Supplementary Material (ESI) for Organic & Biomolecular Chemistry

SUPPORTING INFORMATION FOR:

Design, Synthesis and Cyclization of 4-Aminobutyric Acid Derivatives: Potential Candidates as Self-Immolative Spacers

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Synthesis of phenyl ester 6b. The same procedure described above for the preparation of compound **6a** was followed except that **5** was used as a starting material. The product was purified by column chromatography (9:1 cyclohexane:EtOAc) to provide **6b** (0.128 g, 79%) as a clear, colorless oil. ν_{max}/cm^{-1} 3103, 3074, 3045, 3014, 2979, 2937, 2873, 1762, 1697, 1596, 1494, 1477, 1396, 1366. ^{1}H NMR ($CDCl_3$): δ 7.42 – 7.36 (m, 2H), 7.26 – 7.21 (m, 2H), 7.12 – 7.07 (m, 1H), 3.35 (t, J = 6.6 Hz, 2H), 2.89 (s, 3H), 2.58 (t, J = 7.4 Hz, 2H), 1.97 (quint, J = 7.0 Hz. 2H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 171.6, 155.7, 150.6, 129.3, 125.7, 121.4, 79.4, 48.0 & 47.4 (rotamers), 34.1, 31.3, 28.4, 23.0 & 22.8 (rotamers). HRMS: calc'd $[M+H]^+$ ($C_{16}H_{24}NO_4$): 294.1705. Found: (EI) 294.1711.

Synthesis of α-benzyl *tert*-butyl ester 8c. The same procedure described above for the preparation of compound **8a** was followed except that benzyl bromide was used as the alkyl halide and only 1.2 equiv. of LHMDS was used. The product was purified by column chromatography (99:1 cyclohexane:EtOAc → 19:1 cyclohexane:EtOAc) to provide **8c** (0.188 g, 70%) as a thick, colorless oil. ν_{max}/cm^{-1} 3090, 3066, 3031, 3006, 2978, 2932, 2892, 1727, 1699, 1483, 1456, 1394, 1367. ^{1}H NMR ($CDCl_3$): δ 7.32 – 7.24 (m, 2H), 7.23 – 7.15 (m, 3H), 3.43 – 3.08 (m, 2H), 2.99 – 2.67 (m, 2H), 2.81 (s, 3H), 1.93 – 1.79 (m, 1H), 1.73 – 1.60 (m, 1H), 1.54 – 1.38 (m, 9H), 1.38 – 1.28 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 174.2, 155.5, 139.1, 128.9, 128.2, 126.2, 80.3, 79.2, 47.2, 45.6, 38.5, 34.1, 29.9, 28.3, 27.9. HRMS: calc'd $[M]^+$ ($C_{21}H_{33}NO_4$): 363.2410. Found: (EI) 363.1924.

Synthesis of acid 9b. The same procedure described above for the preparation of compound **9a** was followed except that **8b** was used as a starting material. The product was purified by column chromatography (5:1 cyclohexane:EtOAc) to provide **9b** (0.122 g, 99%) as a thick, colorless oil. ν_{max}/cm^{-1} 3450, 2980, 2941, 1700, 1670, 1489, 1457, 1401, 1368. ^{1}H NMR ($CDCl_3$): δ 10.77 (s, 1H), 5.80 – 5.67 (m, 1H), 5.14 – 5.10 (m, 2H), 3.40 – 3.16 (m, 2H), 2.81 (s, 3H), 2.46 – 2.35 (m, 2H), 2.33 – 2.22 (m, 1H), 1.90 – 1.78 (m, 1H), 1.75 – 1.64 (m, 1H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 180.2, 155.9, 134.7, 117.3, 80.0, 46.9 & 46.5 (rotamers), 42.2, 36.1, 34.1, 29.9, 28.3. HRMS: calc'd $[M]^+$ ($C_{13}H_{23}NO_4$): 257.1627. Found: (EI) 257.1634.

Synthesis of acid 9c. The same procedure described above for the preparation of compound **9a** was followed except that **8c** was used as a starting material. The product was purified by column chromatography (3:1 cyclohexane:EtOAc) to provide **9c** (143 mg, 96%) as a thick, colorless oil. ν_{max}/cm^{-1} 3092, 3180, 3067, 3032, 2980, 2938, 1735, 1700, 1667, 1488, 1456, 1404, 1368. ^{1}H NMR ($CDCl_3$): δ 10.90 (s, 1H), 7.34 – 7.15 (m, 5H), 3.45 – 3.19 (m, 2H), 3.14 – 3.00 (m, 1H), 2.84 – 2.73 (m, 1H), 2.77 (s, 3H), 2.73 – 2.64 (m, 1H), 1.94 – 1.82 (m, 1H), 1.78 – 1.67 (m, 1H), 1.54 – 1.34 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 180.2, 156.3, 138.6, 128.8, 128.4, 126.5, 80.5, 47.1 & 46.6 (rotamers), 44.4, 38.0, 34.1, 29.0, 28.2. HRMS: calc'd $[M]^+$ ($C_{17}H_{25}NO_4$): 307.1784. Found: (EI) 307.1783.

Synthesis of phenyl ester 10b. The same procedure described above for the preparation of compound **10a** was followed except that **9b** was used as a starting material. The product was purified by column chromatography (93:7 cyclohexane:EtOAc) to provide **10b** (0.128 g, 86%) as a colorless oil. ν_{max}/cm^{-1} 3080, 3009, 2979, 2936, 2871, 1758, 1698, 1594, 1493, 1457, 1396, 1367. ^{1}H NMR ($CDCl_3$): δ 7.37 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 5.94 – 5.80 (m, 1H), 5.22 – 5.08 (m, 2H), 3.48 – 3.21 (m, 2H), 2.87 (s, 3H), 2.75 – 2.65 (m, 1H), 2.60 – 2.39 (m, 2H), 2.04 (sextet, J = 7.4 Hz, 1H), 1.80 (sextet, J = 7.4 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.4, 155.6, 150.6, 134.7, 129.3, 125.7, 121.5, 117.5, 79.5, 47.0 & 46.4 (rotamers), 42.5, 36.5, 34.1, 29.4, 28.4. IR (cm^{-1}): HRMS: calc'd $[M]^+$ ($C_{19}H_{27}NO_4$): 333.1940. Found: (EI) 333.1932.

Synthesis of phenyl ester 10c. The same procedure described above for the preparation of compound **10a** was followed except that **9c** was used as a starting material. The product was purified by column chromatography (93:7 cyclohexane:EtOAc) to provide **10c** (0.146 g, 82%) as a colorless oil. ν_{max}/cm^{-1} 3091, 3068, 3033, 2993, 2978, 2931, 2867, 1756, 1696, 1594, 1494, 1481, 1396, 1367. ^{1}H NMR ($CDCl_3$): δ 7.33 – 7.26 (m, 4H), 7.25 – 7.19 (m, 3H), 7.15 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 7.4 Hz, 2H), 3.52 – 3.18 (m, 2H), 3.13 – 2.84 (m, 3H), 2.81 (s, 3H), 2.04 (sextet, J = 7.8 Hz, 1H), 1.89 – 1.73 (m, 1H), 1.52 – 1.35 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 173.5, 155.6, 150.4, 138.5, 129.2, 129.0, 128.4, 126.6, 125.7, 121.4, 79.4, 47.1 & 46.3 (rotamers), 45.0, 38.5, 34.1, 29.8, 28.3. HRMS: calc'd $[M+H]^+$ ($C_{23}H_{30}NO_4$): 384.2169. Found: (EI) 384.2167.

Synthesis of α-dibenzyl *tert*-butyl ester 11c. The same procedure described above for the preparation of compound **11b** was followed except that benzyl bromide was used as the alkyl halide. The product was purified by column chromatography (93:7 cyclohexane:EtOAc) to provide **11c** (0.384 g, 93%) as a thick, colorless oil. ν_{max}/cm^{-1} 3088, 3065, 3032, 3006, 2978, 2935, 1698, 1496, 1482, 1455, 1395, 1366. ^{1}H NMR ($CDCl_3$): δ 7.27 – 7.14 (m, 10H), 3.50 – 3.30 (br m, 2H), 3.02 (d, J=14.1 Hz, 2H), 2.83 (d, J=14.1 Hz, 2H), 2.66 (s, 3H), 1.78 – 1.65 (br m, 2H), 1.45 (s, 9H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.5, 155.5, 137.3, 130.4, 128.0, 126.4, 81.1, 79.5, 50.2, 44.6 & 43.9 (rotamers), 42.0, 33.6, 31.1 & 30.4 (rotamers), 28.5, 27.9. HRMS: calc'd $[M]^+$ ($C_{28}H_{39}NO_4$): 453.2879 Found: (EI) 453.2866.

Synthesis of acid 12a. The same procedure described above for the preparation of compound **9a** was followed except that **11a** was used as a starting material. The product was purified by column chromatography (85:15 cyclohexane:EtOAc) to provide **12a** (0.166 g, 97%) as a thick, colorless oil. ν_{max}/cm^{-1} 3454, 3200, 2980, 2935, 1700, 1694, 1481, 1405, 1368. ^1H NMR ($CDCl_3$): δ 3.24 (br t, J = 7.8 Hz, 2H), 2.83 (s, 3H), 1.82 – 1.74 (m, 2H), 1.46 (s, 9H), 1.25 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 182.9, 155.6, 79.4, 45.4 & 44.9 (rotamers), 40.6, 37.7, 34.0, 28.3, 24.9. HRMS: calc'd $[M]^+$ ($C_{12}H_{23}NO_4$): 245.1627. Found: (EI) 245.1618.

Synthesis of acid 12b. The same procedure described above for the preparation of compound **9a** was followed except that **11b** was used as a starting material. The product was purified by column chromatography (5:1 cyclohexane:EtOAc) to provide **12b** (0.092 g, 90%) as a thick, colorless oil. ν_{max}/cm^{-1} 3430, 3270, 3080, 3010, 2980, 2935, 1730, 1700, 1488, 1454, 1404, 1368. ^1H NMR ($CDCl_3$): δ 5.84 – 5.70 (m, 2H), 5.19 – 5.11 (m, 4H), 3.25 (br t, J = 7.4 Hz, 2H), 2.82 (s, 3H), 2.38 (d, J = 7.4 Hz, 4H), 1.84 – 1.76 (m, 2H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 181.0, 155.6, 132.6, 118.8, 80.3, 47.6, 38.7, 34.1, 32.1, 28.3. HRMS: calc'd $[M]^+$ ($C_{16}H_{27}NO_4$): 297.1940. Found: (EI) 297.1949.

Synthesis of acid 12c. The same procedure described above for the preparation of compound **9a** was followed except that **11c** was used as a starting material. The product was purified by column chromatography (85:15 cyclohexane:EtOAc) to provide **12c** (0.139 g, 94%) as a sticky white solid. ν_{max}/cm^{-1} 3460, 3210, 3090, 3067, 3031, 2979, 2935, 1697, 1665, 1497, 1456, 1404, 1368. ^{1}H NMR ($CDCl_3$): δ 7.33 – 7.19 (m, 10H), 3.55 – 3.31 (m, 2H), 3.13 (d, J = 13.7 Hz), 2.93 (d, J = 14.0 Hz), 2.69 (s, 3H), 1.80 – 1.70 (m, 2H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 181.2, 155.9, 136.8, 130.2, 128.2, 126.8, 80.1, 50.3, 44.8 & 43.9 (rotamers), 42.1, 43.7, 30.6 & 29.4 (rotamers), 28.5. HRMS: calc'd $[M]^+$ ($C_{24}H_{31}NO_4$): 397.2253. Found: (EI) 397.2241.

Synthesis of acid 12d. The same procedure described above for the preparation of compound **9a** was followed except that **11d** was used as a starting material. The product was purified by column chromatography (85:15 cyclohexane:EtOAc) to provide **12d** (0.095 g, 88%) as a thick, colorless oil. ν_{max}/cm^{-1} 3470, 2975, 2876, 1698, 1674, 1468, 1454, 1403, 1368. ^{1}H NMR ($CDCl_3$): δ 3.30 – 3.13 (m, 2H), 2.83 (s, 3H), 2.22 – 2.10 (m, 2H), 1.92 – 1.80 (m, 2H), 1.76 – 1.63 (m, 4H), 1.62 – 1.50 (m, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 182.4, 155.5, 79.3, 51.7, 46.2 & 45.7 (rotamers), 36.4, 36.1, 34.0, 28.3, 24.9. HRMS: calc'd $[M]^+$ ($C_{14}H_{25}NO_4$): 271.1784. Found: (EI) 271.1776.

Synthesis of phenyl ester 13b. The same procedure described above for the preparation of compound **13a** was followed except that **12b** was used as a starting material. The product was purified by column chromatography (97:3 cyclohexane:EtOAc) to provide **13b** (0.085 g, 74%) as a colorless oil. ν_{max}/cm^{-1} 3080, 2979, 2934, 1752, 1697, 1642, 1594, 1494, 1457, 1396, 1367. ^{1}H NMR ($CDCl_3$): δ 7.38 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 7.06 (br d, J = 7.4 Hz, 2H), 5.94 – 5.78 (m, 2H), 5.26 – 5.16 (m, 4H), 3.42 – 3.26 (m, 2H), 2.86 (s, 3H), 2.52 (d, J = 7.8 Hz, 4H), 1.98 – 1.87 (m, 2H), 1.47 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.0, 155.5, 150.7, 132.8, 129.4, 125.8, 121.6, 119.1, 79.6, 48.0, 44.7 & 44.3 (rotamers), 39.1, 34.1, 32.2 & 31.9 (rotamers), 28.5. HRMS: calc'd $[M]^+$ ($C_{22}H_{31}NO_4$): 373.2253. Found: (EI) 373.2267.

Synthesis of phenyl ester 13c. The same procedure described above for the preparation of compound **13a** was followed except that **12c** was used as a starting material. The product was purified by column chromatography (97:3 cyclohexane:EtOAc) to provide **13c** (0.092 g, 60%) as a colorless oil. ν_{max}/cm^{-1} 3091, 3066, 3032, 2980, 2934, 2874, 1750, 1693, 1594, 1495, 1456, 1398, 1367. ^1H NMR ($CDCl_3$): δ 7.44 – 7.26 (m, 12H), 7.23 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.4 Hz), 3.66 – 3.44 (m, 2H), 3.28 (d, J = 13.7 Hz, 2H), 3.05 (d, J = 14.0 Hz, 2H), 2.73 (s, 3H), 2.02 – 1.86 (m, 2H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.9, 155.5, 150.5, 136.8, 130.3, 129.3, 128.3, 126.9, 125.8, 121.4, 79.6, 50.8, 44.7 & 43.7 (rotamers), 42.3, 36.7, 30.5 & 29.5 (rotamers), 28.5. HRMS: calc'd $[M]^+$ ($C_{30}H_{35}NO_4$): 473.2566. Found: (EI) 473.2557.

Synthesis of phenyl ester 13d. The same procedure described above for the preparation of compound **13a** was followed except that **12d** was used as a starting material. The product was purified by column chromatography (98:2 cyclohexane:EtOAc → 97:3 cyclohexane:EtOAc) to provide **13d** (0.135 g, 76%) as a colorless oil. ν_{max}/cm^{-1} 3103, 3095, 3047, 2974, 2934, 2878, 1750, 1699, 1597, 1494, 1458, 1399, 1367. ^1H NMR ($CDCl_3$): δ 7.38 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.07 (br d, J = 7.4 Hz, 2H), 3.38 – 3.24 (m, 2H), 2.87 (s, 3H), 2.38 – 2.26 (m, 2H), 2.00 (br t, J = 7.8 Hz, 2H), 1.83 – 1.60 (m, 6H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 175.8, 155.5, 150.9, 129.3, 125.6, 121.4, 79.4, 52.3, 46.3 & 45.9 (rotamers), 36.6 & 36.2 (rotamers), 36.4, 34.2, 28.4, 25.0. HRMS: calc'd $[M+H]^+$ ($C_{20}H_{30}NO_4$): 348.2169. Found: (EI) 348.2169.

Synthesis of phenyl ester 17b. The same procedure described above for the preparation of compound **17a** was followed except that **16b** was used as a starting material. The product was purified by column chromatography (93:7 cyclohexane:EtOAc) to provide **17b** (0.096 g, 58%) as a colorless oil. ν_{max}/cm^{-1} 3120, 3084, 3024, 3008, 2982, 2938, 2898, 1778, 1747, 1698, 1593, 1493, 1476, 1396, 1369. ^{1}H NMR ($CDCl_3$): δ 7.38 (t, J = 7.8 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 7.8 Hz, 2H), 5.05 (dd, J = 4.3 & 8.6 Hz, 1H), 3.64 – 3.48 (m, 1H), 3.43 – 3.29 (m, 1H), 2.89 (s, 3H), 2.38 – 2.13 (m, 2H), 1.51 (s, 9H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 168.7, 155.6, 152.8, 150.2, 129.5, 126.1, 121.2, 83.3, 79.8, 72.2, 45.0, 34.5, 29.7, 28.4, 27.7. HRMS: calc'd $[M+H]^+$ ($C_{21}H_{31}NO_7$): 410.2173. Found: (EI) 410.2173.

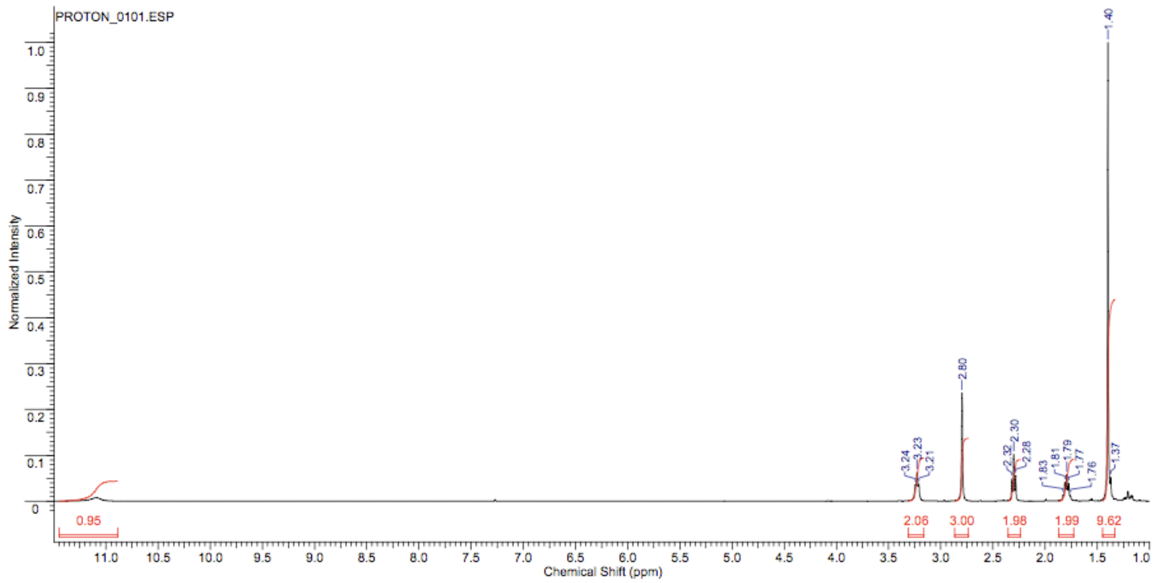

Figure S1. ^{1}H NMR Spectrum of Compound **5** (400 MHz, $CDCl_3$)

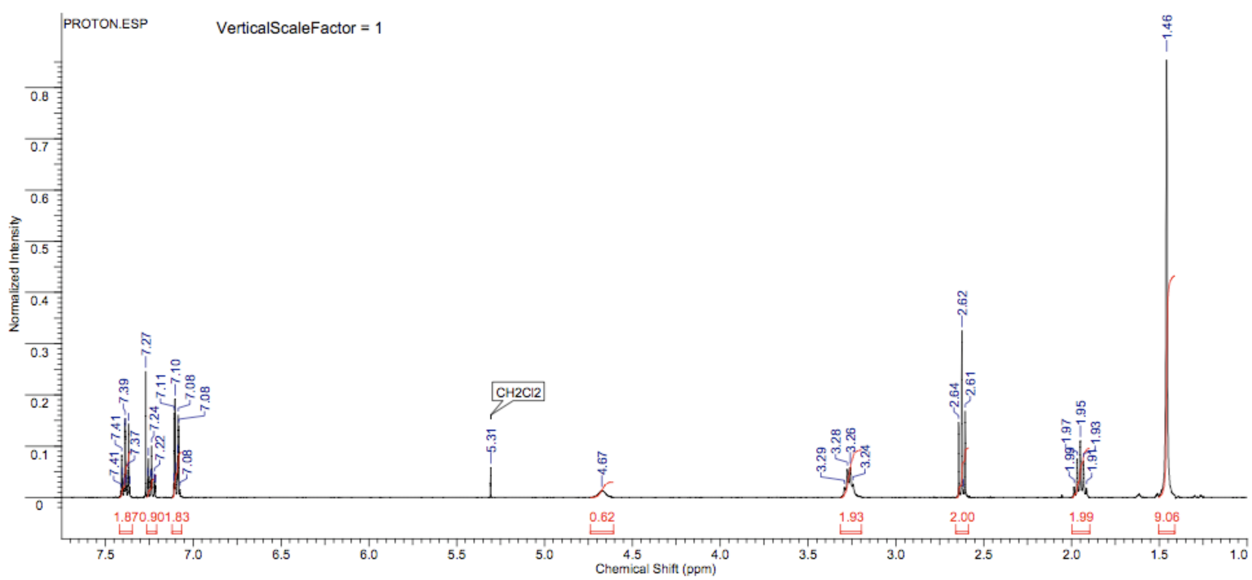

Figure S2. ^{1}H NMR Spectrum of Compound **6a** (400 MHz, $CDCl_3$)

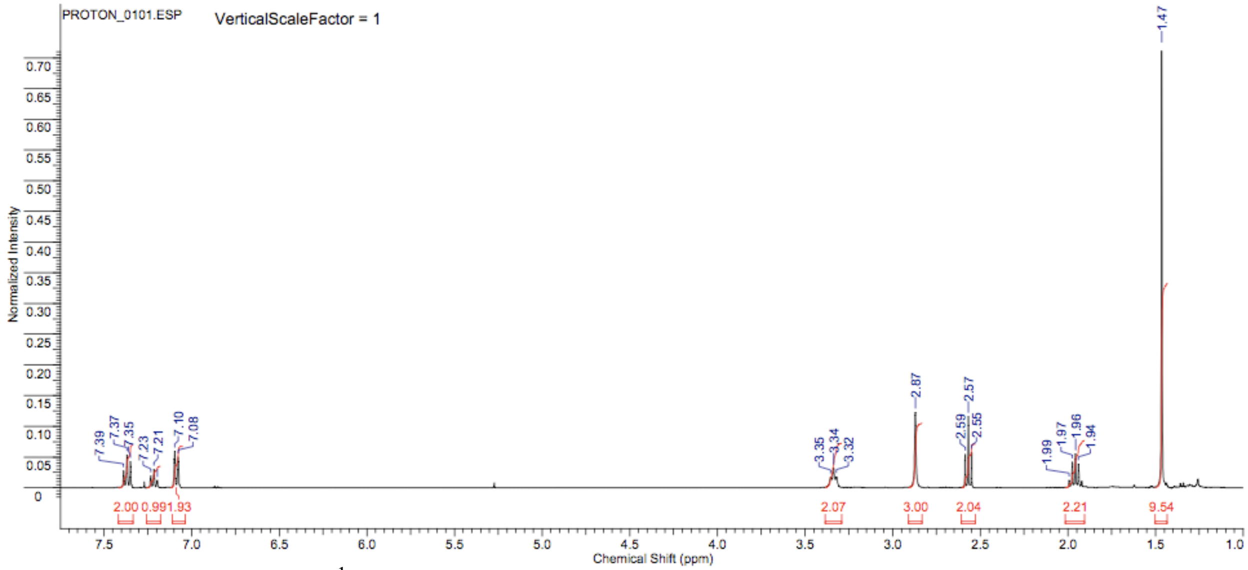

Figure S3. ^{1}H NMR Spectrum of Compound **6b** (400 MHz, $CDCl_3$)

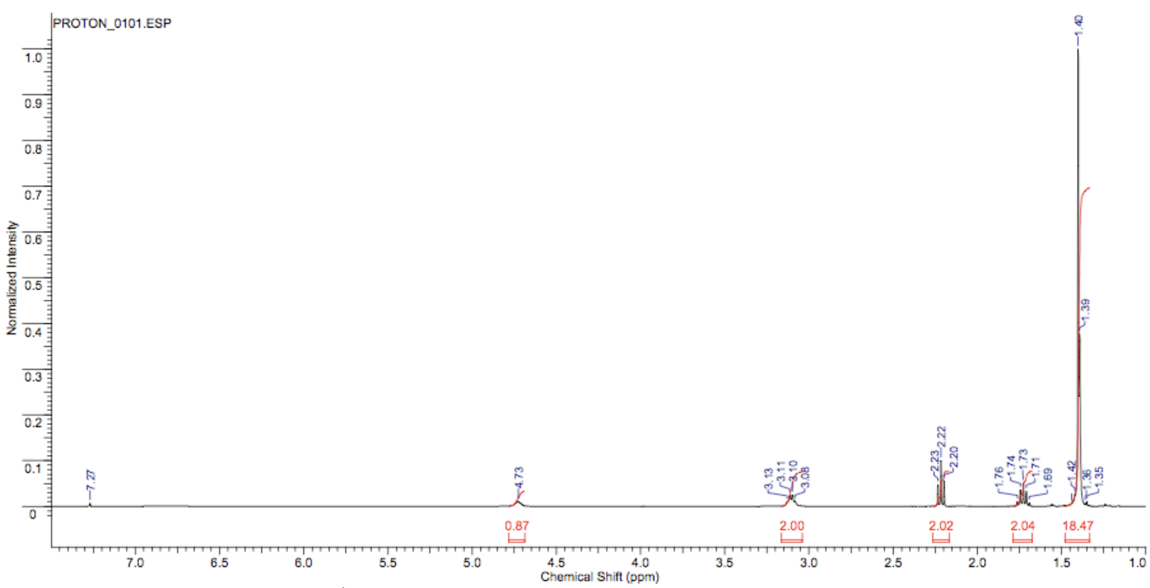

Figure S4. ^{1}H NMR Spectrum of Compound **7a** (400 MHz, $CDCl_3$)

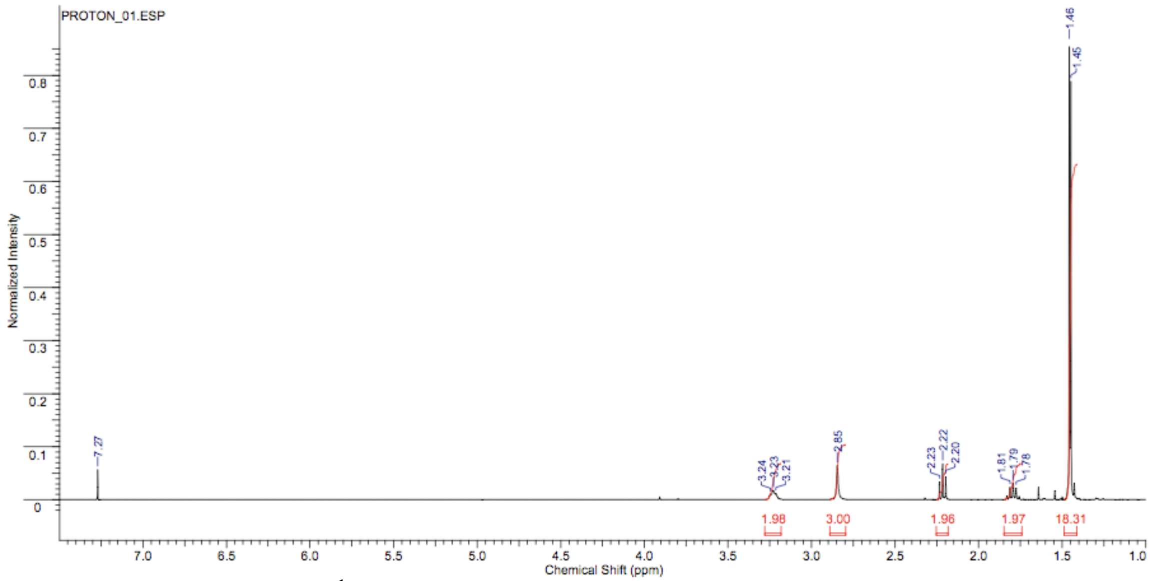

Figure S5. ^{1}H NMR Spectrum of Compound **7b** (400 MHz, $CDCl_3$)

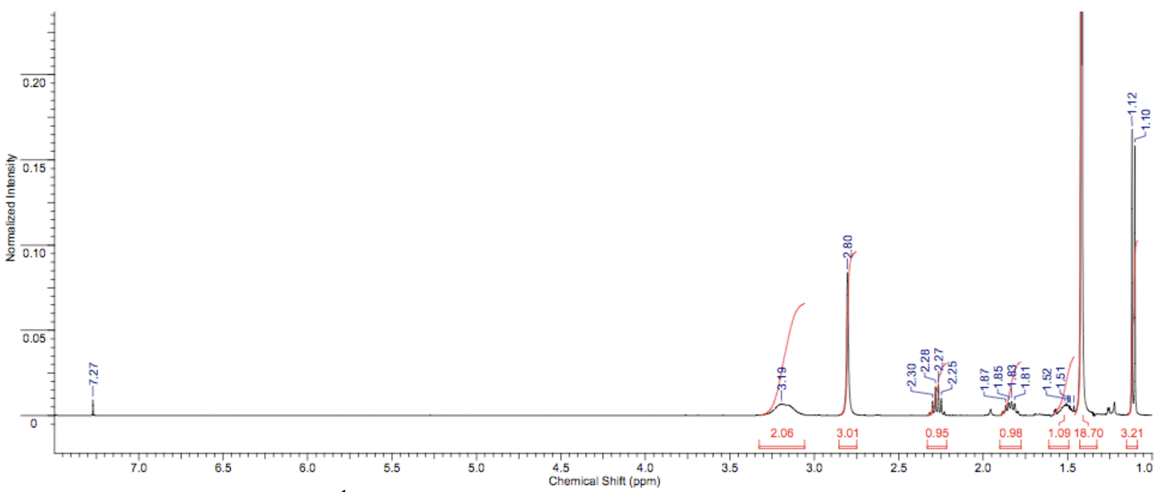

Figure S6. ^{1}H NMR Spectrum of Compound **8a** (400 MHz, $CDCl_3$)

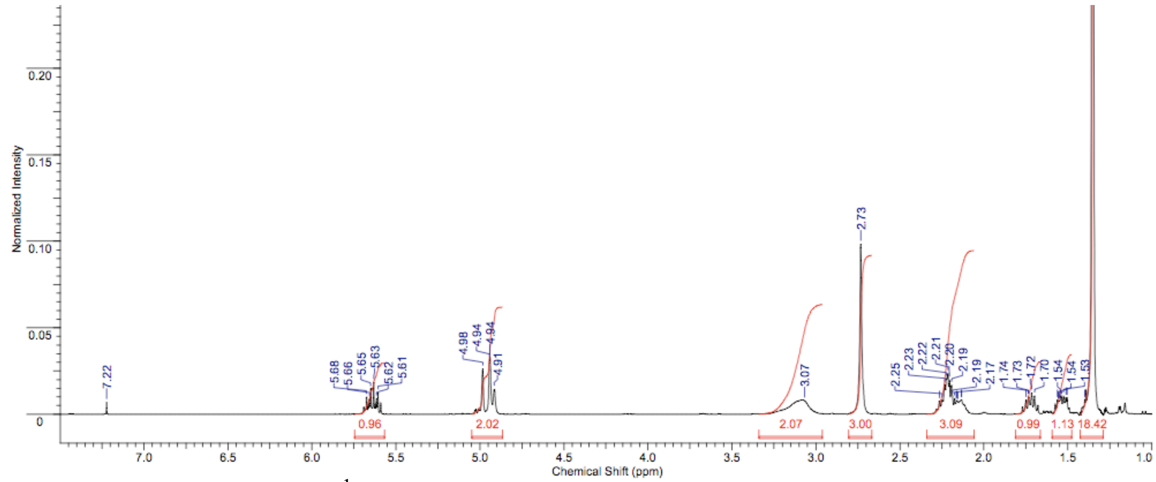

Figure S7. ^{1}H NMR Spectrum of Compound **8b** (400 MHz, $CDCl_3$)

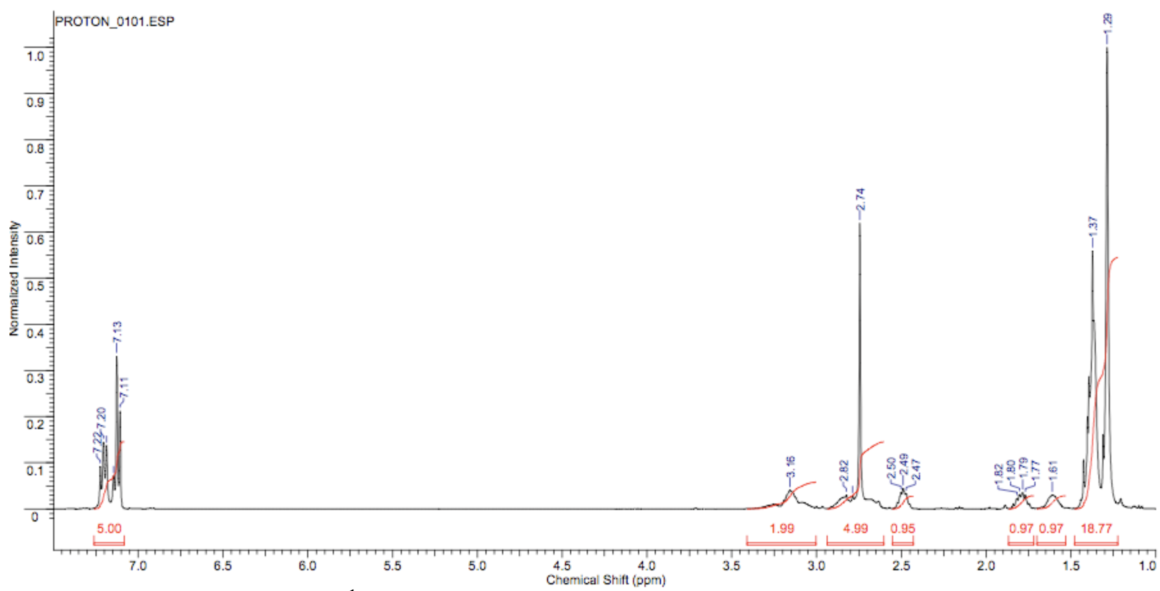

Figure S8. ^{1}H NMR Spectrum of Compound **8c** (400 MHz, $CDCl_3$)

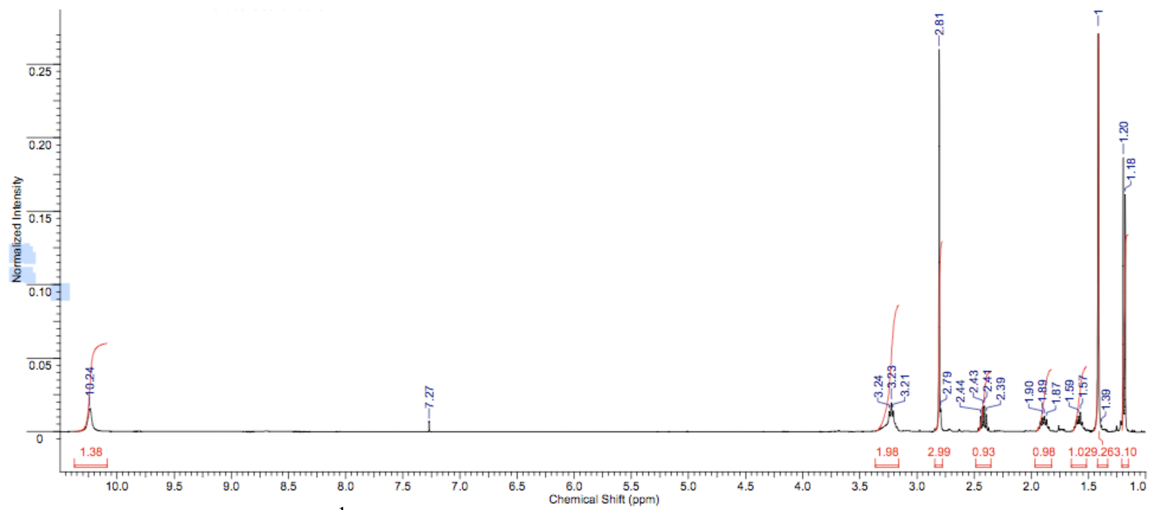

Figure S9. ^{1}H NMR Spectrum of Compound **9a** (400 MHz, $CDCl_3$)

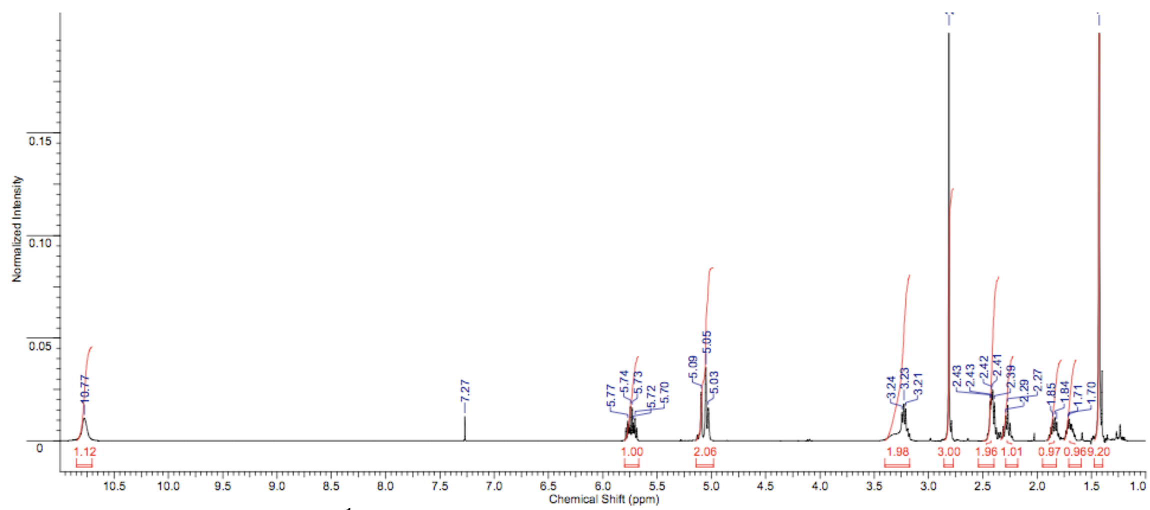

Figure S10. ^{1}H NMR Spectrum of Compound **9b** (400 MHz, $CDCl_3$)

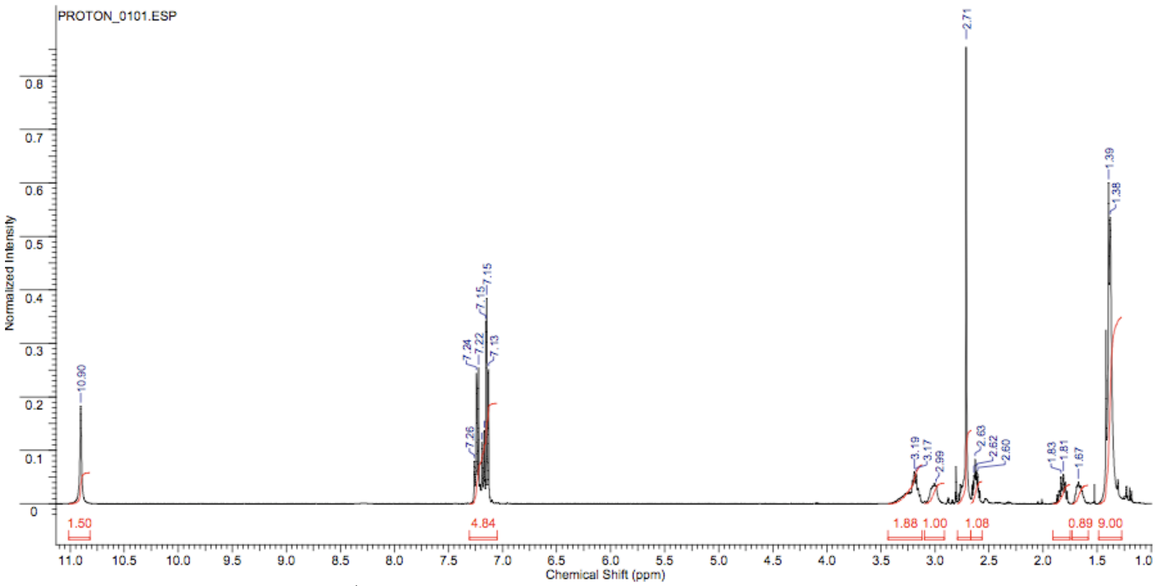

Figure S11. ^{1}H NMR Spectrum of Compound **9c** (400 MHz, $CDCl_3$)

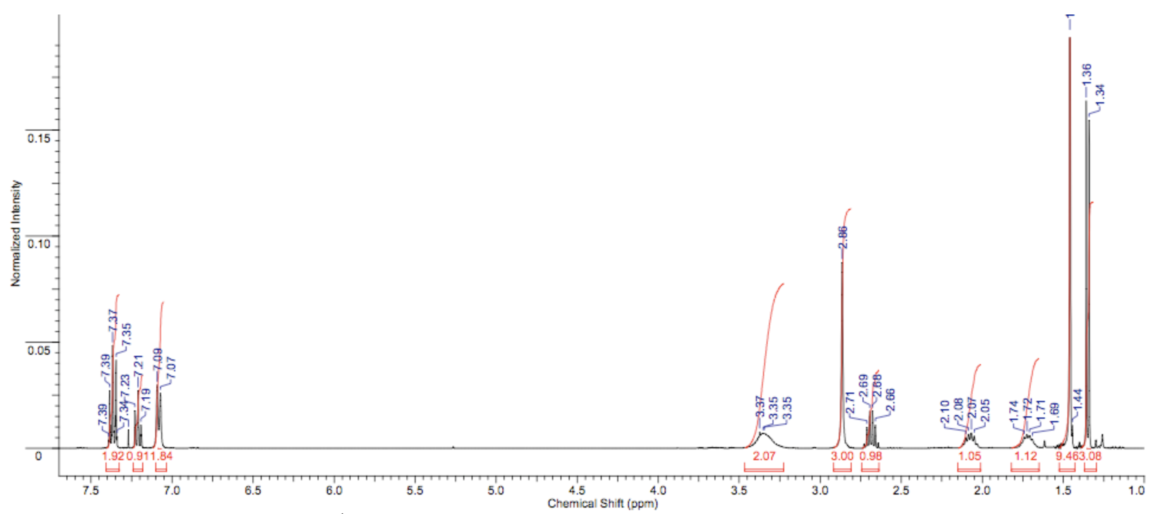

Figure S12. ^{1}H NMR Spectrum of Compound **10a** (400 MHz, $CDCl_3$)

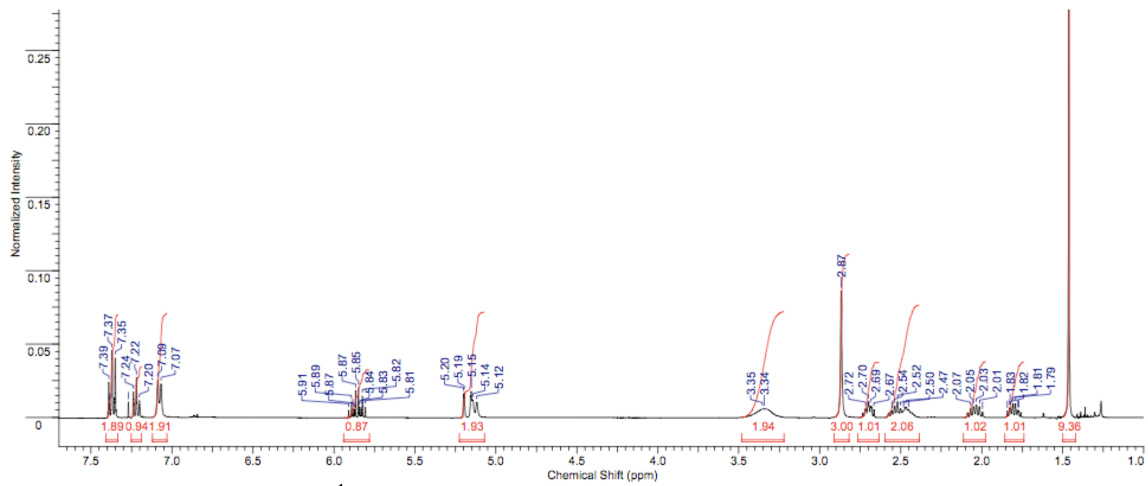

Figure S13. ^{1}H NMR Spectrum of Compound **10b** (400 MHz, $CDCl_3$)

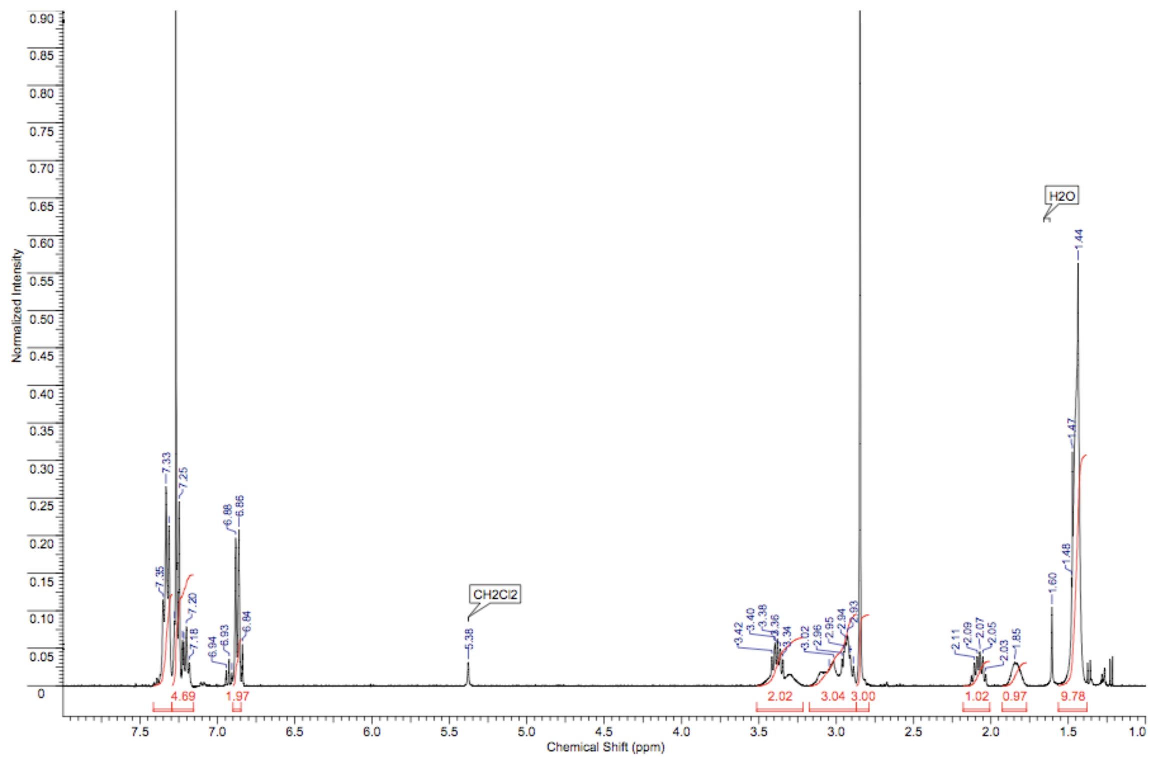

Figure S14. ^{1}H NMR Spectrum of Compound **10c** (400 MHz, $CDCl_3$)

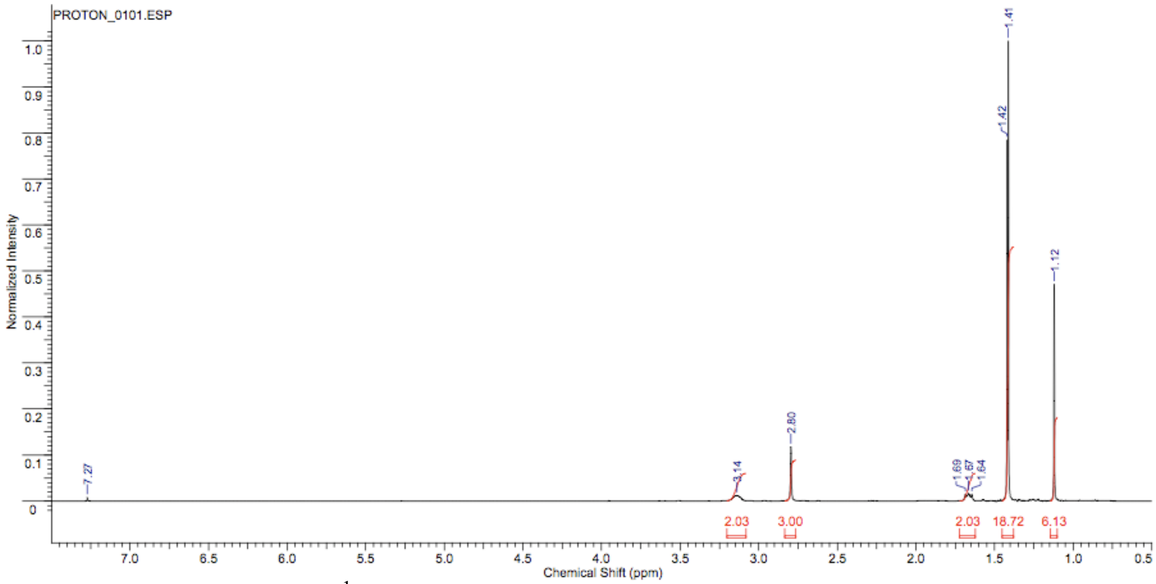

Figure S15. ^{1}H NMR Spectrum of Compound **11a** (400 MHz, $CDCl_3$)

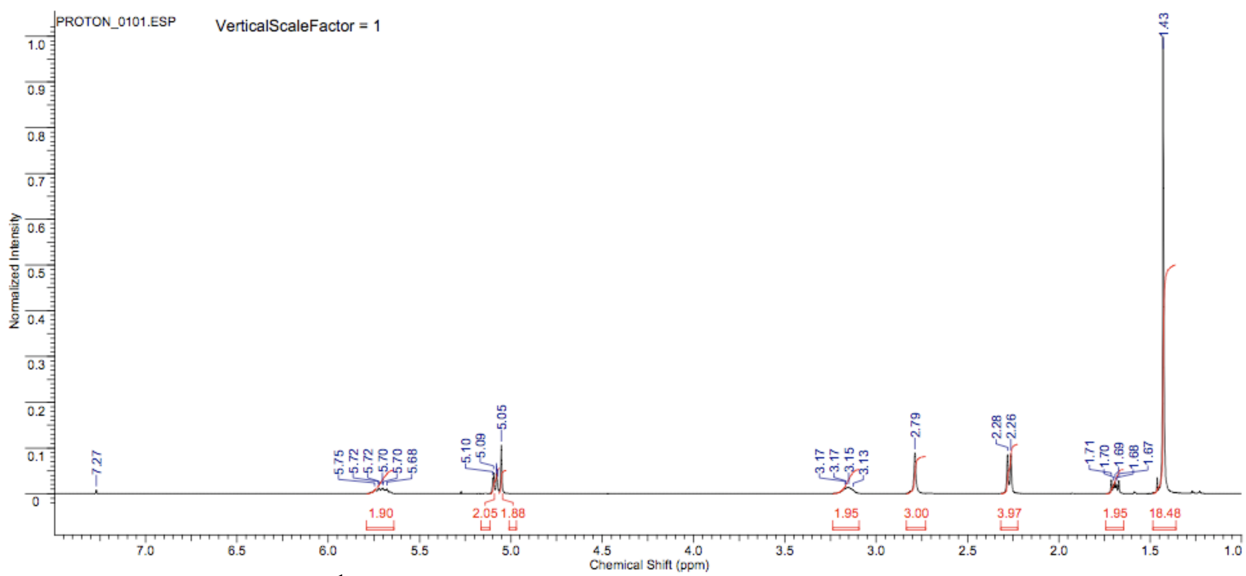

Figure S16. ^{1}H NMR Spectrum of Compound **11b** (400 MHz, $CDCl_3$)

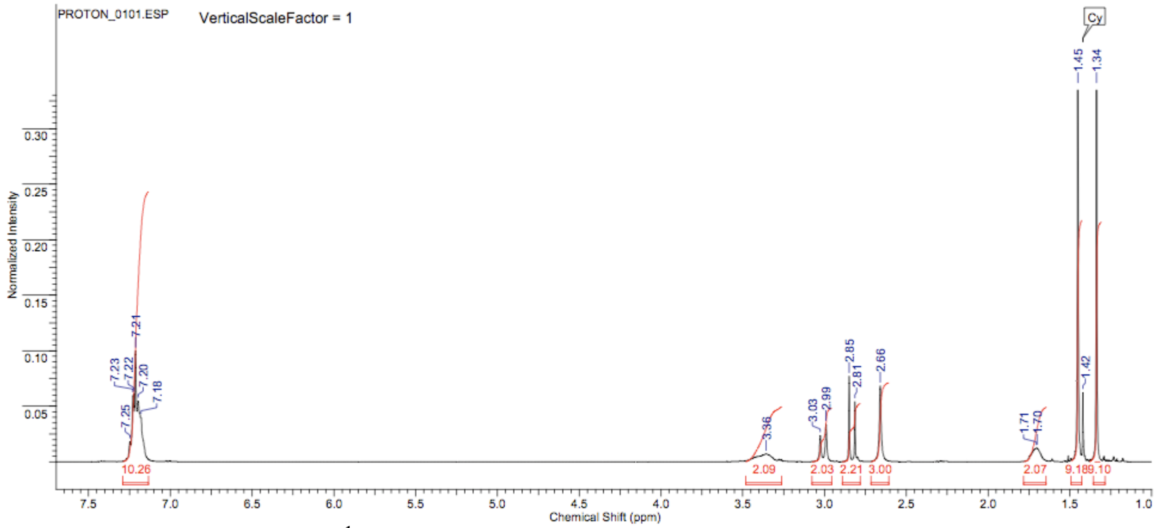

Figure S17. ^{1}H NMR Spectrum of Compound **11c** (400 MHz, $CDCl_3$)

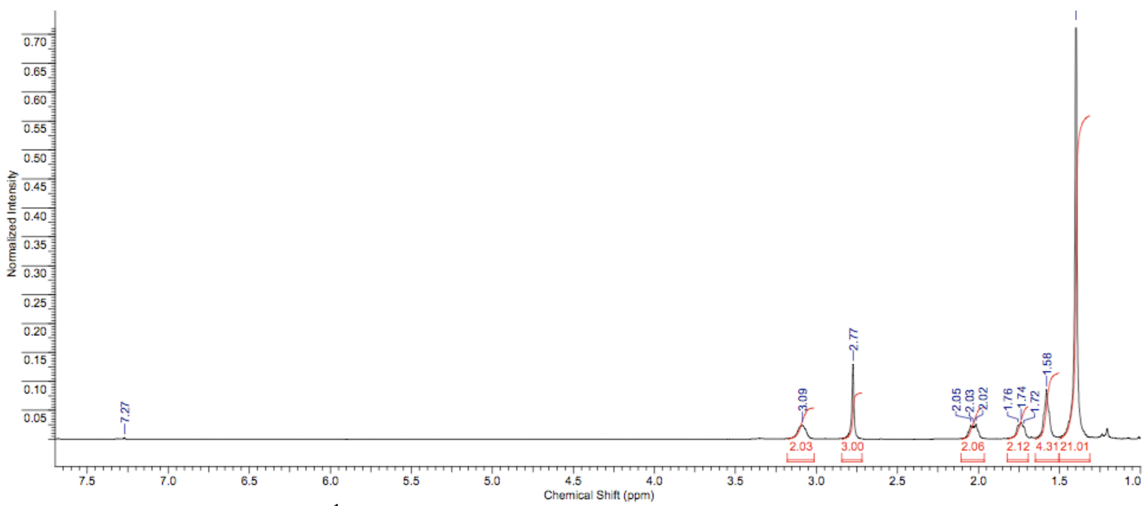

Figure S18. ^{1}H NMR Spectrum of Compound **11d** (400 MHz, $CDCl_3$)

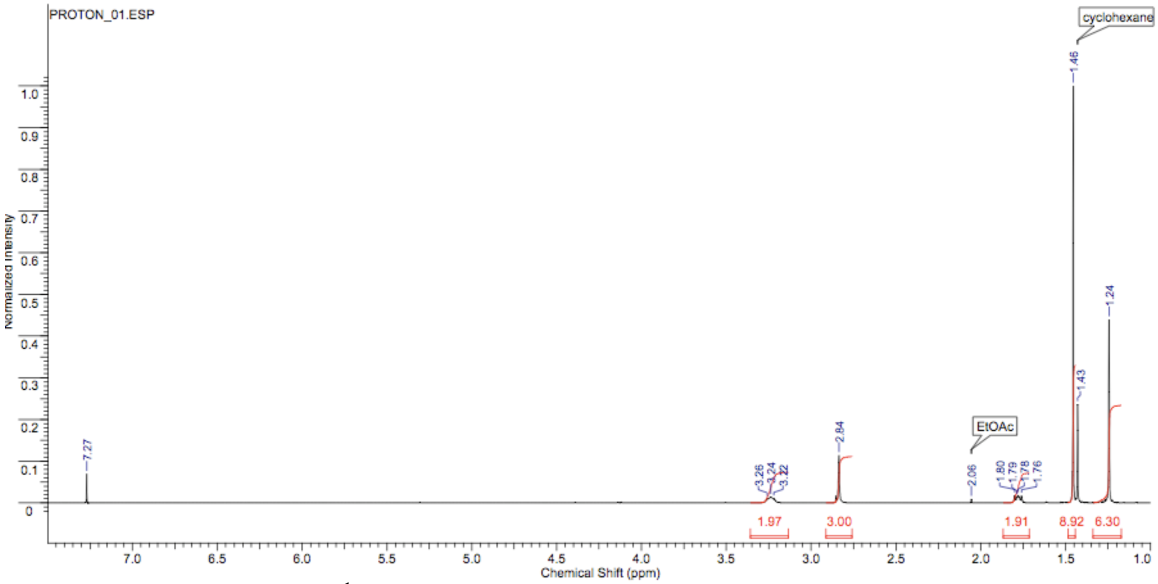

Figure S19. ^{1}H NMR Spectrum of Compound **12a** (400 MHz, $CDCl_3$)

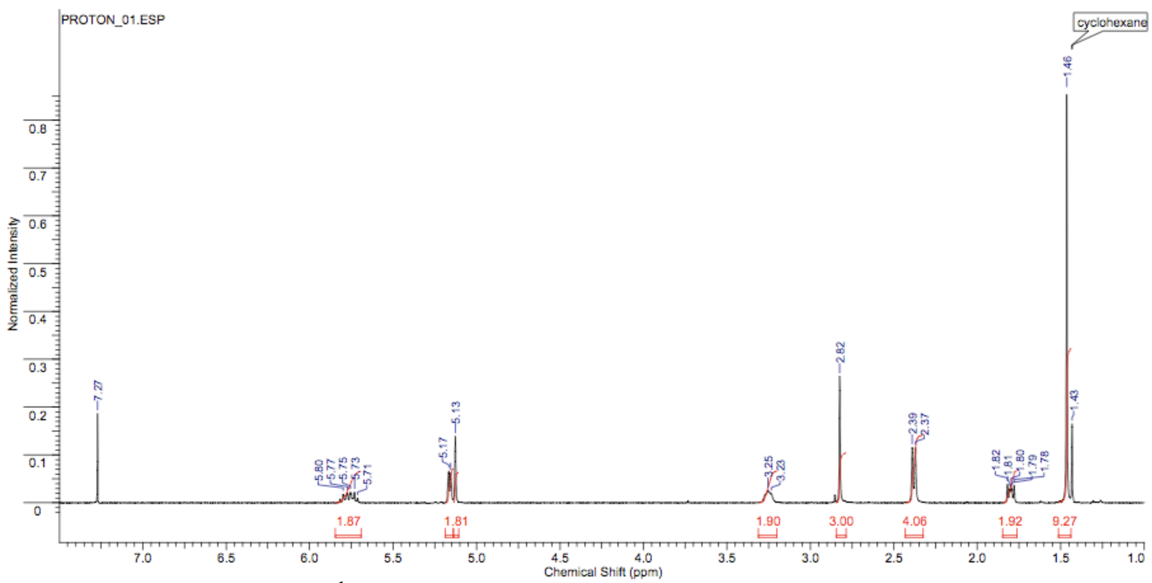

Figure S20. ^{1}H NMR Spectrum of Compound **12b** (400 MHz, $CDCl_3$)

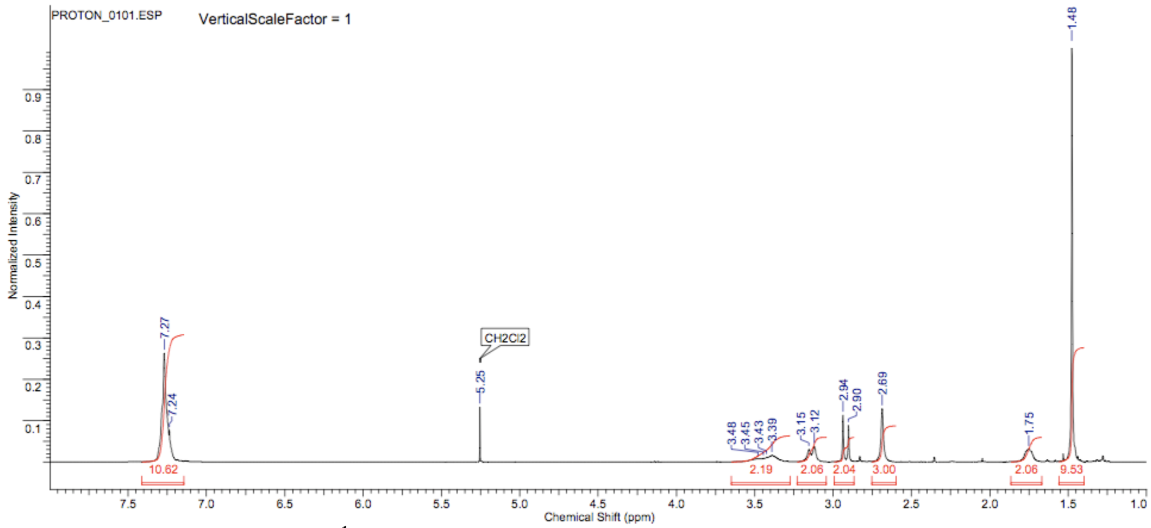

Figure S21. ^{1}H NMR Spectrum of Compound **12c** (400 MHz, $CDCl_3$)

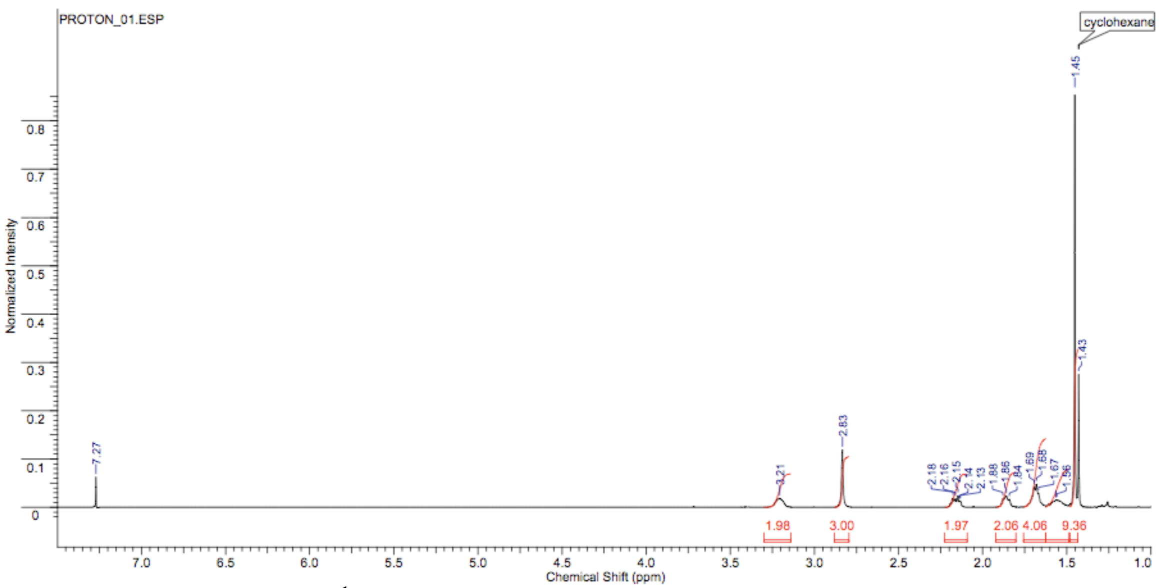

Figure S22. ^{1}H NMR Spectrum of Compound **12d** (400 MHz, $CDCl_3$)

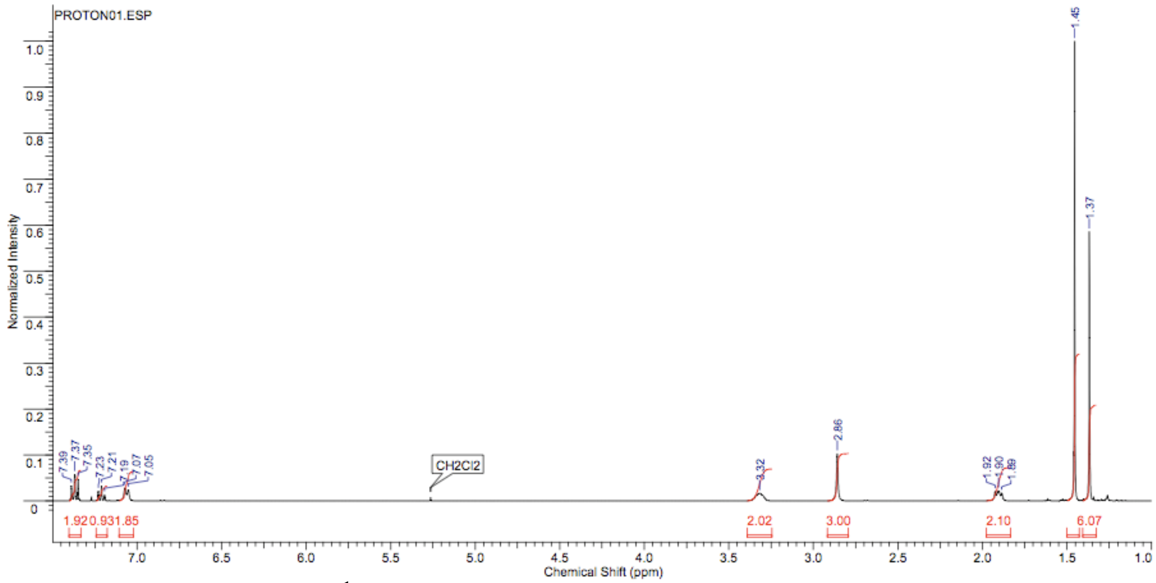

Figure S23. ^{1}H NMR Spectrum of Compound **13a** (400 MHz, $CDCl_3$)

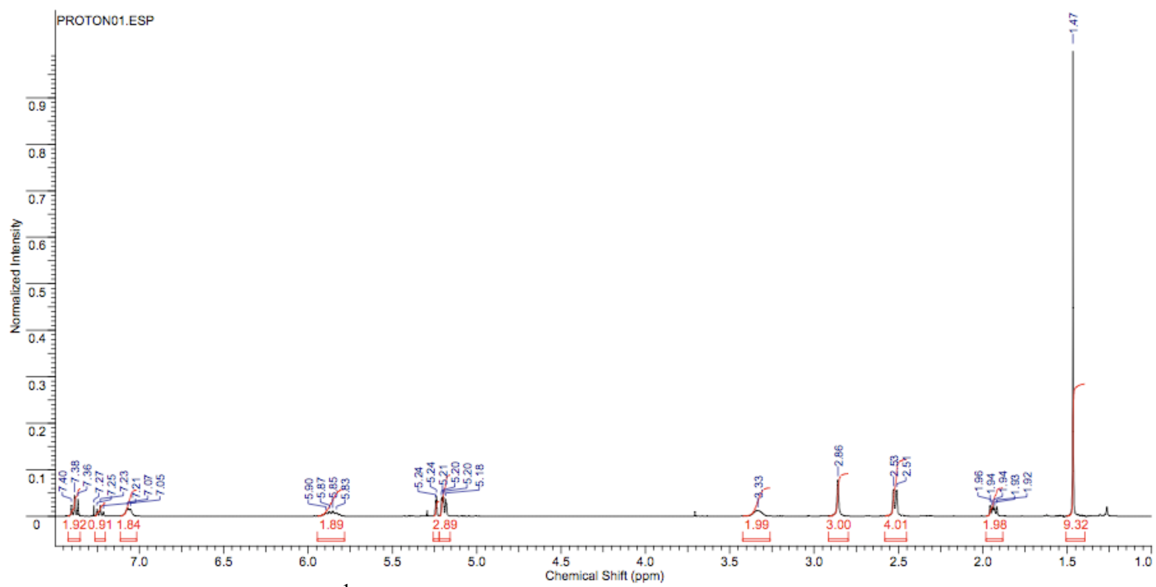

Figure S24. ^{1}H NMR Spectrum of Compound **13b** (400 MHz, $CDCl_3$)

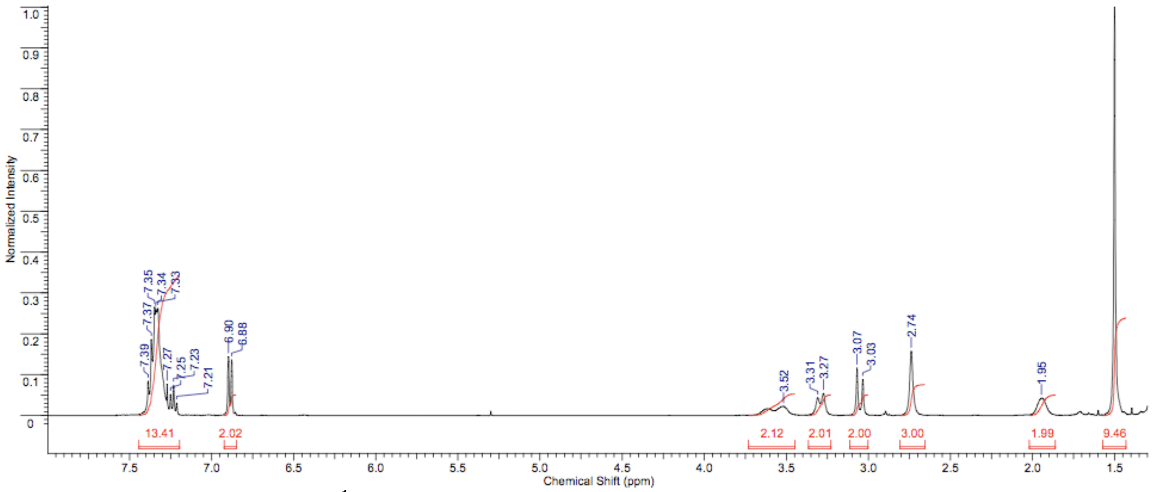

Figure S25. ^{1}H NMR Spectrum of Compound **13c** (400 MHz, $CDCl_3$)

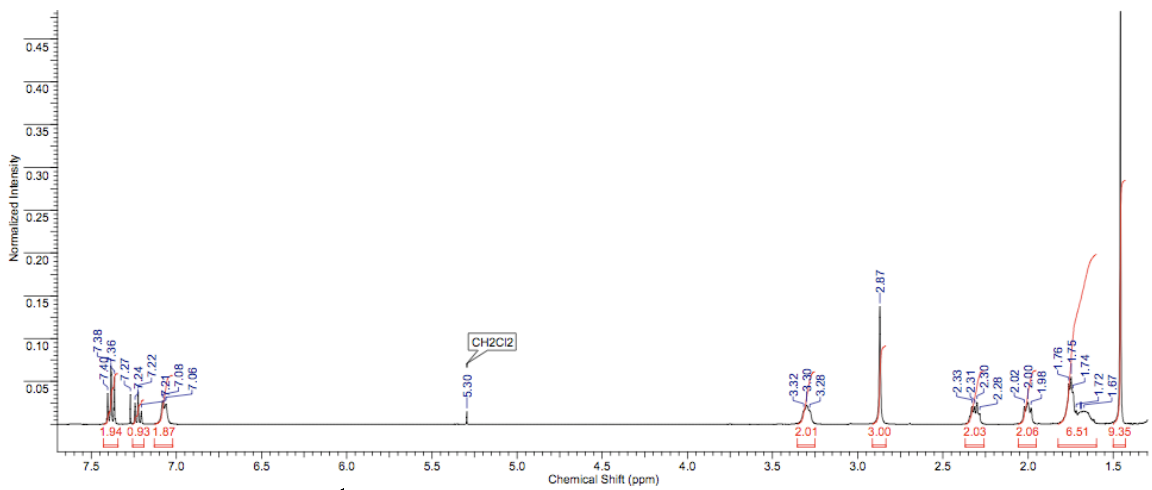

Figure S26. ^{1}H NMR Spectrum of Compound **13d** (400 MHz, $CDCl_3$)

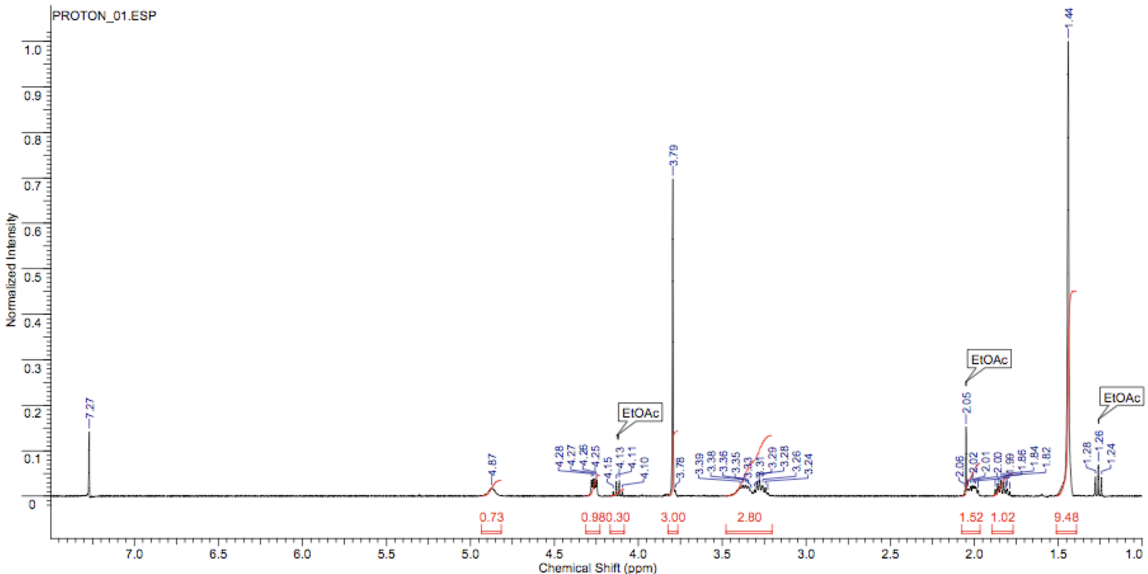

Figure S27. ^{1}H NMR Spectrum of Compound **15** (400 MHz, $CDCl_3$)

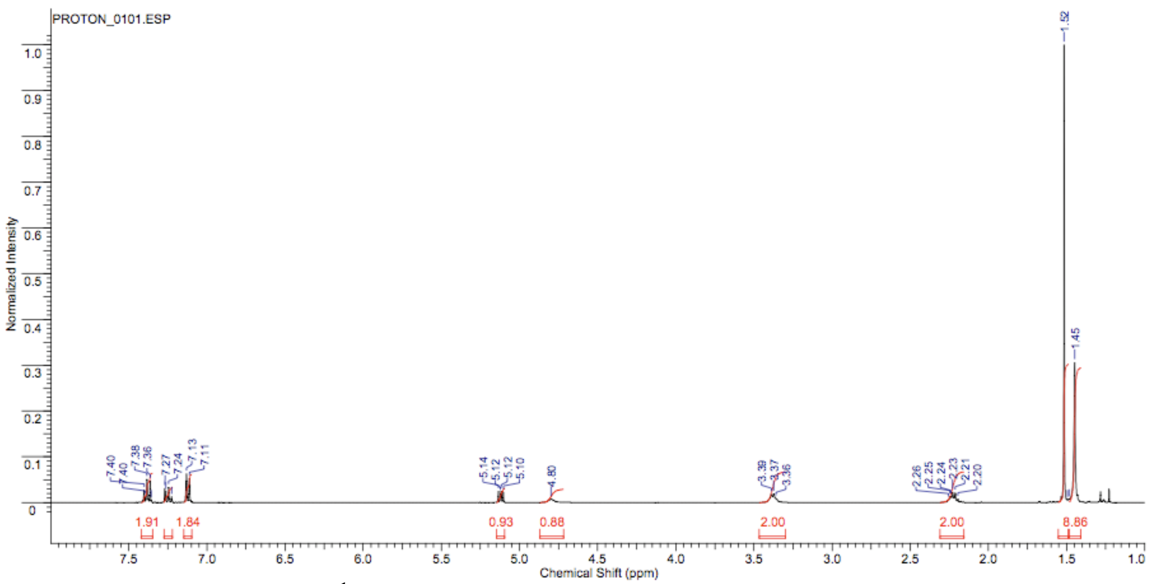

Figure S28. ^{1}H NMR Spectrum of Compound **16a** (400 MHz, $CDCl_3$)

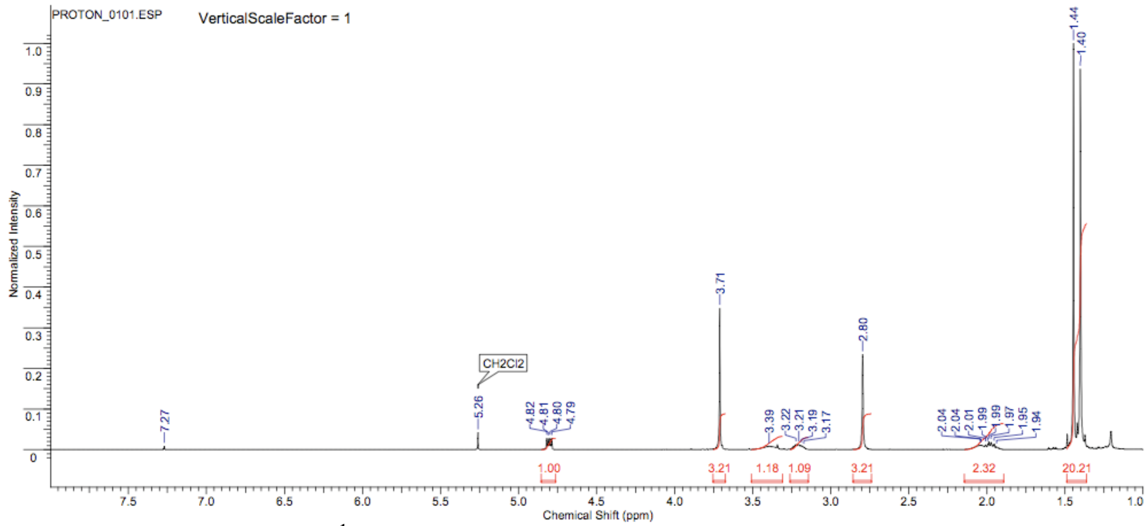

Figure S29. ^{1}H NMR Spectrum of Compound **16b** (400 MHz, $CDCl_3$)

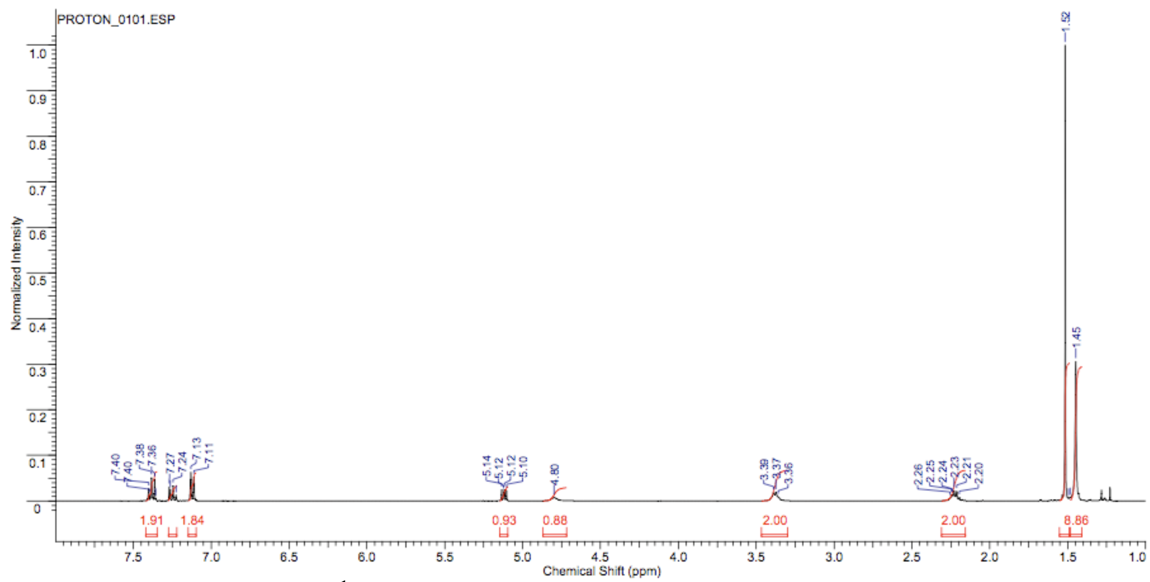

Figure S30. ^{1}H NMR Spectrum of Compound **17a** (400 MHz, $CDCl_3$)

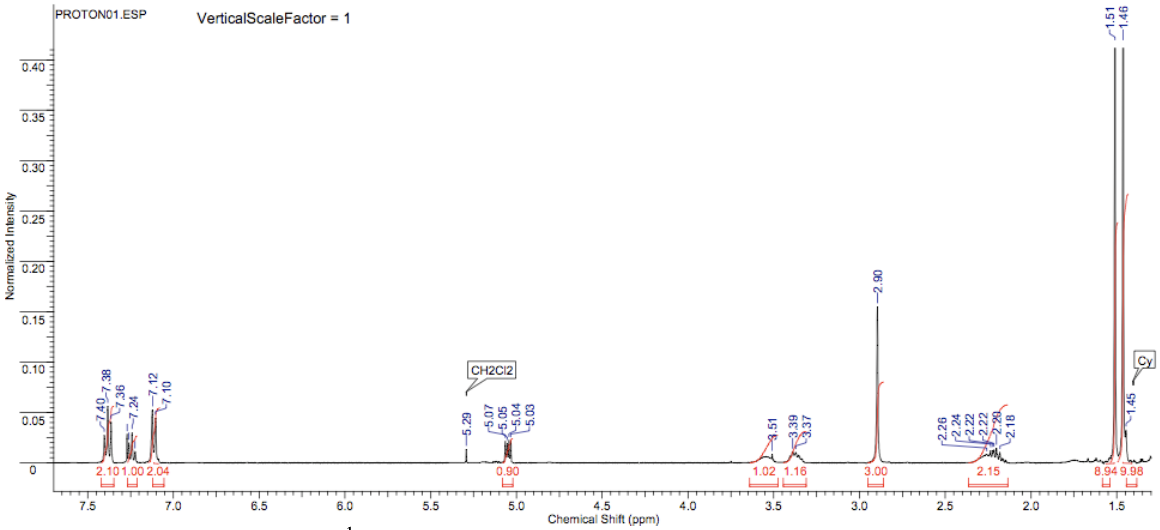

Figure S31. ^{1}H NMR Spectrum of Compound **17b** (400 MHz, $CDCl_3$)

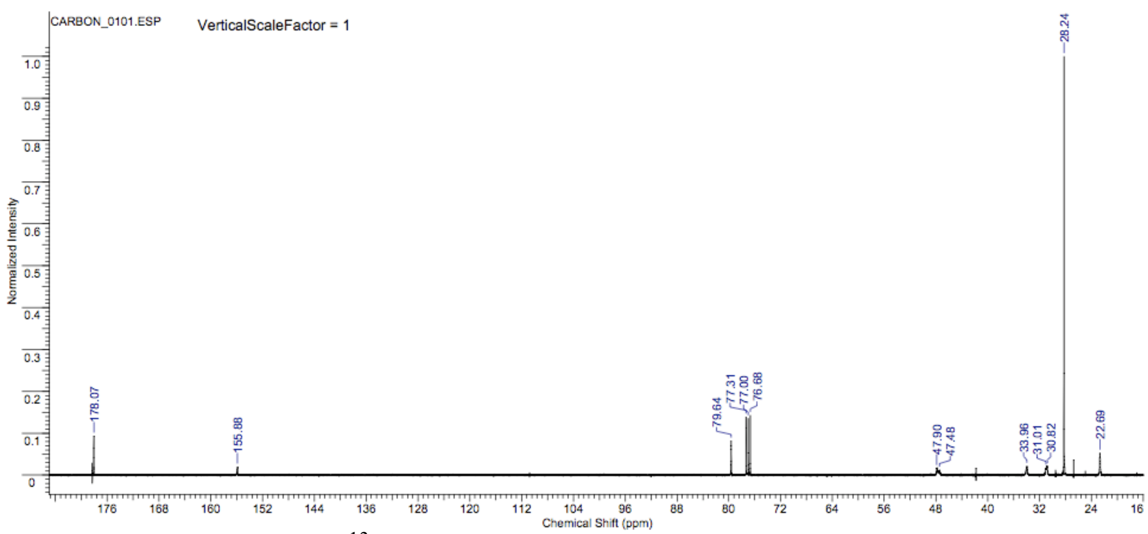

Figure S32. ^{13}C NMR Spectrum of Compound **5** (100 MHz, $CDCl_3$)

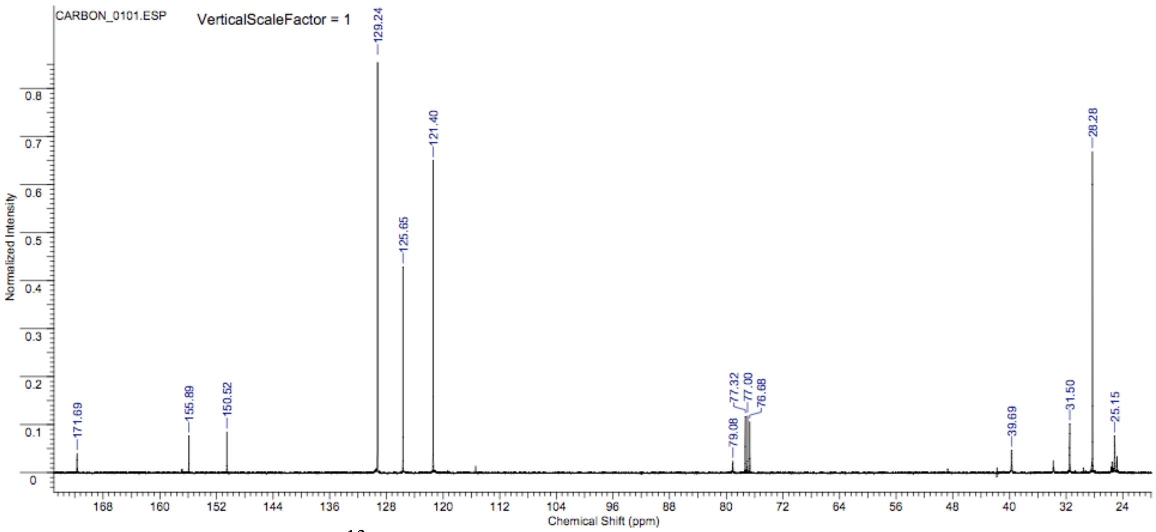

Figure S33. ^{13}C NMR Spectrum of Compound **6a** (100 MHz, $CDCl_3$)

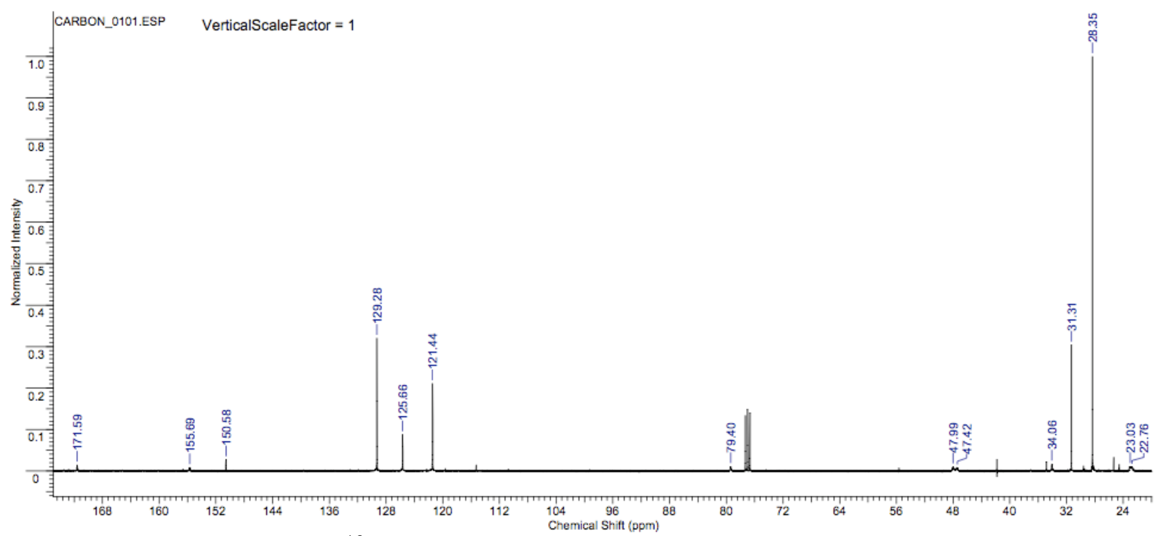

Figure S34. ^{13}C NMR Spectrum of Compound **6b** (100 MHz, $CDCl_3$)

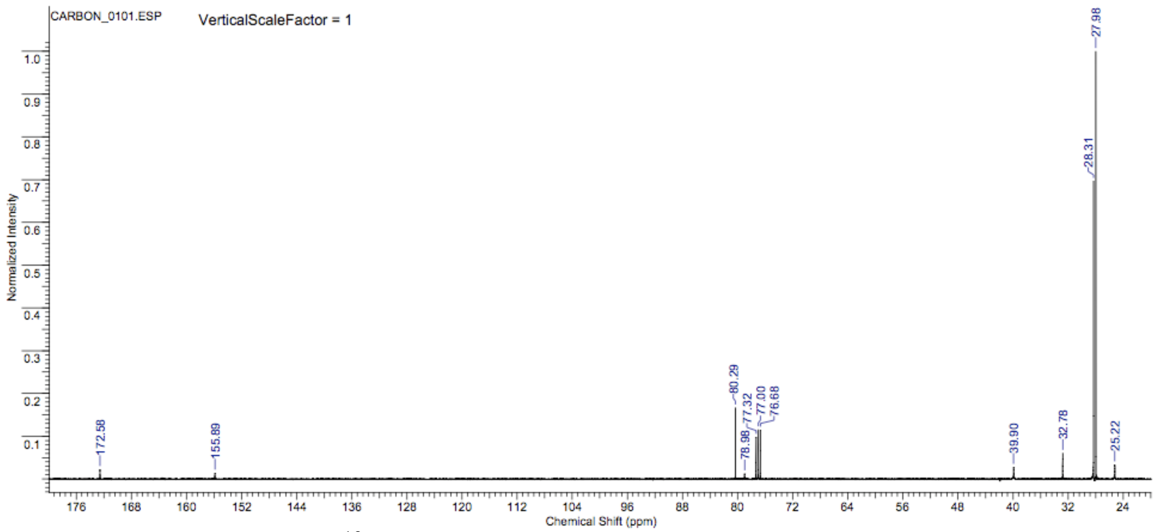

Figure S35. ^{13}C NMR Spectrum of Compound **7a** (100 MHz, $CDCl_3$)

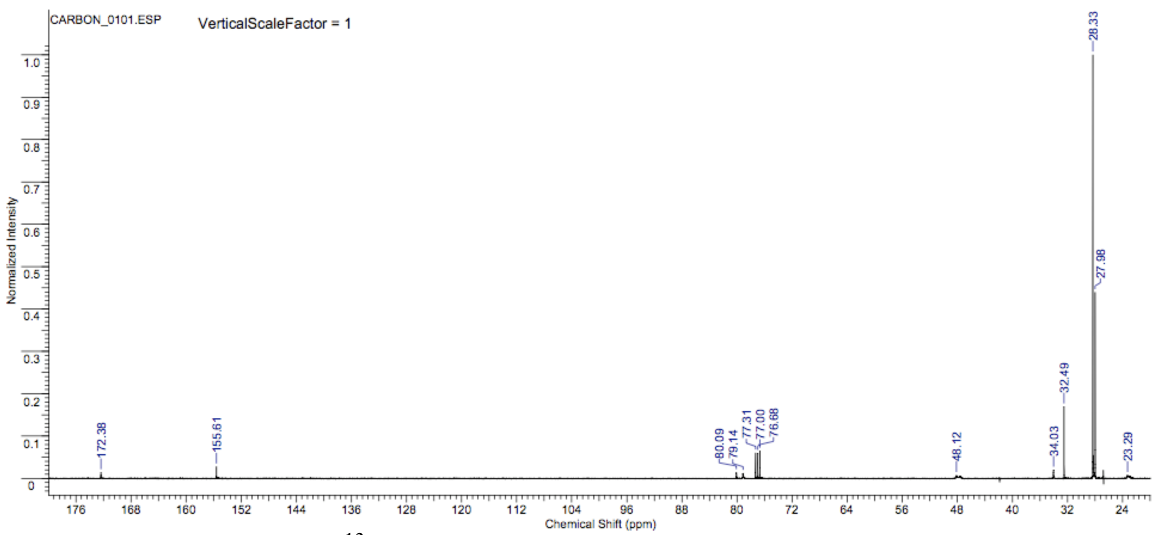

Figure S36. ^{13}C NMR Spectrum of Compound **7b** (100 MHz, $CDCl_3$)

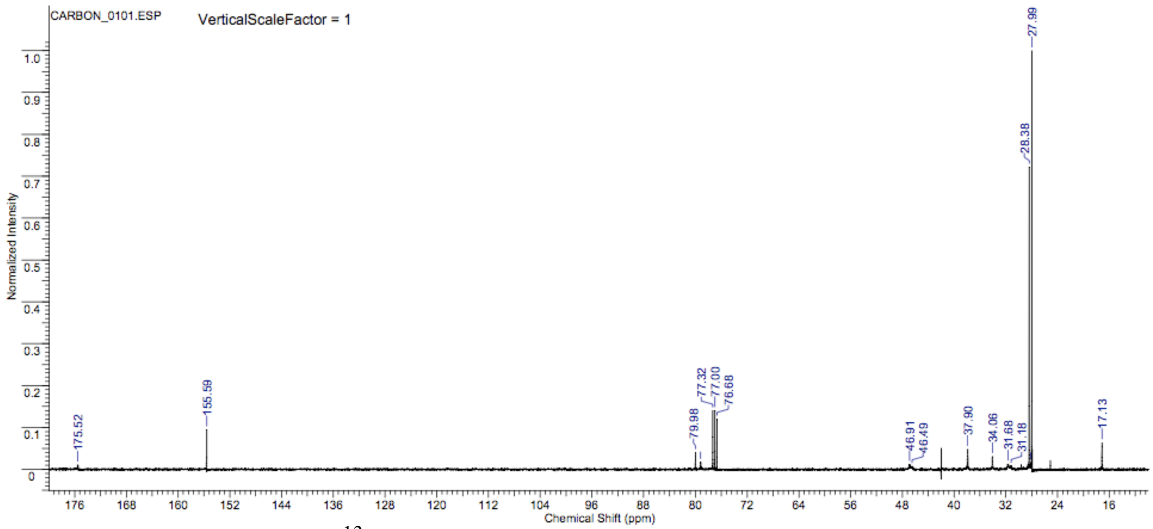

Figure S37. ^{13}C NMR Spectrum of Compound **8a** (100 MHz, $CDCl_3$)

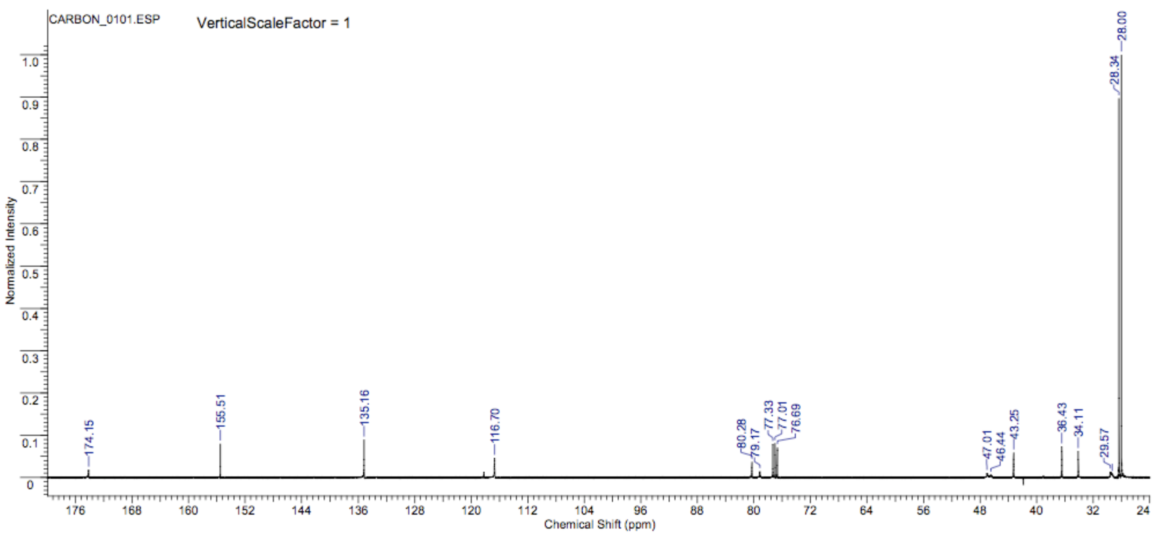

Figure S38. ^{13}C NMR Spectrum of Compound **8b** (100 MHz, $CDCl_3$)

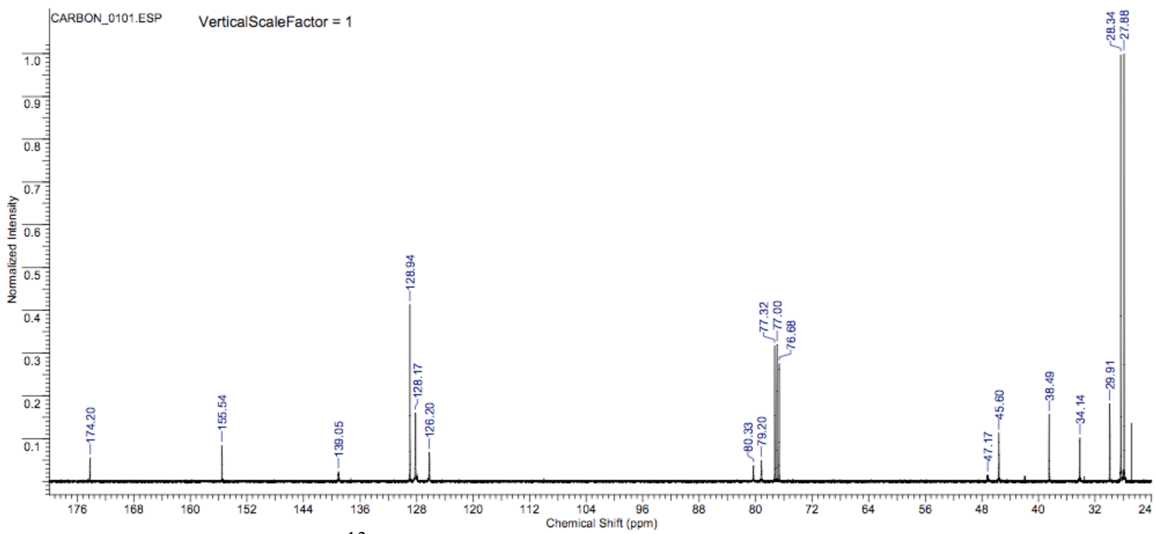

Figure S39. ^{13}C NMR Spectrum of Compound **8c** (100 MHz, $CDCl_3$)

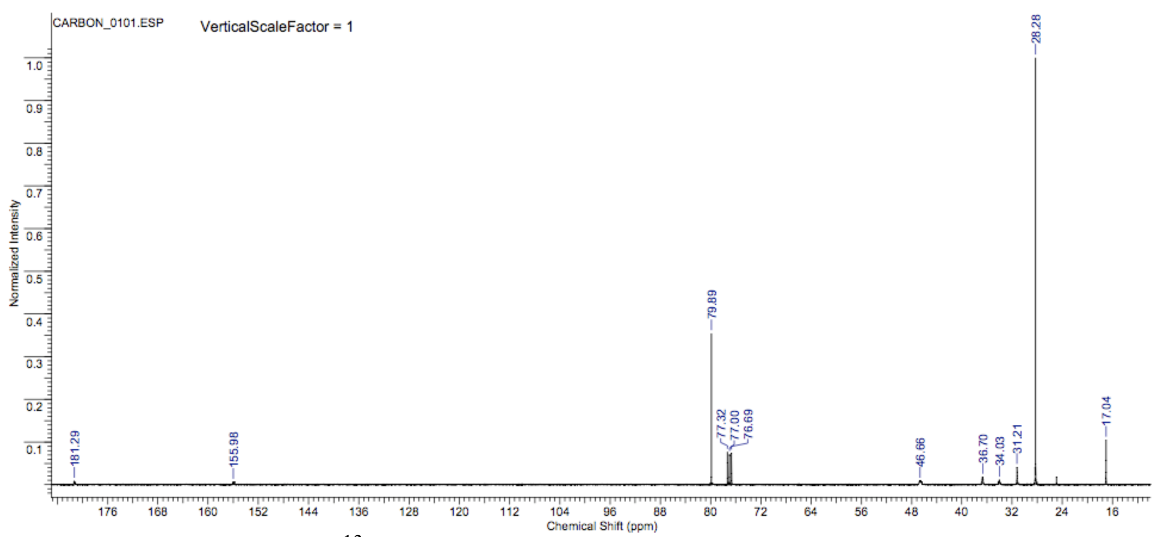

Figure S40. ^{13}C NMR Spectrum of Compound **9a** (100 MHz, $CDCl_3$)

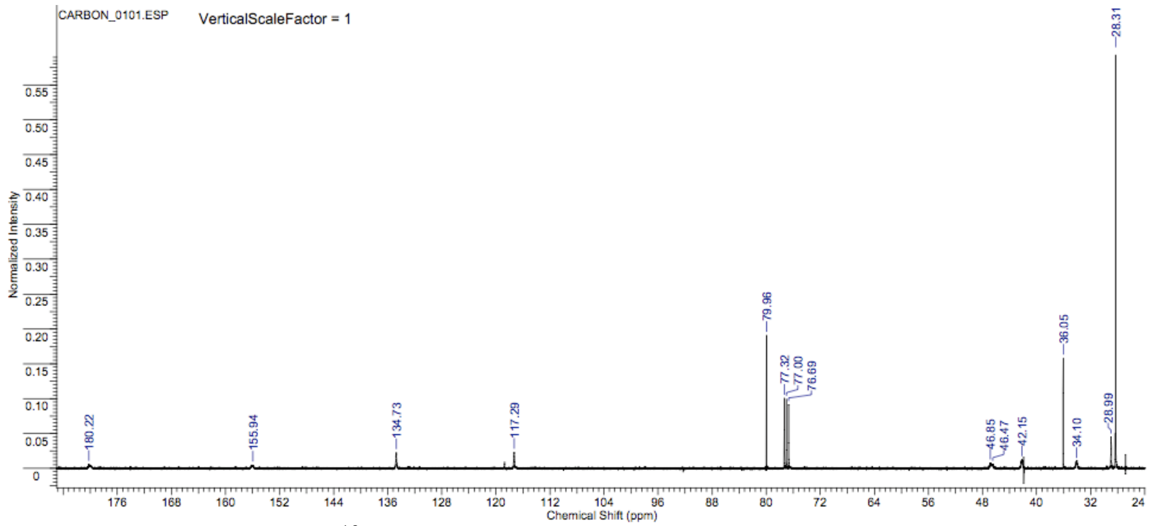

Figure S41. ^{13}C NMR Spectrum of Compound **9b** (100 MHz, $CDCl_3$)

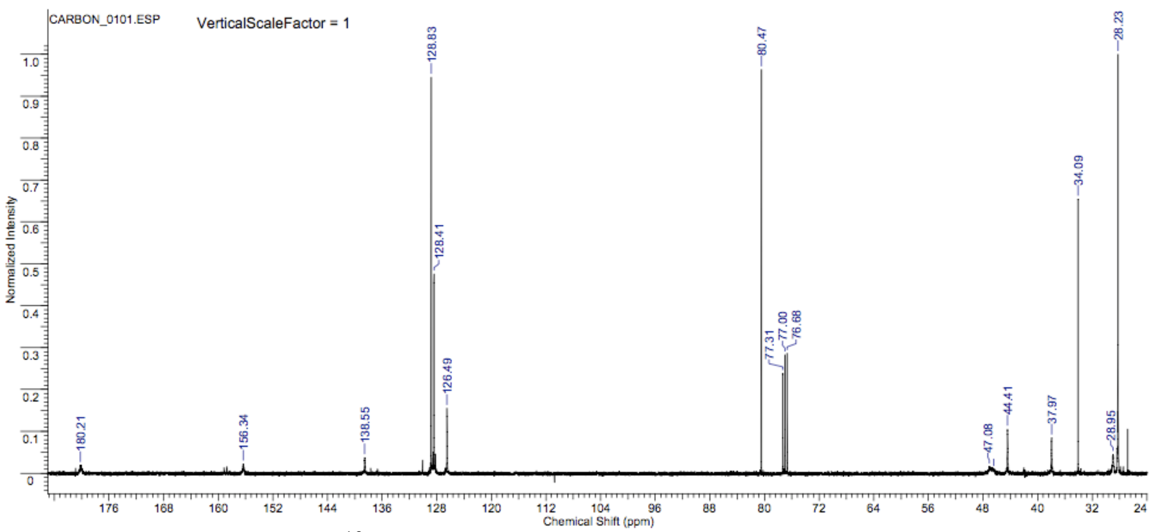

Figure S42. ^{13}C NMR Spectrum of Compound **9c** (100 MHz, $CDCl_3$)

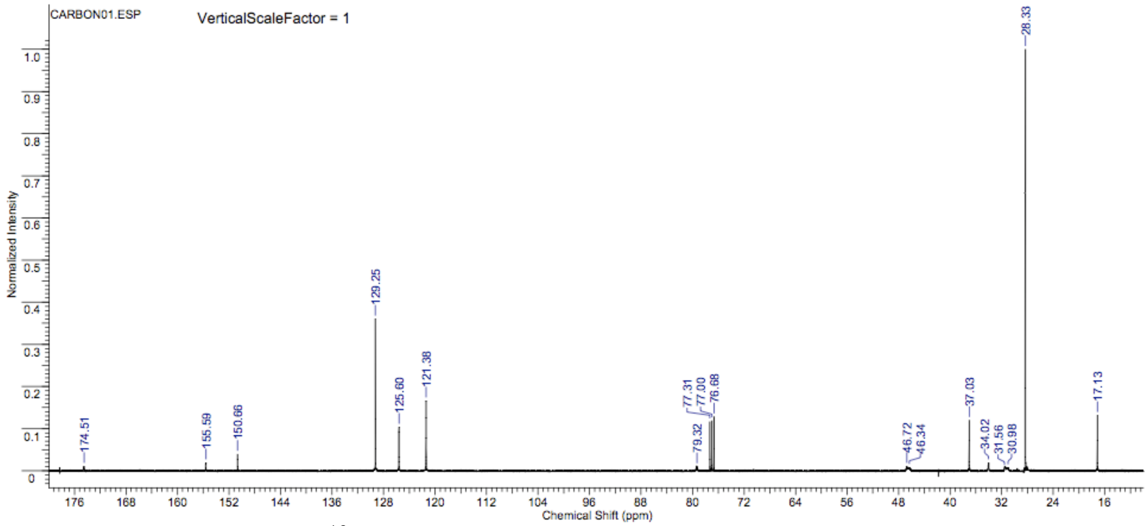

Figure S43. ^{13}C NMR Spectrum of Compound **10a** (100 MHz, $CDCl_3$)

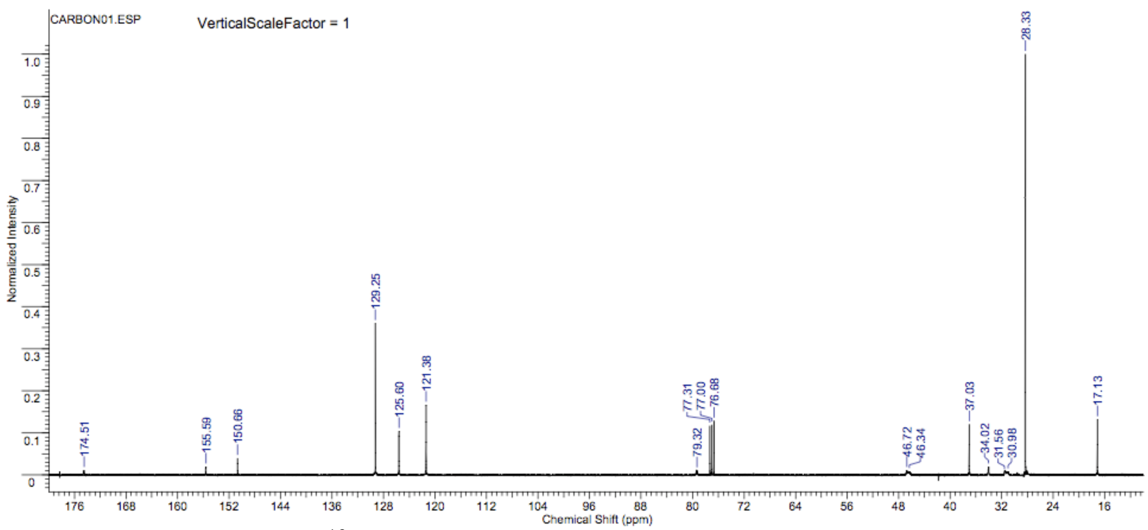

Figure S44. ^{13}C NMR Spectrum of Compound **10b** (100 MHz, $CDCl_3$)

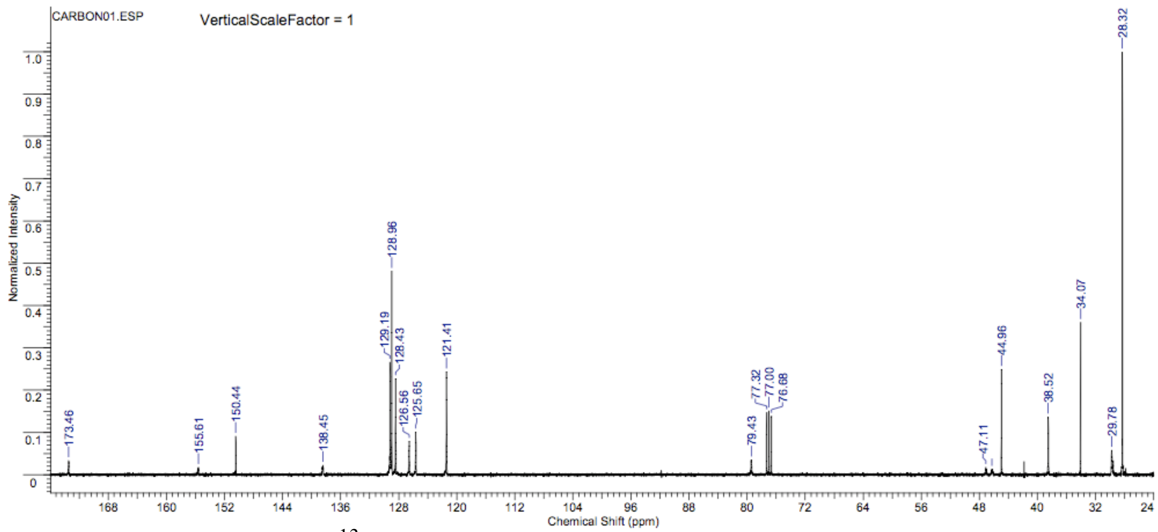

Figure S45. ^{13}C NMR Spectrum of Compound **10c** (100 MHz, $CDCl_3$)

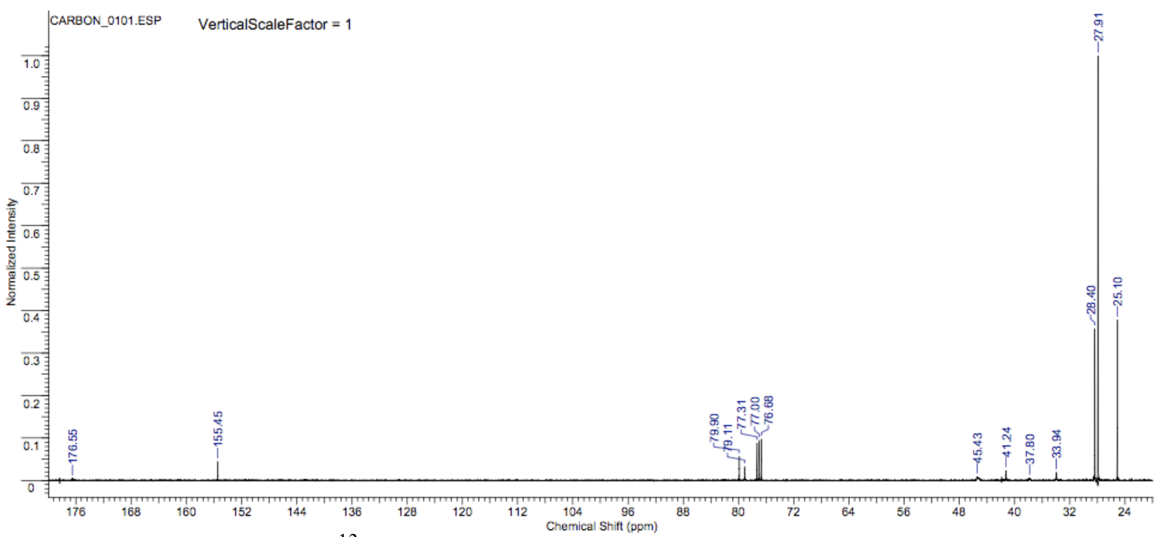

Figure S46. ^{13}C NMR Spectrum of Compound **11a** (100 MHz, $CDCl_3$)

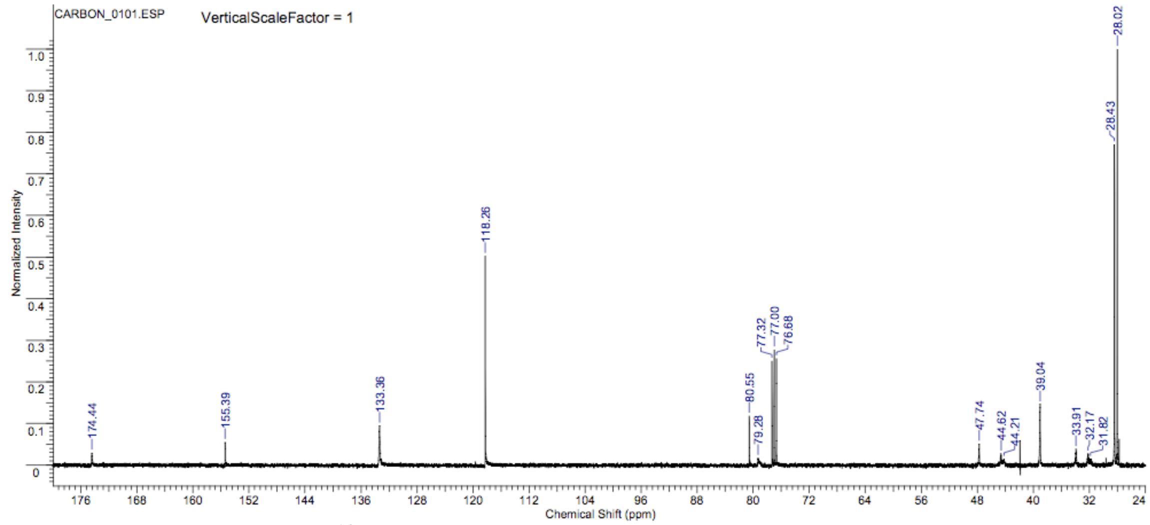

Figure S47. ^{13}C NMR Spectrum of Compound **11b** (100 MHz, $CDCl_3$)

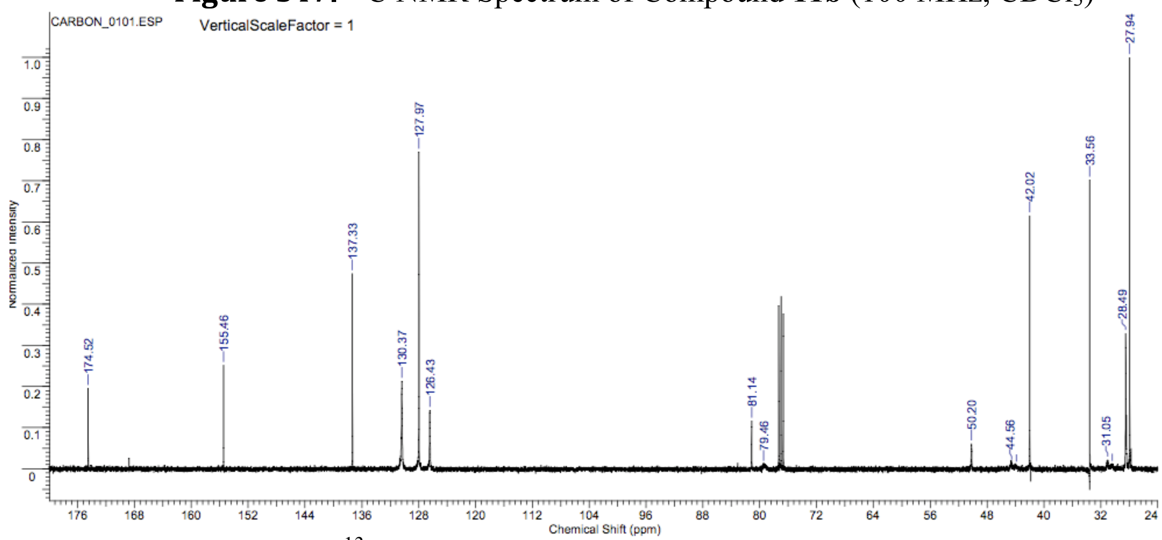

Figure S48. ^{13}C NMR Spectrum of Compound **11c** (100 MHz, $CDCl_3$)

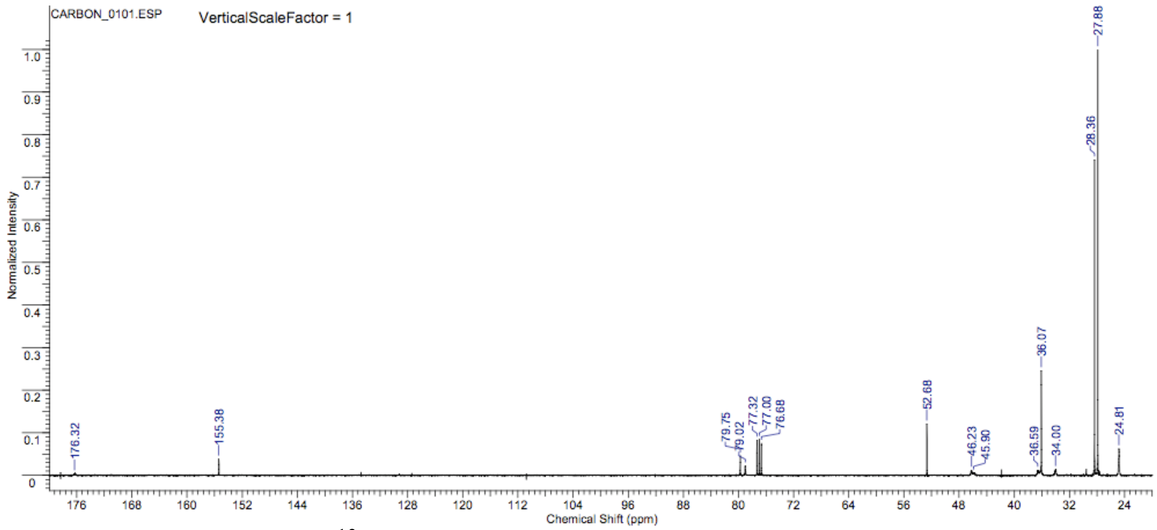

Figure S49. ^{13}C NMR Spectrum of Compound **11d** (100 MHz, $CDCl_3$)

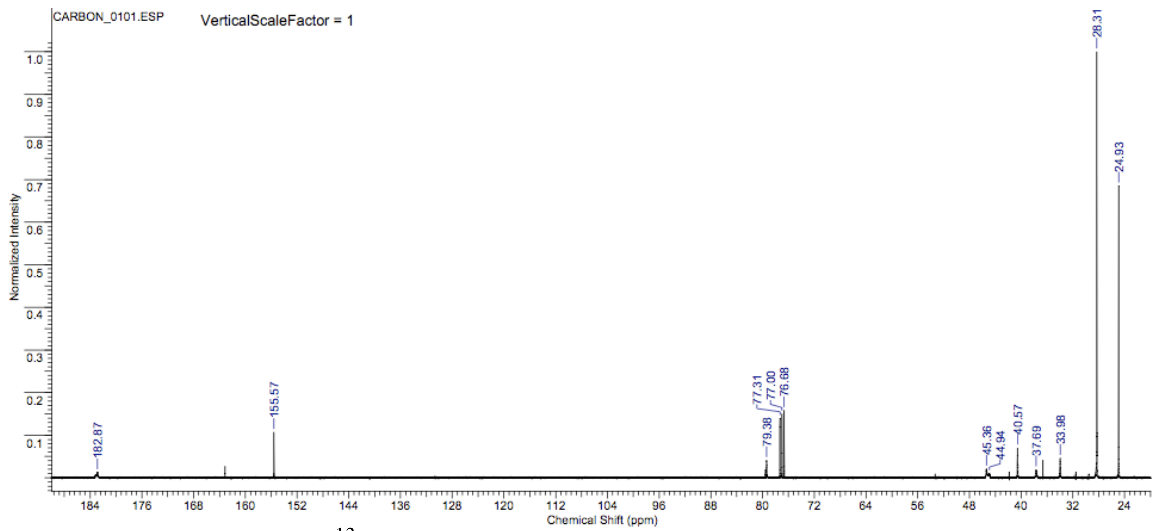

Figure S50. ^{13}C NMR Spectrum of Compound **12a** (100 MHz, $CDCl_3$)

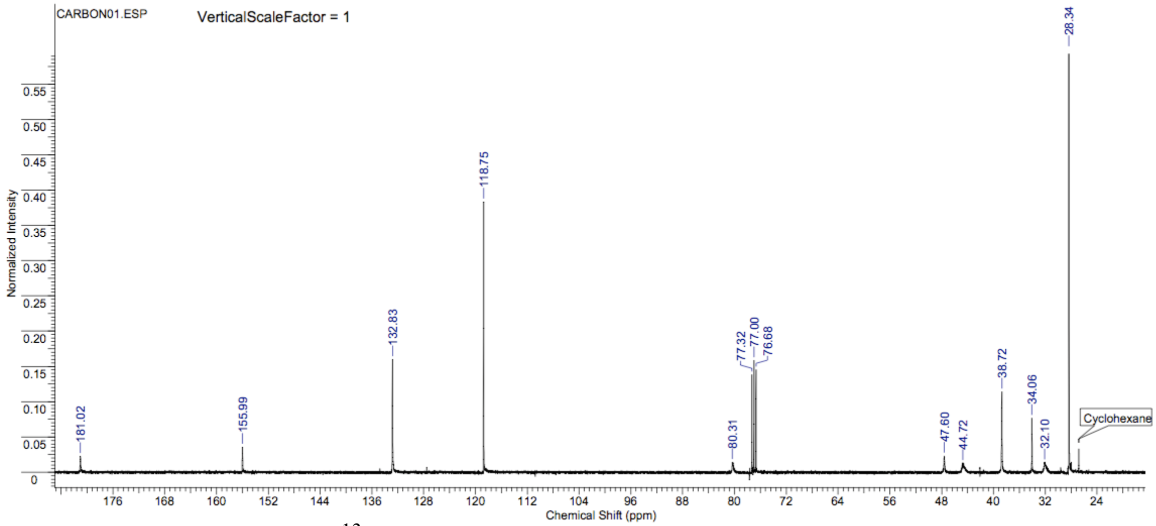

Figure S51. ^{13}C NMR Spectrum of Compound **12b** (100 MHz, $CDCl_3$)

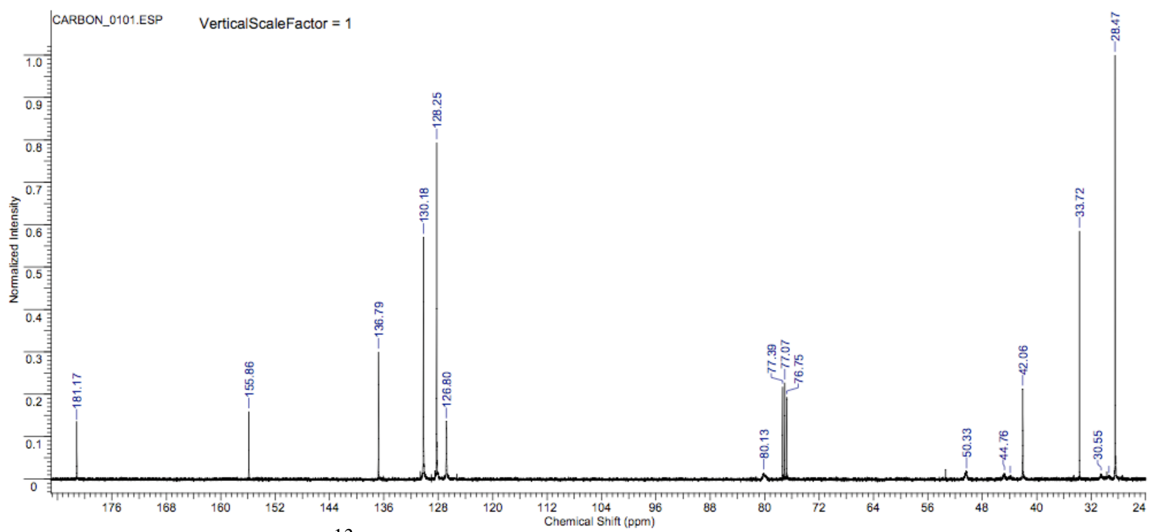

Figure S52. ^{13}C NMR Spectrum of Compound **12c** (100 MHz, $CDCl_3$)

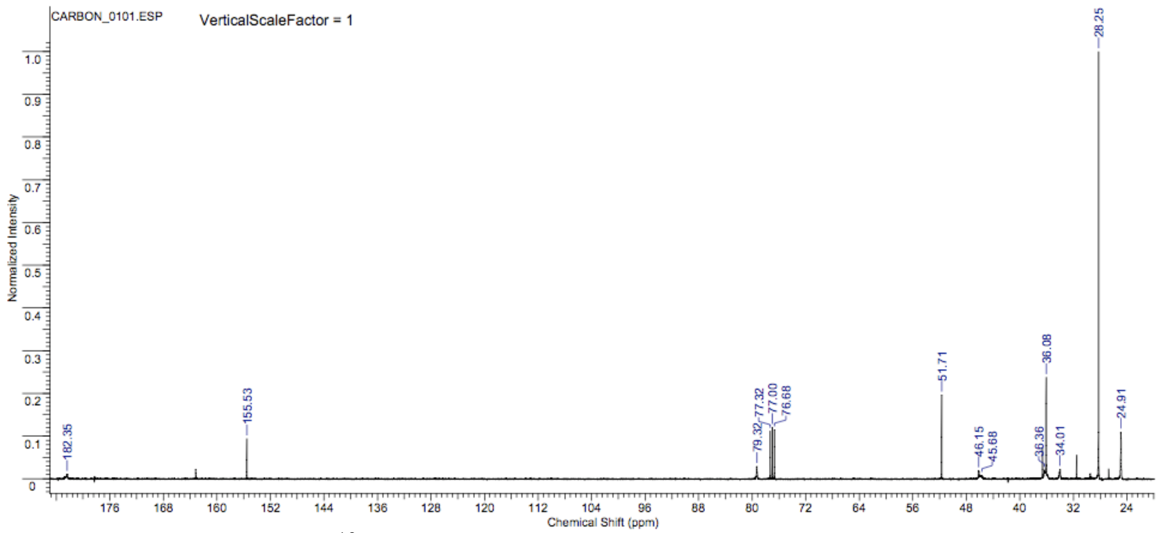

Figure S53. ^{13}C NMR Spectrum of Compound **12d** (100 MHz, $CDCl_3$)

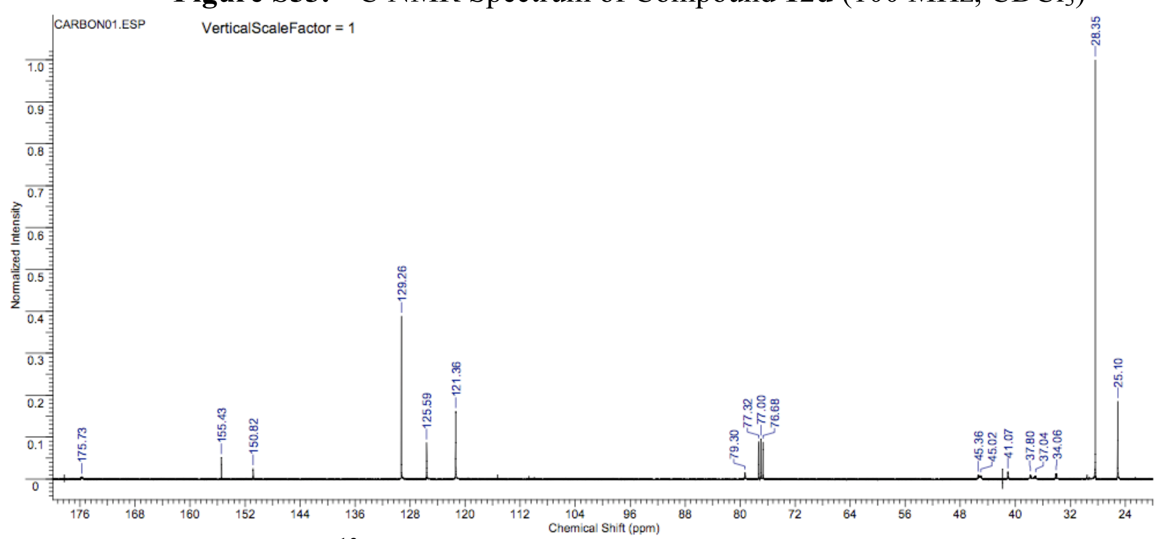

Figure S54. ^{13}C NMR Spectrum of Compound **13a** (100 MHz, $CDCl_3$)

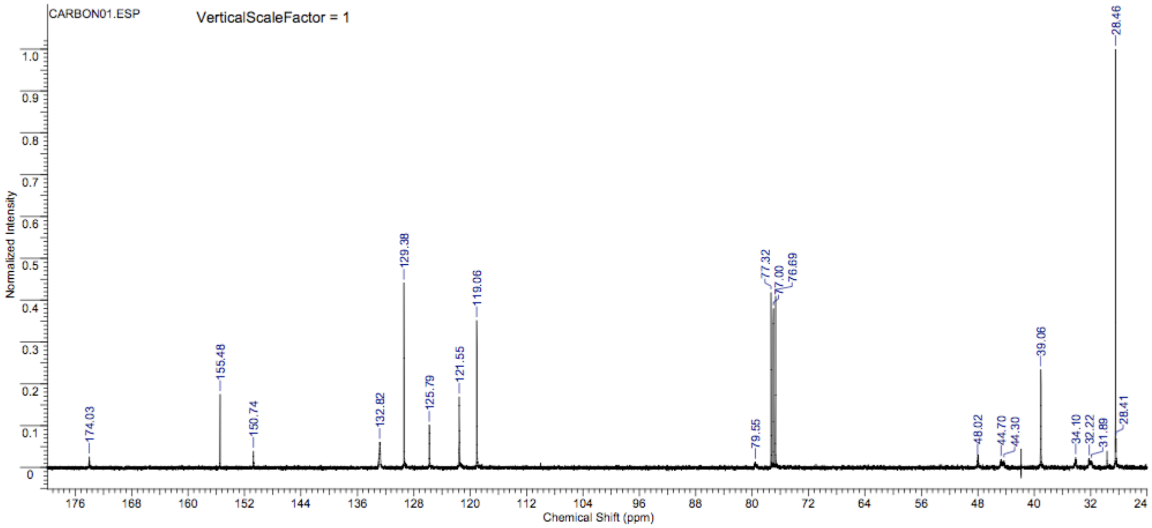

Figure S55. ^{13}C NMR Spectrum of Compound **13b** (100 MHz, $CDCl_3$)

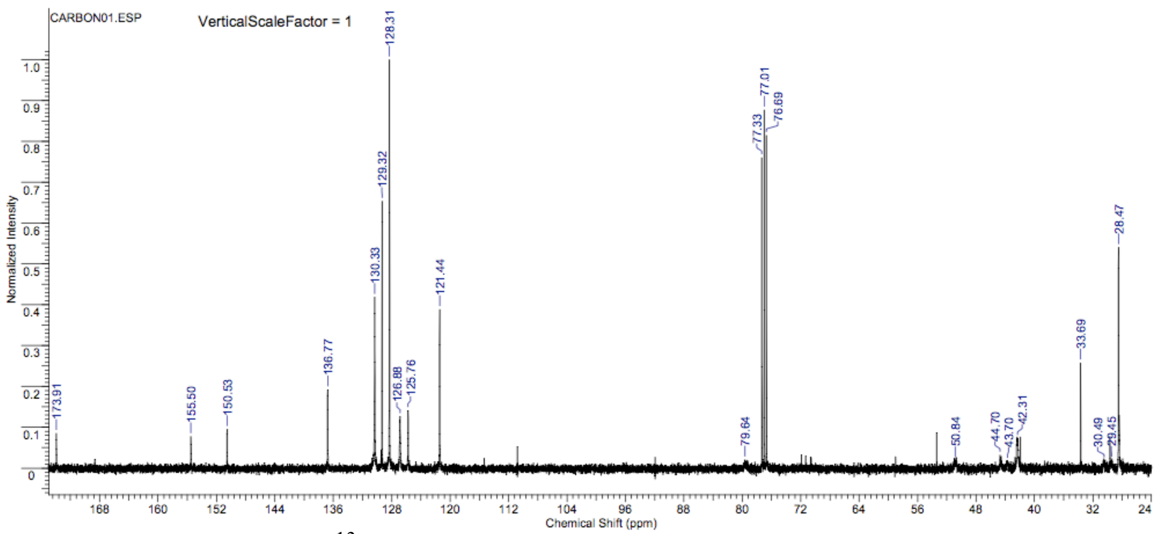

Figure S56. ^{13}C NMR Spectrum of Compound **13c** (100 MHz, $CDCl_3$)

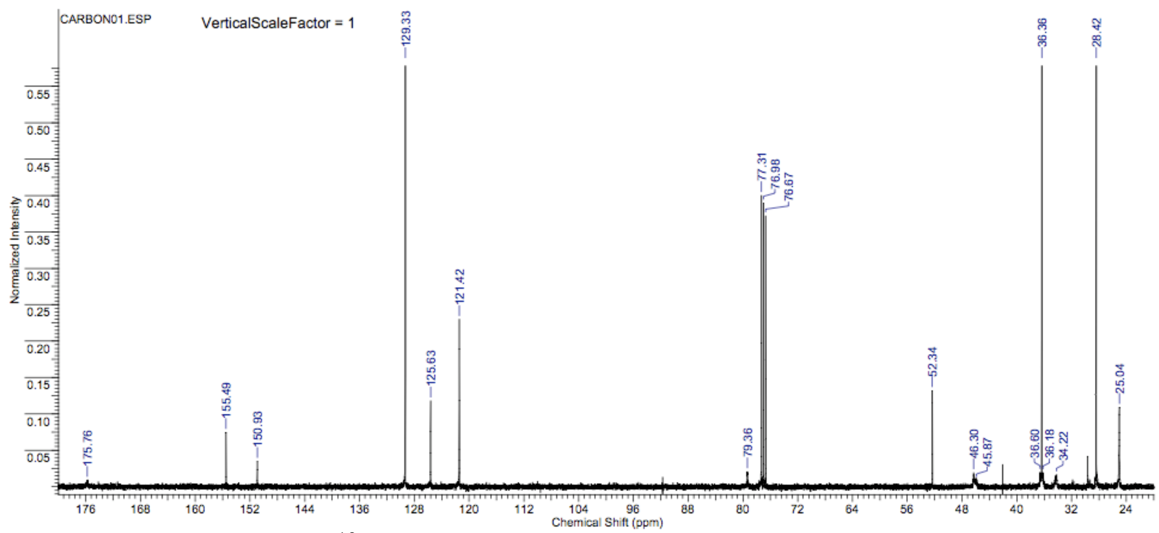

Figure S57. ^{13}C NMR Spectrum of Compound **13d** (100 MHz, $CDCl_3$)

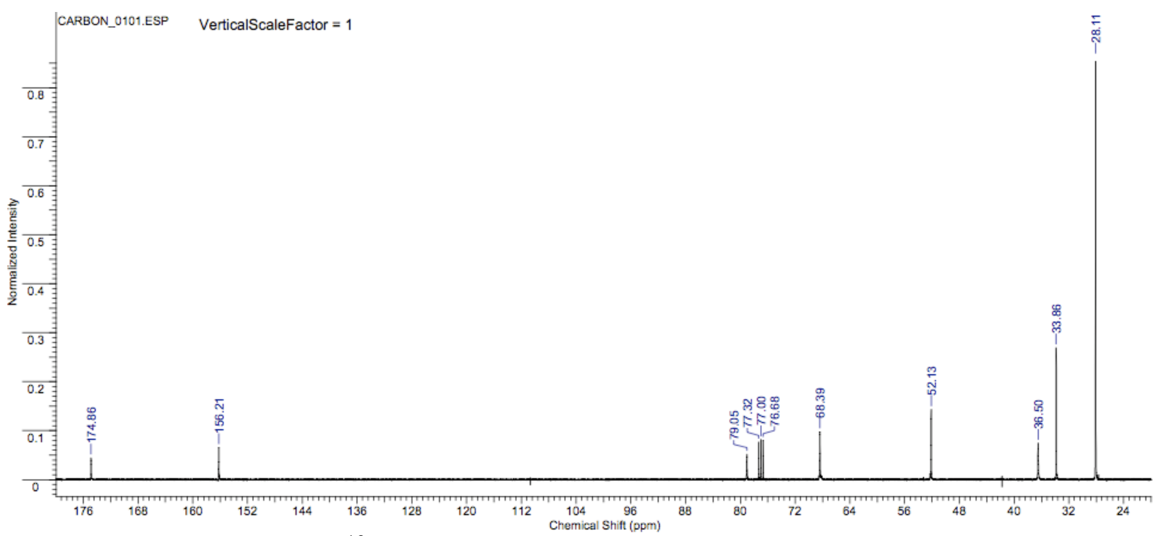

Figure S58. ^{13}C NMR Spectrum of Compound **15** (100 MHz, $CDCl_3$)

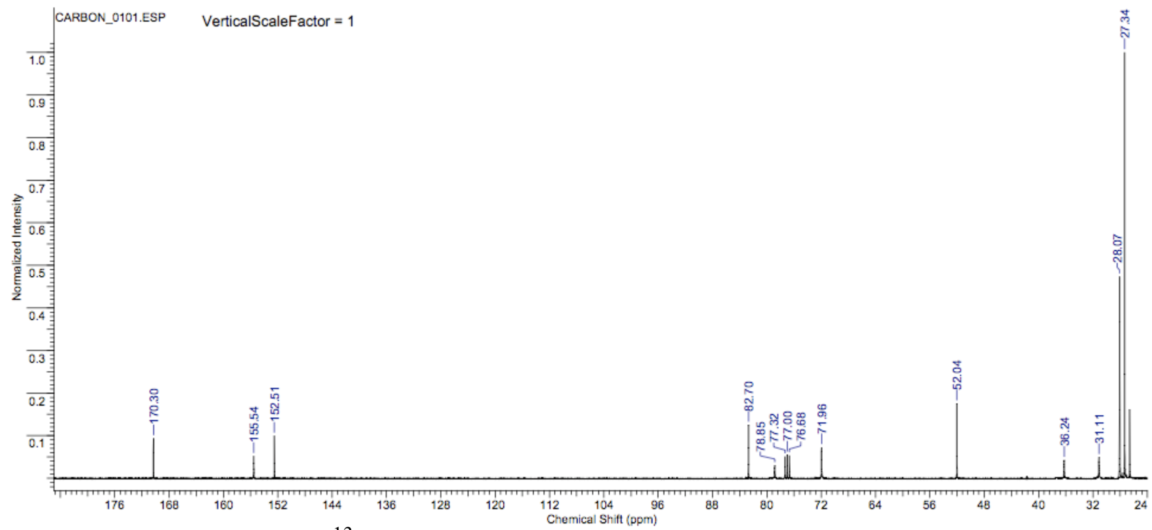

Figure S59. ^{13}C NMR Spectrum of Compound **16a** (100 MHz, $CDCl_3$)

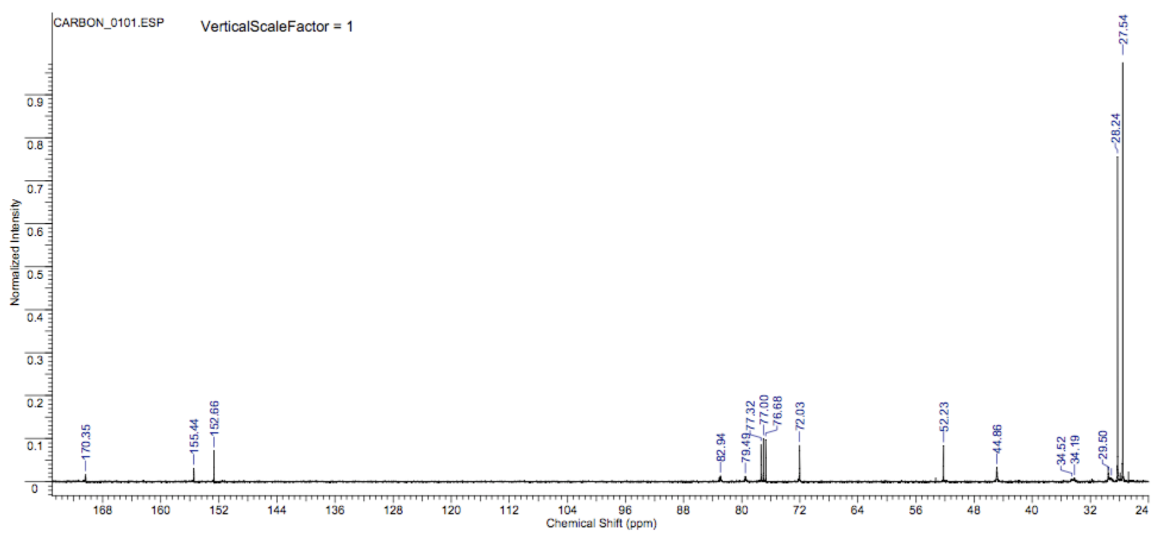

Figure S60. ^{13}C NMR Spectrum of Compound **16b** (100 MHz, $CDCl_3$)

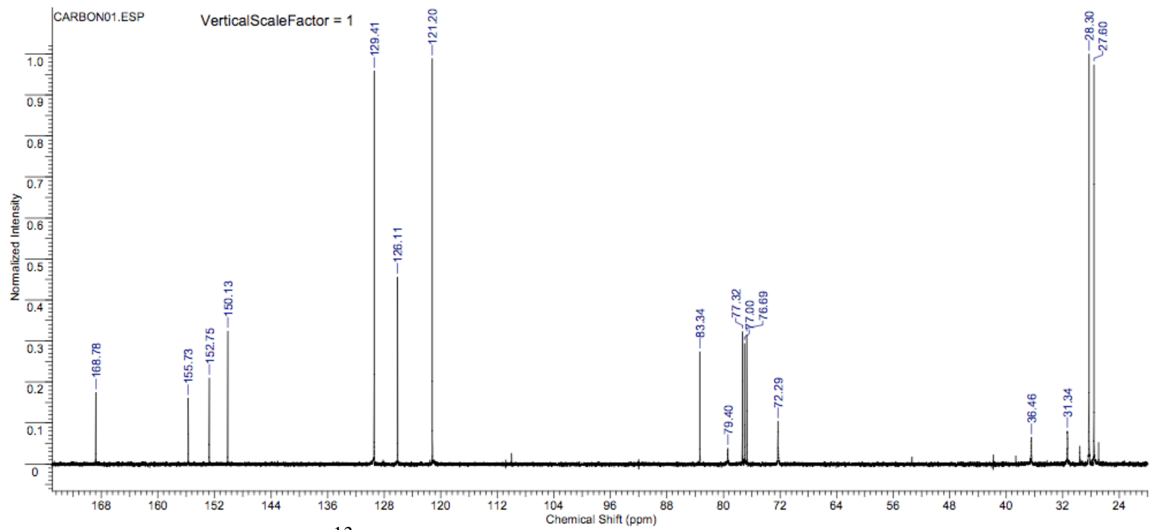

Figure S61. ^{13}C NMR Spectrum of Compound **17a** (100 MHz, $CDCl_3$)

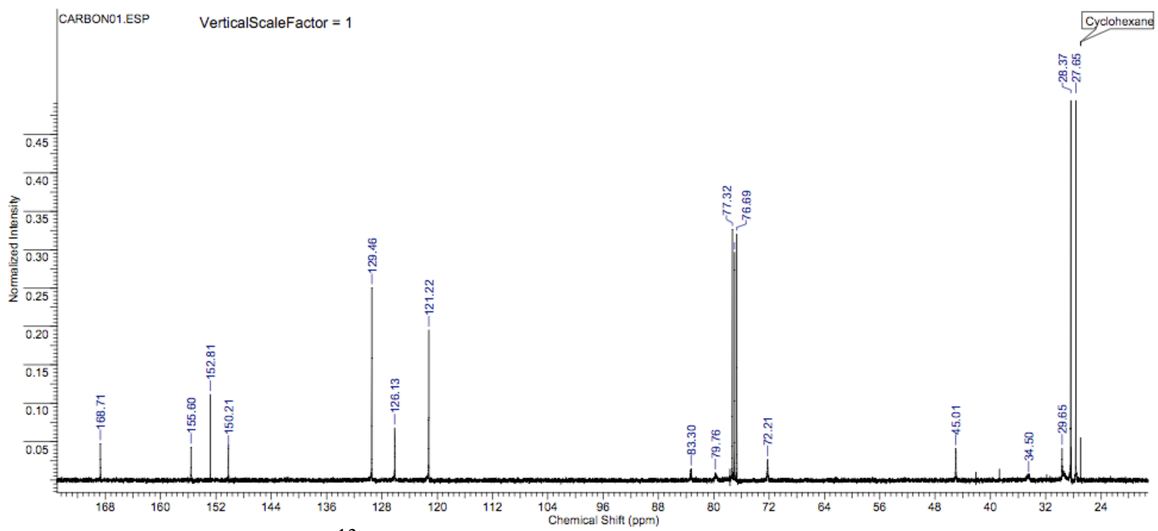

Figure S62. ^{13}C NMR Spectrum of Compound **17b** (100 MHz, $CDCl_3$)

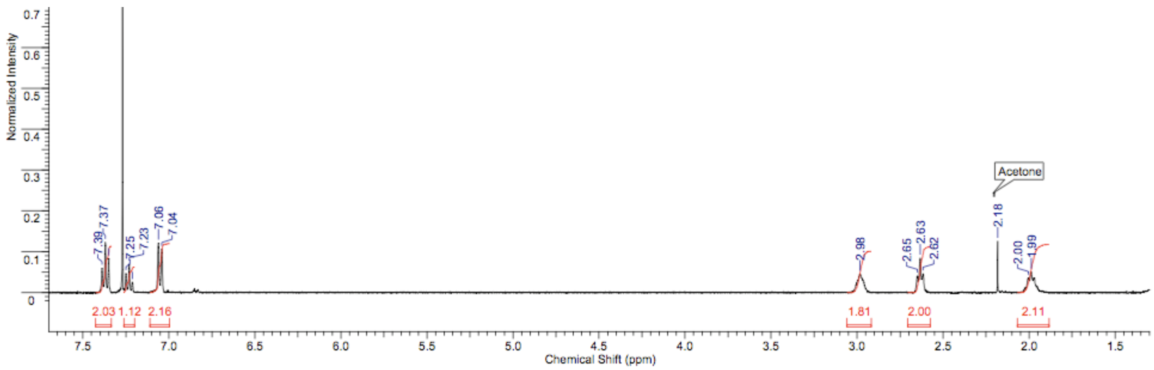

Figure S63. ^{1}H NMR Spectrum of **3a**·TFA (400 MHz, $CDCl_3$)

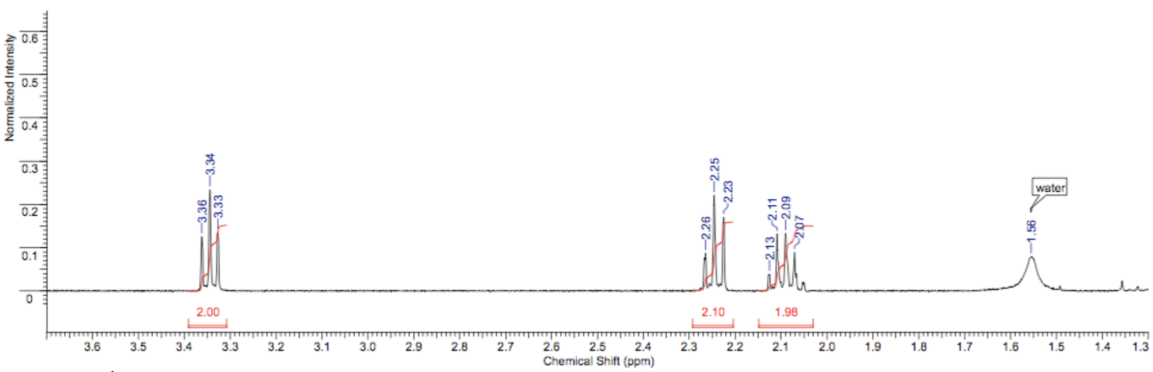

Figure 64. ^{1}H NMR Spectrum of **18a** (400 MHz, $CDCl_3$). HRMS calc'd $[M]^+$ (C_4H_7NO): 85.0528. Found: (EI) 85.0530.

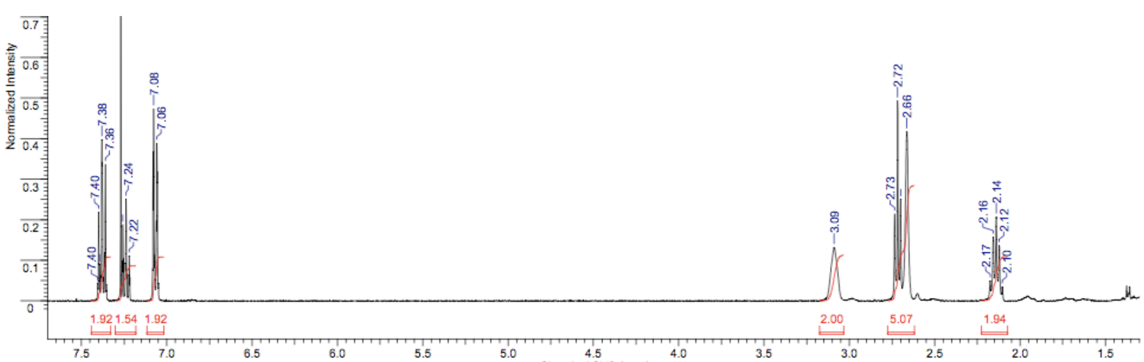

Figure S65. ^{1}H NMR Spectrum of **3b**·TFA (400 MHz, $CDCl_3$)

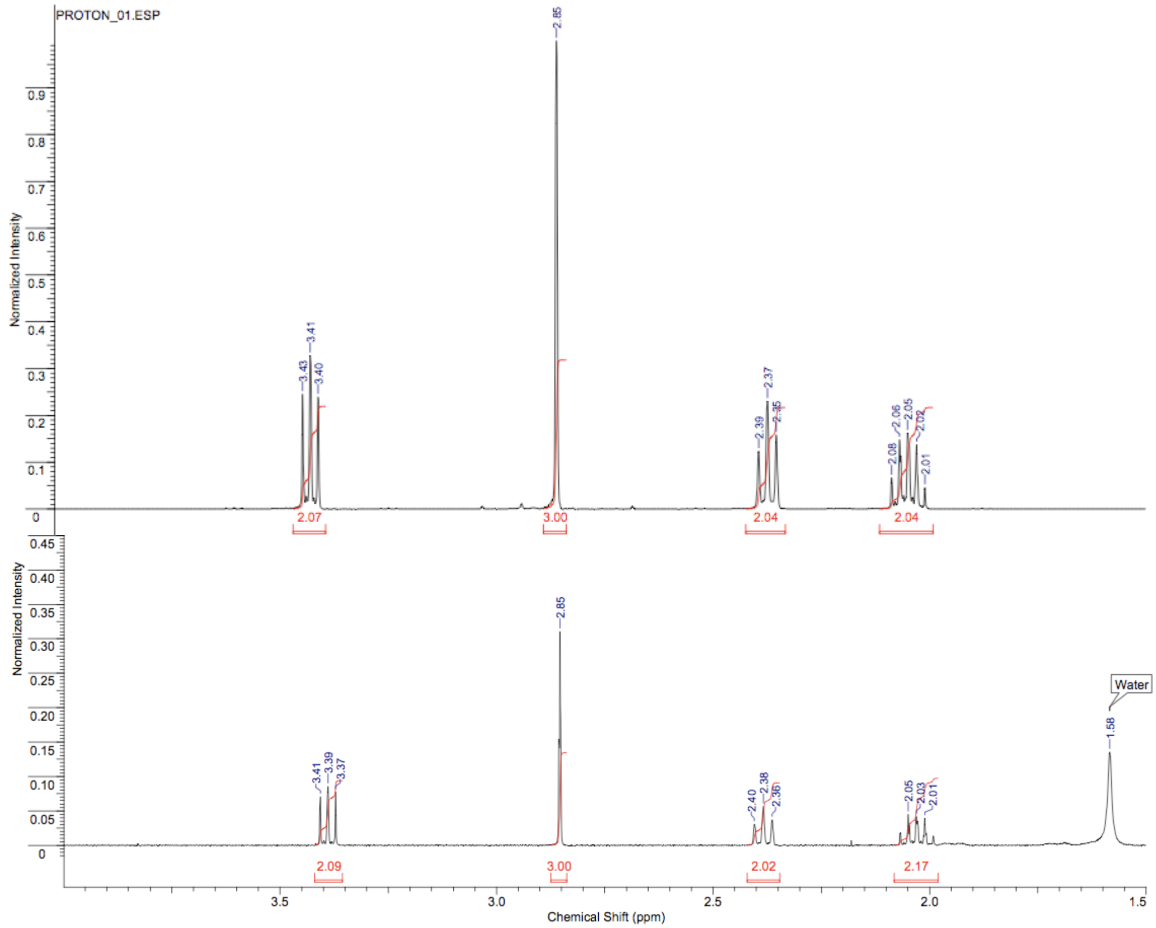

Figure S66. ^{1}H NMR Spectrum of a) Commercial NMP and b) **18b** (400 MHz, $CDCl_3$). HRMS calc'd $[M]^+$ (C_5H_9NO): 99.0684. Found: (EI) 99.0681.

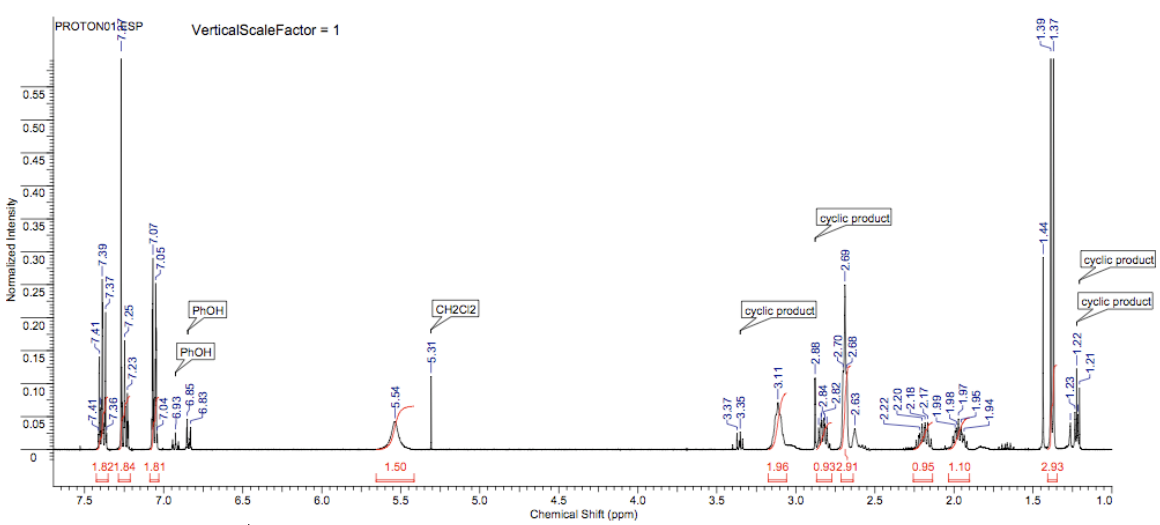

Figure S67. ^{1}H NMR Spectrum of **3c**·TFA (400 MHz, $CDCl_3$). Upon addition of H_2O immediately prior to freeze drying, some material cyclized to form **18c** and PhOH.

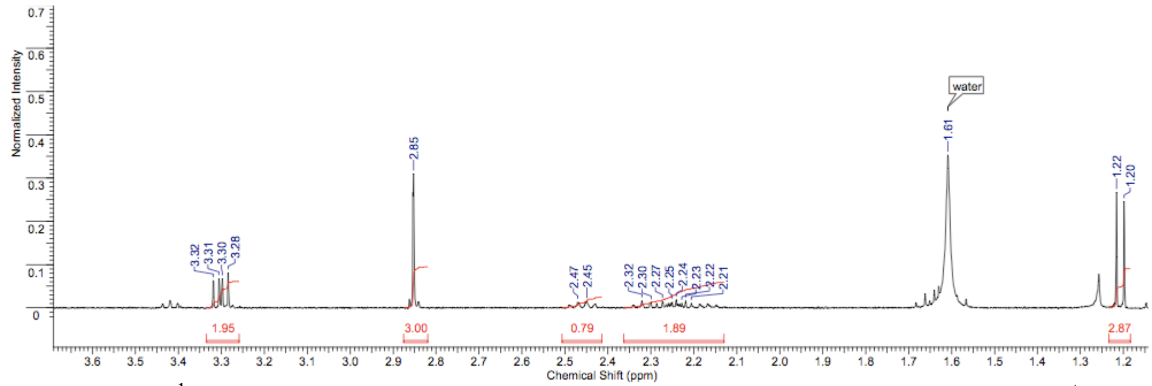

Figure S68. ^{1}H NMR Spectrum of **18c** (400 MHz, $CDCl_3$). HRMS calc'd $[M]^+$ ($C_6H_{11}NO$): 113.0841. Found: (EI) 113.0841.

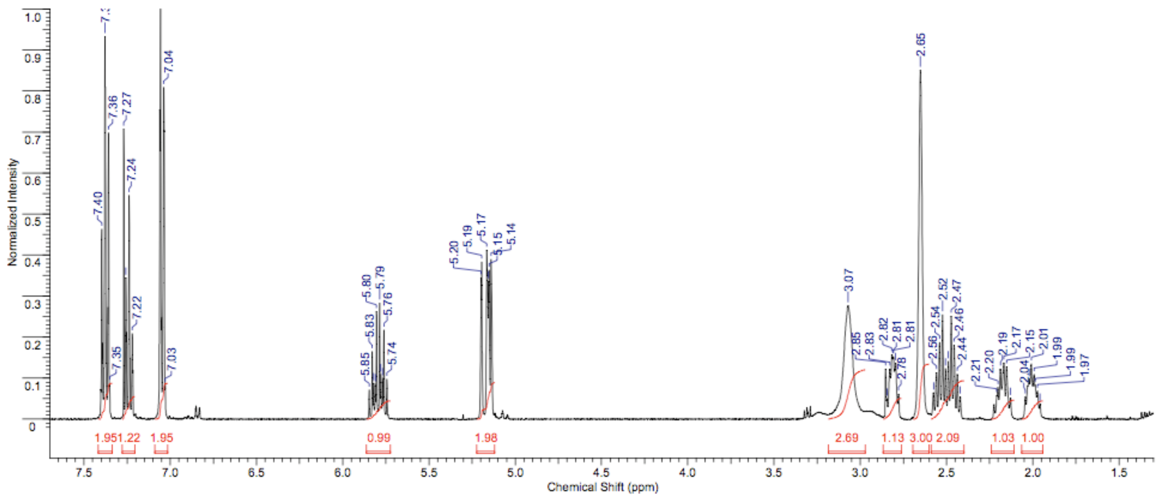

Figure S69. ^{1}H NMR Spectrum of **3d**·TFA (400 MHz, $CDCl_3$)

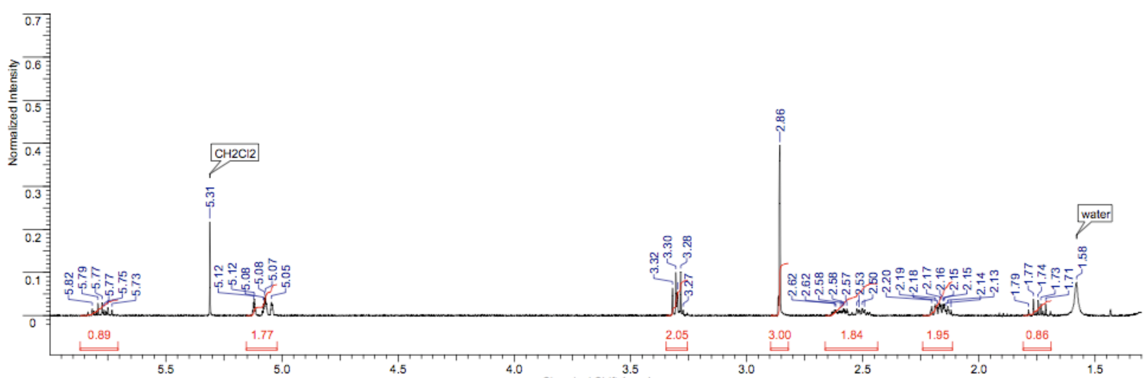

Figure S70. ^{1}H NMR Spectrum of **18d** (400 MHz, $CDCl_3$). HRMS calc'd $[M+H]^+$ $(C_8H_{14}NO)^+$: 140.1070. Found: (EI) 140.1079.

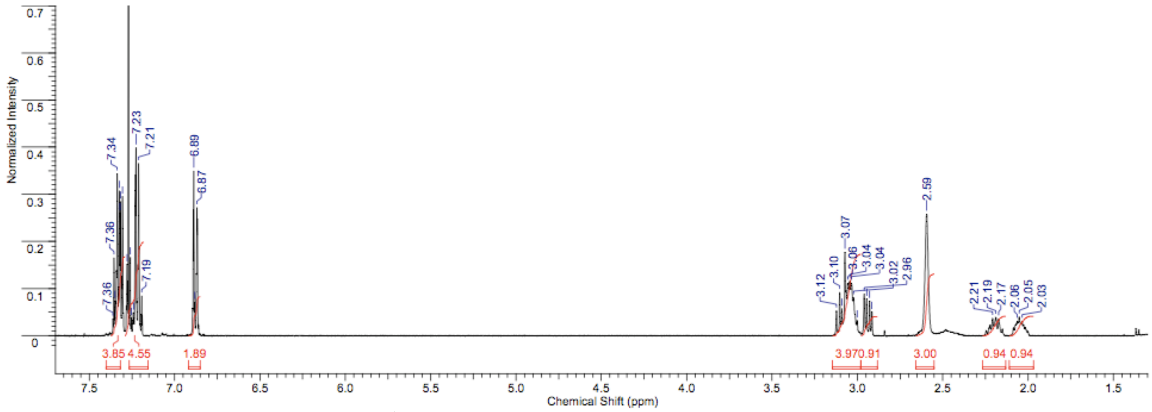

Figure S71. ^{1}H NMR Spectrum of **3e**·TFA (400 MHz, $CDCl_3$)

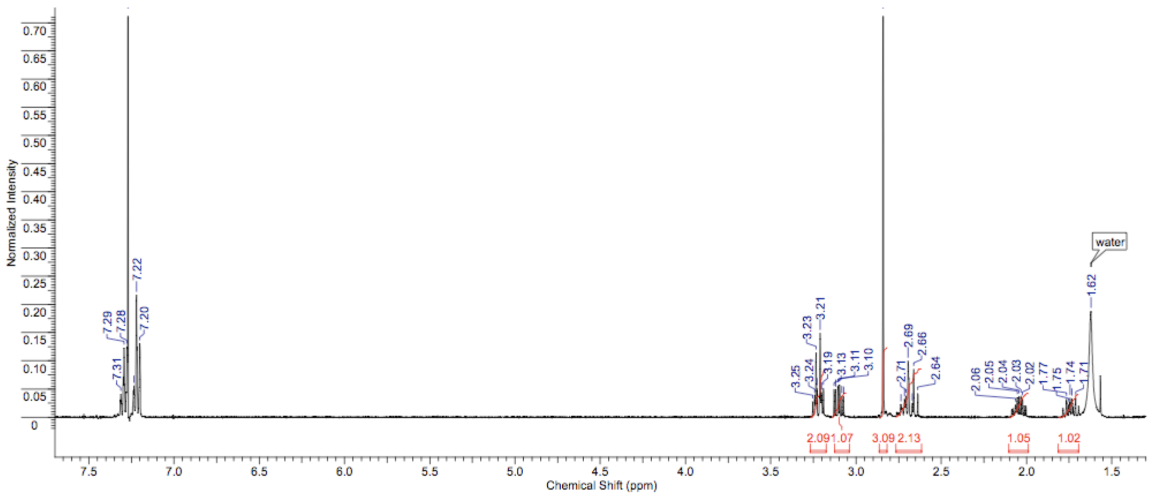

Figure S72. ^{1}H NMR Spectrum of **18e** (400 MHz, $CDCl_3$). HRMS calc'd $[M]^+$ ($C_{12}H_{15}NO$): 189.1154. Found: (EI) 181.1156.

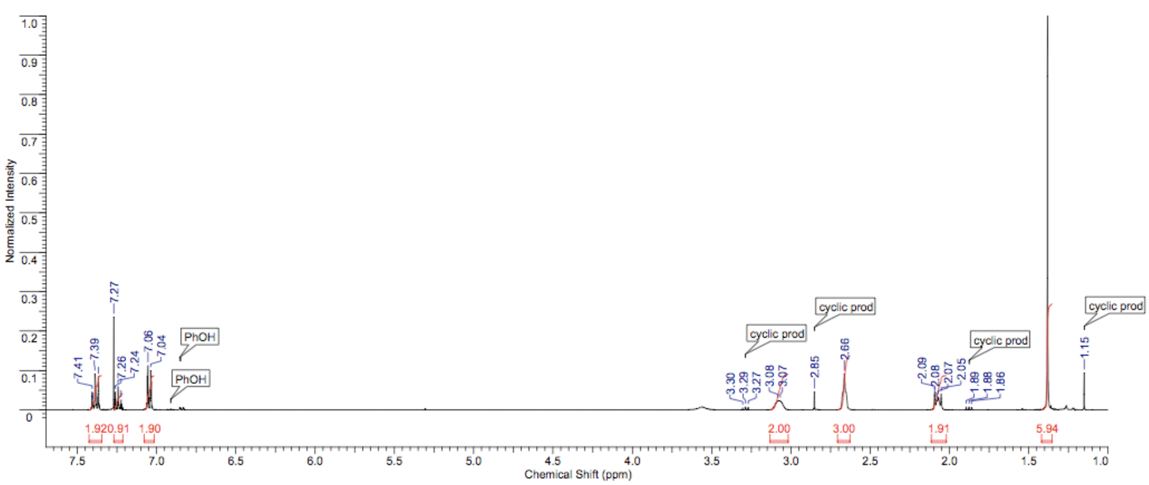

Figure S73. ^{1}H NMR Spectrum of **3f**·TFA (400 MHz, $CDCl_3$)

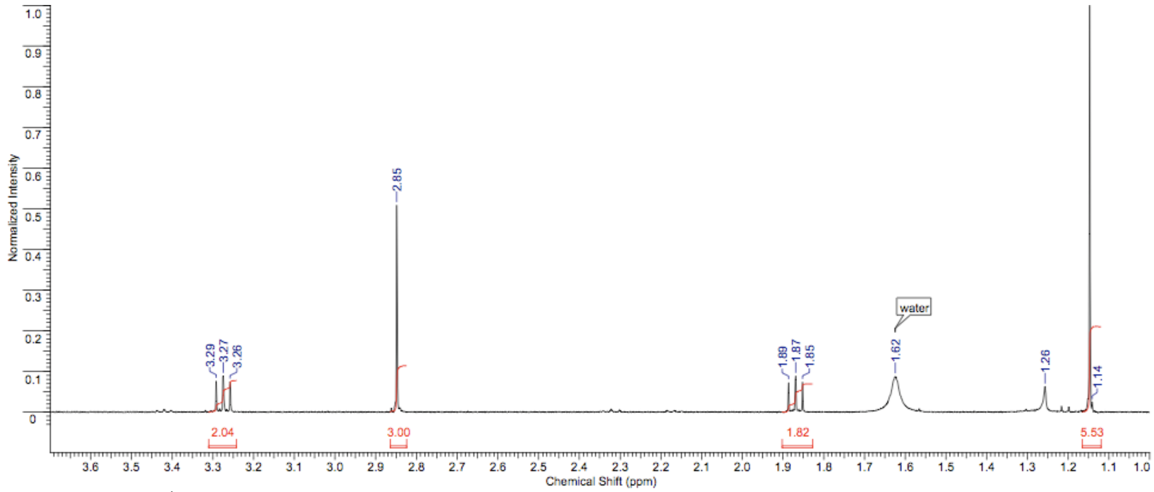

Figure S74. [1]H NMR Spectrum of **18f** (400 MHz, $CDCl_3$). HRMS calc'd $[M+H]^+$ ($C_7H_{14}NO$): 128.1070. Found: (EI) 128.1079.

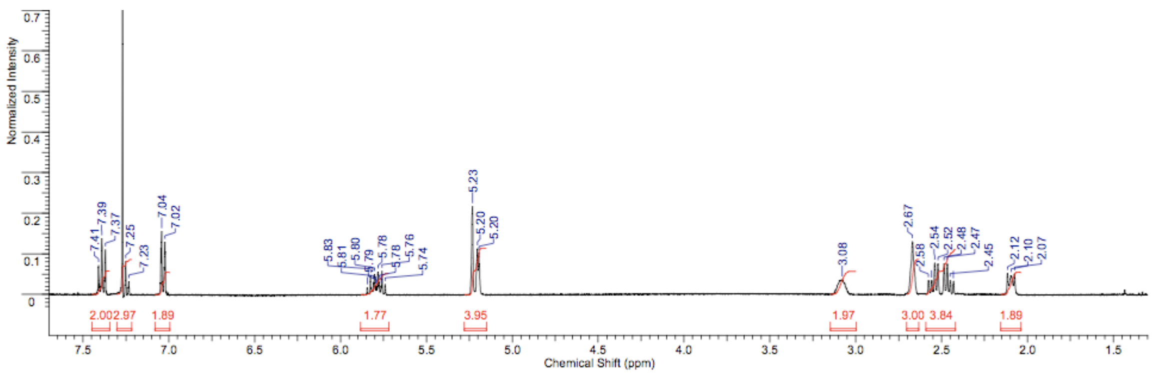

Figure S75. [1]H NMR Spectrum of **3g**·TFA (400 MHz, $CDCl_3$)

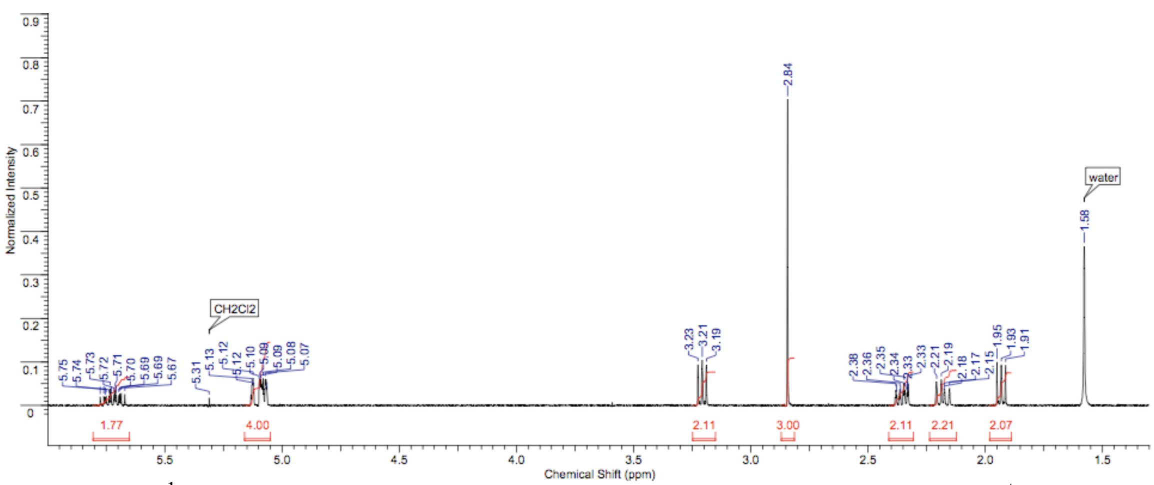

Figure S76. [1]H NMR Spectrum of **18g** (400 MHz, $CDCl_3$). HRMS calc'd $[M]^+$ ($C_{11}H_{17}NO$): 179.1310. Found: (EI) 179.1308.

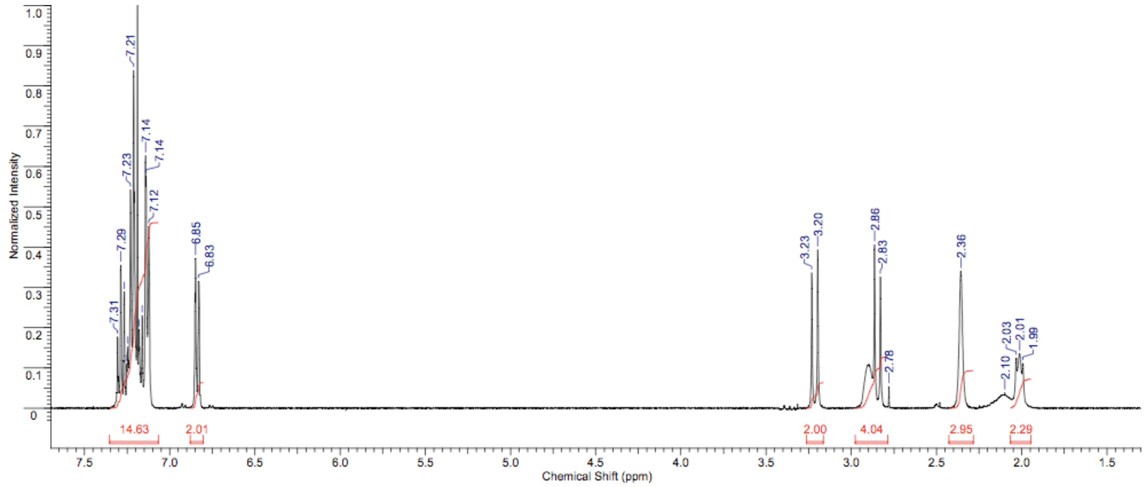

Figure S77. ^{1}H NMR Spectrum of **3h**·TFA (400 MHz, $CDCl_3$)

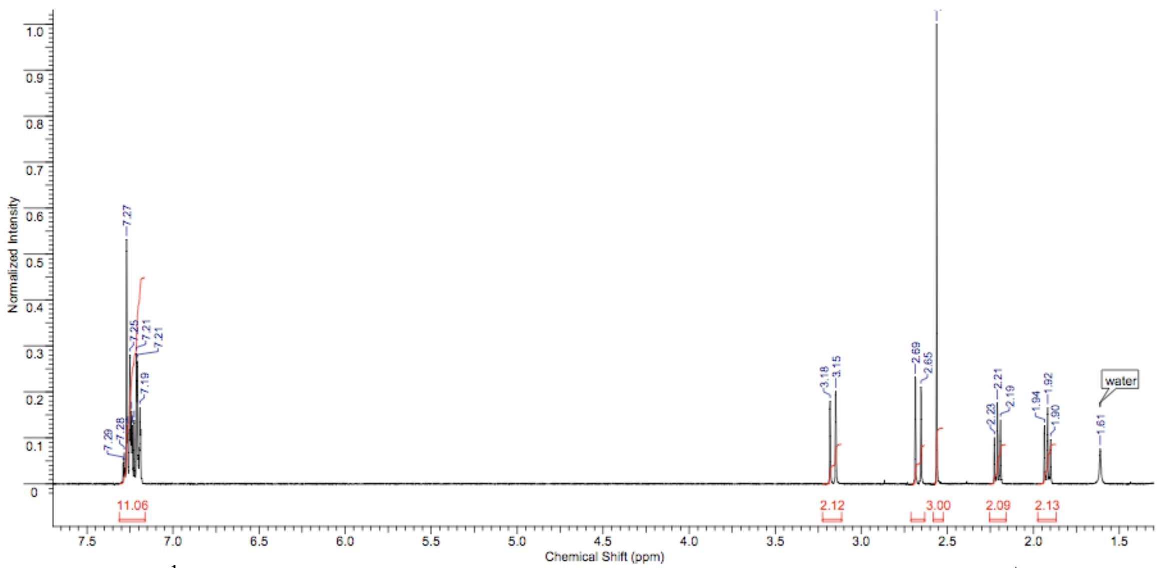

Figure S78. ^{1}H NMR Spectrum of **18h** (400 MHz, $CDCl_3$). HRMS calc'd $[M]^+$ ($C_{19}H_{21}NO$): 279.1623. Found: (EI) 279.1623.

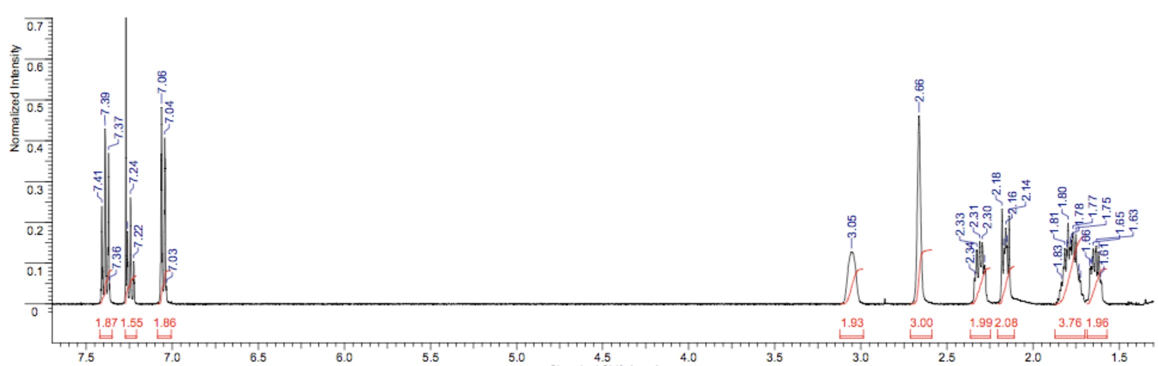

Figure S79. ^{1}H NMR Spectrum of **3i**·TFA (400 MHz, $CDCl_3$)

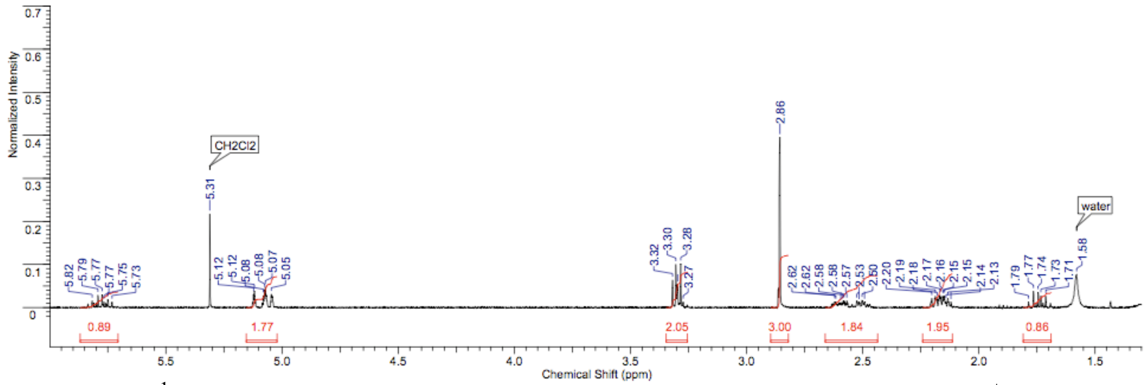

Figure S80. ^{1}H NMR Spectrum of **18i** (400 MHz, $CDCl_3$). HRMS calc'd $[M]^+$ ($C_9H_{15}NO$): 153.1154. Found: (EI) 153.1156.

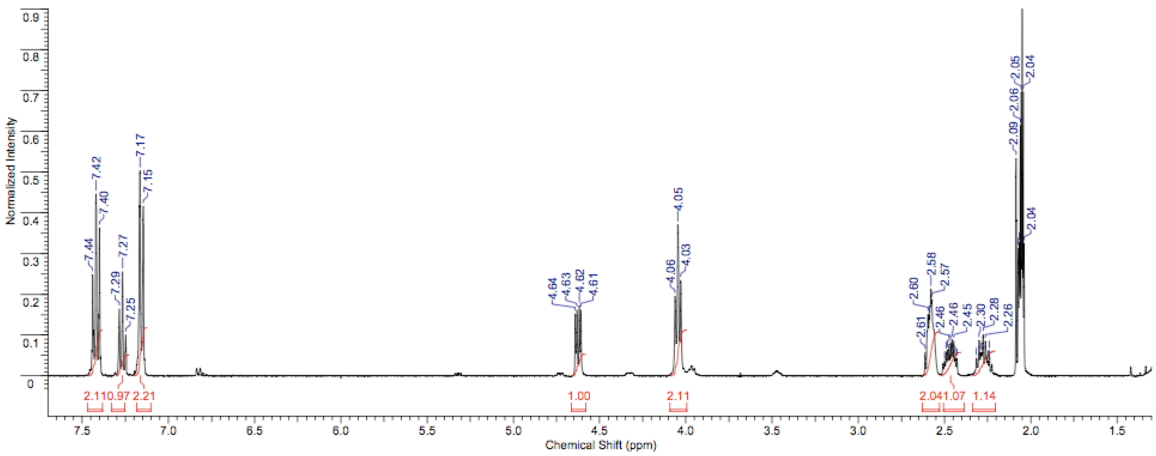

Figure S81. ^{1}H NMR Spectrum of **3j**·TFA (400 MHz, Acetone-d_6)

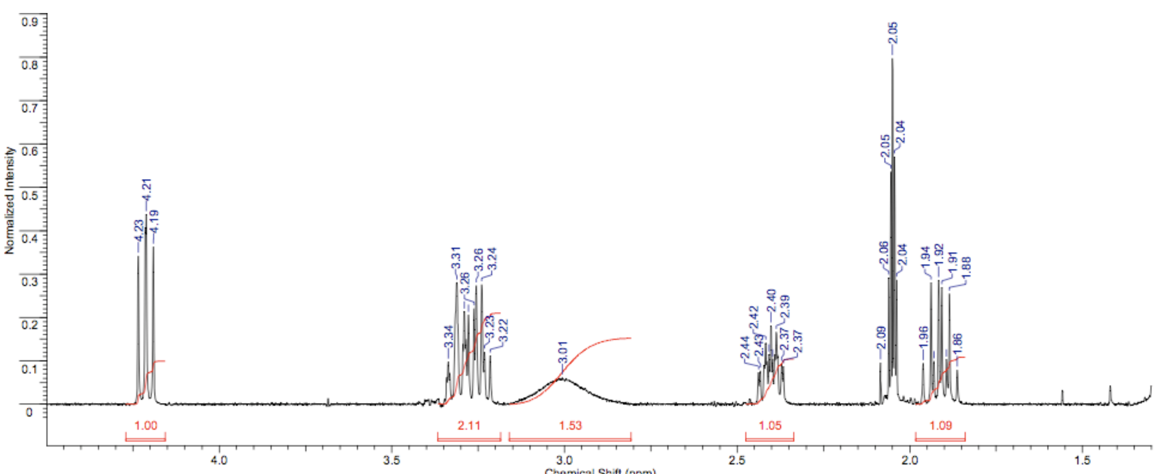

Figure S82. ^{1}H NMR Spectrum of **18j** (400 MHz, Acetone-d_6). HRMS calc'd $[M]^+$ ($C_4H_7NO_2$): 101.0477. Found: (EI) 101.0479.

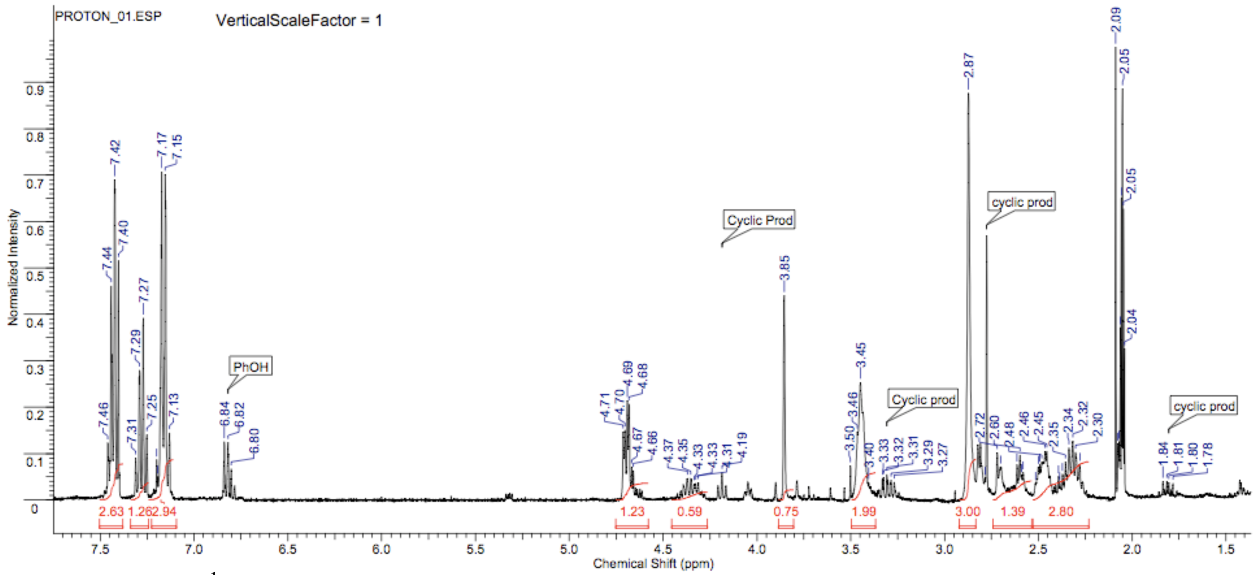

Figure S83. ^{1}H NMR Spectrum of **3k**·TFA (400 MHz, Acetone-d_6). Upon addition of H_2O immediately prior to freeze drying, some material cyclized to form **18k** and PhOH.

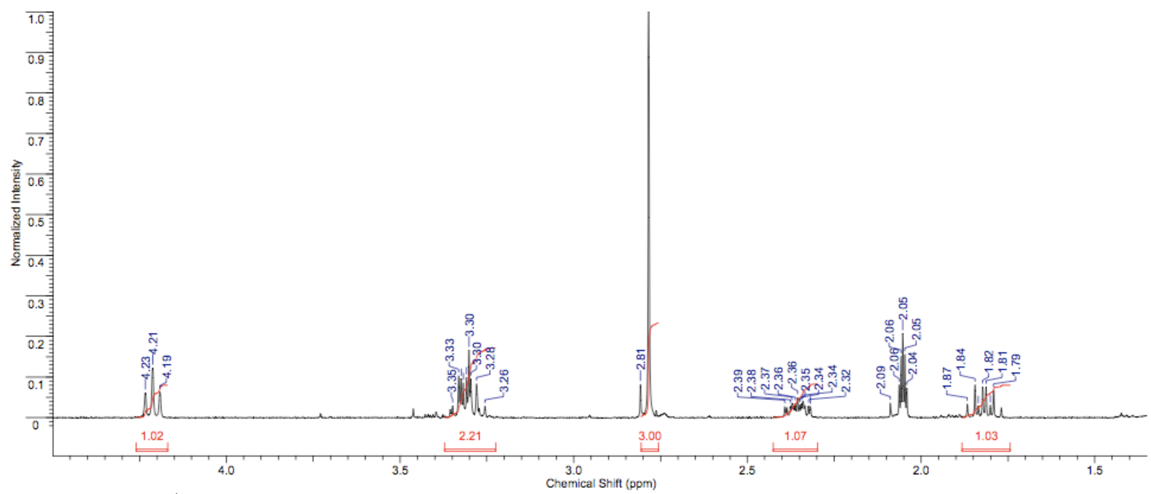

Figure S84. ^{1}H NMR Spectrum of **18k** (400 MHz, Acetone-d_6). HRMS calc'd $[M]^+$ ($C_5H_9NO_2$): 115.0633. Found: (EI) 115.0633.

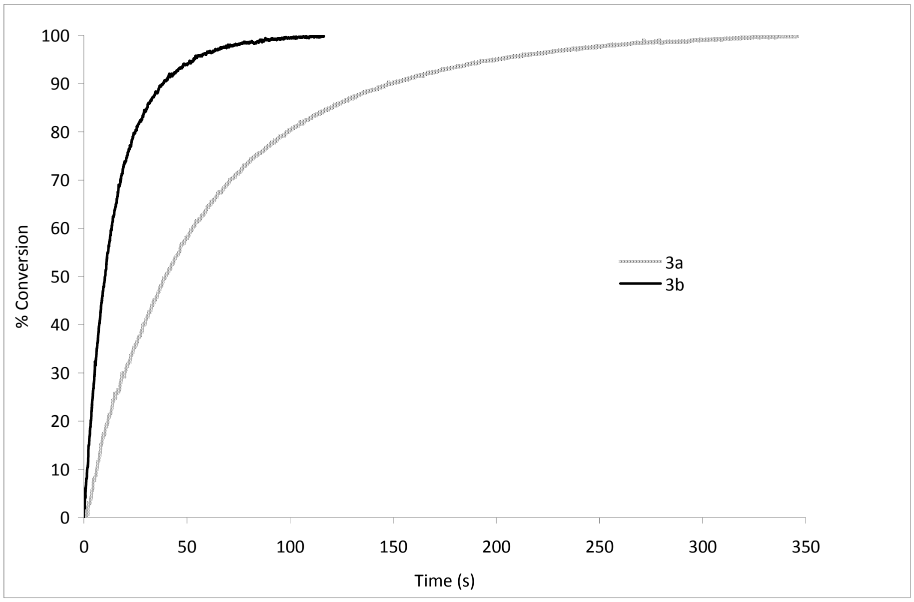

Figure S85. Cyclization kinetics for compounds **3a** and **3b**.

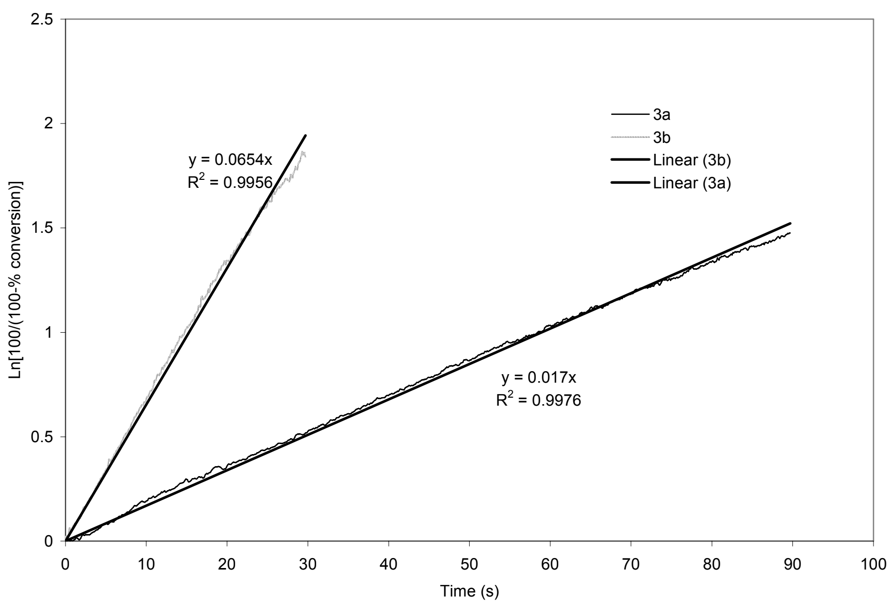

Figure 86. Determination of first order rate constant by $\ln[A]_0/[A]$ vs t graph for compounds **3a** and **3b**.

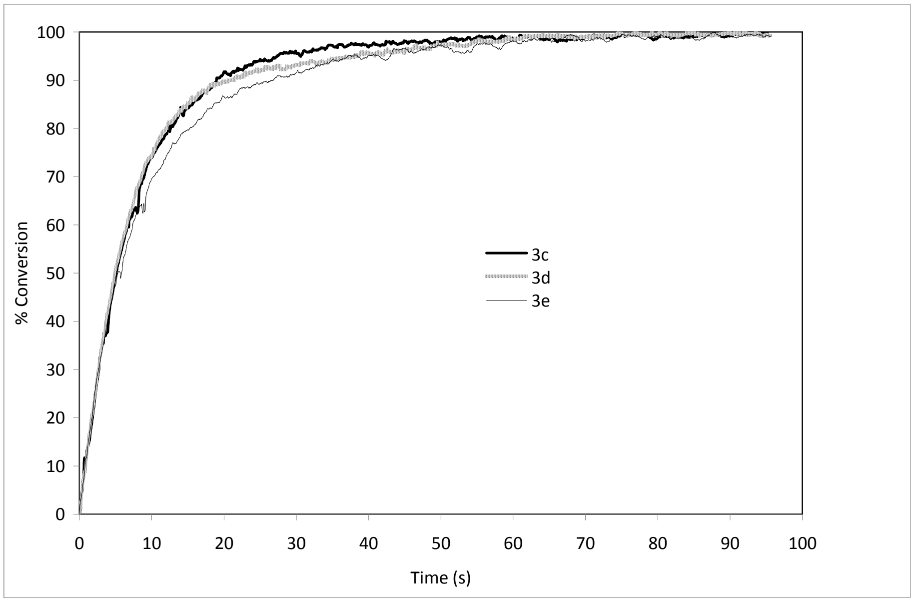

Figure S87. Cyclization kinetics for compounds **3c**, **3d**, and **3e**.

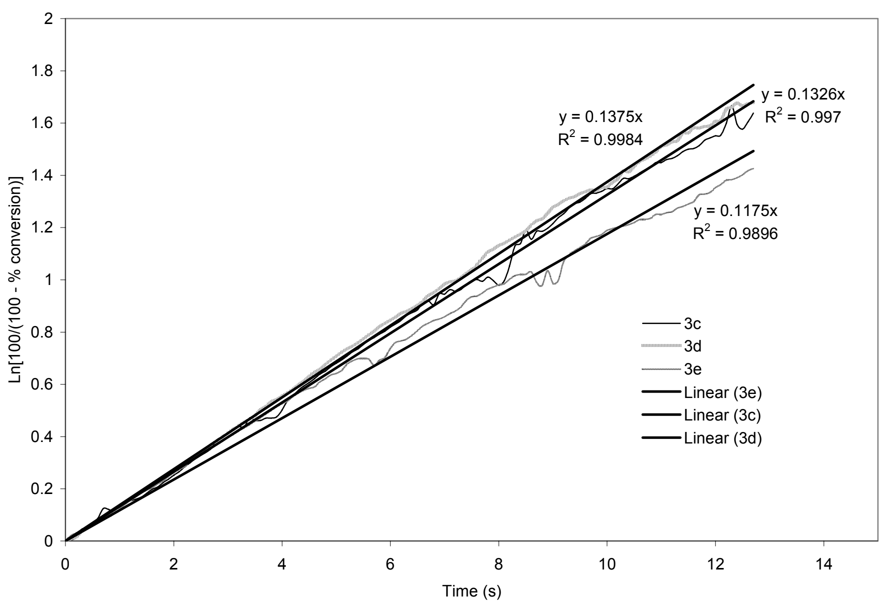

Figure 88. Determination of first order rate constant by $\ln[A]_0/[A]$ vs t graph for compounds **3c**, **3d**, and **3e**.

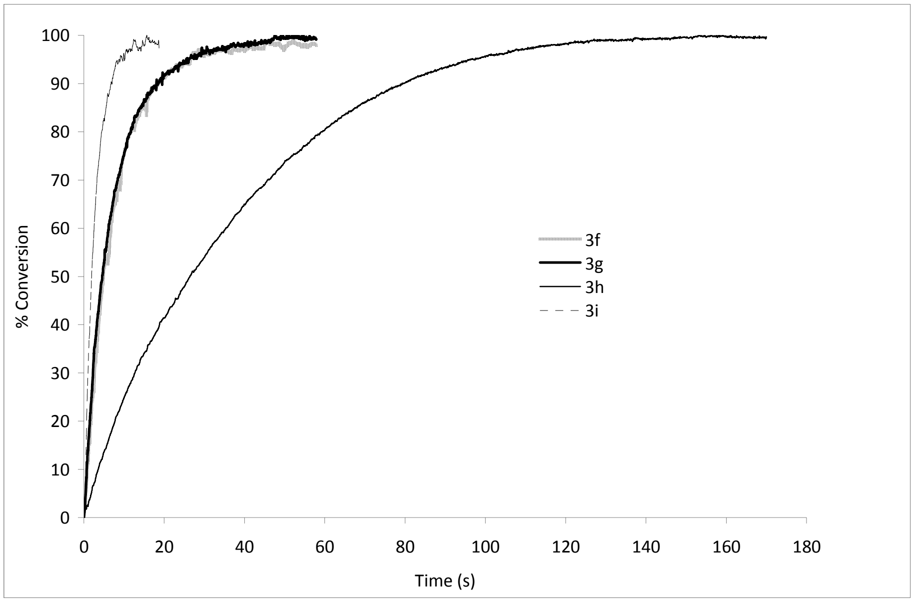

Figure S89. Cyclization kinetics for compounds **3f**, **3g**, **3h**, and **3i**.

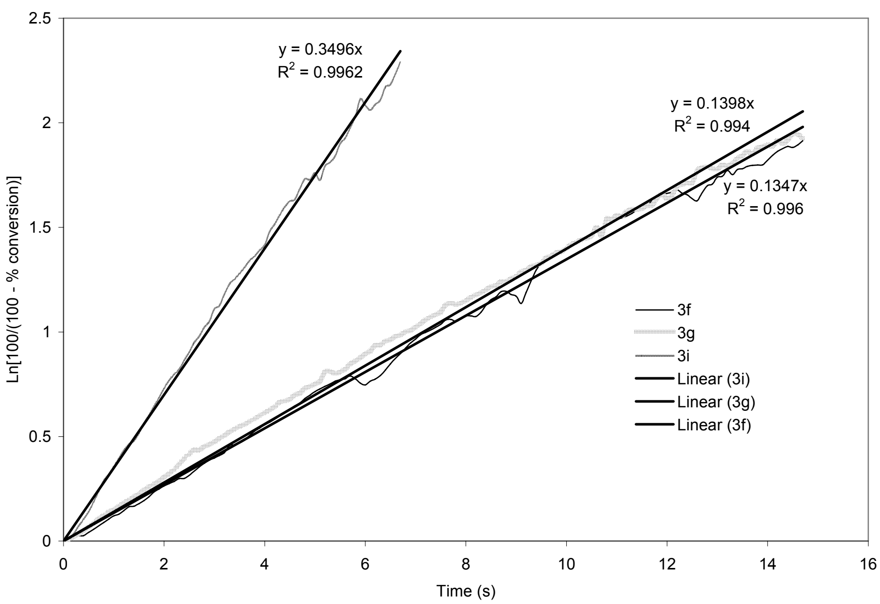

Figure 90. Determination of first order rate constant by $\ln[A]_0/[A]$ vs t graph for compounds **3f**, **3g**, and **3i**.

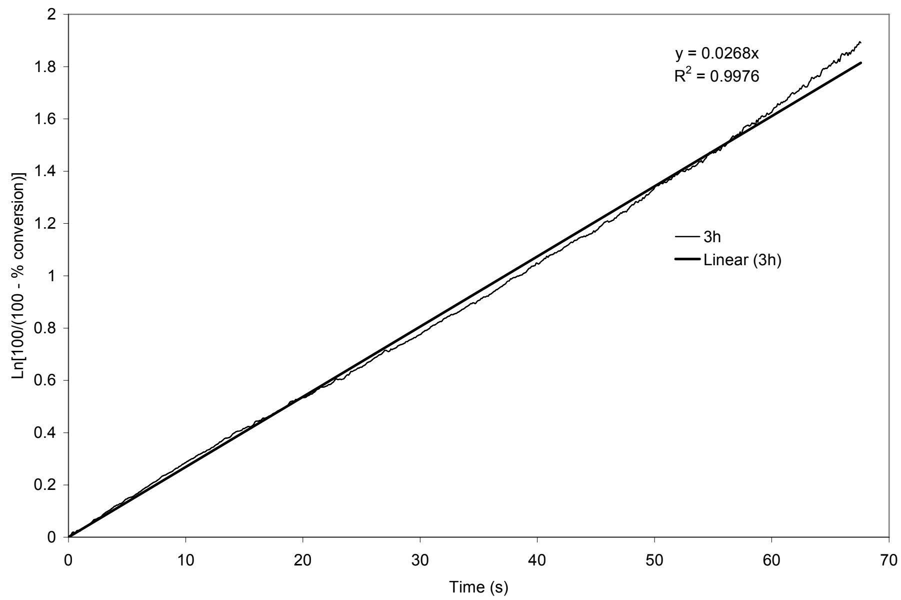

Figure 91. Determination of first order rate constant by $\ln[A]_0/[A]$ vs t graph for compound **3h**.

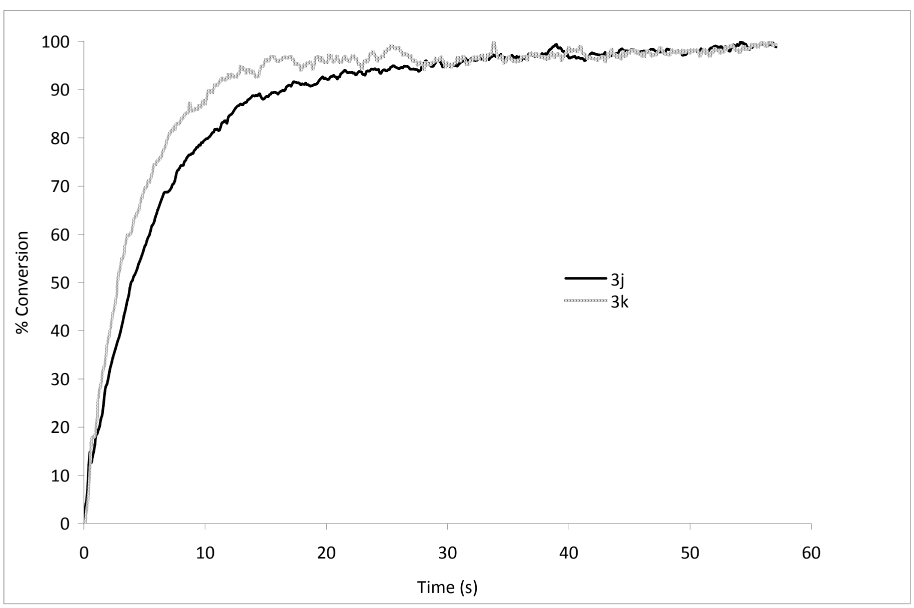

Figure S92. Cyclization kinetics for compounds **3j** and **3k**.

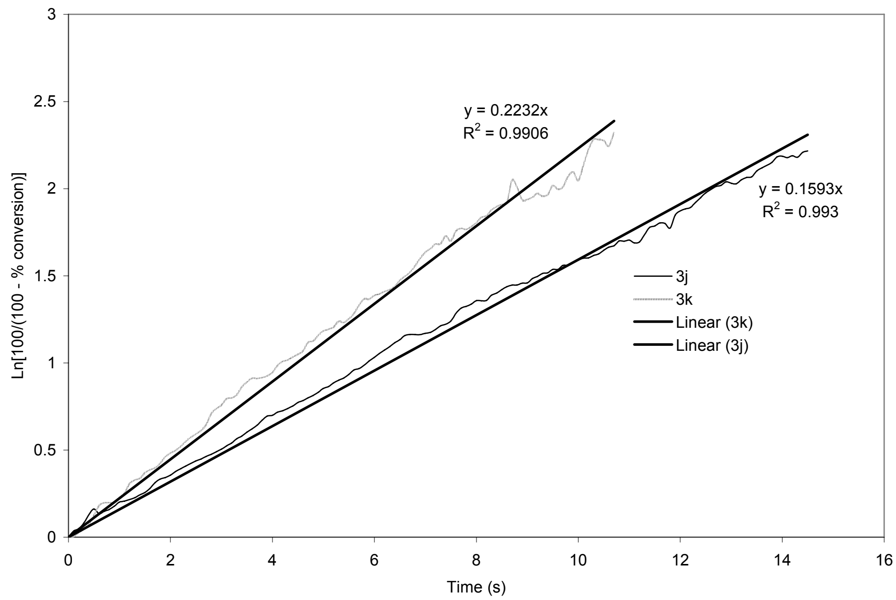

Figure 93. Determination of first order rate constant by ln$[A]_0/[A]$ vs t graph for compounds **3j** and **3k.**

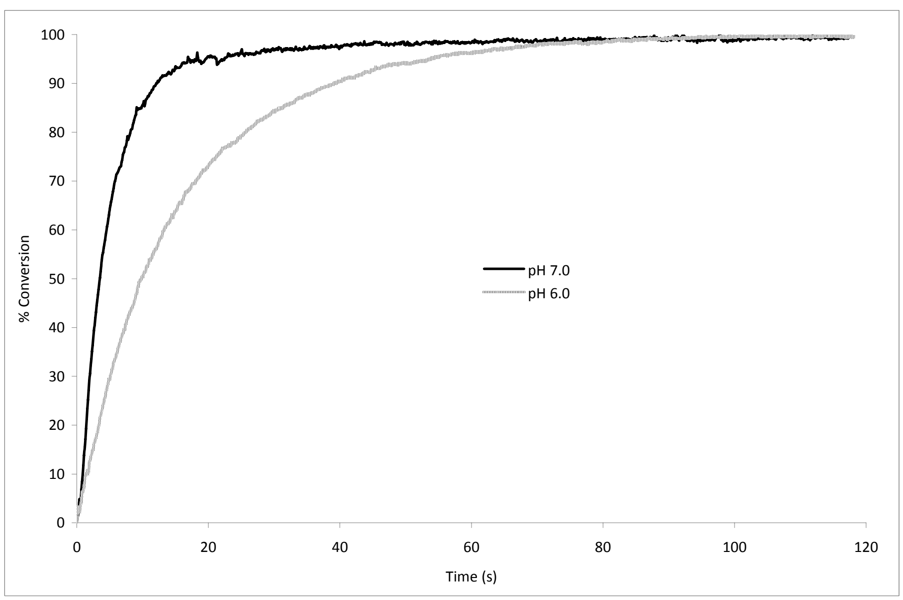

Figure S94. Cyclization rate of **3i** at pH 7.0 and 6.0.

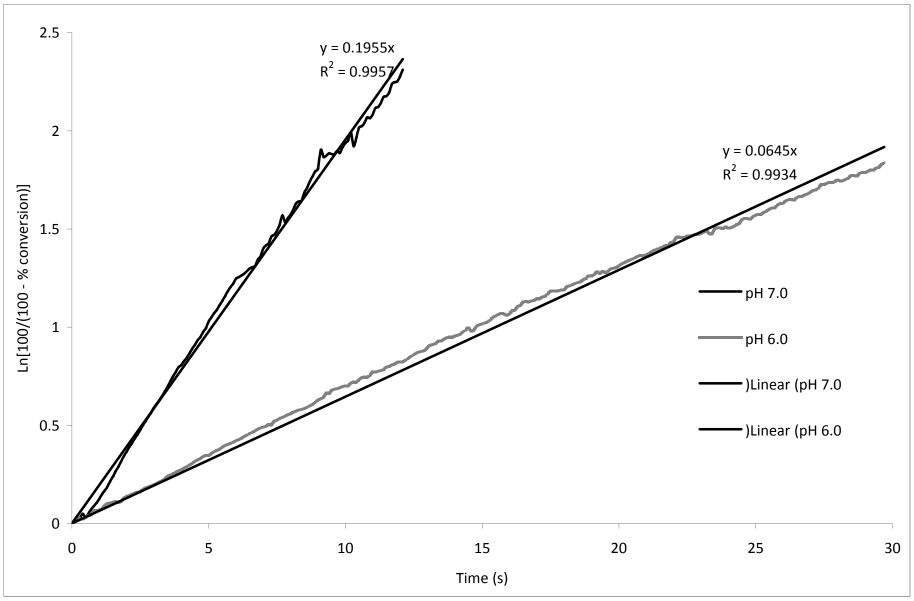

Figure 95. Determination of first order rate constant by $\ln[A]_0/[A]$ vs t graph for compounds **3i** at pH 7.0 and 6.0.

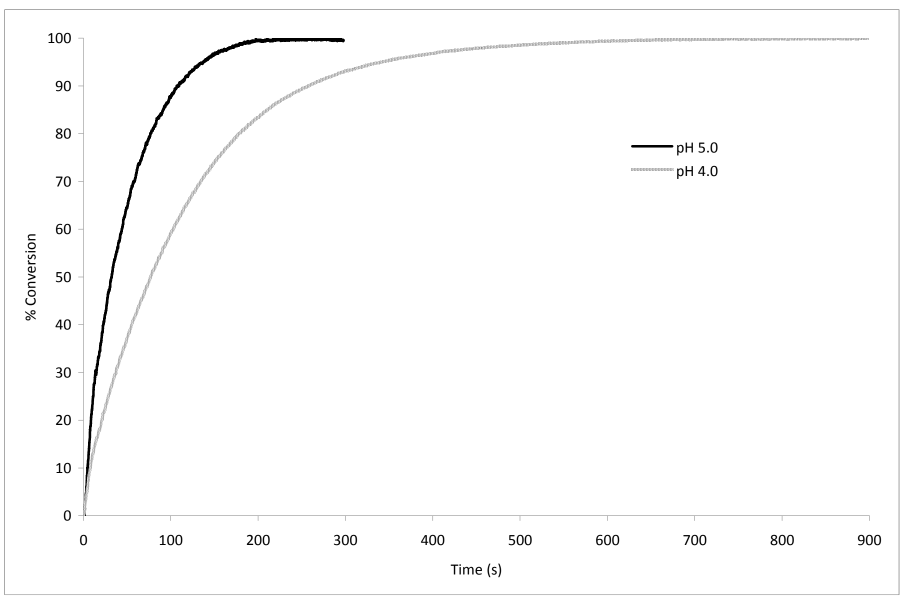

Figure 96. Cyclization of **3i** and pH 5.0 and 4.0.

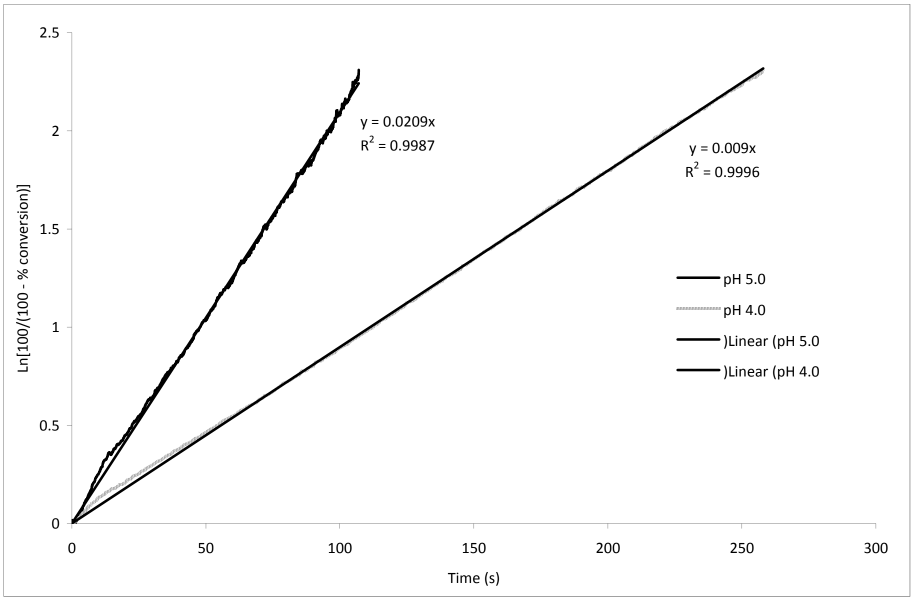

Figure 97. Determination of first order rate constant by $\ln[A]_0/[A]$ vs t graph for compounds **3i** at pH 5.0 and 4.0.

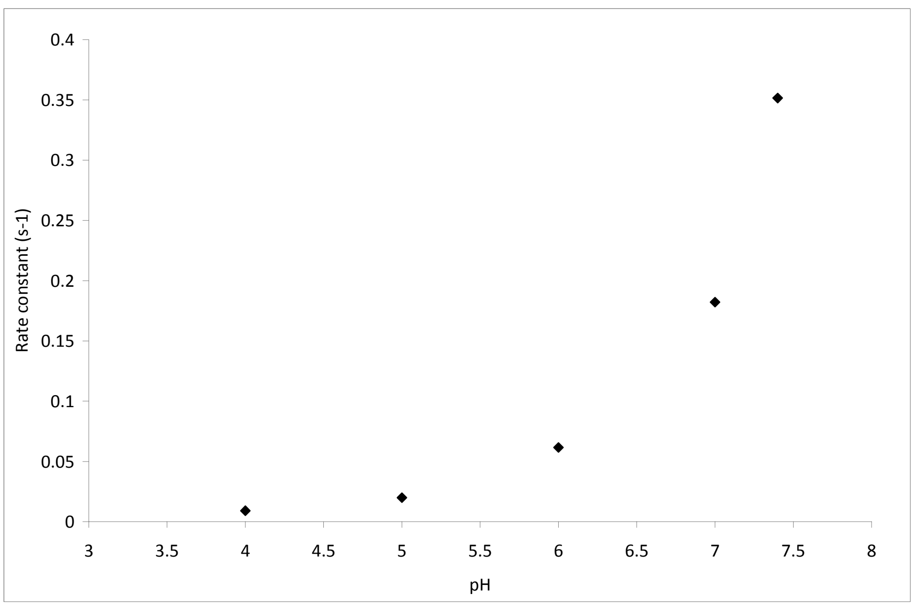

Figure S98. pH dependence of the cyclization rate of **3i.**