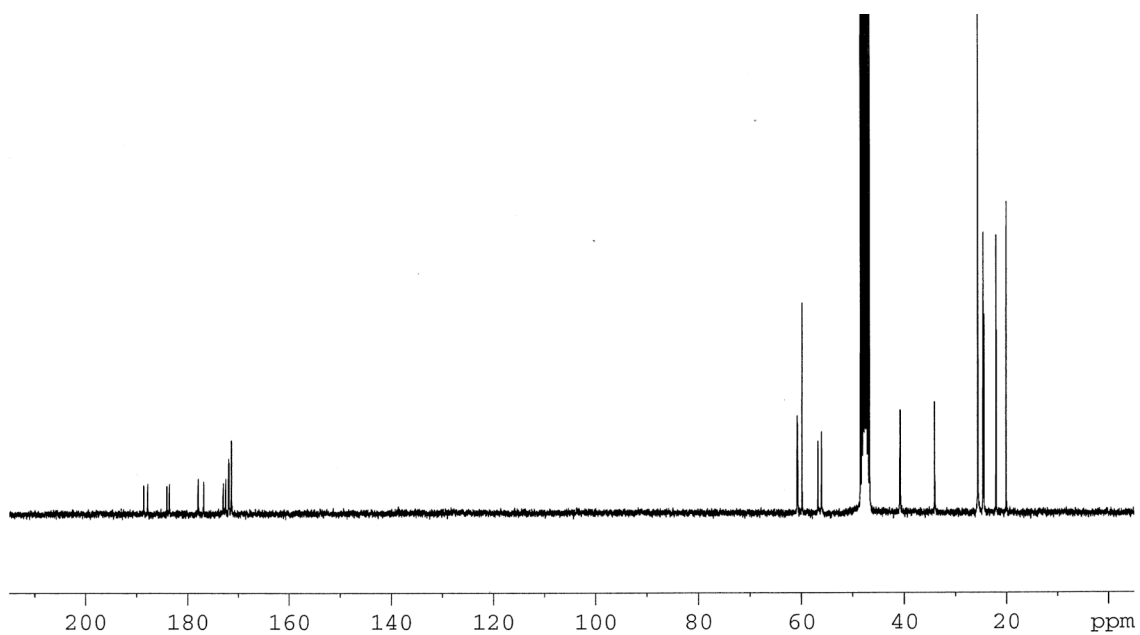


Figure S76. ¹³C NMR spectrum of compound **13**.

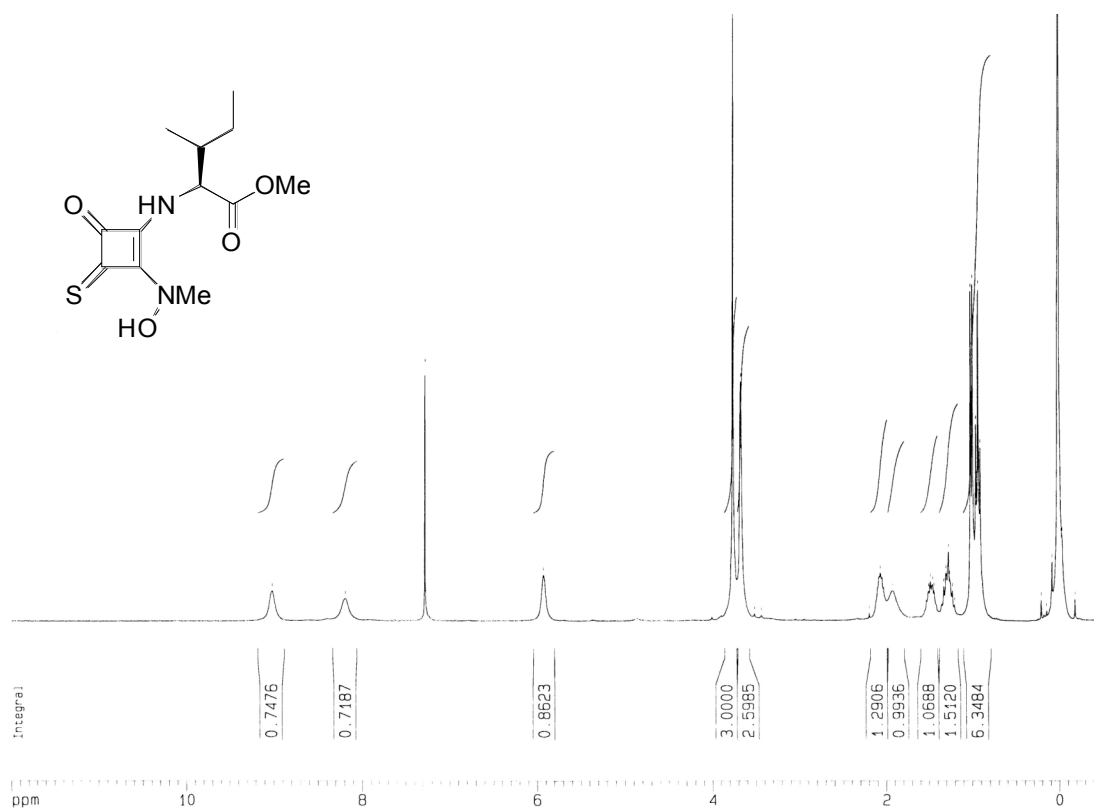


Figure S79. ¹H NMR spectrum of compound 15.

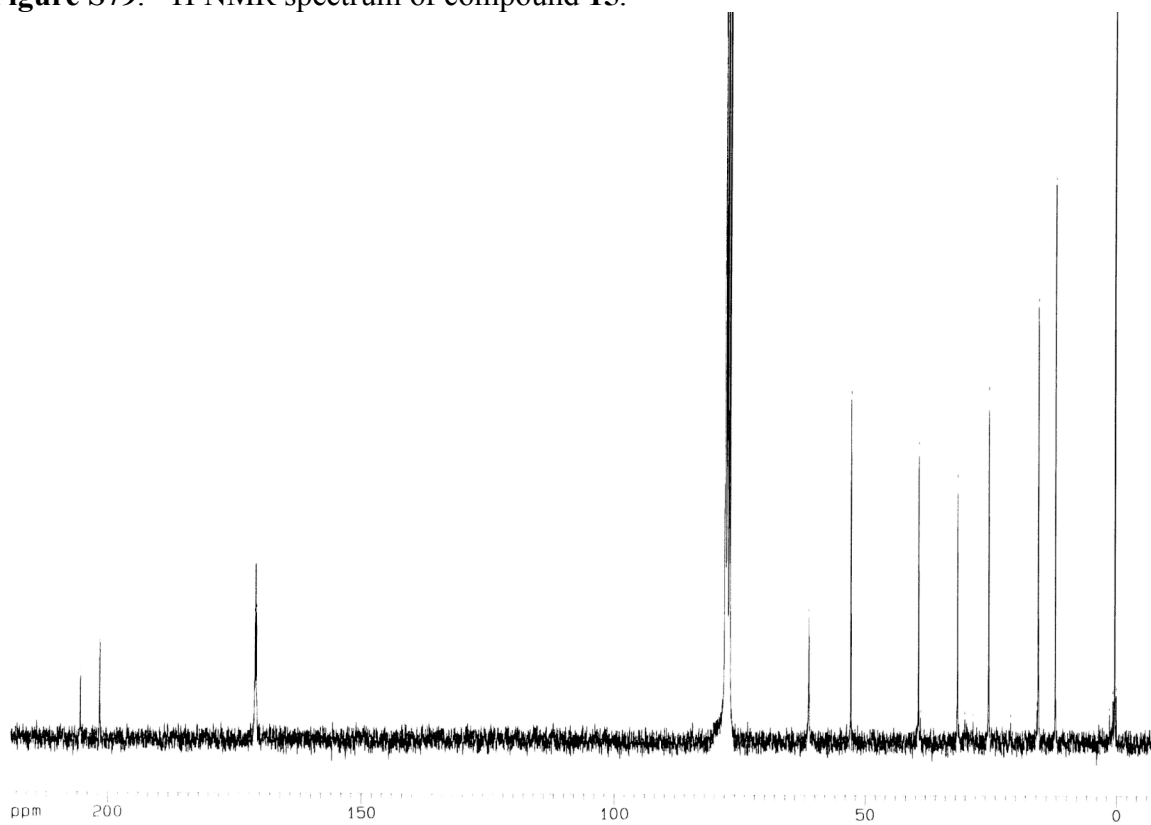


Figure S80. ¹³C NMR spectrum of compound 15.

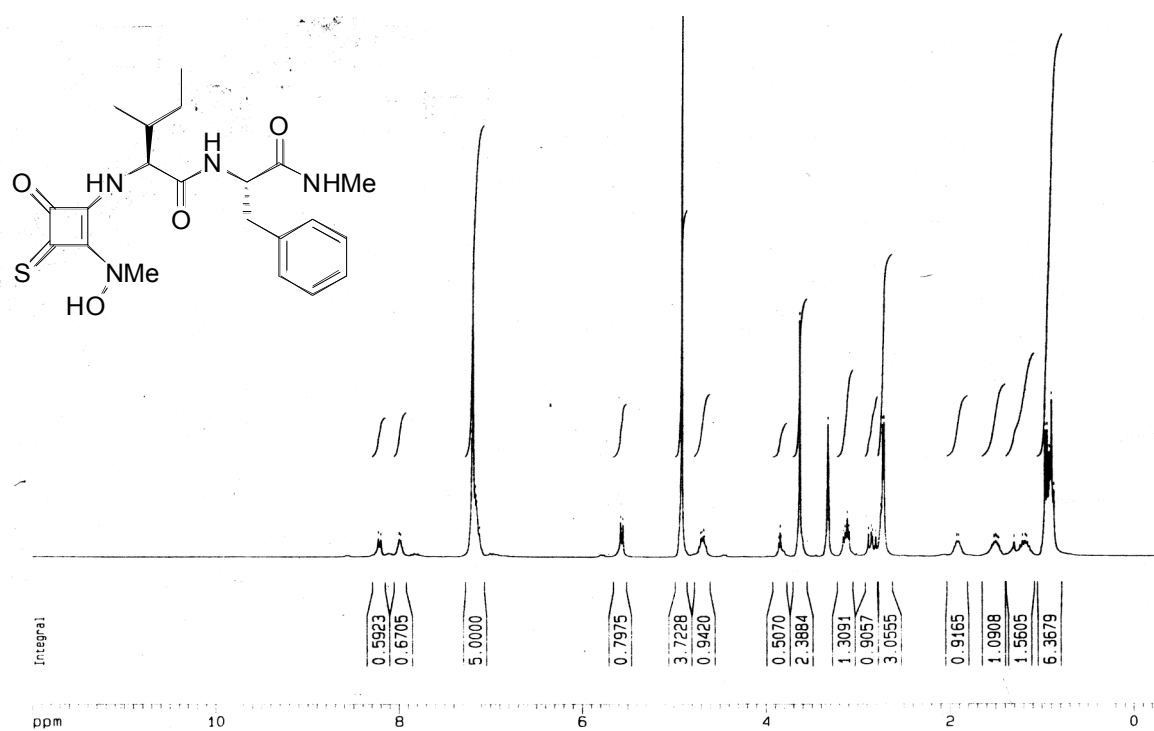


Figure S81. ¹H NMR spectrum of compound 16.

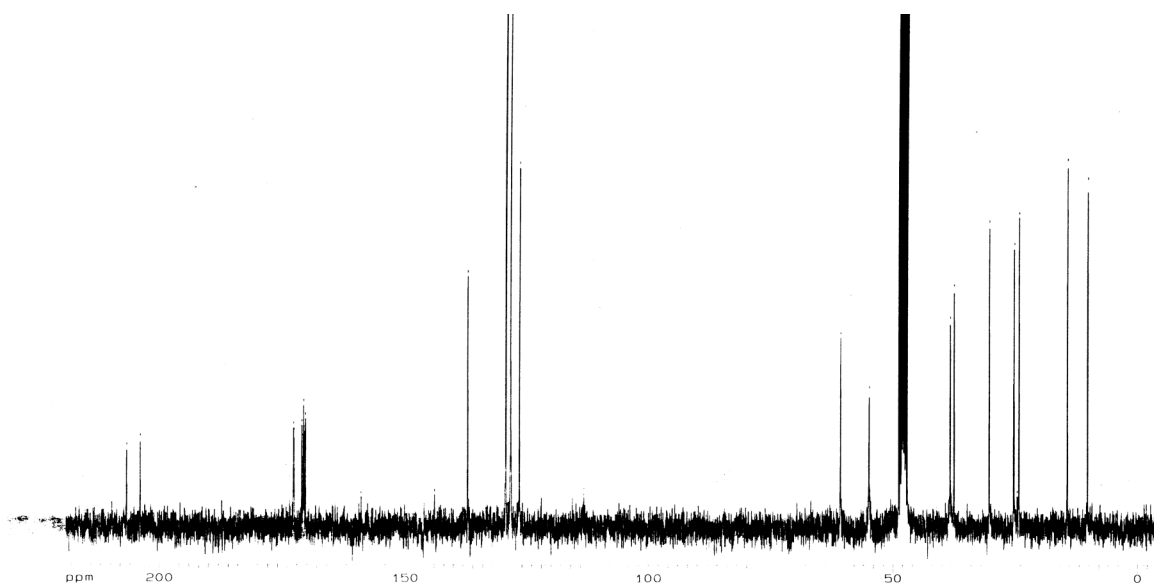
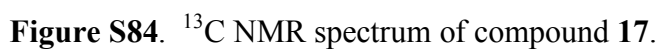
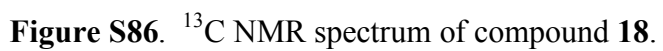


Figure S82. ¹³C NMR spectrum of compound 16.





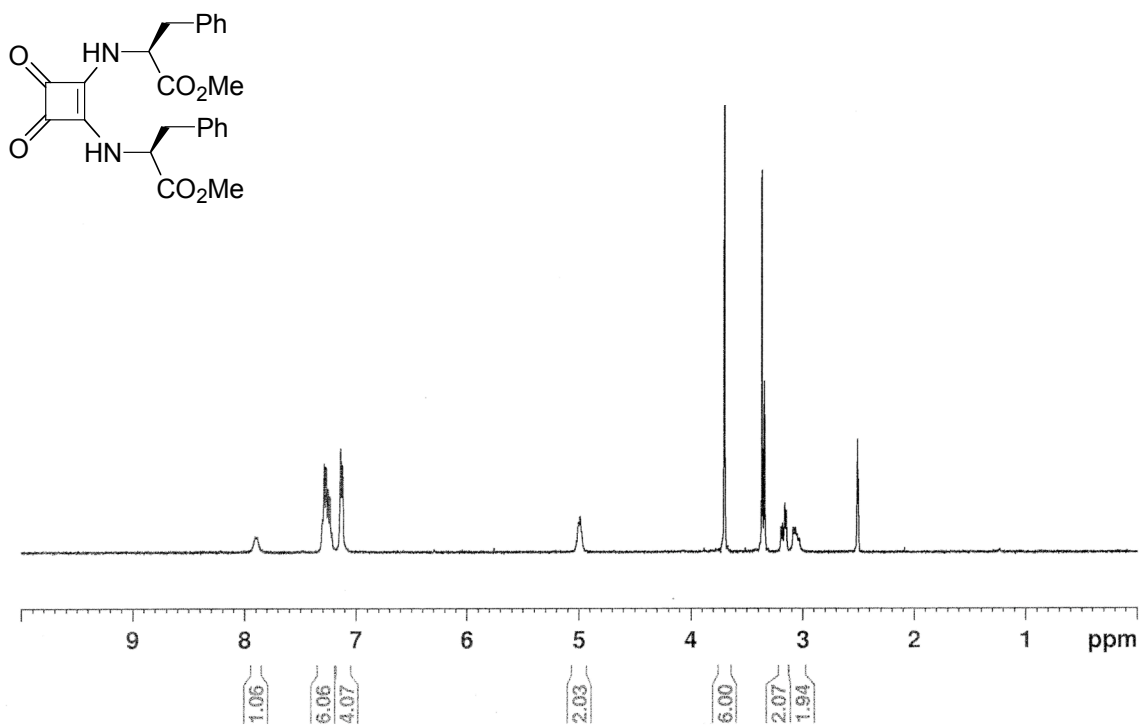


Figure S87. ¹H NMR spectrum of compound 19.

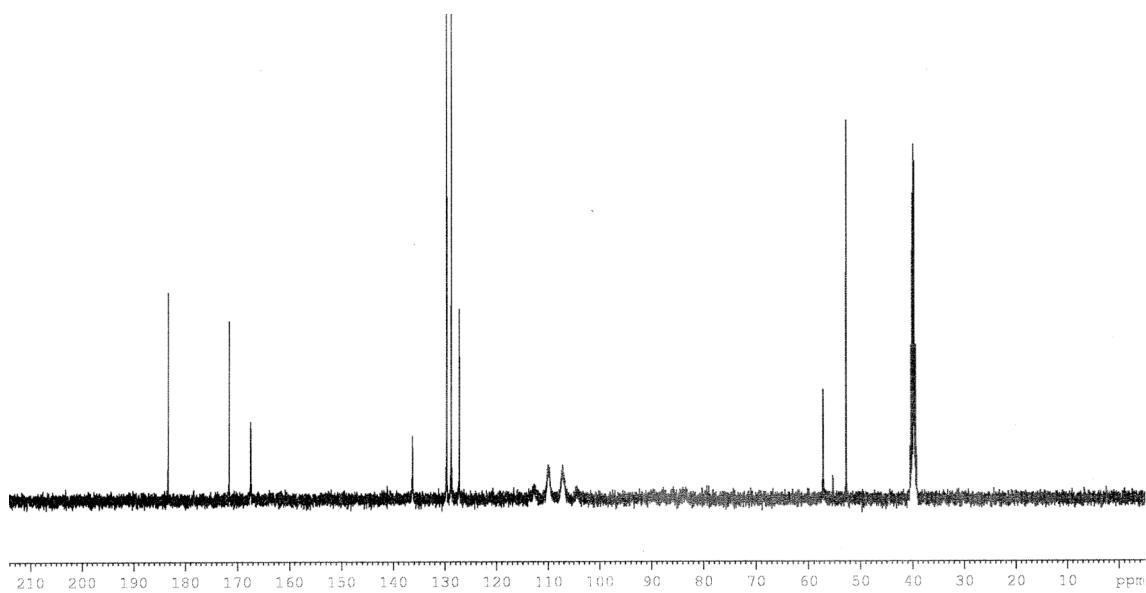


Figure S88. ¹³C NMR spectrum of compound 19.

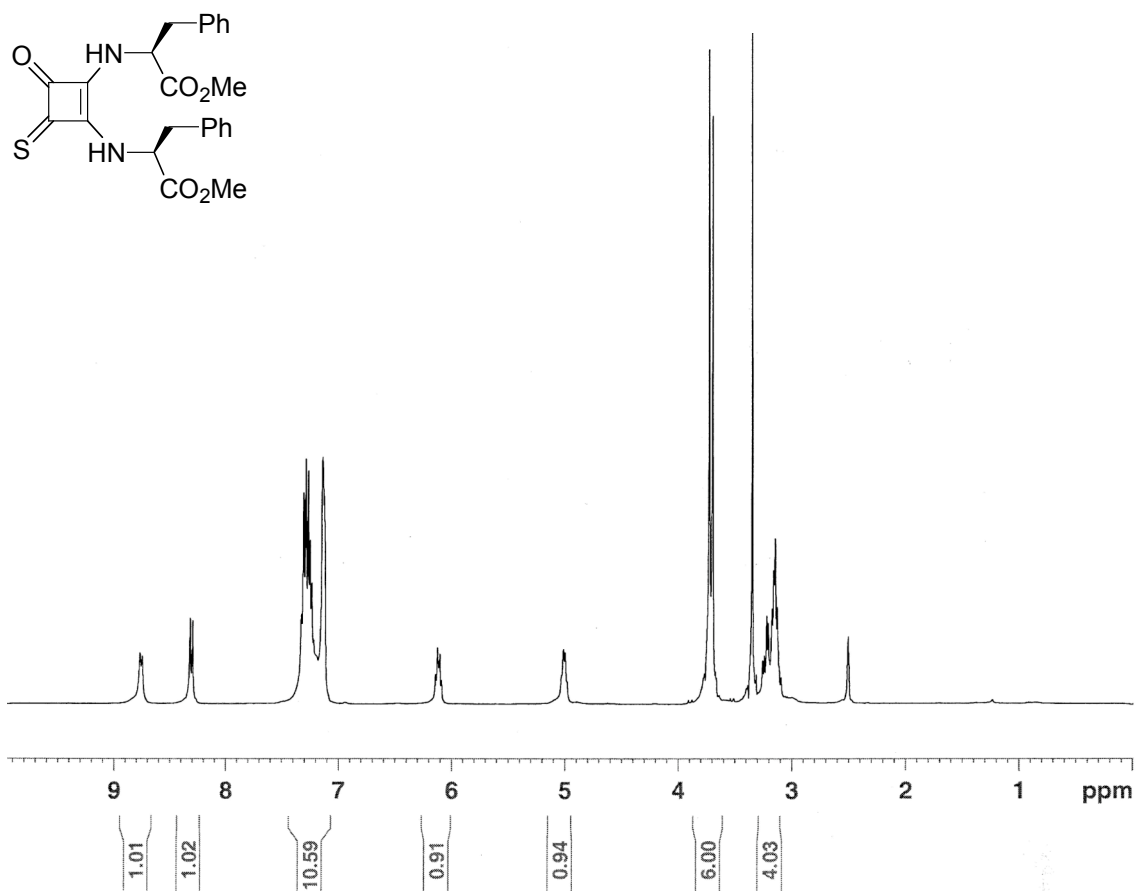


Figure S89. ¹H NMR spectrum of compound 20.

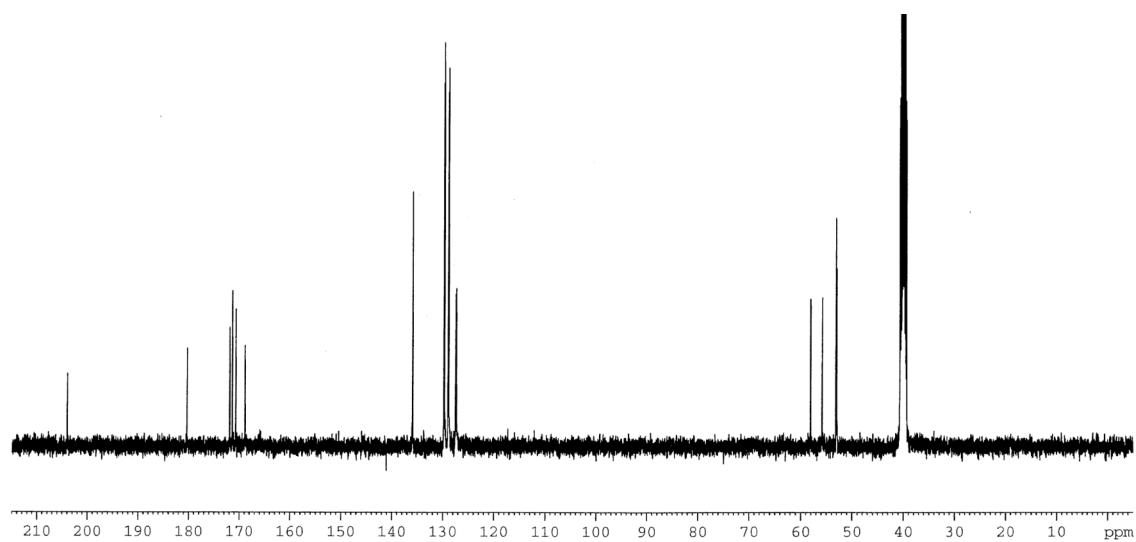


Figure S90. ¹³C NMR spectrum of compound 20.

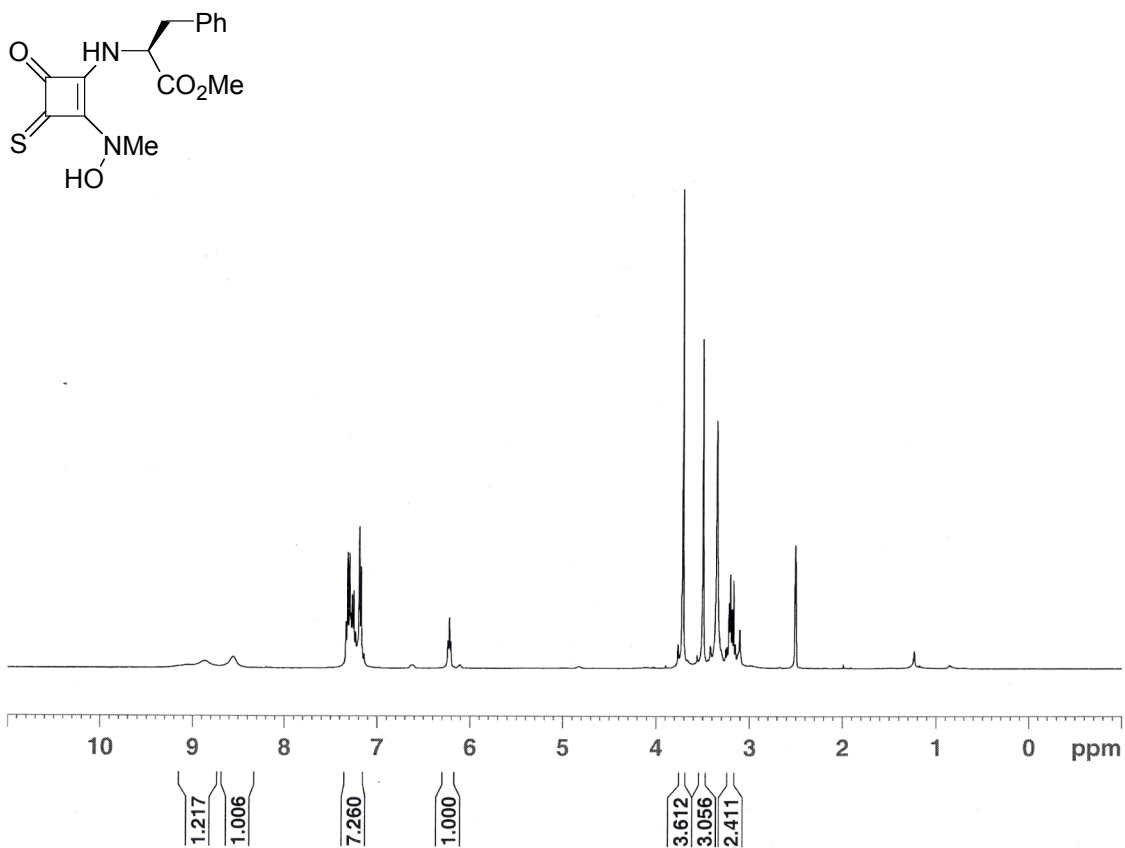


Figure S91. ¹H NMR spectrum of compound 21.

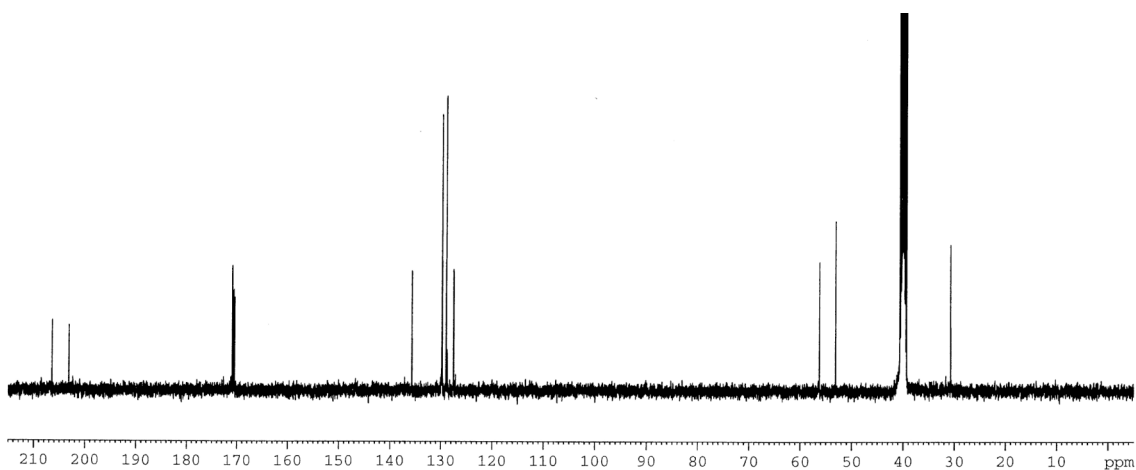


Figure S92. ¹³C NMR spectrum of compound 21.

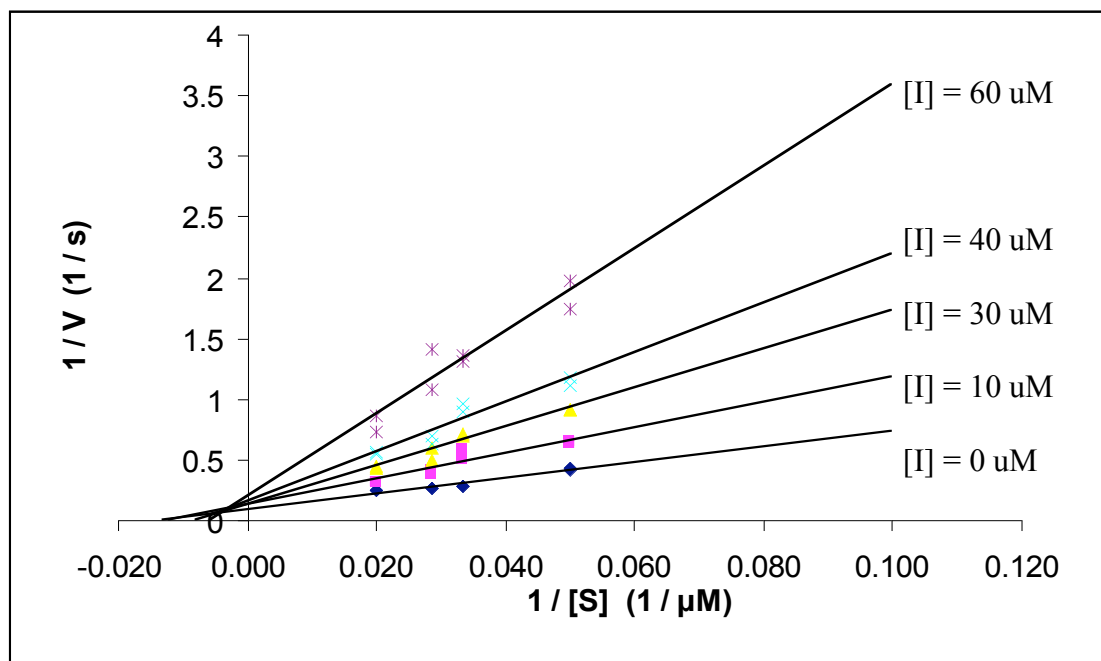


Figure S93. Lineweaver-Burk plot for the inhibition of MMP-1 by compound **16**. The activity of MMP-1 was measured under the same conditions as described in the experimental section in the presence of the following concentrations of **16**: 60 uM, 40 uM, 30 uM, 10 uM and 0 uM. The substrate concentrations used in the assays were 20, 30, 35, and 50 uM.

References

- ¹ Lim, N. C.; Morton, M. D.; Jenkins, H. A.; Bruckner, C. *J. Org. Chem.* **2003**, *68*, 9233-9241.
- ² Reichard, G. A.; Stengone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Wang, C.; Tiberi, R.; McPhail, A. T.; Piwinski, J. J. and Shih, N.-Y. *Org. Lett.* **2003**, *5*, 4249-4251.
- ³ Kortylewicz, Z. P. and Galardy, R. E. *J. Med. Chem.* **1990**, *33*, 263-273.