

Supporting Information

Mn(III)-Driven Oxidative Cyclisation via C(sp³)-H Functionalisation: An Efficient Strategy for Benzo-fused Aza-Heterocycle Synthesis

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1. General information.

All commercial reagents and solvents were used without purification. TLC analyses were carried out on pre-coated silica gel plates with F254 indicator. Visualization was accomplished by UV light (254 nm). Purification of reaction products was carried out by flash chromatography using E. Merck silica gel 60 (230-400 mesh). ¹H NMR and ¹³C NMR spectra were recorded at 400 MHz and 100 MHz respectively, on a Jeol ECS 400 MHz NMR spectrometer. Chemical shift values are reported in ppm relative to Me₄Si as the internal reference. Mass spectra (MS-EI, 70 eV) were conducted on GC-MS Shimadzu QP2010. High resolution mass spectra were measured on Jeol HX110/110A using electrospray ionization technique.

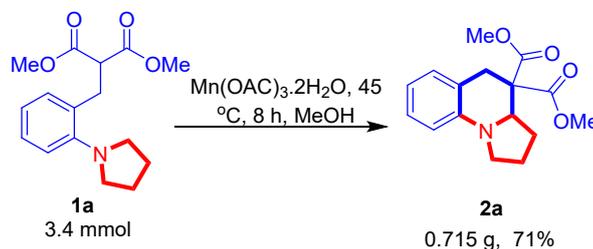
2. Preparation of starting materials.

All starting material were prepared in accordance with literature methods.¹

3. General procedure for the synthesis of benzo-fused aza-heterocycles.

A mixture of 2-(*o*-dialkylamino)benzyl malonates **1** (0.34 mmol), Mn(OAc)₃·2H₂O (50 mol%, 0.17 mmol) was stirred at 45 °C for 5-9 h in MeOH (3 mL). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water (5 mL), the aqueous layer was extracted with EtOAc (2 x 10 mL). The organic content was concentrated under reduced pressure to get the crude product which was further purified through silica gel (60-120 mesh) column chromatography using EtOAc/hexane (5:95, v/v) as an eluent to afford the analytically pure product **2**.

4. Gram scale synthesis of **2a**.

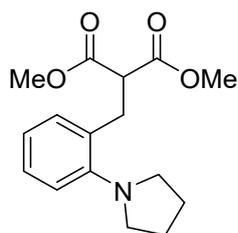


A mixture of dimethyl 2-(2-(pyrrolidin-1-yl)benzyl)malonate (**1a**, 3.4 mmol) and Mn(OAc)₃·2H₂O (50 mol%, 1.7 mmol) was stirred in methanol (8 mL) at 45 °C for 8 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (60-120 mesh) using ethyl acetate/hexane (5:95, v/v) as the eluent. The desired product **2a** was obtained as an analytically pure pale-yellow viscous oil in 71% yield.

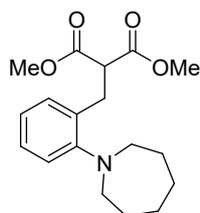
5. References.

(1). (a) M. Sandip, C. Zhang, M. D. Konieczynska and D. Seidel, *Org. Lett.*, 2009, **11**, 129; (b) K. L. Ivanov, M. Ya. Melnikov and E. M. Budynina, *Synthesis*, 2021, **53**, 1285; (c) K. L. Ivanov, E. V. Villemson, G. V. Latyshev, S. Bezzubov, A. Majouga, M. Ya. Melnikov and E. M. Budynina, *J. Org. Chem.*, 2017, **82**, 9537.

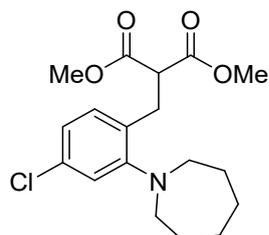
6. Characterization data of benzo-fused aza-heterocycles.



Dimethyl 2-(2-(pyrrolidin-1-yl)benzyl)malonate (1a) Yield: 88% as a colourless oil; $R_f = 0.41$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max}(\text{cm})^{-1} = 2915, 1754, 1735, 1588, 1491$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.16-7.07 (m, 2H, ArH), 6.99-6.97 (m, 1H, ArH), 6.86-6.82 (m, 1H, ArH), 4.05 (t, $J = 7.4$ Hz, 1H), 3.64 (s, 6H, CO_2Me), 3.31 (d, $J = 7.6$ Hz, 2H), 3.14 (t, $J = 6.4$ Hz, 4H), 1.94 - 1.90 (m, 4H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.90, 149.31, 131.46, 129.16, 127.71, 121.22, 117.54, 52.48, 51.55, 49.97, 33.54, 25.22 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 292.1543, found: 292.1535.

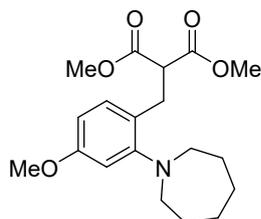


Dimethyl 2-(2-(azepan-1-yl)benzyl)malonate (1b) Yield: 80% as colourless oil; $R_f = 0.47$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max}(\text{cm})^{-1} = 2944, 1753, 1730, 1594, 1491, 1466$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.19-7.10 (m, 3H, ArH), 6.97-6.93 (m, 1H, ArH), 4.17 (t, $J = 7.6$ Hz, 1H), 3.66 (s, 6H, CO_2Me), 3.26 (d, $J = 7.8$ Hz, 2H), 3.04 (t, $J = 5.5$ Hz, 4H), 1.77-1.70 (m, 8H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ = 169.34, 155.04, 132.71, 130.38, 127.64, 123.35, 122.38, 57.07, 51.85, 51.33, 31.62, 29.31, 26.48 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 320.1856, found: 320.1843.

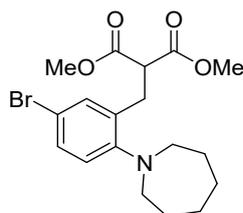


Dimethyl 2-(2-(azepan-1-yl)-4-chlorobenzyl)malonate (1c) Yield: 85% as a yellow solid; mp: 66-67 °C, $R_f = 0.42$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max}(\text{cm})^{-1} = 2875, 1736, 1587, 1472, 1454$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.09-7.04 (m, 2H, ArH), 6.93 (dd, $J_1 = 8.2, J_2 = 2.2$ Hz, 1H, ArH), 4.11 (t, $J = 7.6$ Hz, 1H), 3.68 (s, 6H, CO_2Me), 3.21 (d, $J = 7.6$ Hz, 2H), 3.03 (t, $J = 5.4$ Hz, 4H), 1.77-1.69 (m, 8H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ = 169.51, 156.25, 132.96, 131.75, 131.31, 123.50, 123.05, 57.10,

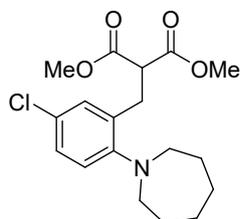
52.34, 51.27, 31.40, 29.34, 26.75 ppm; HRMS (ESI) m/z : calcd. for $C_{18}H_{24}ClNO_4$ $[M + H^+]$: 354.1467, found: 354.1465.



Dimethyl 2-(2-(azepan-1-yl)-4-methoxybenzyl)malonate (1d) Yield: 65% as a colourless oil; R_f = 0.37 (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{max} (cm) $^{-1}$ = 2912, 1754, 1730, 1577, 1433; 1H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.4 Hz, 1H, ArH), 6.68 (m, 1H, ArH), 6.51-6.49 (m, 1H, ArH), 4.15 (t, J = 7.8 Hz, 1H), 3.75 (s, 3H, OMe), 3.67 (s, 6H, CO_2Me), 3.19 (d, J = 8 Hz, 2H), 3.03 (t, J = 5.4 Hz, 4H), 1.77 - 1.70 (m, 8H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3$) δ 169.89, 159.40, 156.50, 131.47, 125.07, 109.12, 108.07, 57.36, 55.08, 52.35, 52.14, 31.53, 29.65, 26.91 ppm; HRMS (ESI) m/z : calcd. for $C_{19}H_{27}NO_5$ $[M + H^+]$: 350.1962, found: 350.1960.

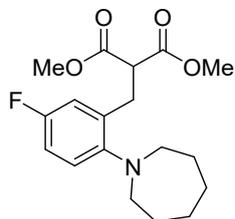


Dimethyl 2-(2-(azepan-1-yl)-5-bromobenzyl)malonate (1e) Yield: 75% as a yellow oil; R_f = 0.39 (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{max} (cm) $^{-1}$ = 2921, 1754, 1737, 1482, 1342; 1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 2H, ArH), 7.00 (d, J = 8.4 Hz, 1H, ArH), 4.11 (t, J = 7.4 Hz, 1H), 3.70 (s, 6H, CO_2Me), 3.21 (d, J = 7.6 Hz, 2H), 3.00 (t, J = 5.4 Hz, 4H), 1.76-1.68 (m, 8H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3$) δ 169.46, 154.38, 135.39, 133.39, 130.84, 124.50, 116.35, 57.23, 52.42, 51.43, 31.56, 29.45, 26.78 ppm; HRMS (ESI) m/z : calcd. for $C_{18}H_{24}BrNO_4$ $[M + H^+]$: 398.0961, $[M + 2 + H^+]$: 400.0941 found: 398.0960 (100%), 400.0930 (97%).

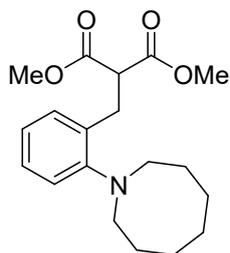


Dimethyl 2-(2-(azepan-1-yl)-5-chlorobenzyl)malonate (1f) Yield: 86% as a pale oil; R_f = 0.46 (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{max} (cm) $^{-1}$ = 2921, 1754, 1732, 1435, 1403; 1H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J_1 = 8.4, J_2 = 2.4 Hz, 1H, ArH), 7.15-7.04 (m, 2H, ArH), 4.11 (t, J = 7.6 Hz, 1H),

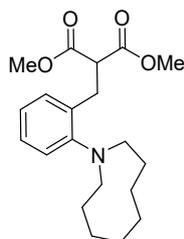
3.70 (s, 6H, CO₂Me), 3.21 (d, $J = 7.6$ Hz, 2H), 3.00 (t, $J = 5.8$ Hz, 4H), 1.77-1.69 (m, 8H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 169.45, 153.88, 134.98, 130.43, 128.53, 127.84, 124.08, 57.30, 52.39, 51.41, 31.58, 29.45, 26.75 ppm; HRMS (ESI) m/z : calcd. for C₁₈H₂₄ClNO₄ [M + H⁺]: 354.1467, found: 354.1450.



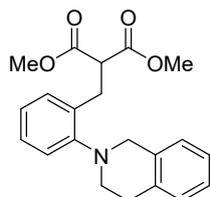
Dimethyl 2-(2-(azepan-1-yl)-5-fluorobenzyl)malonate (1g) Yield: 66% as a yellow oil; $R_f = 0.36$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2915, 1754, 1735, 1588, 1491; ¹H NMR (400 MHz, CDCl₃) δ 7.09 (dd, $J_1 = 8.6$, $J_2 = 5.4$ Hz, 1H, ArH), 6.89-6.82 (m, 2H, ArH), 4.11 (t, $J = 7.6$ Hz, 1H), 3.70 (s, 6H, CO₂Me), 3.23 (d, $J = 7.6$ Hz, 2H), 2.98 (t, $J = 5.8$ Hz, 4H), 1.76 - 1.70 (m, 8H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 169.22, 158.67 (d, $J_{C-F} = 241$ Hz), 151.27, 135.28, 124.13 (d, $J_{C-F} = 8.6$ Hz), 116.76 (d, $J_{C-F} = 22$ Hz), 114.09 (d, $J_{C-F} = 21.9$ Hz), , 57.47, 52.06, 51.44, 31.38, 29.39, 26.53 ppm; HRMS (ESI) m/z : calcd. for C₁₈H₂₄FNO₄ [M + H⁺]: 338.1762, found: 338.1755.



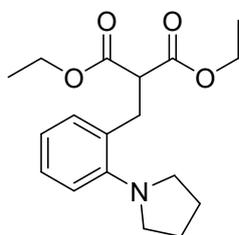
Dimethyl 2-(2-(azocan-1-yl)benzyl)malonate (1h) Yield: 89% as a colourless oil; $R_f = 0.47$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2714, 1754, 1734, 1433, 1343, ¹H NMR (400 MHz, CDCl₃) δ 7.22-7.17 (m, 2H, ArH), 7.12 -7.10 (m, 1H, ArH), 7.00-6.96 (m, 1H, ArH), 3.98 (t, $J = 8.0$ Hz, 1H), 3.68 (s, 6H, CO₂Me), 3.34 (d, $J = 8$ Hz, 2H), 3.03 (m, 4H), 1.69 (m, 10H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 169.59, 155.97, 133.74, 130.25, 128.09, 124.52, 124.02, 56.97, 52.31, 31.26, 28.43, 27.43, 25.07 ppm; HRMS (ESI) m/z : calcd. for C₁₉H₂₇NO₄ [M + H⁺]: 334.2013, found: 334.2010.



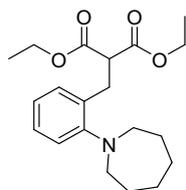
Dimethyl 2-(2-(azonan-1-yl)benzyl)malonate (1i) Yield: 60% as a colourless oil; $R_f = 0.47$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2758, 2372, 1749, 1735, 1435, 1280$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.30-7.26 (m, 1H, ArH), 7.24-7.20 (m, 1H, ArH), 7.10 (dd, $J_1 = 7.6, J_2 = 1.6$ Hz, 1H, ArH), 7.03-7.00 (m, 1H, ArH), 3.85 (t, $J = 7.8$ Hz, 1H), 3.69 (s, 6H, CO_2Me), 3.39 (d, $J = 7.6$ Hz, 2H), 3.00 (t, $J = 5.8$ Hz, 4H), 1.74-1.58 (m, 12H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.57, 155.39, 134.76, 130.02, 128.17, 125.72, 124.47, 55.86, 52.39, 30.96, 27.46, 25.55, 23.36 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 348.2169, found: 348.2155.



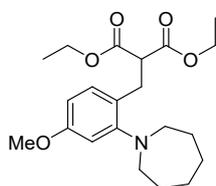
Dimethyl 2-(2-(3,4-dihydroisoquinolin-2(1H)-yl)benzyl)malonate (1j) Yield: 80% as a colourless oil; $R_f = 0.39$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2888, 2752, 1745, 1730, 1430$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.25-7.18 (m, 3H, ArH), 7.16 (d, $J = 5.5$ Hz, 3H, ArH), 7.08-7.03 (m, 2H, ArH), 4.10 (s, 2H), 4.03 (t, $J = 7.4$ Hz, 1H), 3.57 (s, 6H, CO_2Me), 3.30 (d, $J = 7.2$ Hz, 2H), 3.18 (t, $J = 5.8$ Hz, 2H), 3.02 (t, $J = 5.0$ Hz, 2H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.58, 151.73, 135.15, 134.25, 133.54, 130.66, 128.78, 127.97, 126.26, 126.01, 125.52, 124.43, 121.14, 54.76, 52.20, 51.64, 51.31, 31.42, 29.70 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 354.1700, found: 354.1701.



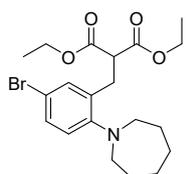
Diethyl 2-(2-(azepan-1-yl)benzyl)malonate (1k) Yield: 66% as a pale oil; $R_f = 0.41$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2995, 2834, 1749, 1729, 1635, 1430$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.15 - 7.09 (m, 2H, ArH), 6.98 (d, $J = 8.2$ Hz, 1H, ArH), 6.84 (t, $J = 7.3$ Hz, 1H, ArH), 4.15-4.07 (m, 4H), 4.02 (t, $J = 7.8$ Hz, 1H), 3.30 (d, $J = 7.8$ Hz, 2H), 3.15 (t, $J = 6.2$ Hz, 4H), 1.96 - 1.89 (m, 4H), 1.17 (t, $J = 7.4$ Hz, 6H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.52, 149.32, 131.56, 129.30, 127.60, 121.12, 117.44, 61.27, 51.48, 50.48, 33.45, 25.19, 14.07 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{18}\text{H}_{25}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 320.1856, found: 320.1844.



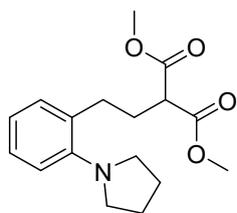
Diethyl 2-(2-(azepan-1-yl)benzyl)malonate (1l) Yield: 57% as a colourless oil; $R_f = 0.46$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm) $^{-1} = 2950, 2350, 1750, 1733, 1433$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.19-7.11 (m, 3H, ArH), 6.96-6.92 (m, 1H, ArH), 4.18- 4.10 (m, 5H), 3.25 (d, $J = 7.2$ Hz, 2H), 3.04 (t, $J = 5.4$ Hz, 4H), 1.78 -1.70 (m, 8H), 1.18 (t, $J = 7.0$ Hz, 6H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.41, 155.41, 133.17, 130.83, 127.81, 123.53, 122.60, 61.04, 57.31, 51.81, 31.94, 29.60, 26.82, 13.93 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{20}\text{H}_{29}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 348.2169, found: 348.2160.



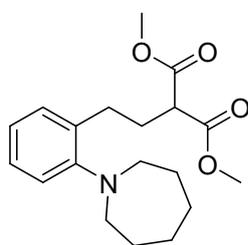
Diethyl 2-(2-(azepan-1-yl)-5-methoxybenzyl)malonate (1m) Yield: 60% as a yellow oil; $R_f = 0.41$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm) $^{-1} = 2950, 1740, 1725, 1580, 1450$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.04 (d, $J = 8.4$ Hz, 1H, ArH), 6.68 (d, $J = 2.8$ Hz, 1H, ArH), 6.50 (dd, $J_1 = 8.6, J_2 = 2.6$ Hz, 1H, ArH), 4.22 (t, $J = 7.0$ Hz, 1H), 4.16-4.10 (m, 4H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.75 (s, 3H, OCH_3), 3.18 (d, $J = 7.6$ Hz, 2H), 3.04 (t, $J = 5.6$ Hz, 4H), 1.78 - 1.69 (m, 8H), 1.20 (t, $J = 7.0$ Hz, 6H, $\text{CO}_2\text{CH}_2\text{CH}_3$) $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.46, 159.16, 156.39, 131.43, 125.12, 108.91, 107.78, 61.02, 57.15, 55.04, 51.87, 31.35, 29.47, 26.77, 13.93 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{21}\text{H}_{31}\text{NO}_5$ [$\text{M} + \text{H}^+$]: 378.2275, found: 378.2268.



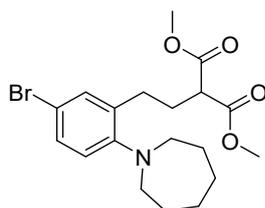
Diethyl 2-(2-(azepan-1-yl)-5-bromobenzyl)malonate(1n) Yield: 61% as a yellow oil; $R_f = 0.48$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm) $^{-1} = 2931, 1738, 1730, 1692, 1483$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.29 - 7.25 (m, 2H, ArH), 6.99 (d, $J = 8.4$ Hz, 1H, ArH), 4.20-4.13 (m, 4H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.09 (t, $J = 7.6$ Hz, 1H), 3.20 (d, $J = 8$ Hz, 2H), 3.01 (t, $J = 5.6$ Hz, 4H), 1.77-1.69 (m, 8H), 1.21 (t, $J = 7.2$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.03, 154.33, 135.40, 133.46, 130.64, 124.31, 116.14, 61.22, 57.12, 51.39, 31.57, 29.40, 26.71, 13.92 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{20}\text{H}_{28}\text{BrNO}_4$ [$\text{M} + \text{H}^+$]: 426.1274, [$\text{M} + 2 + \text{H}^+$]: 428.1254 found: 426.1271 (100%), 428.1250 (97%).



Dimethyl 2-(2-(pyrrolidin-1-yl)phenethyl)malonate (3a) Yield: 70% as a colourless oil; $R_f = 0.37$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max}(\text{cm})^{-1} = 2947, 1748, 1732, 1558, 1433$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.15-7.11 (m, 2H, ArH), 6.97 (d, $J = 8$ Hz, 1H, ArH), 6.89 (t, $J = 7.6$ Hz, 1H, ArH), 3.73 (s, 6H, CO_2Me), 3.38 (t, $J = 7.4$ Hz, 1H), 3.11 (t, $J = 6.4$ Hz, 4H), 2.72 (t, $J = 7.8$ Hz, 2H), 2.27-2.21 (m, 2H), 1.93-1.90 (m, 4H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.75, 148.76, 132.09, 130.42, 126.78, 121.14, 117.12, 52.32, 51.65, 51.17, 30.18, 28.84, 24.81 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{17}\text{H}_{23}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 306.1700, found: 306.1701.

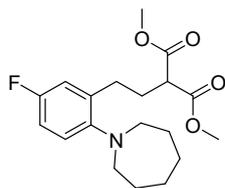


Dimethyl 2-(2-(azepan-1-yl)phenethyl)malonate (3b) Yield: 88% as a brown oil; $R_f = 0.47$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max}(\text{cm})^{-1} = 2914, 2902, 1732, 1488, 1273$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.17 - 7.10 (m, 3H, ArH), 6.99 (t, $J = 7.2$ Hz, 1H, ArH), 3.73 (s, 6H, CO_2Me), 3.42 (t, $J = 7.6$ Hz, 1H), 3.01 (t, $J = 5.4$ Hz, 4H), 2.73 (t, $J = 7.8$ Hz, 2H), 2.28 (q, $J = 7.2$ Hz, 2H), 1.72 (m, 8H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.85, 155.11, 136.03, 129.64, 127.06, 123.44, 122.51, 57.05, 52.37, 51.47, 29.54, 29.47, 29.04, 26.95 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{19}\text{H}_{27}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 334.2013, found: 334.2002.

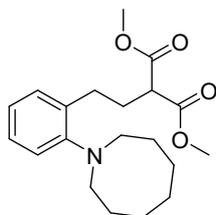


Dimethyl 2-(2-(azepan-1-yl)-5-bromophenethyl)malonate (3c) Yield: 80% as a pale oil; $R_f = 0.49$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max}(\text{cm})^{-1} = 2908, 1738, 1443, 1350$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.27 - 7.23 (m, 2H, ArH), 6.97 (d, $J = 8.4$ Hz, 1H, ArH), 3.75 (s, 6H, CO_2Me), 3.40 (t, $J = 7.6$ Hz, 1H), 2.98 (t, $J = 5.5$ Hz, 4H), 2.69 (t, $J = 7.8$ Hz, 2H), 2.28-2.22 (m, 2H), 1.70 (m, 8H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.61, 154.05, 138.35, 132.31, 129.91, 124.19, 116.17, 56.87, 52.42, 51.34,

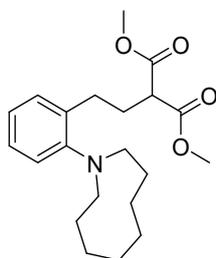
29.36, 29.16, 28.86, 26.88 ppm; HRMS (ESI) m/z: calcd. for $C_{19}H_{26}BrNO_4[M + H^+]$: 412.1118, $[M + 2 + H^+]$: 414.1098, found: 412.1106 (100%), 414.1090 (97%).



Dimethyl 2-(2-(azepan-1-yl)-5-fluorophenethyl)malonate (3d) Yield: 70% as a pale oil; $R_f = 0.41$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{max} (cm)^{-1} = 2750, 1730, 1440, 1380$; 1H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, $J_1 = 8.1, J_2 = 5.4$ Hz, 1H, ArH), 6.86-6.81 (m, 2H, ArH), 3.75 (s, 6H, CO_2Me), 3.41 (t, $J = 7.6$ Hz, 1H), 2.95 (t, $J = 5.0$ Hz, 4H), 2.74-2.70 (m, 2H), 2.25 (q, $J = 7.7$ Hz, 2H), 1.71 (m, 8H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3$) δ 169.66, 160.18, 157.77, 151.16, 138.48 (d, $J_{C-F} = 7.1$ Hz), 124.08 (d, $J_{C-F} = 7.7$ Hz), 115.76 (d, $J_{C-F} = 21.9$ Hz), 113.40 (d, $J_{C-F} = 21$ Hz), 57.35, 52.38, 51.30, 29.51, 29.28, 28.86, 26.86 ppm. HRMS (ESI) m/z: calcd. for $C_{19}H_{26}FNO_4[M + H^+]$: 352.1919, found: 352.1918.

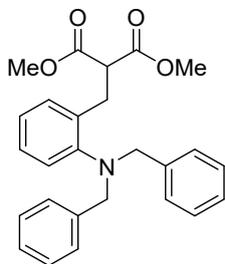


Dimethyl 2-(2-(azocan-1-yl)phenethyl)malonate (3e) Yield : 80% as a pale oil; $R_f = 0.49$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{max} (cm)^{-1} = 2972, 1754, 1730, 1434, 1275$; 1H NMR (400 MHz, $CDCl_3$) δ 7.18 - 7.16 (m, 3H, ArH), 7.04-7.00(m, 1H, ArH), 3.74 (s, 6H, CO_2Me), 3.45 (t, $J = 7.6$ Hz, 1H), 3.00 (t, $J = 5.2$ Hz, 4H), 2.79 (t, $J = 7.6$ Hz, 2H), 2.29-2.23(m, 2H), 1.70 (m, 10H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3$) δ 169.75, 155.50, 136.86, 129.48, 127.22, 124.38, 123.91, 56.62, 52.32, 51.42, 29.66, 28.85, 28.42, 27.59, 25.22 ppm; HRMS (ESI) m/z: calcd. for $C_{20}H_{29}NO_4 [M + H^+]$: 348.2169, found: 348.2151.

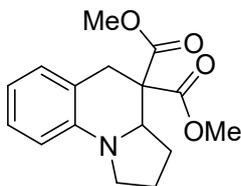


Dimethyl 2-(2-(azonan-1-yl)phenethyl)malonate (3f) Yield : 80% as a yellow oil; $R_f = 0.57$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{max} (cm)^{-1} = 2955, 1733, 1433, 1257$; 1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, $J = 8.4$ Hz, 1H, ArH), 7.20-7.17 (t, $J = 6.4$ Hz, 2H, ArH), 7.05 (t, $J = 6.8$ Hz, 1H, ArH), 3.74

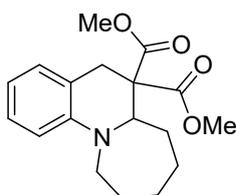
(s, 6H, CO₂Me), 3.47 (t, *J* = 7.6 Hz, 1H), 2.97 (t, *J* = 5.8 Hz, 4H), 2.83 (t, *J* = 8.2 Hz, 2H), 2.27-2.21 (m, 2H), 1.72-1.57 (m, 12H) ppm, ¹³C-NMR (100 MHz, CDCl₃) δ = 169.77, 154.71, 137.88, 129.53, 127.27, 125.55, 124.41, 55.57, 52.41, 51.53, 29.89, 28.88, 27.38, 25.52, 23.35 ppm; HRMS (ESI) *m/z*: calcd. for C₂₁H₃₁NO₄[M + H⁺]:362.2326, found: 362.2310.



Dimethyl 2-(2-(dibenzylamino)benzyl)malonate (6) Yield : 50% as a blue oil; *R_f* = 0.41 (hexane/EtOAc, 95:5, v/v); IR (neat): *v*_{max} (cm)⁻¹ = 2856, 1758, 1733, 1430, 1350; ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.20 (m, 10H, ArH), 7.17-7.10 (m, 3H, ArH), 7.02-6.98 (m, 1H, ArH), 4.03 (s, 4H), 3.80 (t, *J* = 8 Hz, 1H), 3.66 (s, 6H, CO₂Me), 3.34 (d, *J* = 8 Hz, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 169.57, 149.89, 137.91, 134.23, 130.01, 129.00, 128.05, 127.23, 126.95, 124.50, 123.89, 58.07, 52.27, 51.81, 30.33 ppm; HRMS (ESI) *m/z*: calcd. for C₂₆H₂₇NO₄[M + H⁺]:418.2013, found: 418.2005.

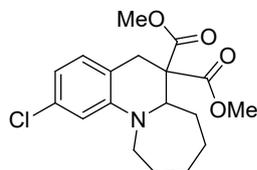


Dimethyl 1,2,3,3a-tetrahydropyrrolo[1,2-*a*]quinoline-4,4(5*H*)-dicarboxylate: (2a) Yield: 78% as white solid, mp: 130-133 °C; *R_f* = 0.47 (hexane/EtOAc, 95:5, v/v); IR (neat): *v*_{max} (cm)⁻¹ = 2329, 1724, 1507, 1451; ¹H NMR (400 MHz, CDCl₃) δ 7.07 (t, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.61-6.57 (m, 1H), 6.45 (d, *J* = 8.2 Hz, 1H), 3.78-3.75 (m, 4H), 3.56 (s, 3H), 3.37-3.25 (m, 4H), 2.46-2.36 (m, 1H), 2.16-2.11 (m, 1H), 2.05-2.02 (m, 1H), 1.94-1.89 (m, 1H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 171.48, 169.07, 143.75, 128.47, 127.53, 118.61, 115.95, 110.91, 62.07, 53.16, 52.69, 52.15, 47.35, 36.86, 27.83, 23.48 ppm; HRMS (ESI) *m/z*: calcd. for C₁₆H₁₉NO₄[M + H⁺]:290.1387, found: 290.1397.



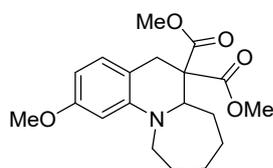
Dimethyl 6a,7,8,9,10,11-hexahydroazepino[1,2-*a*]quinoline-6,6(5*H*)-dicarboxylate (2b) Yield : 71% as a yellow solid; mp: 111-114 °C, *R_f* = 0.38 (hexane/EtOAc, 95:5, v/v); IR (neat): *v*_{max} (cm)⁻¹ = 2353, 1744, 1499, 1273; ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, *J* = 7.4 Hz, 2H, ArH), 6.57 (t, *J* = 7.3

Hz, 1H, ArH), 6.53 (d, $J = 8.0$ Hz, 1H, ArH), 4.10 (dd, $J = 11.2, 4.0$ Hz, 1H), 3.90-3.84 (m, 1H), 3.76 (s, 3H, CO₂Me), 3.62 (s, 3H, CO₂Me), 3.39 (d, $J = 17.0$ Hz, 1H), 3.28 (d, $J = 17.0$ Hz, 1H), 3.22-3.14 (m, 1H), 2.06-1.97 (m, 1H), 1.65-1.38 (m, 7H) ppm; ¹³C-NMR (100 MHz, CDCl₃) $\delta = 169.66, 169.49, 142.34, 128.98, 127.27, 116.87, 115.27, 109.72, 60.25, 55.31, 52.61, 52.56, 49.67, 30.56, 28.41, 27.17, 25.93, 25.56$ ppm; HRMS (ESI) m/z : calcd. for C₁₈H₂₃NO₄[M + H⁺]: 318.1700 found: 318.1701.



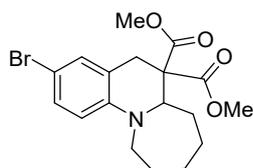
Dimethyl 2-chloro-6a,7,8,9,10,11-hexahydroazepino[1,2-*a*]quinoline-6,6(5*H*)-dicarboxylate (2c)

Yield : 65% as a yellow solid; mp: 115-118 °C; $R_f = 0.47$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2952, 1735, 1227, 1194; ¹H NMR (400 MHz, CDCl₃) δ 6.93 (d, $J = 8.2$ Hz, 1H), 6.54-6.52 (m, 1H), 6.49 (d, $J = 1.8$ Hz, 1H), 4.10 (dd, $J = 11.4, 4.1$ Hz, 1H), 3.84-3.78 (m, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.35 (d, $J = 17.0$ Hz, 1H), 3.20 (d, $J = 15.6$ Hz, 2H), 2.06-1.95 (m, 1H), 1.67-1.35 (m, 7H) ppm; ¹³C-NMR (100 MHz, CDCl₃) $\delta = 169.48, 169.39, 143.43, 133.01, 130.04, 115.45, 115.20, 109.57, 60.18, 55.17, 52.87, 52.83, 50.01, 30.83, 28.03, 26.84, 25.90, 25.61$ ppm; HRMS (ESI) m/z : calcd. for C₁₈H₂₂ClNO₄[M + H⁺]: 352.1310 found: 352.1317.



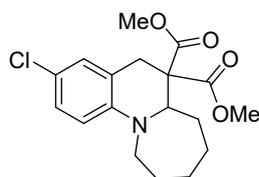
Dimethyl 2-methoxy-6a,7,8,9,10,11-hexahydroazepino[1,2-*a*]quinoline-6,6(5*H*)-dicarboxylate (2d)

Yield : 70% as a white solid; mp: 125-128 °C; $R_f = 0.50$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2546, 1733, 1610, 1505, 1436; ¹H NMR (400 MHz, CDCl₃) δ 6.94 (d, $J = 7.6$ Hz, 1H, ArH), 6.17 (dd, $J_1 = 8.2, J_2 = 2.2$ Hz, 1H, ArH), 6.10 (d, $J = 2.4$ Hz, 1H, ArH), 4.08 (dd, $J_1 = 11.4, J_2 = 3.4$ Hz, 1H, ArH), 3.87 - 3.81 (m, 1H), 3.76 (s, 3H, CO₂Me), 3.75 (s, 3H, CO₂Me), 3.63 (s, 3H, CH₃), 3.36-3.32 (m, 1H), 3.23-3.14 (m, 2H), 2.08 - 1.97 (m, 1H), 1.70-1.34 (m, 7H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 169.99, 169.82, 159.44, 143.58, 129.72, 110.04, 100.04, 96.56, 60.41, 55.71, 55.03, 52.87, 50.03, 30.91, 27.96, 27.24, 26.13, 25.78 ppm; HRMS (ESI) m/z : calcd. for C₁₉H₂₅NO₅[M + H⁺]: 348.1805 found: 348.1810.

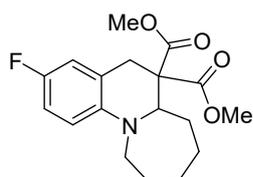


Dimethyl 3-bromo-6a,7,8,9,10,11-hexahydroazepino[1,2-a]quinoline-6,6(5H)-dicarboxylate (2e)

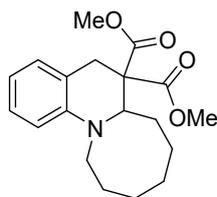
Yield : 69% as a yellow solid; mp: 131-134 °C; $R_f = 0.43$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2830, 1728, 1494, 1197; ¹H NMR (400 MHz, CDCl₃) δ 7.13-7.09 (m, 2H, ArH), 6.40 (d, $J = 8.7$ Hz, 1H, ArH), 4.09 (dd, $J = 11.0, 4.1$ Hz, 1H), 3.84-3.78 (m, 1H), 3.77 (s, 3H, CO₂Me), 3.64 (s, 3H, CO₂Me), 3.35 (d, $J = 17.4$ Hz, 1H), 3.24 (d, $J = 17.4$ Hz, 1H), 3.20-3.14 (m, 1H), 2.20-1.94 (m, 1H), 1.66-1.33 (m, 7H) ppm; ¹³C-NMR (100 MHz, CDCl₃) $\delta = 169.38, 169.32, 141.51, 131.42, 130.02, 119.20, 111.46, 106.92, 60.39, 55.18, 52.85, 52.81, 49.94, 30.63, 28.27, 26.94, 25.90, 25.59$ ppm; HRMS (ESI) m/z : calcd. for C₁₈H₂₂BrNO₄[M + H⁺]: 396.0805, [M + 2 + H⁺]: 398.0785, found: 396.0802 (100%), 398.0780 (97%).

**Dimethyl 3-chloro-6a,7,8,9,10,11-hexahydroazepino[1,2-a]quinoline-6,6(5H)-dicarboxylate (2f)**

Yield : 67% as a yellow solid; mp: 120-123 °C; $R_f = 0.52$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2932, 1750, 1728, 1500, 1428; ¹H NMR (400 MHz, CDCl₃) δ 7.00-6.96 (m, 2H, ArH), 6.44 (d, $J = 8.7$ Hz, 1H, ArH), 4.09 (dd, $J = 11.2, 4.3$ Hz, 1H), 3.85-3.79 (m, 1H), 3.77 (s, 3H, CO₂Me), 3.63 (s, 3H, CO₂Me), 3.36 (d, $J = 17.4$ Hz, 1H), 3.23 (d, $J = 17.4$ Hz, 1H), 3.20-3.14 (m, 1H), 2.04-1.94 (m, 1H), 1.67-1.34 (m, 7H) ppm; ¹³C-NMR (100 MHz, CDCl₃) $\delta = 169.45, 169.38, 141.12, 128.66, 127.19, 119.87, 118.70, 110.96, 60.44, 55.29, 52.86, 52.82, 49.97, 30.64, 28.38, 27.02, 25.93, 25.63$ ppm; HRMS (ESI) m/z : calcd. for C₁₈H₂₂ClNO₄[M + H⁺]: 352.1310, found: 352.1311.

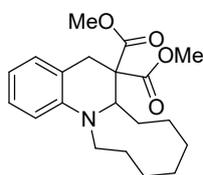
**Dimethyl 3-fluoro-6a,7,8,9,10,11-hexahydroazepino[1,2-a]quinoline-6,6(5H)-dicarboxylate (2g)**

Yield: 63% as a yellow solid; mp: 128-131 °C; $R_f = 0.49$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2834, 1727, 1503, 1454, 1266; ¹H NMR (400 MHz, CDCl₃) δ 6.80-6.72 (m, 2H, ArH), 6.43 (q, $J = 4.4$ Hz, 1H, ArH), 4.10 (dd, $J_1 = 11.0, J_2 = 3.6$ Hz, 1H), 3.83-3.78 (m, 1H), 3.77 (s, 3H, CO₂Me), 3.64 (s, 3H, CO₂Me), 3.38 (d, $J = 17.6$ Hz, 1H), 3.26-3.13 (m, 2H), 2.06-1.95 (m, 1H), 1.71-1.32 (m, 7H) ppm; ¹³C-NMR (100 MHz, CDCl₃) $\delta 169.29, 169.21, 154.13$ (d, $J_{C-F} = 154.51$ Hz), 138.74 118.28 (d, $J_{C-F} = 6.6$ Hz), 115.22 (d, $J_{C-F} = 21.9$ Hz), 113.42 (d, $J_{C-F} = 20.9$ Hz), 110.10 (d, $J_{C-F} = 7.7$ Hz), 60.28, 55.40, 52.53, 52.47, 49.73, 30.16, 28.47, 27.01, 25.80, 25.47 ppm; HRMS (ESI) m/z : calcd. for C₁₈H₂₂FNO₄[M + H⁺]: 336.1606, found: 336.1609.



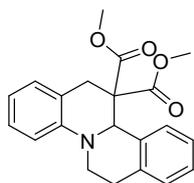
Dimethyl 7,8,9,10,11,12-hexahydro-5H-azocino[1,2-a]quinoline-6,6(6aH)-dicarboxylate (2h)

Yield: 75% as colourless oil, $R_f = 0.49$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2550, 1730, 1510, 1412$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.07-7.04 (m, 2H, ArH), 6.63-6.59 (m, 2H, ArH), 4.16 (dd, $J = 9.6, 4.1$ Hz, 1H), 3.78 (s, 3H), 3.60 (s, 3H), 3.37 (d, $J = 16.0$ Hz, 1H), 3.26 (d, $J = 16.5$ Hz, 1H), 1.85-1.33 (m, 12H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.69, 169.31, 142.44, 128.94, 127.03, 117.48, 115.48, 111.19, 59.99, 54.09, 52.44, 52.21, 30.27, 28.23, 27.31, 27.03, 25.57 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_4[\text{M} + \text{H}^+]$: 332.1856 found: 332.1890.



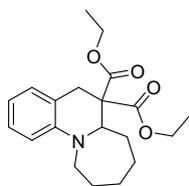
Dimethyl 6a,7,8,9,10,11,12,13-octahydroazonino[1,2-a]quinoline-6,6(5H)-dicarboxylate (2i)

Yield: 75% as a white solid, mp: 135-138 °C; $R_f = 0.51$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2917, 1734, 1602, 1496, 1348$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.11-7.04 (m, 2H, ArH), 6.67-6.63 (m, 2H, ArH), 4.13-4.10 (m, 1H), 3.78 (s, 3H, CO_2Me), 3.70-3.63 (m, 1H), 3.59 (s, 3H, CO_2Me), 3.44-3.34 (m, 2H), 3.23 (d, $J = 16.8$ Hz, 1H), 1.88-1.43 (m, 12H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 170.30, 169.65, 143.37, 129.28, 127.28, 118.57, 116.39, 113.15, 63.64, 57.08, 55.82, 52.89, 52.61, 29.87, 28.67, 28.39, 26.65, 26.48, 26.19, 25.17 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_4[\text{M} + \text{H}^+]$: 346.2013, found: 346.2018.

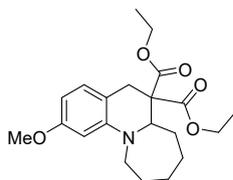


Dimethyl 11b,13-dihydro-6H-isoquinolino[2,1-a]quinoline-12,12(7H)-dicarboxylate (2j).

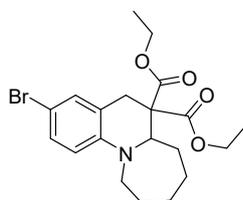
Yield: 70% as a yellow solid, mp: 124-127 °C; $R_f = 0.40$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2937, 1740, 1534, 1375$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.16-7.08 (m, 6H), 6.79-6.72 (m, 2H), 5.04 (s, 1H), 3.94-3.90 (m, 1H), 3.75 (s, 4H), 3.70 (s, 3H), 3.62 (s, 1H), 3.29-3.18 (m, 2H), 2.75 (d, $J = 14.6$ Hz, 1H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 170.73, 169.58, 145.20, 136.78, 134.78, 128.80, 128.53, 126.87, 126.79, 125.78, 125.59, 121.31, 118.06, 112.00, 61.17, 59.27, 52.82, 52.45, 43.70, 33.97, 28.00 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}_4[\text{M} + \text{H}^+]$: 352.1543, found: 352.1533.



Diethyl 6a,7,8,9,10,11-hexahydroazepino[1,2-*a*]quinoline-6,6(5*H*)-dicarboxylate (2k). Yield: 58% as a white solid, mp: 120 -123 °C; $R_f = 0.47$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2942, 1729, 1321, 1221$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.02 (d, $J = 7.6$ Hz, 2H, ArH), 6.57-6.51 (m, 2H, ArH), 4.25-4.16 (m, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.14-3.99 (m, 3H, comp, $\text{CO}_2\text{CH}_2\text{CH}_3$, H), 3.89-3.83 (m, 1H), 3.37 (d, $J = 16.8$ Hz, 1H), 3.26-3.13 (m, 2H), 2.06-1.96(m, 1H), 1.77-1.34 (m, 7H), 1.34-1.25 (t, $d = 7.8$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.11-1.05 (t, $d = 7$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.31, 169.06, 142.44, 129.02, 127.26, 117.03, 115.19, 109.60, 61.50, 61.22, 60.19, 55.32, 49.79, 30.79, 28.47, 27.17, 26.00, 25.69, 13.87, 13.78 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_4$ [$\text{M} + \text{H}^+$]:346.2013, found: 346.2010.

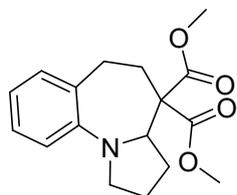


Diethyl 2-methoxy-6a,7,8,9,10,11-hexahydroazepino[1,2-*a*]quinoline-6,6(5*H*)-dicarboxylate (2l) Yield: 67% as yellow solid, mp: 125-128 °C; $R_f = 0.41$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2912, 1729, 1604, 1494$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.06-6.93 (m, 1H, ArH), 6.18-6.10 (m, 2H, ArH), 4.27-4.19 (m, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.18-4.02 (m, 3H, Comp, COCH_2CH_3 , H), 3.87-3.80 (m, 1H), 3.76 (s, 3H, CH_3), 3.33 (d, $J = 16.4$ Hz, 1H), 3.26-3.13 (m, 2H), 2.07-2.00 (m, 1H), 1.78-1.52 (m, 7H), 1.29 (t, $J = 7.2$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.12 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.67, 169.41, 159.51, 143.76, 129.81, 110.33, 99.99, 96.53, 61.78, 61.22, 60.42, 57.34, 55.27, 55.13, 50.20, 29.66, 28.11, 26.99, 26.00, 14.14, 14.09 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_5$ [$\text{M} + \text{H}^+$]:376.2118, found: 376.2122.



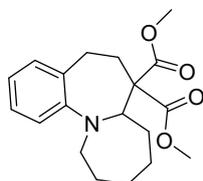
Diethyl 3-bromo-6a,7,8,9,10,11-hexahydroazepino[1,2-*a*]quinoline-6,6(5*H*)-dicarboxylate (2m). Yield: 62% as a colourless oil, $R_f = 0.44$ (hexane/EtOAc, 95:5, v/v); IR (neat): $\nu_{\max} (\text{cm})^{-1} = 2941, 1747, 1736, 1591, 1494$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.06-7.02 (m, 2H, ArH), 6.32 (d, $J = 8.8$ Hz, 1H, ArH), 4.19-4.12 (m, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.10-3.96 (complex, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.76-3.70 (m, 1H), 3.27

(d, $J = 17.2$ Hz, 1H), 3.16-3.04 (m, 2H), 1.97-1.88 (m, 1H), 1.71-1.43 (m, 7H), 1.21 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.05 (t, $J = 7.0$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$) ppm; ^{13}C -NMR (100 MHz, CDCl_3) δ 169.16, 169.04, 141.83, 131.62, 130.17, 119.62, 111.53, 107.04, 61.54, 60.53, 55.44, 50.22, 41.72, 30.99, 28.54, 27.14, 26.17, 25.92, 14.12, 14.05 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{20}\text{H}_{26}\text{BrNO}_4$ [$\text{M} + \text{H}^+$]: 424.1118, [$\text{M} + 2 + \text{H}^+$]: 426.1098, found: 424.1110 (100%), 426.1090 (97%).



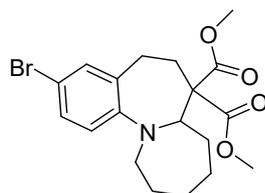
Dimethyl 3,3a,5,6-tetrahydro-1H-benzo[*f*]pyrrolo[1,2-*a*]azepine-4,4(2*H*)-dicarboxylate (4a).

Yield: 70% as a colourless oil, $R_f = 0.45$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{max} (cm^{-1}) = 2927, 2850, 1725, 1587, 1495, 1442; ^1H -NMR (400 MHz, CDCl_3) δ 7.10-6.99 (m, 2H, ArH), 6.75-6.69 (m, 2H, ArH), 4.37 (m, 1H), 3.75 (s, 6H, CO_2CH_3), 3.28 (t, $J = 7.8$ Hz, 1H), 3.15-3.03 (m, 2H), 2.96-2.90 (m, 1H), 2.76-2.70 (m, 1H), 2.30-2.26 (m, 2H), 2.12-2.01 (m, 2H), 1.90-1.84 (m, 1H) ppm; ^{13}C -NMR (100 MHz, CDCl_3) δ 172.29, 171.00, 149.46, 130.86, 127.72, 126.65, 118.62, 113.51, 64.73, 62.07, 52.50, 50.23, 31.77, 30.21, 29.69, 29.50, 23.55 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{17}\text{H}_{21}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 304.1543, found: 304.1540.

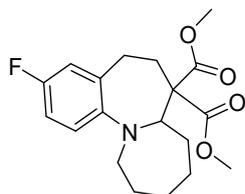


Dimethyl 7a,8,9,10,11,12-hexahydro-5*H*-azepino[1,2-*a*]benzo[*f*]azepine-7,7(6*H*)-dicarboxylate (4b).

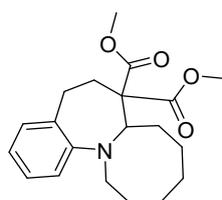
Yield: 79% as a colourless oil, $R_f = 0.48$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{max} (cm^{-1}) = 2929, 2853, 1722, 1584, 1492, 1440; ^1H -NMR (400 MHz, CDCl_3) δ 7.07-7.03 (m, 1H), 6.98 (d, $J = 7.5$ Hz, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 6.72-6.68 (m, 1H), 4.25 (dd, $J = 11.0, 5.4$ Hz, 1H), 3.75 (s, 6H), 3.57-3.49 (m, 1H), 3.42-3.35 (m, 1H), 3.02-2.95 (m, 1H), 2.72-2.56 (m, 2H), 2.33-2.27 (m, 1H), 1.97-1.90 (m, 2H), 1.79-1.62 (m, 4H), 1.45-1.34 (m, 2H) ppm; ^{13}C -NMR: 172.07, 171.46, 150.57, 131.14, 128.16, 126.28, 118.35, 115.70, 63.46, 62.43, 52.47, 52.32, 48.19, 30.63, 30.04, 29.97, 28.59, 27.33, 25.93 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_4$ [$\text{M} + \text{H}^+$]: 332.1856, found: 332.1860.



Dimethyl 3-bromo-7a,8,9,10,11,12-hexahydro-5H-azepino[1,2-*a*]benzo[*f*]azepine-7,7(6*H*)-dicarboxylate (4c). Yield: 70% as a yellow oil, $R_f = 0.48$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2940, 1723, 1684, 1584, 1458; ¹H-NMR (400 MHz, CDCl₃) δ 7.13-7.08 (m, 2H), 6.75 (d, $J = 8.7$ Hz, 1H), 4.21 (dd, $J = 12.4$ Hz, 1H), 3.76 (s, 6H), 3.51-3.32 (m, 2H), 2.98-2.90 (m, 1H), 2.54 (dd, $J = 16.5, 6.9$ Hz, 1H), 2.53 (t, $J = 13.5$ Hz, 1H), 2.29 (dd, $J = 14.2, 6.9$ Hz, 1H), 1.93-1.78 (m, 3H), 1.70-1.61 (m, 3H), 1.45-1.32 (m, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 171.83, 171.18, 149.63, 133.38, 130.26, 128.89, 117.21, 110.19, 63.45, 62.09, 52.57, 52.43, 48.39, 30.35, 29.82, 29.56, 28.32, 27.18, 25.83 ppm; HRMS (ESI) m/z : calcd. for C₁₉H₂₅BrNO₄ [M + H⁺]: 410.0961, [M + 2 + H⁺] 412.0941, found: 410.0969 (100%), 412.0935 (97%)

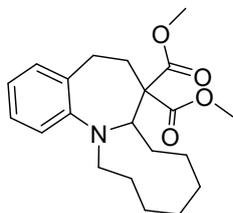


Dimethyl 3-fluoro-7a,8,9,10,11,12-hexahydro-5H-azepino[1,2-*a*]benzo[*f*]azepine-7,7(6*H*)-dicarboxylate (4d). Yield: 68% as a yellow oil, $R_f = 0.49$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2976, 1733, 1666, 1545, 1401; ¹H-NMR (400 MHz, CDCl₃) δ 7.08-7.05 (m, 1H, ArH), 6.69-6.88 (m, 3H, ArH), 4.21 (dd, $J_1 = 12.4, J_2 = 3.6$ Hz, 1H), 3.76 (s, 3H, CO₂CH₃), 3.75 (s, 3H, CO₂CH₃), 3.54-3.35 (m, 1H), 2.95-2.83 (m, 2H), 2.74-2.62 (m, 1H), 2.53-2.22 (m, 2H), 1.91-1.78 (m, 2H), 1.70 (m, 4H), 1.60-1.44 (m, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 171.80, 171.26, 156.08 (d, $J_{C-F} = 237$ Hz), 146.74, 130.49, 124.14 (d, $J_{C-F} = 8$ Hz), 116.98 (d, $J_{C-F} = 22$ Hz), 112.42 (d, $J_{C-F} = 22$ Hz), 63.19, 62.47, 52.52, 52.43, 49.23, 30.74, 29.58, 28.93, 26.92, 26.86, 25.67 ppm; HRMS (ESI) m/z : calcd. for C₁₉H₂₄FNO₄[M + H⁺]: 350.1762, found: 350.1767.

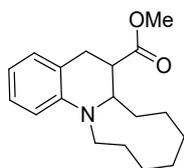


Dimethyl 5,6,8,9,10,11,12,13-octahydrobenzo[6,7]azepino[1,2-*a*]azocine-7,7(7*a*H)-dicarboxylate (4e). Yield: 72% as a white solid, mp: 78-81 °C, $R_f = 0.57$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm)⁻¹ = 2949, 2922, 2848, 1734, 1585, 1494; ¹H-NMR (400 MHz, CDCl₃) δ 7.17 (d, $J = 8$ Hz, 1H, ArH), 7.11 (t, $J = 7.6$ Hz, 1H, ArH), 7.02 (d, $J = 7.2$ Hz, 1H, ArH), 6.78 (t, $J = 7.2$ Hz, 1H, ArH), 4.59 (dd, $J_1 = 12.8, J_2 = 3.2$ Hz, 1H), 3.76 (s, 3H, CO₂Me), 3.73 (m, 4H, CO₂Me, H), 3.60-3.53 (m, 1H), 2.80-2.71 (m, 1H), 2.58-2.51 (m, 1H), 2.46-2.41 (m, 1H), 2.14-2.04 (m, 2H), 2.00-1.84 (m, 3H), 1.68-1.64 (m, 1H), 1.52-1.43 (m, 3H), 1.30-1.22 (m, 2H) ppm; ¹³C-NMR (100 MHz, CDCl₃) δ 171.12,

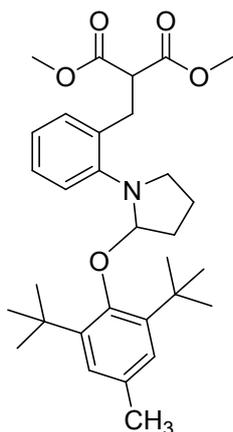
149.09, 132.94, 130.07, 126.65, 120.16, 119.65, 62.70, 59.37, 55.84, 52.74, 52.49, 31.79, 28.50, 26.74, 26.05, 21.76 ppm; HRMS (ESI) m/z : calcd. for $C_{20}H_{27}NO_4$ [$M + H^+$]: 346.2013, found: 346.2010.



Dimethyl 7a,8,9,10,11,12,13,14-octahydro-5H-benzo[6,7]azepino[1,2-a]azonine-7,7(6H)-dicarboxylate (4f). Yield: 66% as a white solid, mp: 87-88 °C; R_f = 0.55 (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{max} (cm^{-1}) = 2928, 2842, 1738, 1718, 1587, 1492; 1H -NMR (400 MHz, $CDCl_3$) δ 7.12-7.05 (m, 2H, ArH), 7.00 (d, J = 7.6 Hz, 1H, ArH), 6.82-6.78 (m, 1H, ArH), 4.52-4.50 (m, 1H), 3.73 (s, 6H, CO_2CH_3), 3.64-3.61 (m, 1H), 3.48-3.42 (m, 1H), 2.82-2.68 (m, 2H), 2.41-2.18 (m, 2H), 1.97- 1.88 (m, 3H), 1.81-1.72 (m, 2H), 1.64-1.42 (m, 6H), 1.27-1.18 (m, 1H) ppm; ^{13}C -NMR (100 MHz, $CDCl_3$) δ 171.44, 149.79, 133.81, 130.30, 126.64, 121.27, 120.98, 63.25, 60.90, 54.76, 52.33, 31.38, 29.65, 29.55, 28.27, 26.53, 25.85, 23.35 ppm; HRMS (ESI) m/z : calcd. for $C_{21}H_{29}NO_4$ [$M + H^+$]: 360.2169, found: 360.2155.

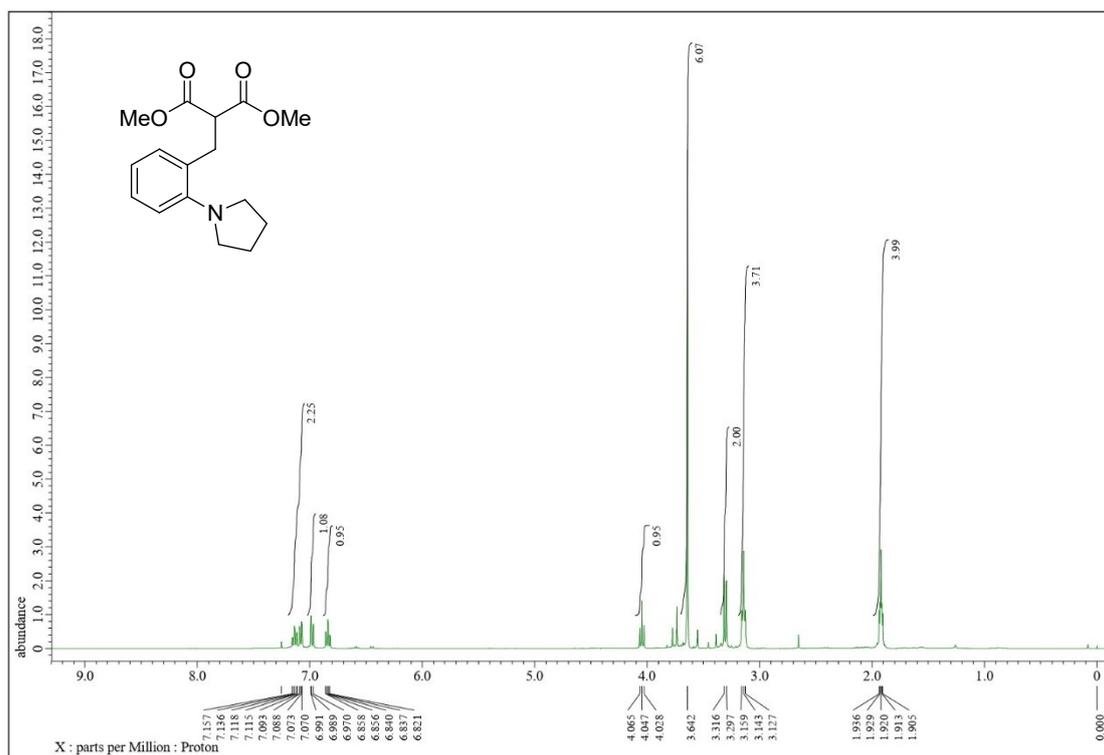


Methyl 5,6,6a,7,8,9,10,11,12,13-decahydroazonino[1,2-a]quinoline-6-carboxylate (5). Yield: 55% as yellow oil; R_f = 0.45 (hexane/EtOAc, 95:5, v/v); 1H -NMR (600 MHz, $CDCl_3$) δ 7.10 (t, J = 9 Hz, 1H, ArH), 7.05 (d, J = 6 Hz, 1H, ArH), 6.76 (d, J = 6 Hz, 1H, ArH), 6.67 (t, J = 9 Hz, 1H, ArH), 3.75 (s, 3H, CO_2CH_3), 3.70-3.63 (m, 2H), 3.25-3.20 (m, 1H), 3.07-2.98 (m, 1H), 2.85 (dd, J_1 = 18 Hz, J_2 = 6 Hz, 1H), 2.74-2.71 (m, 1H), 1.73-1.47 (m, 12H), ppm; ^{13}C -NMR (150 MHz, $CDCl_3$) δ 174.04, 144.68, 129.57, 127.14, 120.86, 116.69, 114.84, 60.58, 56.76, 55.70, 51.88, 40.81, 28.21, 27.68, 27.30, 25.46, 25.09, 24.86 ppm; HRMS (ESI) m/z : calcd. for $C_{18}H_{25}NO_2$ [$M + H^+$]: 288.1958 found: 288.1955.

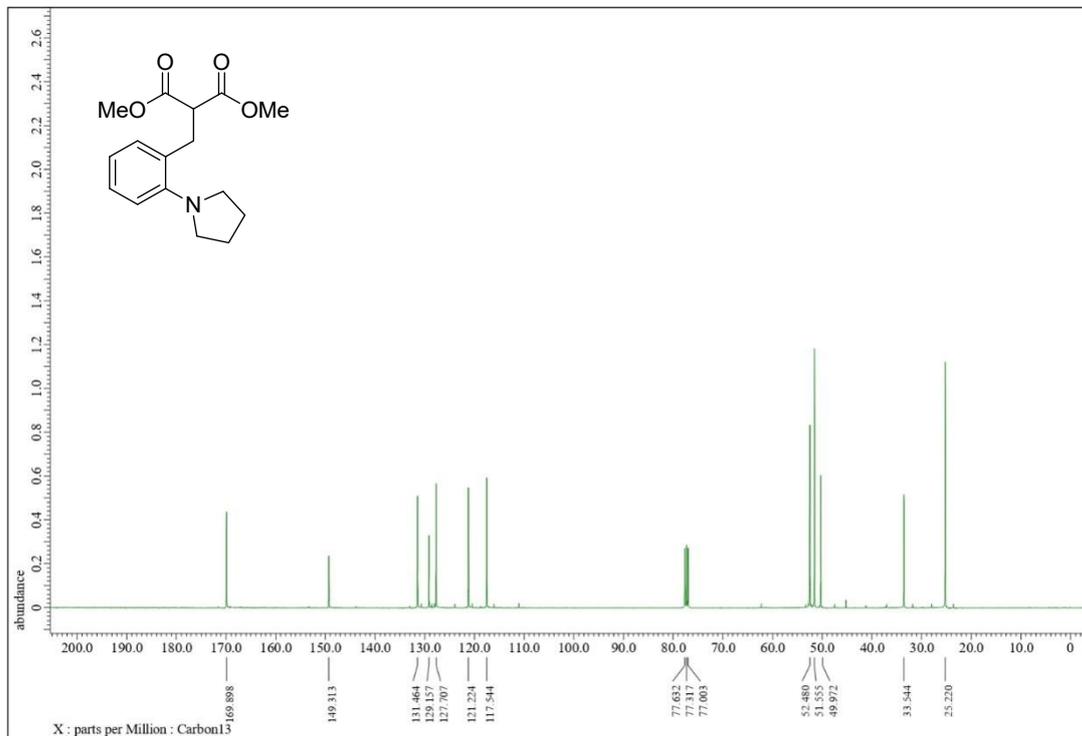


Dimethyl 2-(2-(2-(2,6-di-tert-butyl-4-methylphenoxy)pyrrolidin-1-yl)benzyl)malonate (8). Yield: 53% as a colourless liquid, $R_f = 0.55$ (hexane/EtOAc, 95:5, v/v); IR (neat): ν_{\max} (cm) $^{-1} = 2988, 1740, 1720, 1587, 1492$; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.23-6.83 (m, 4H, ArH), 6.56 (s, 2H, ArH), 4.09-3.96 (m, 1H), 3.79-3.76 (m, 1H), 3.67 (s, 3H, CO_2Me), 3.64 (s, 3H, CO_2Me), 3.29 (d, $J = 7.8$ Hz, 3H), 3.15 (t, $J = 6.4$ Hz, 3H), 2.66 (s, 3H, CH_3), 1.94-1.91 (m, 3H), 1.59 (s, 8H), 1.24 (s, 10H) ppm; $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 169.94, 169.72, 147.24, 144.32, 134.22, 131.45, 129.40, 127.68, 125.63, 125.44, 121.21, 117.55, 116.08, 111.03, 52.54, 51.55, 50.31, 47.48, 42.83, 37.11, 34.73, 33.74, 29.58, 25.28 ppm; HRMS (ESI) m/z : calcd. for $\text{C}_{31}\text{H}_{43}\text{NO}_5$ [$\text{M} + \text{H}^+$]: 510.3214 found: 510.3215.

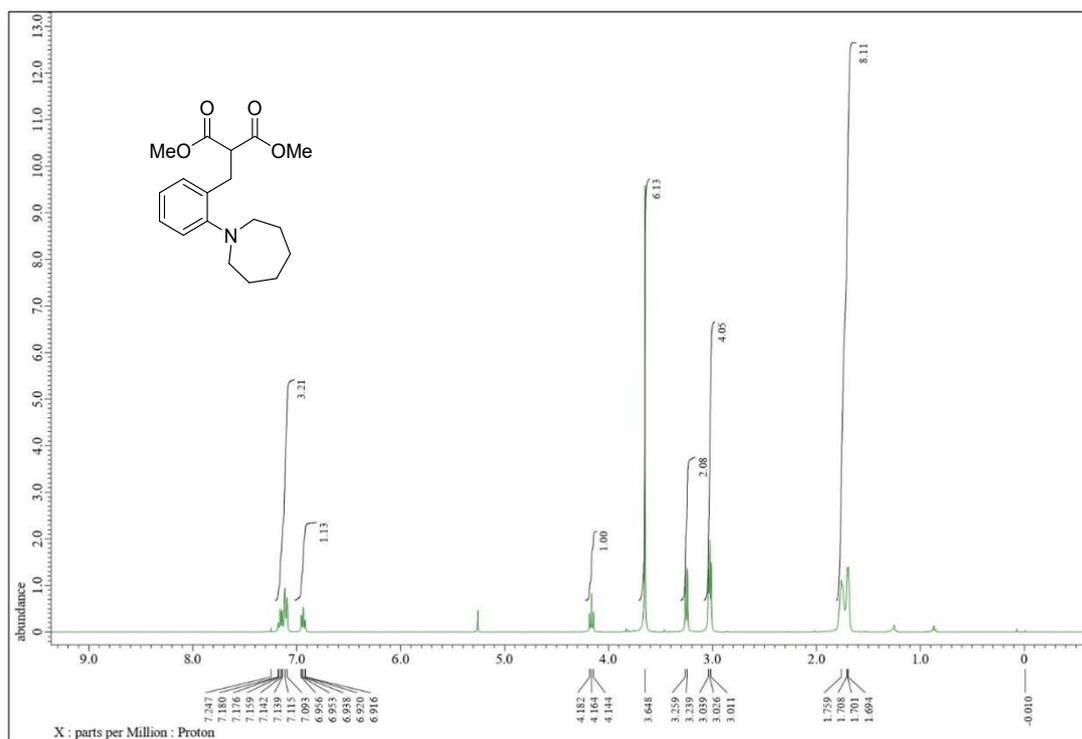
7. NMR spectra.



^1H -NMR spectra of **1a** in CDCl_3



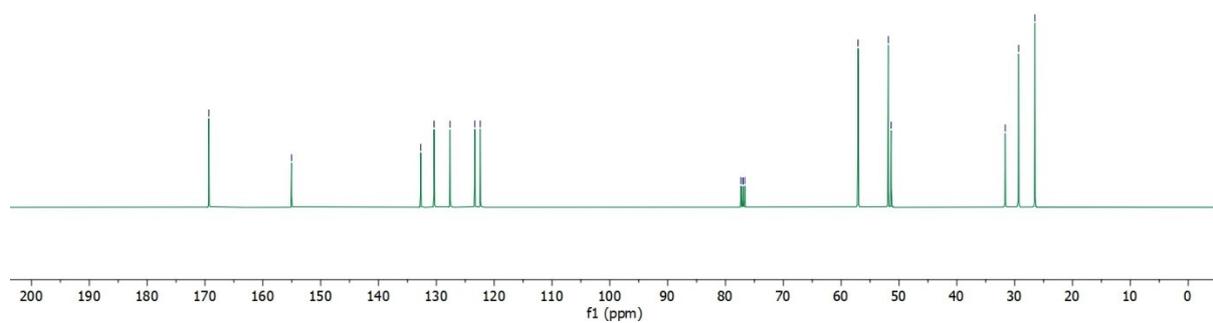
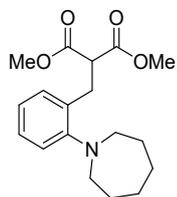
^{13}C -NMR of spectra of **1a** in CDCl_3



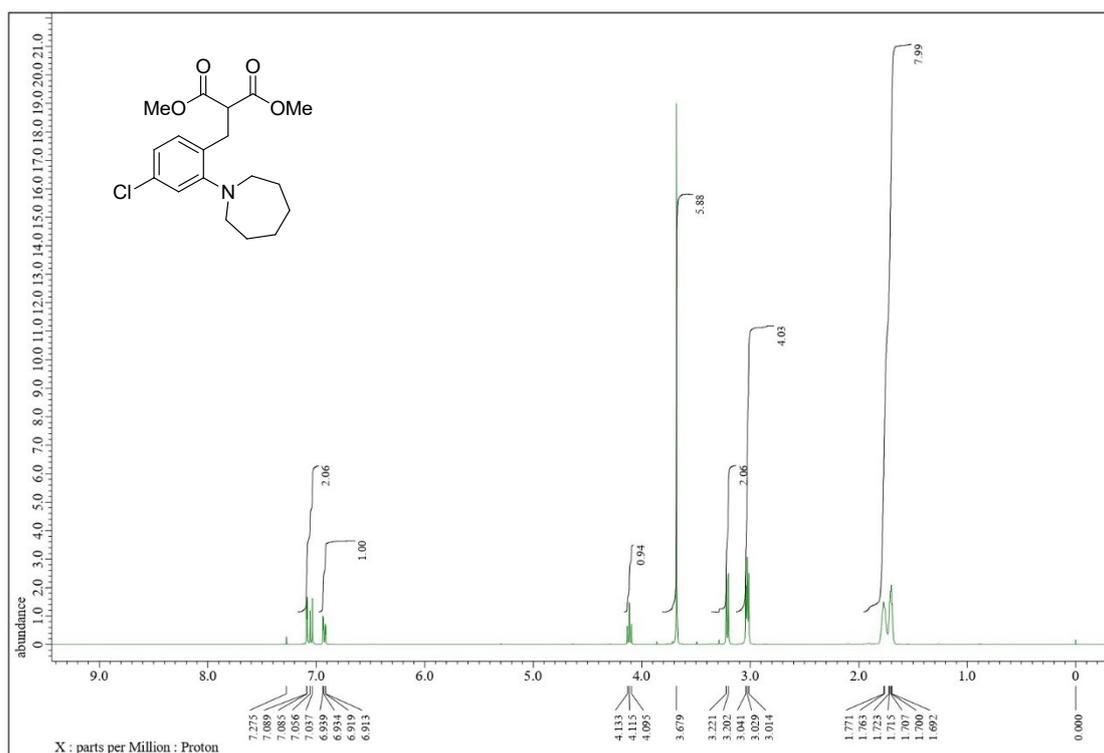
$^1\text{H-NMR}$ spectra of **1b** in CDCl_3

ms-27

single pulse decoupled gated NOE

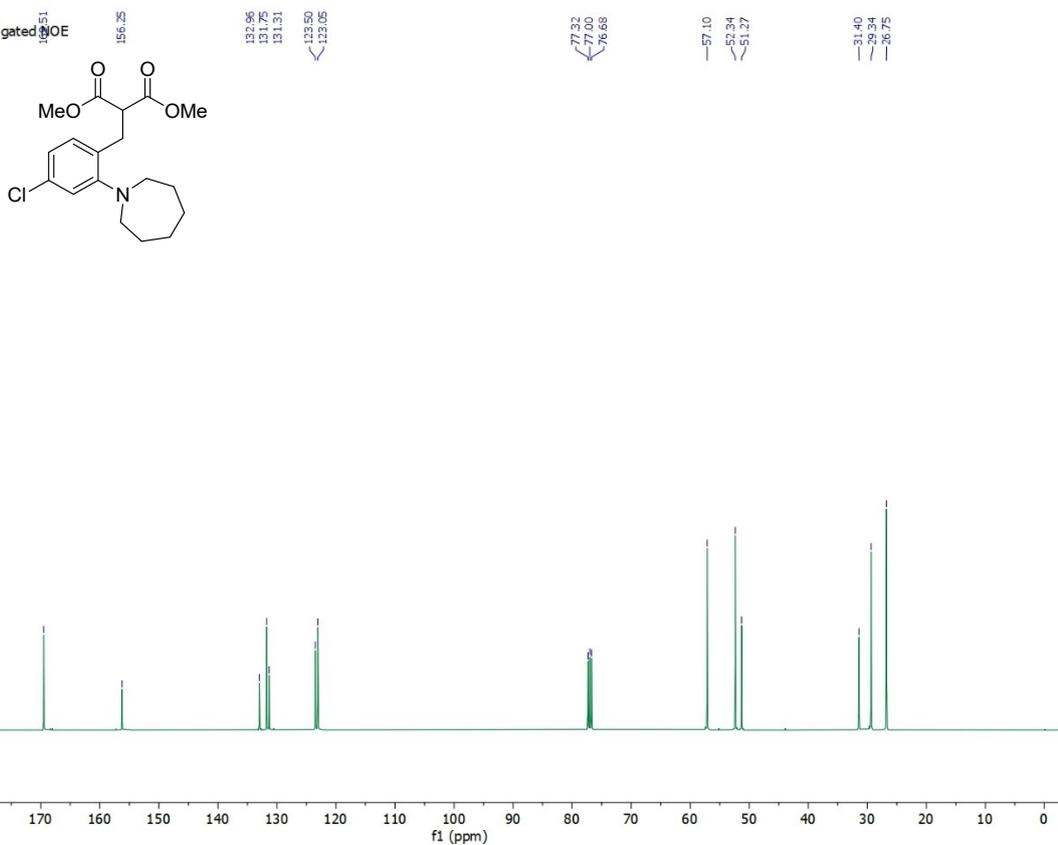


$^{13}\text{C-NMR}$ spectra of **1b** in CDCl_3

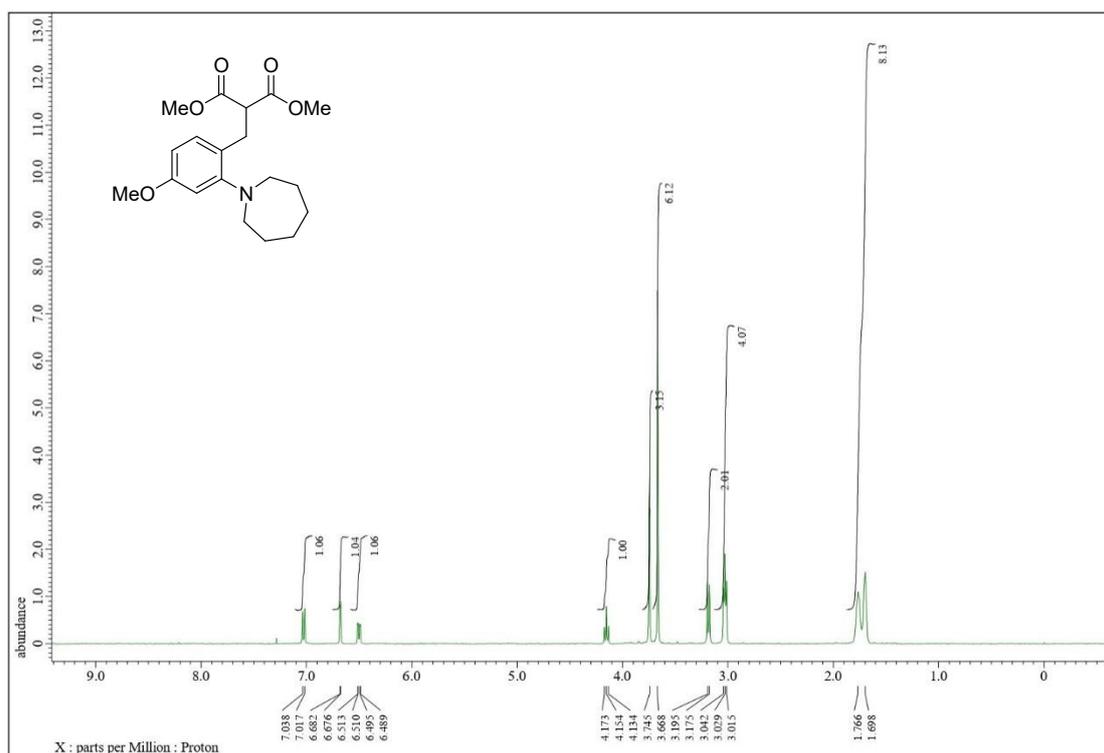


¹H-NMR spectra of **1c** in CDCl₃

MS-115 UPPER
single pulse decoupled gated NOE



¹³C-NMR spectra of **1c** in CDCl₃

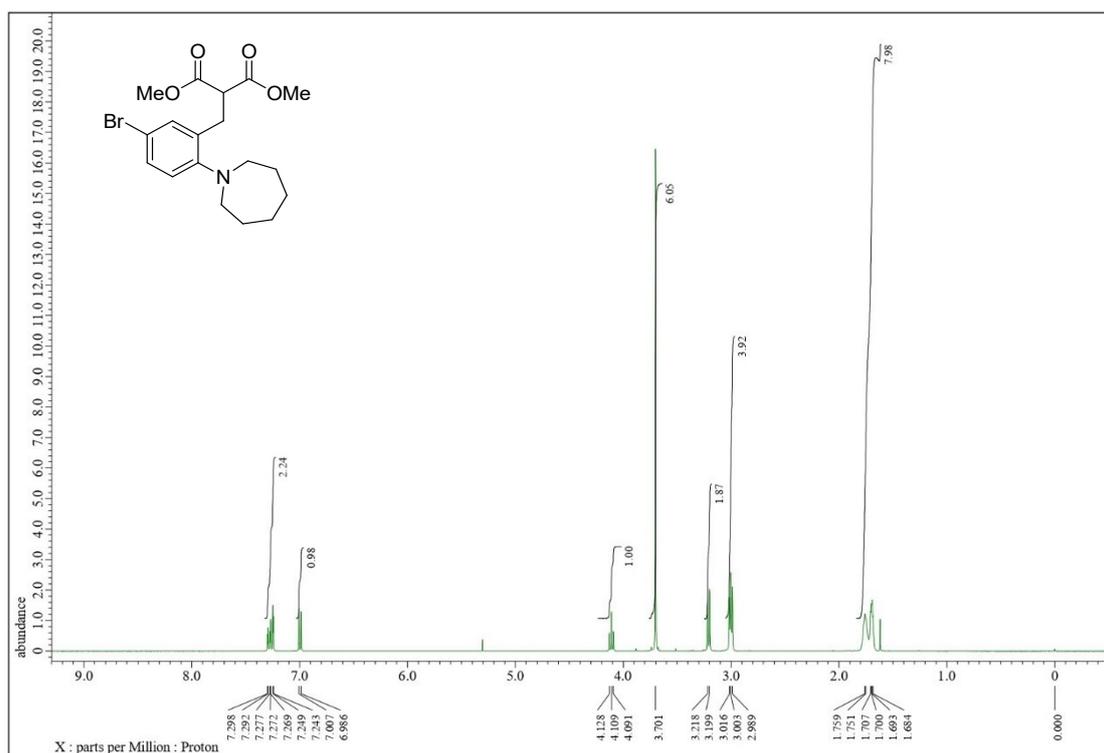


$^1\text{H-NMR}$ spectra of **1d** in CDCl_3

Ms-94 upper $^{13}\text{C-NMR}$
single pulse decoupled gated NOESY

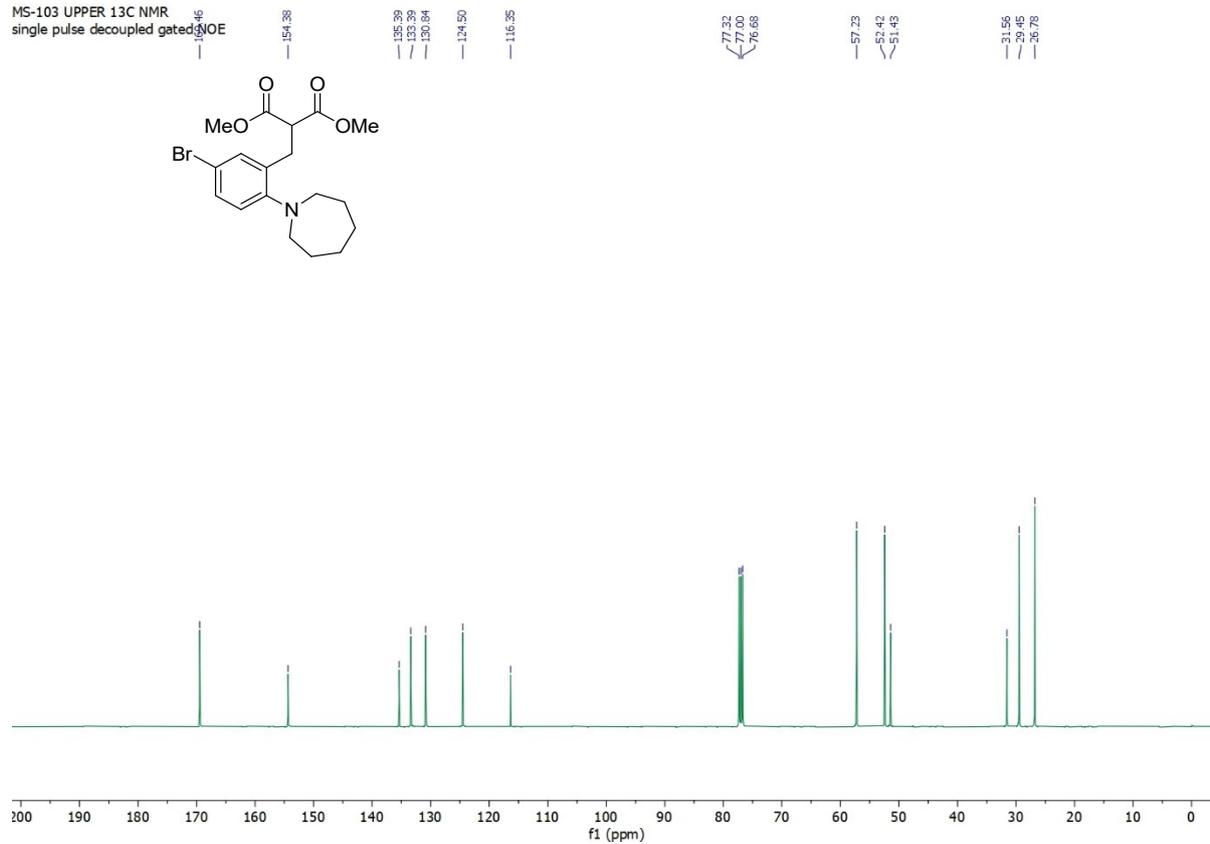


$^{13}\text{C-NMR}$ spectra of **1d** in CDCl_3

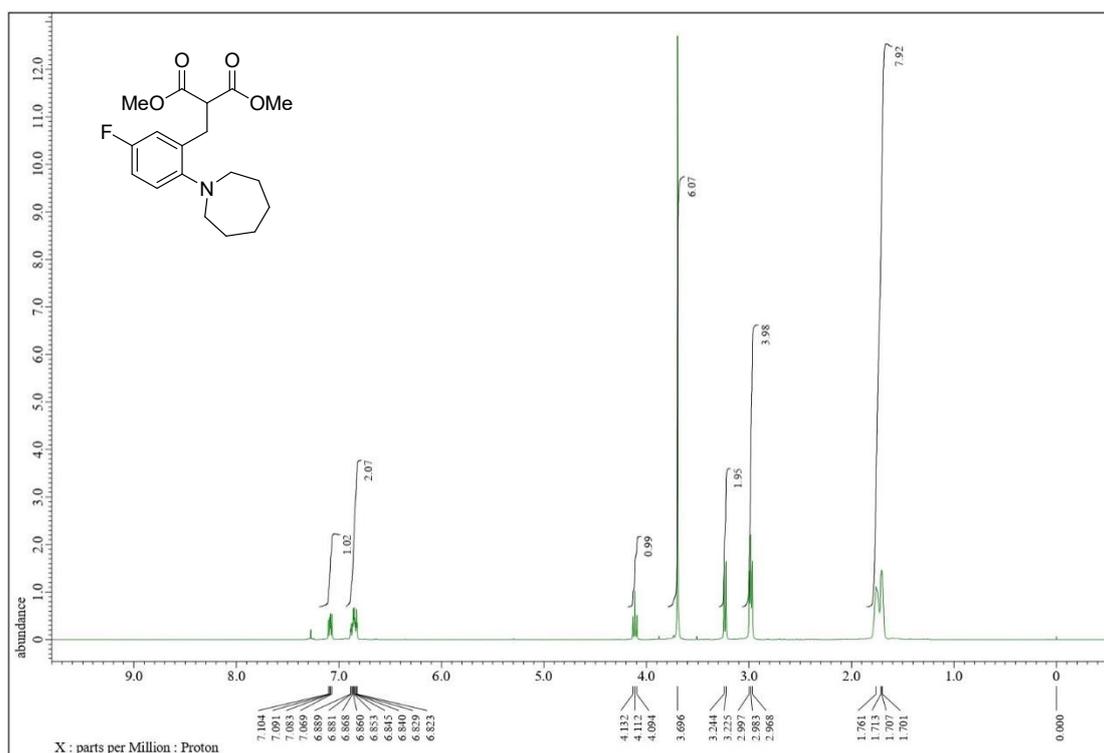


¹H-NMR spectra of **1e** in CDCl₃

MS-103 UPPER 13C NMR
single pulse decoupled gated NOE

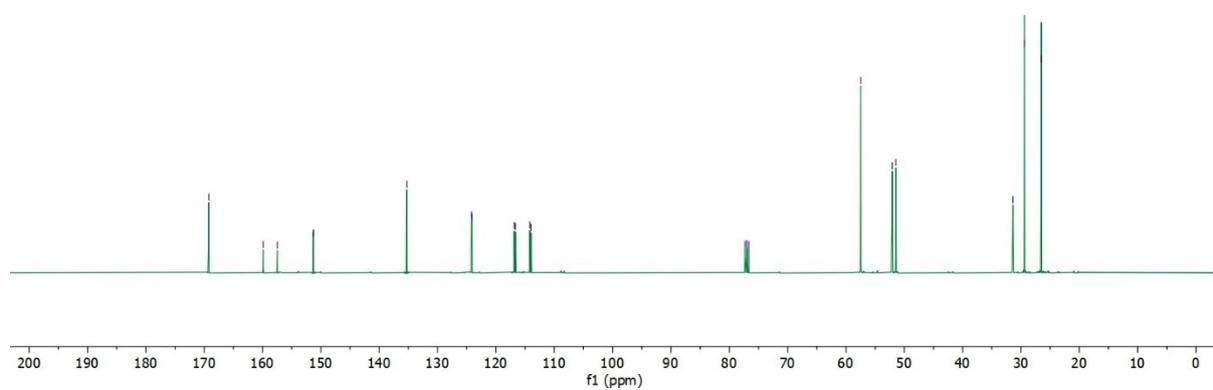
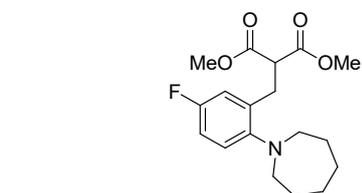
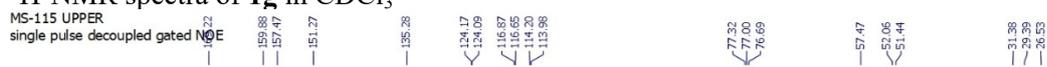


¹³C-NMR spectra of **1e** in CDCl₃

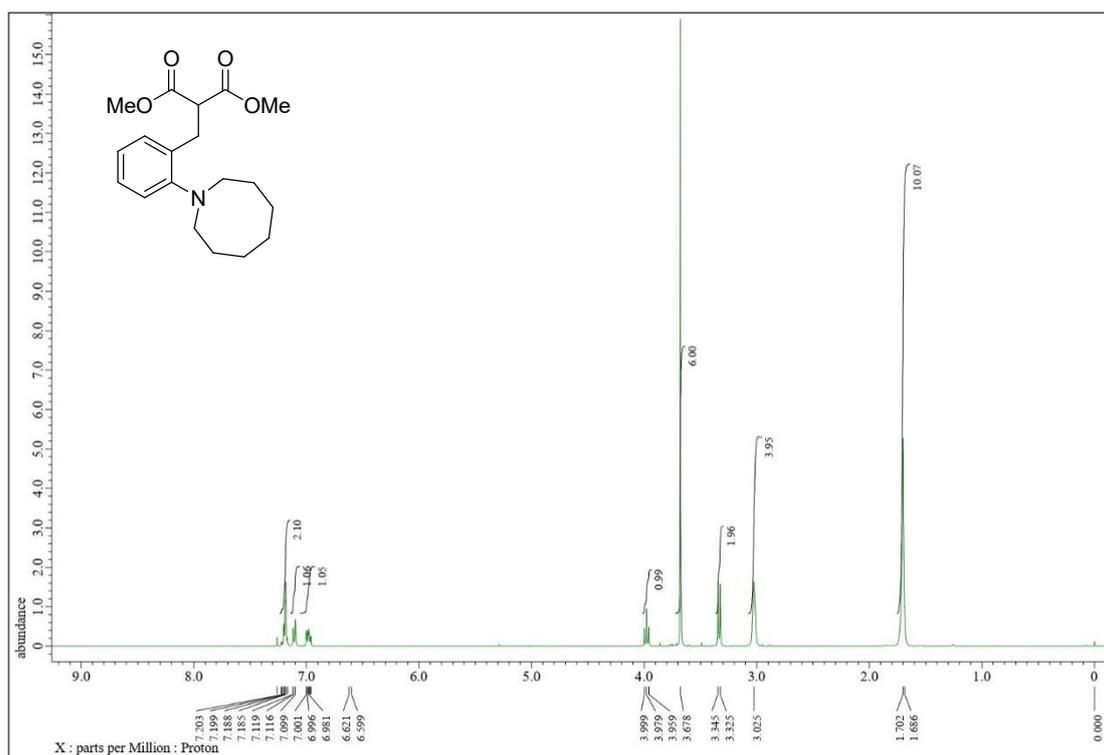


¹H-NMR spectra of **1g** in CDCl₃

MS-115 UPPER
single pulse decoupled gated NOE



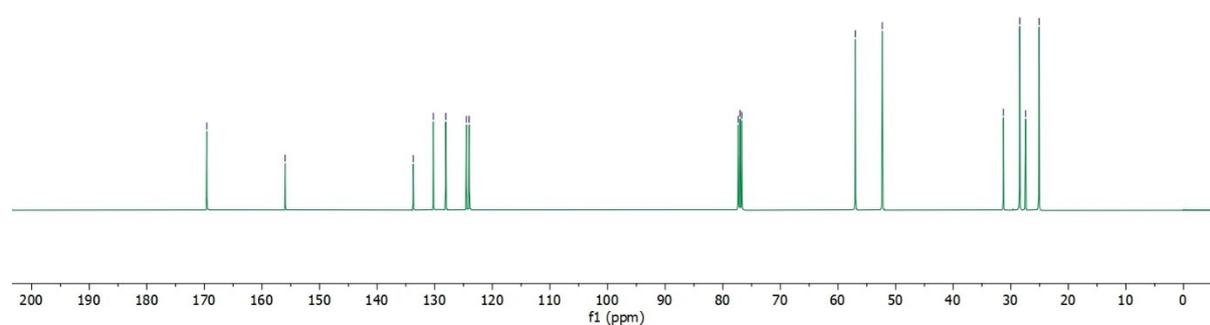
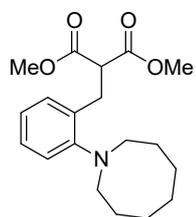
¹³C-NMR spectra of **1g** in CDCl₃



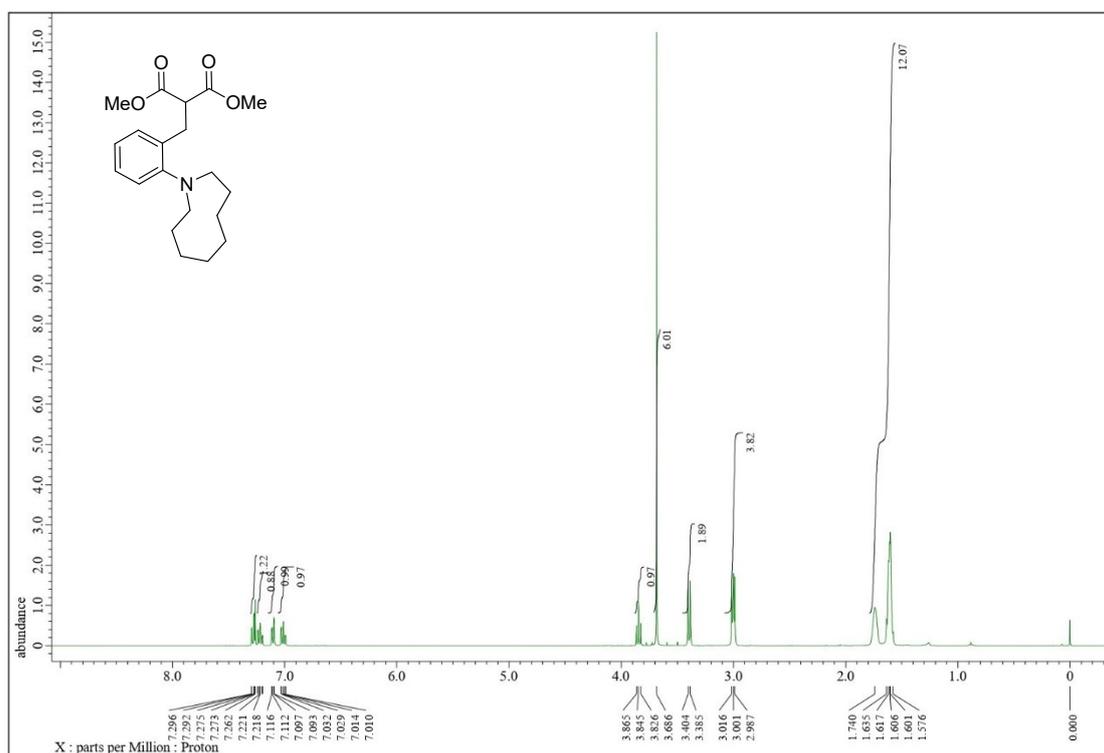
¹H-NMR spectra of **1h** in CDCl₃

ms-157

single pulse decoupled gated NDE

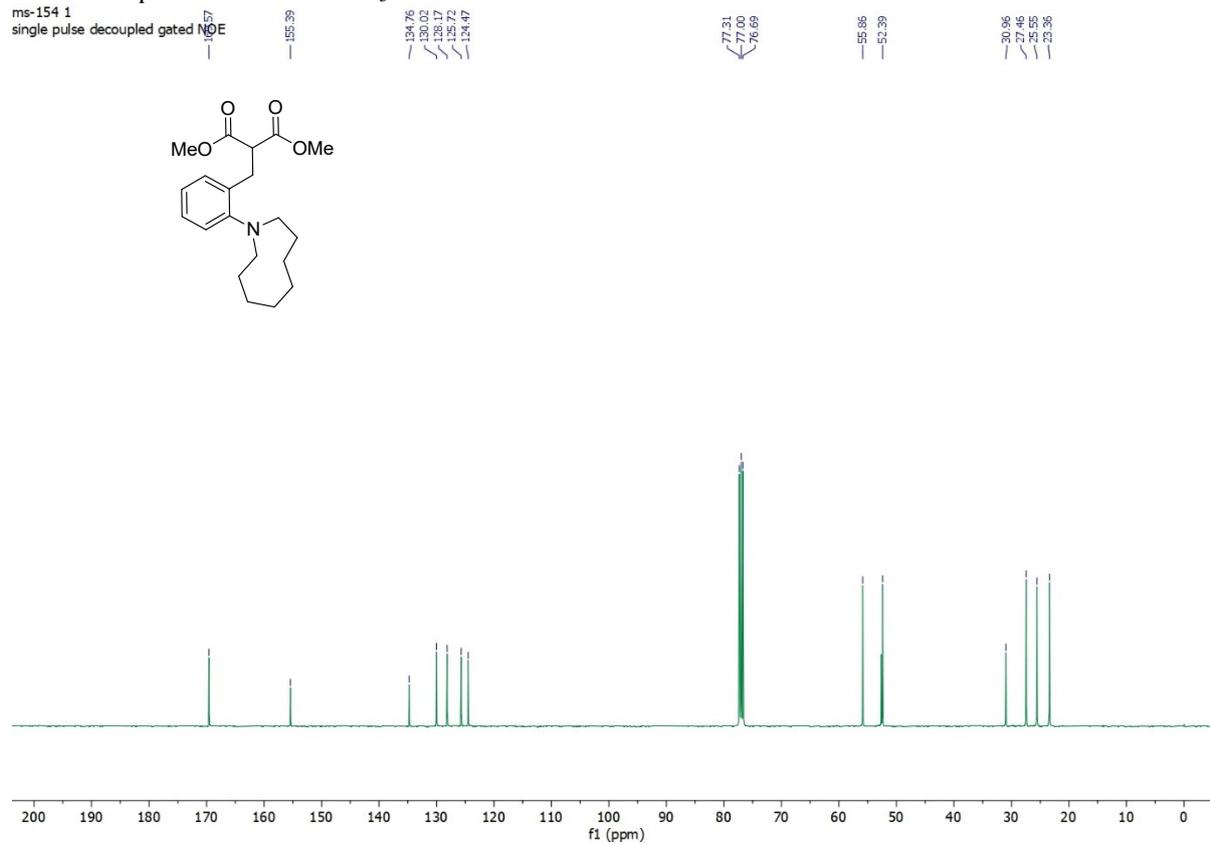
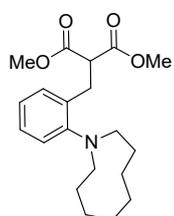


¹³C-NMR of spectra of **1h** in CDCl₃

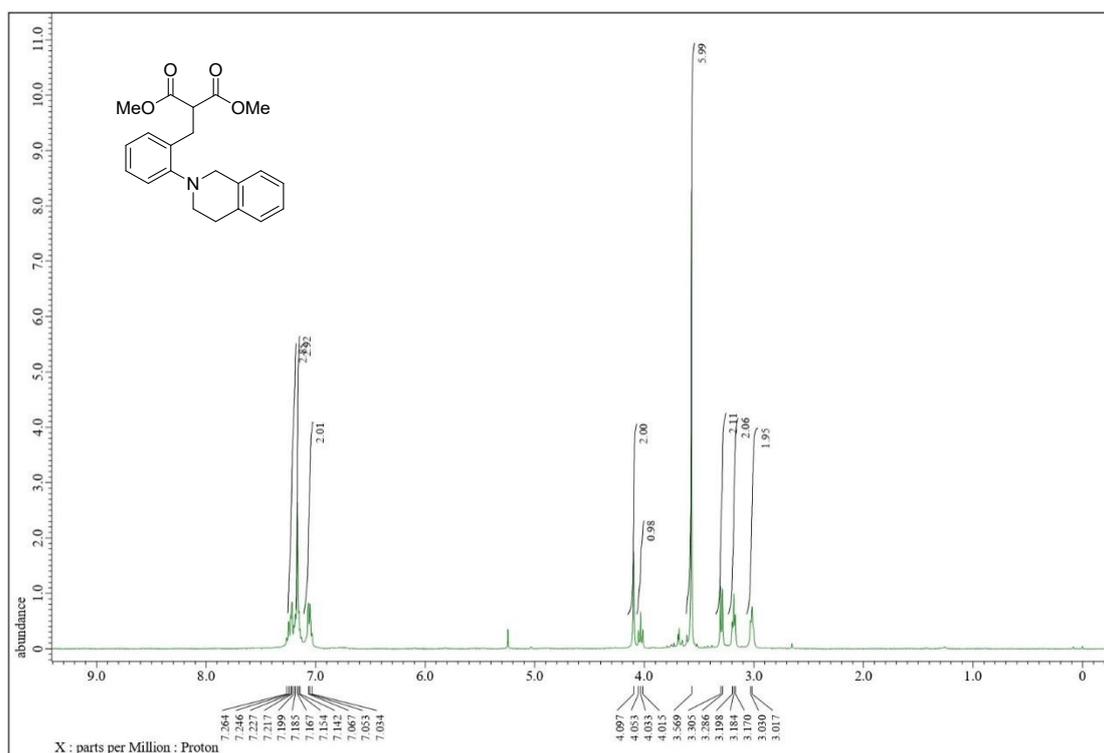


¹H-NMR spectra of **1i in CDCl₃**

ms-154 1
single pulse decoupled gated NOE

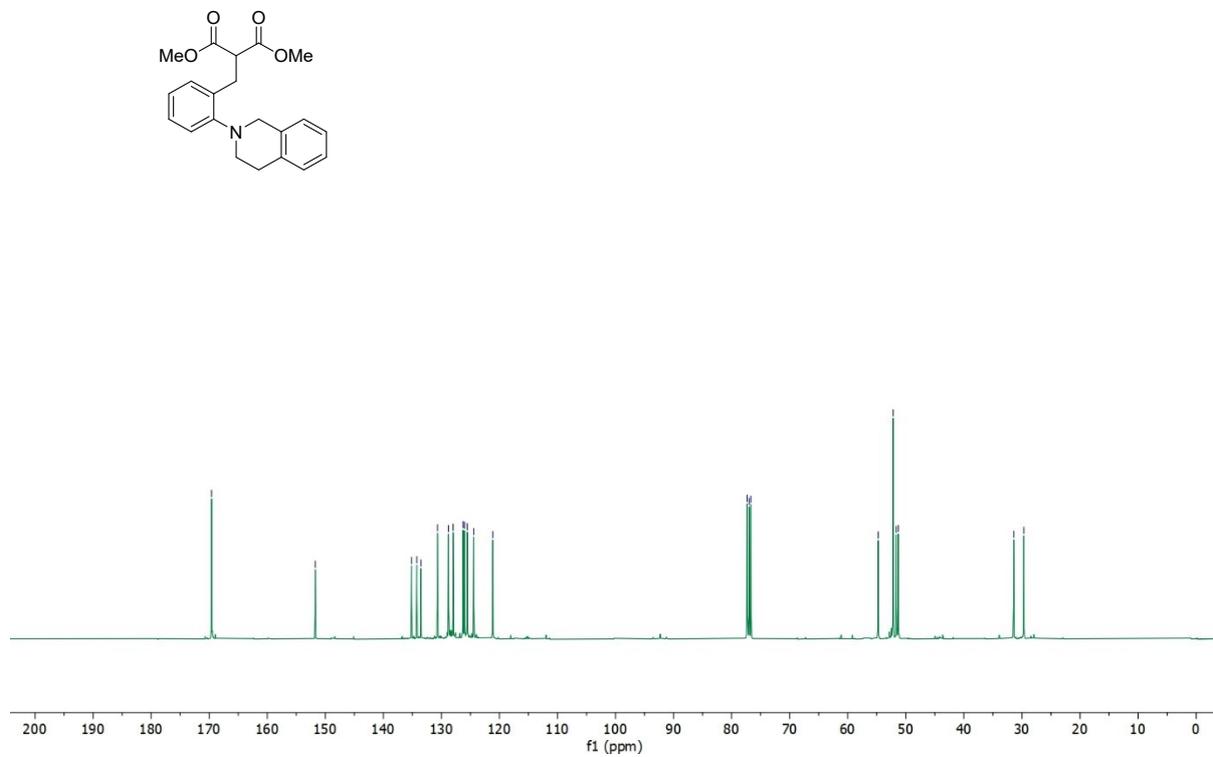


¹³C-NMR spectra of **1i in CDCl₃**

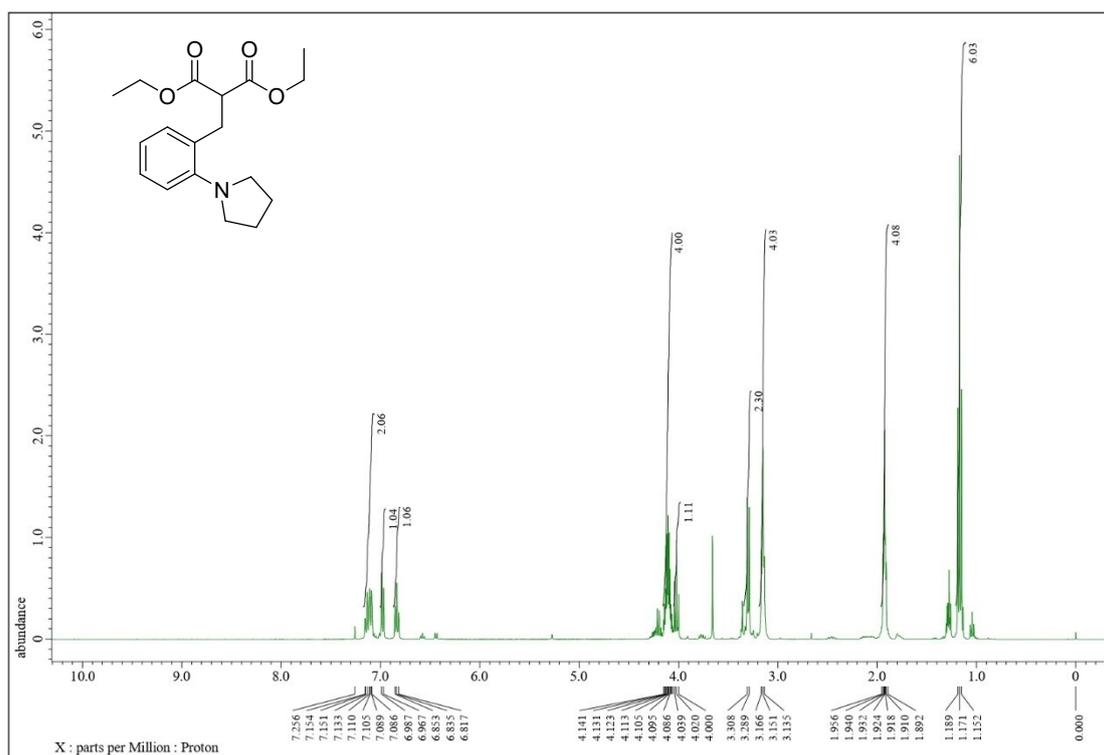


¹H-NMR spectra of **1j** in CDCl₃

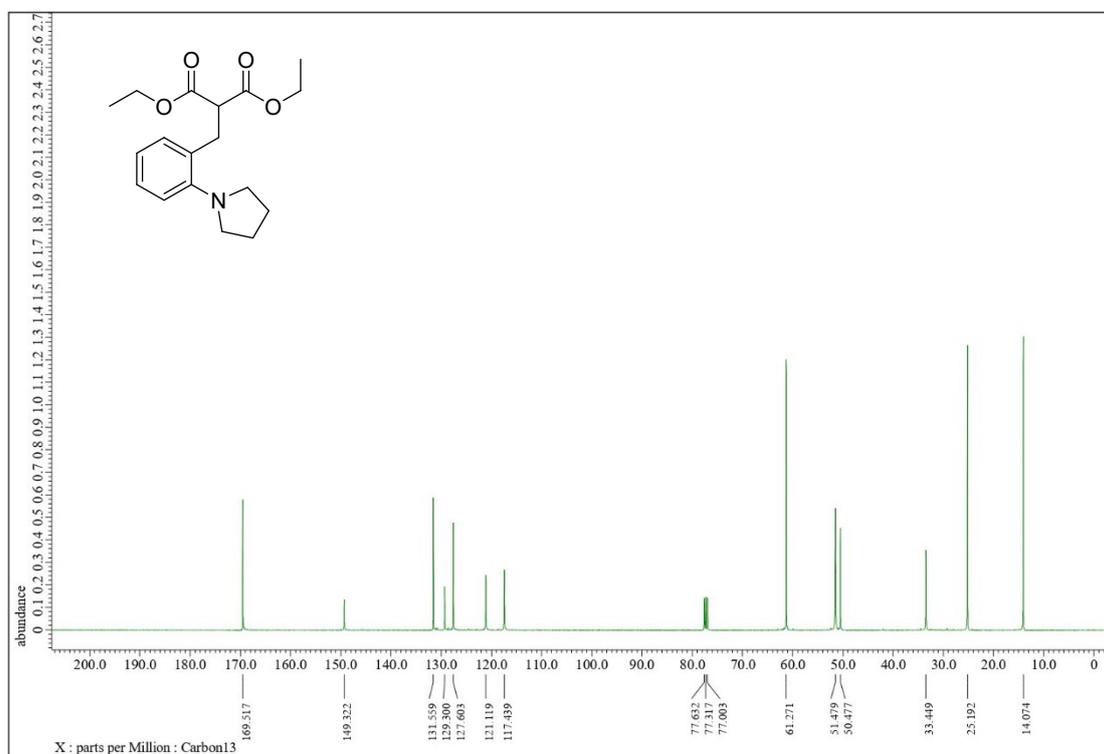
Ms-93 upper 13C-nmr
single pulse decoupled gated NOE



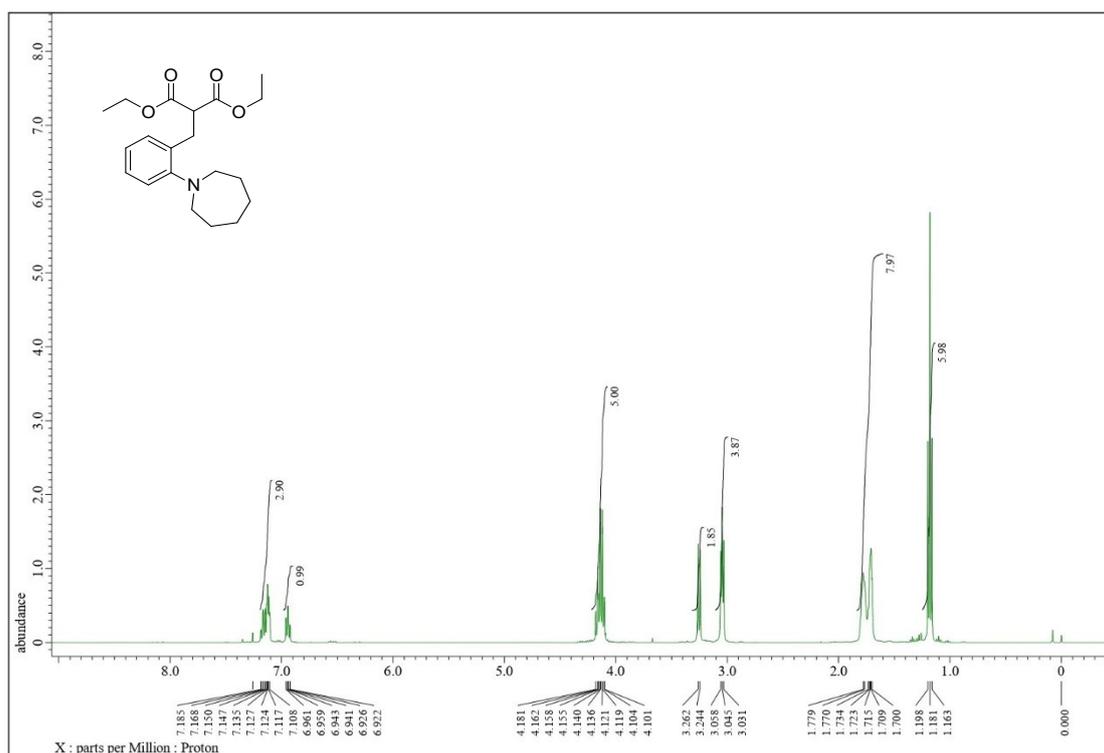
¹³C-NMR spectra of **1j** in CDCl₃



¹H-NMR spectra of **1k** in CDCl₃



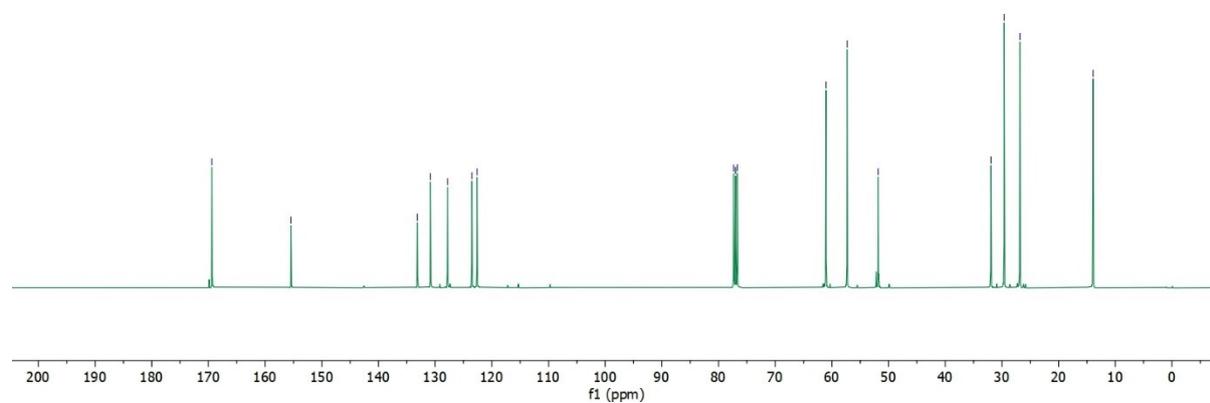
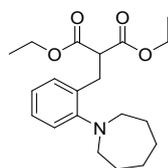
¹³C-NMR spectra of **1k** in CDCl₃



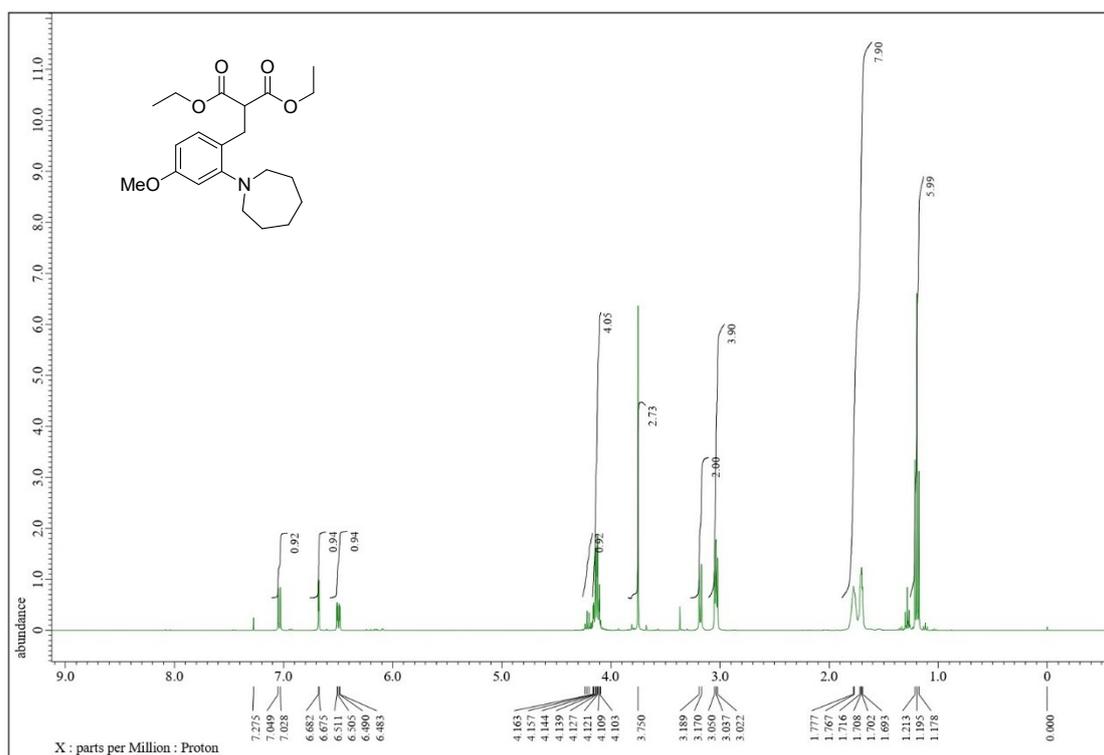
¹H-NMR spectra of **11** in CDCl₃

13

single pulse decoupled gated NQE



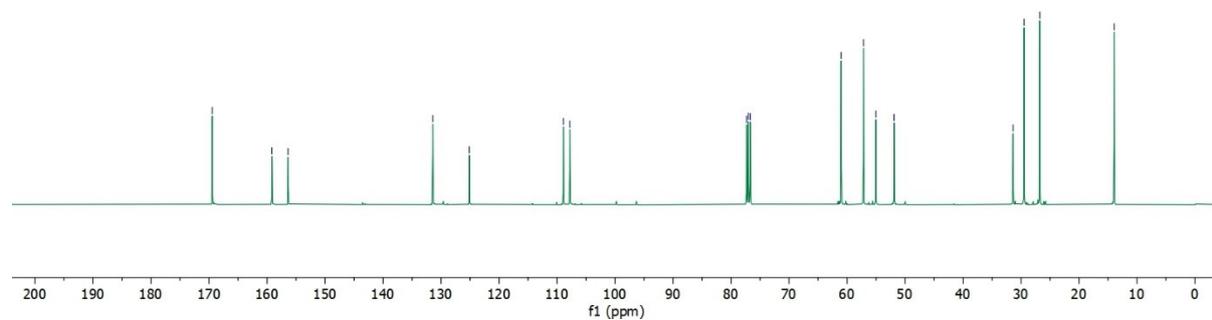
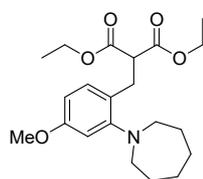
¹³C-NMR spectra of **11** in CDCl₃



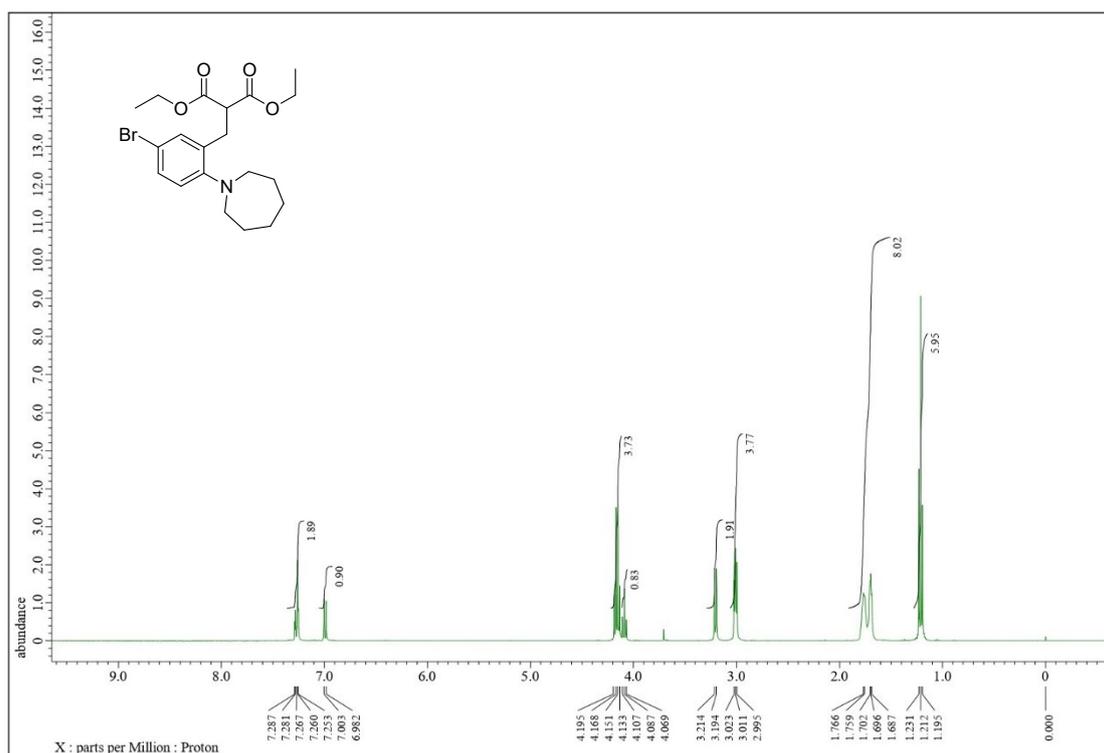
¹H-NMR spectra of **1m** in CDCl₃

ms-132

single pulse decoupled gated NOE



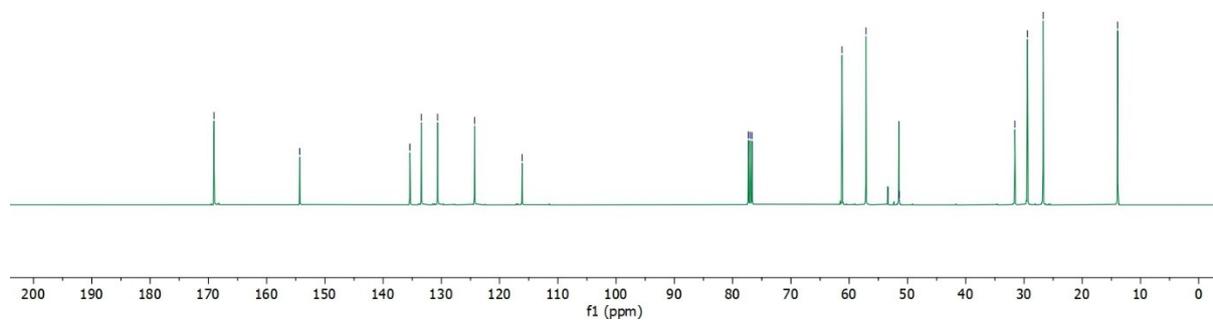
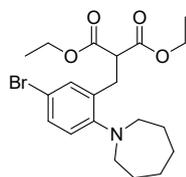
¹³C-NMR spectra of **1m** in CDCl₃



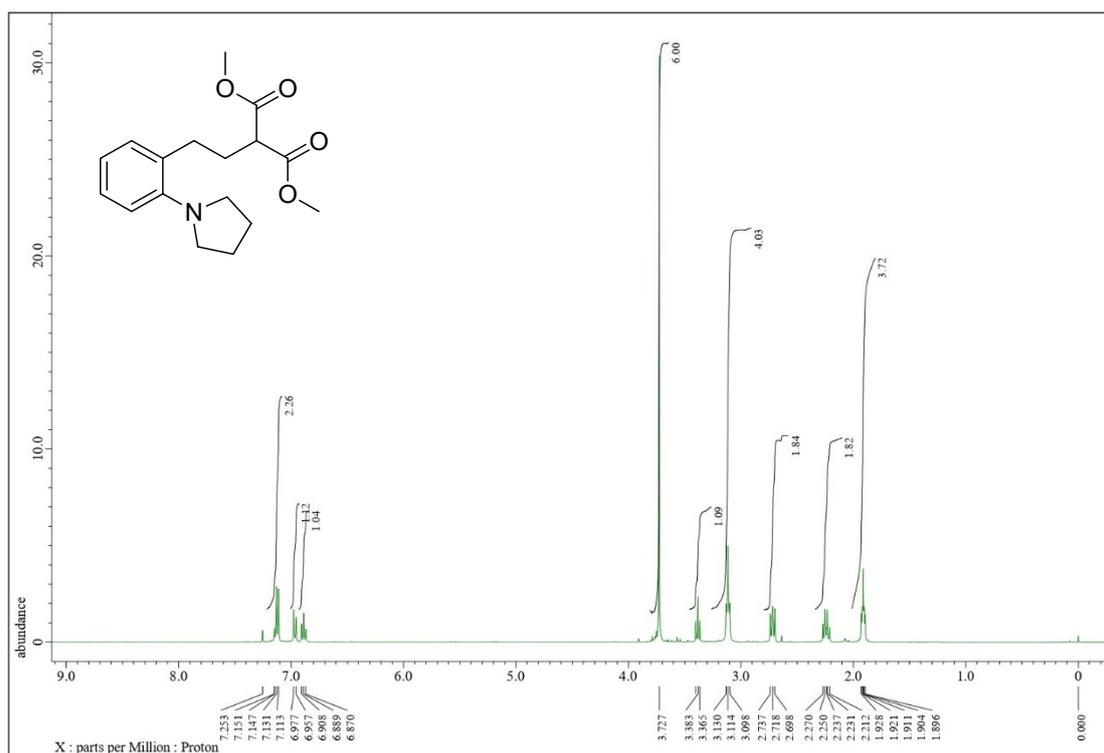
¹H-NMR spectra of **1n in CDCl₃**

ms-131

single pulse decoupled gated NQE



¹³C-NMR spectra of **1n in CDCl₃**



¹H-NMR spectra of **3a** in CDCl₃

ms-47

single pulse decoupled gated NOESY

168.75

148.76

132.09

130.42

126.78

121.14

117.12

77.32

77.00

76.68

52.32

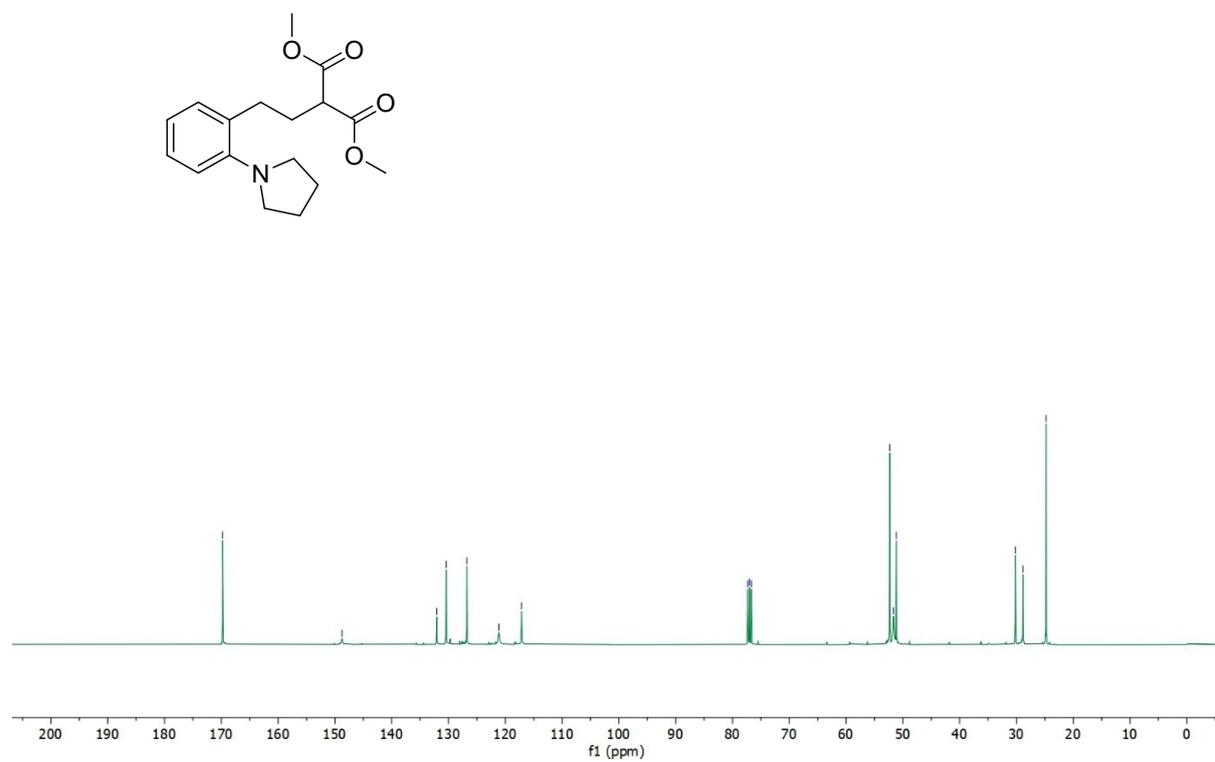
51.65

51.17

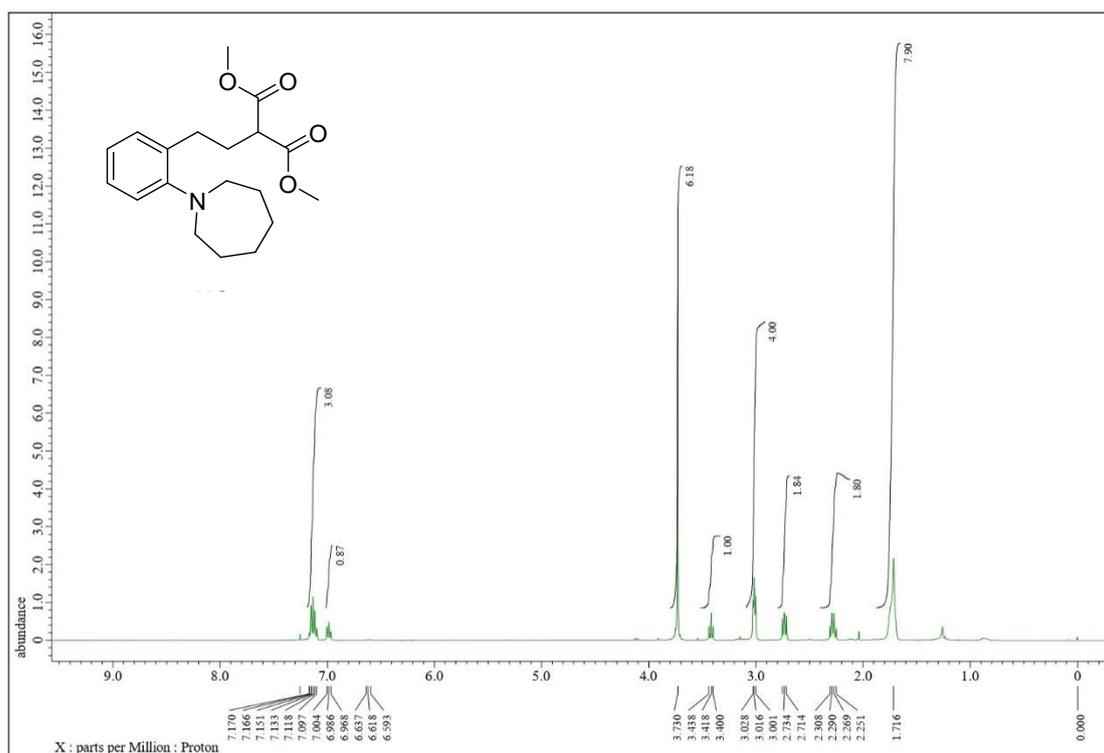
30.18

28.84

24.81

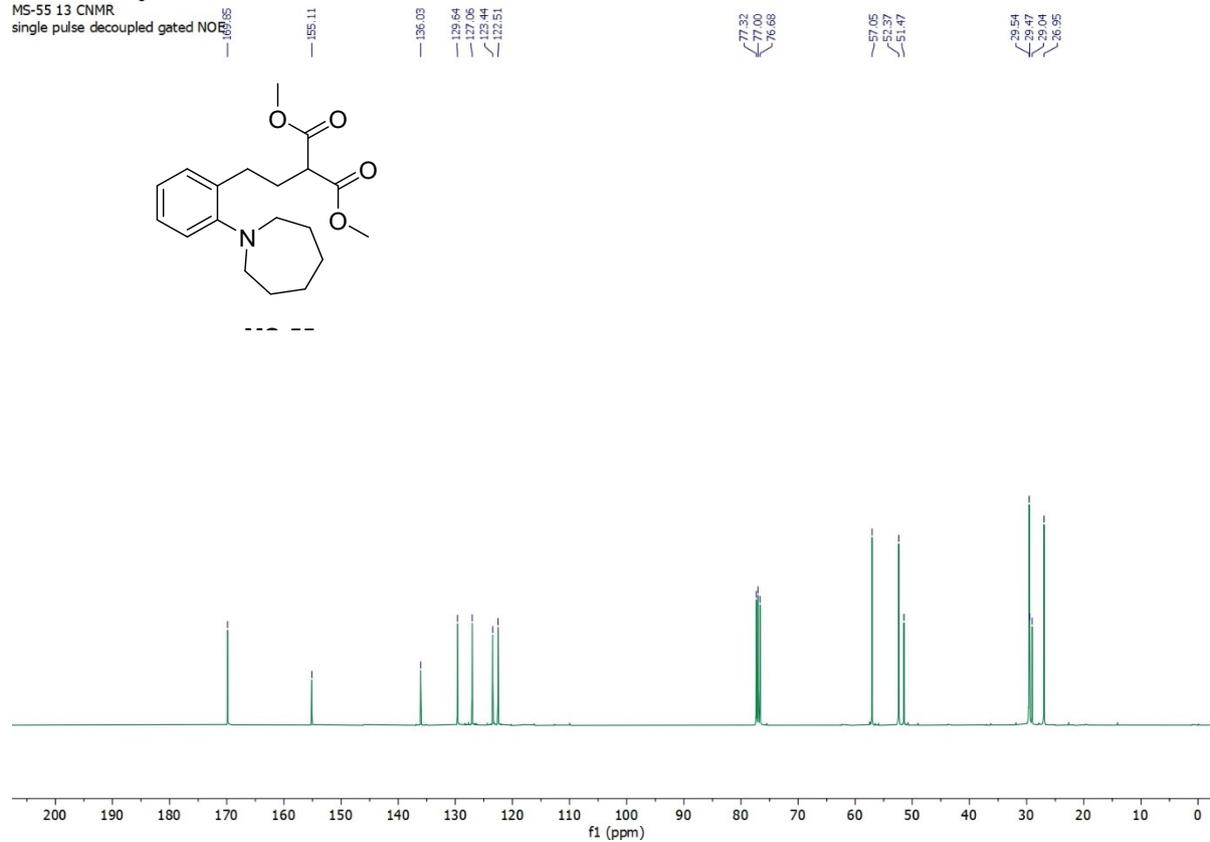


¹³C-NMR spectra of **3a** in CDCl₃

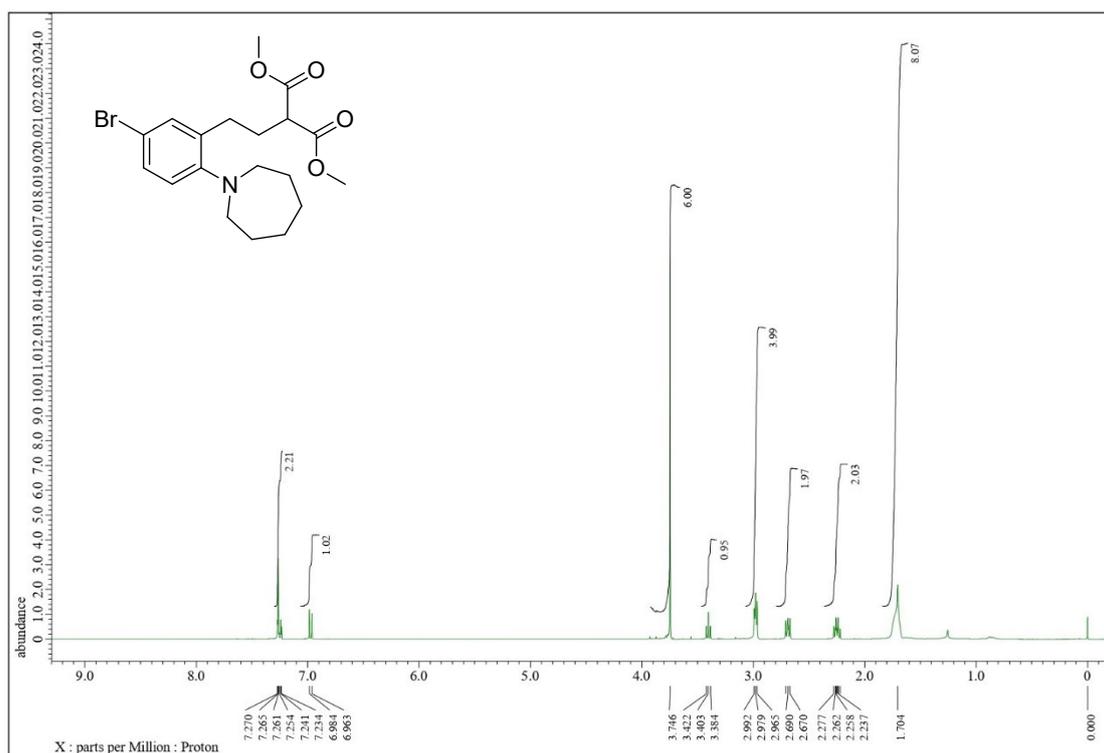


¹H-NMR spectra of 3b in CDCl₃

MS-55 13 CNMR
single pulse decoupled gated NOE

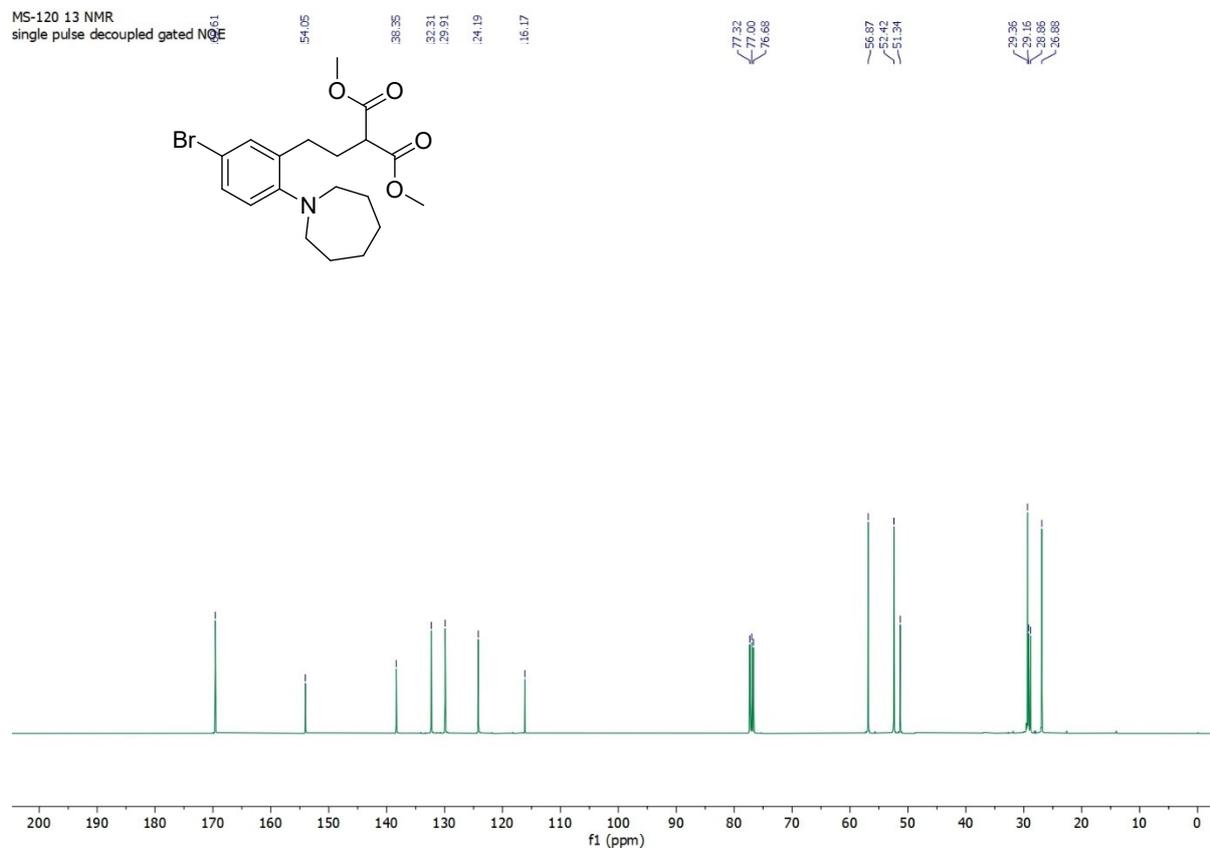


¹³C-NMR spectra of 3b in CDCl₃

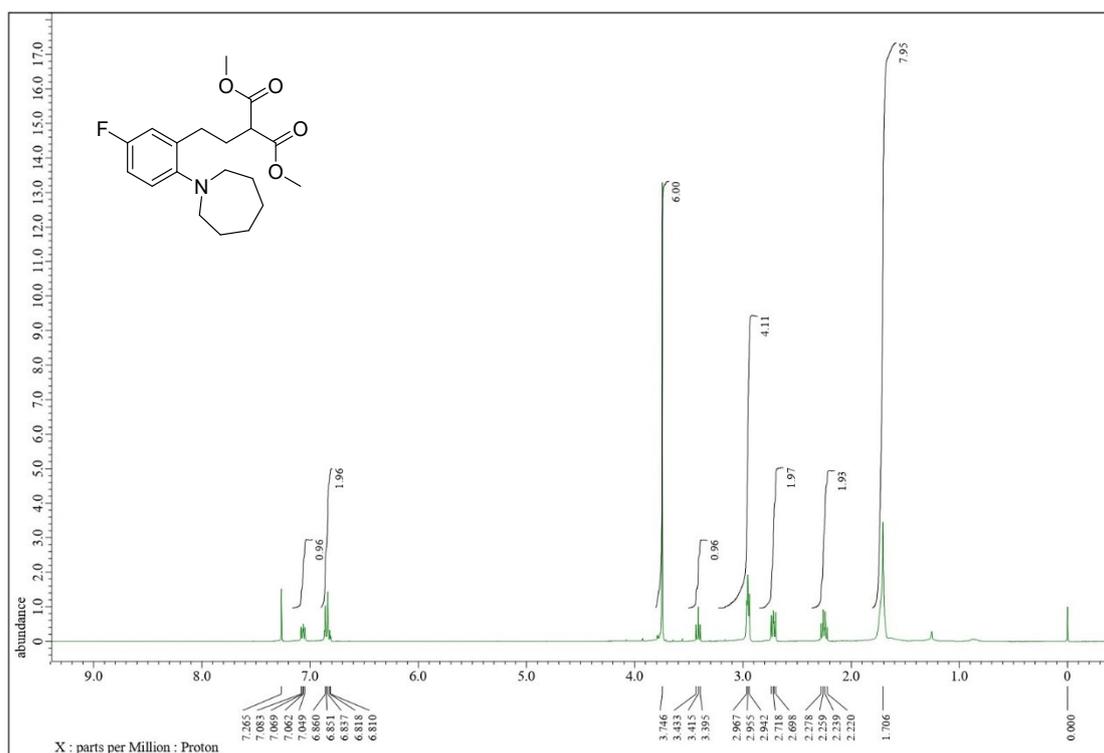


¹H-NMR spectra of **3c** in CDCl₃

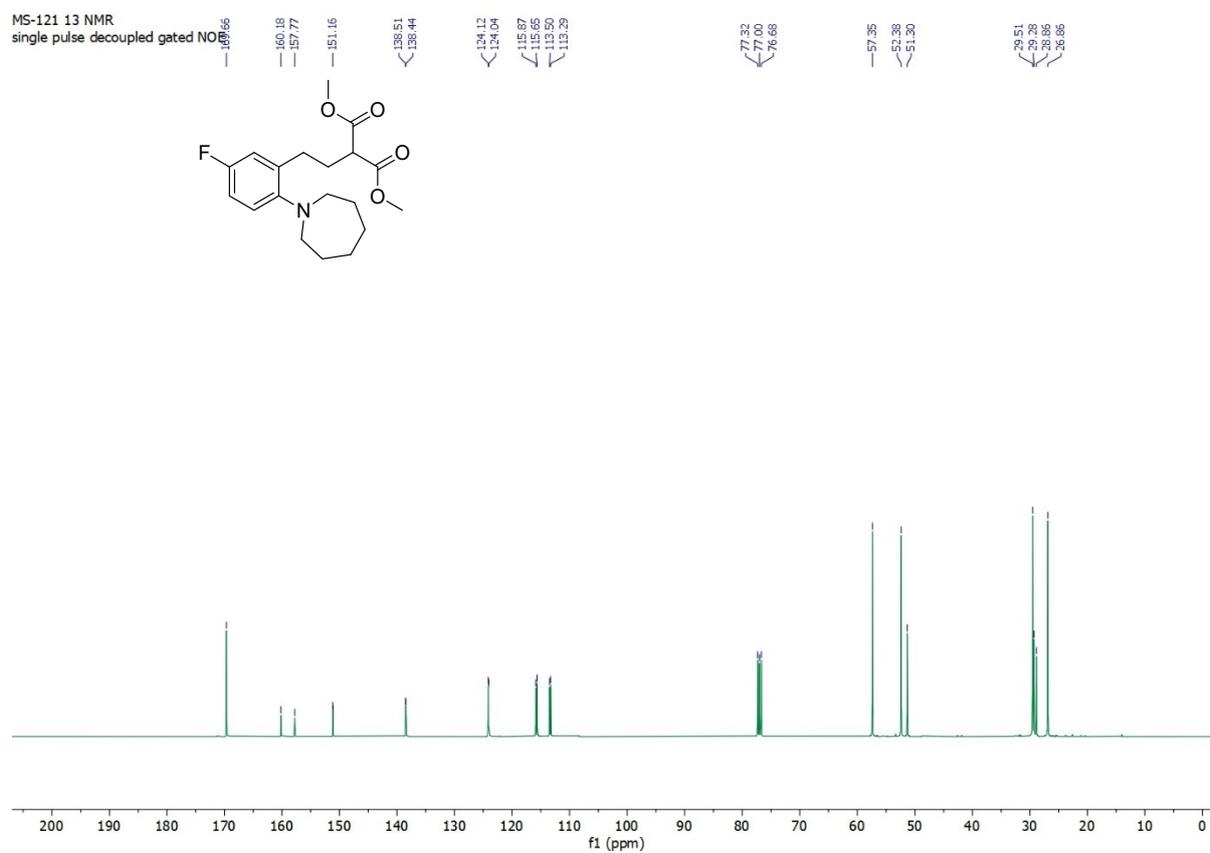
MS-120 13 NMR
single pulse decoupled gated NOE



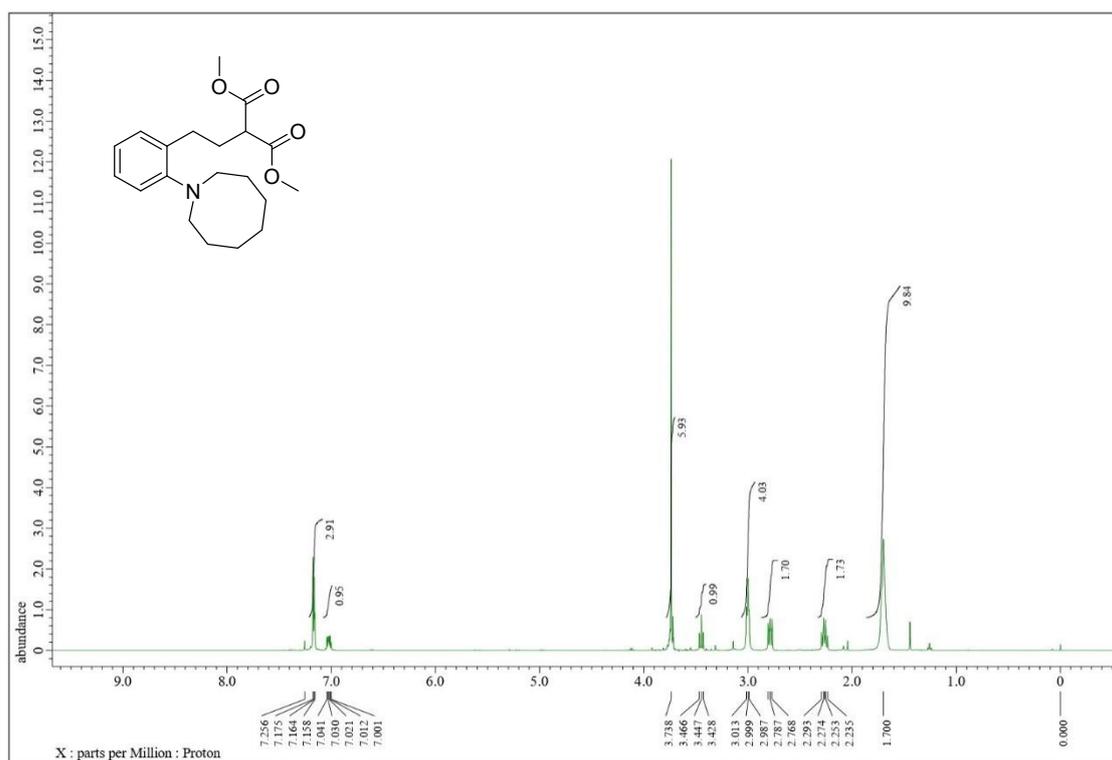
¹³C-NMR spectra of **3c** in CDCl₃



¹H-NMR spectra of **3d** in CDCl₃



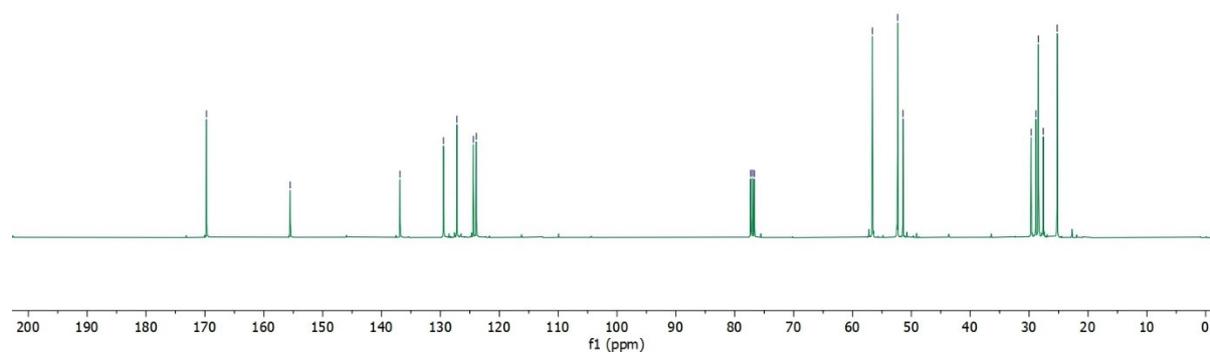
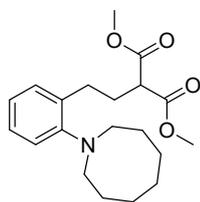
¹³C-NMR spectra of **3d** in CDCl₃



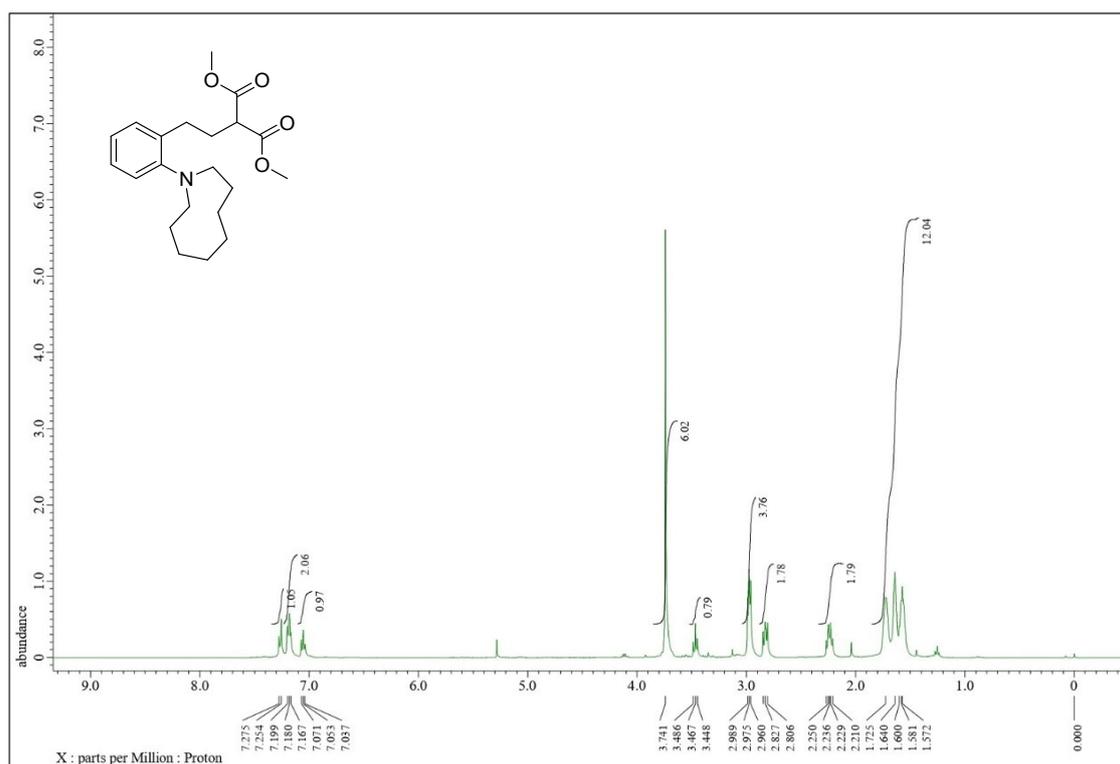
$^1\text{H-NMR}$ spectra of **3e** in CDCl_3

ms-155 13 cnmr

single pulse decoupled gated NOE



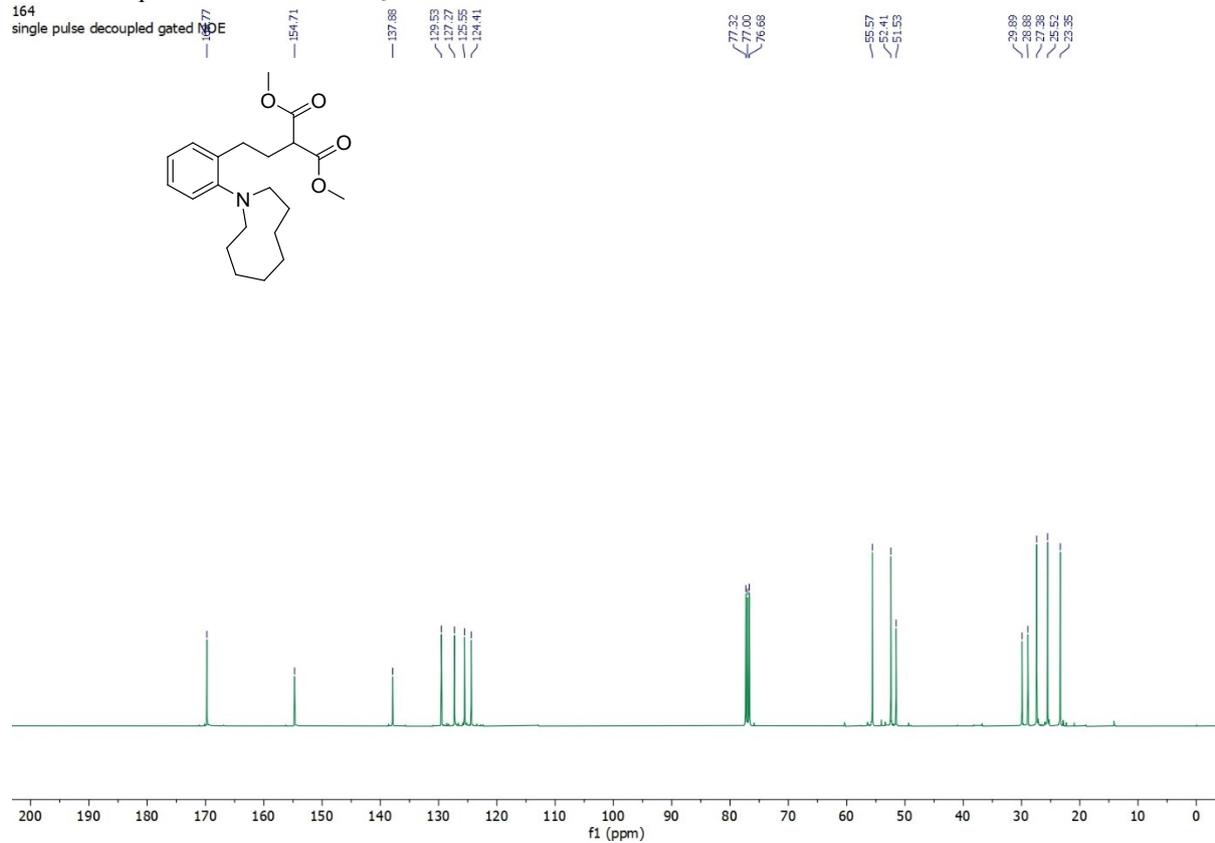
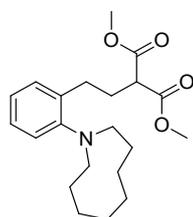
$^{13}\text{C-NMR}$ spectra of **3e** in CDCl_3



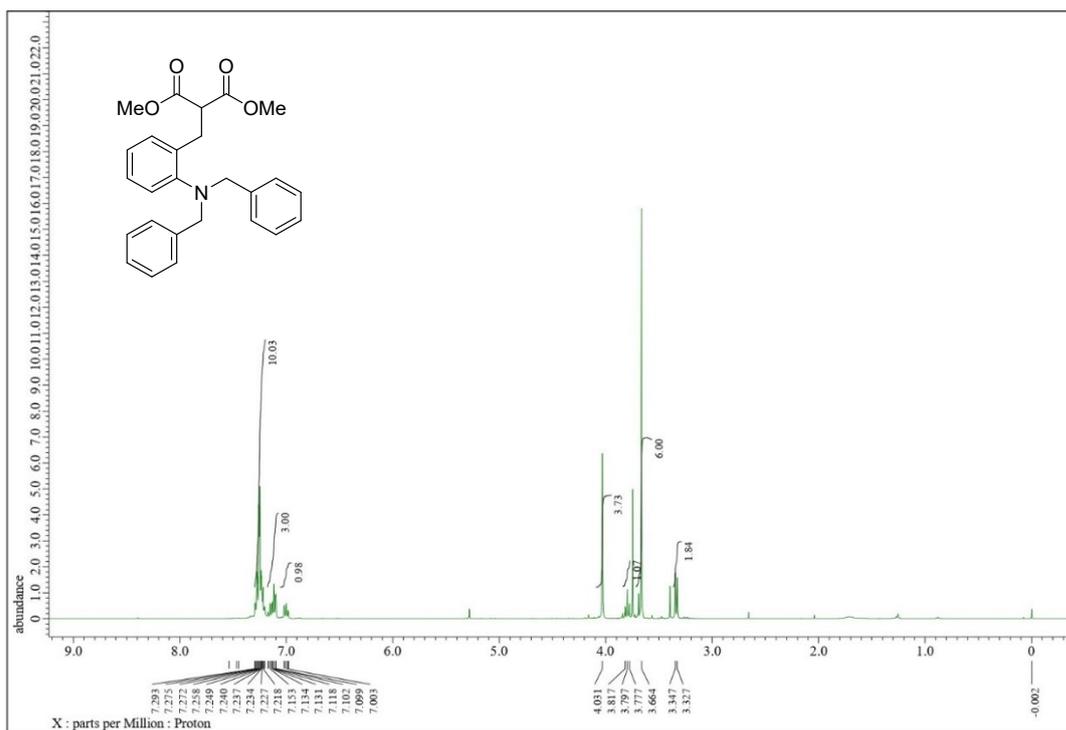
¹H-NMR spectra of 3f in CDCl₃

164

single pulse decoupled gated NMR



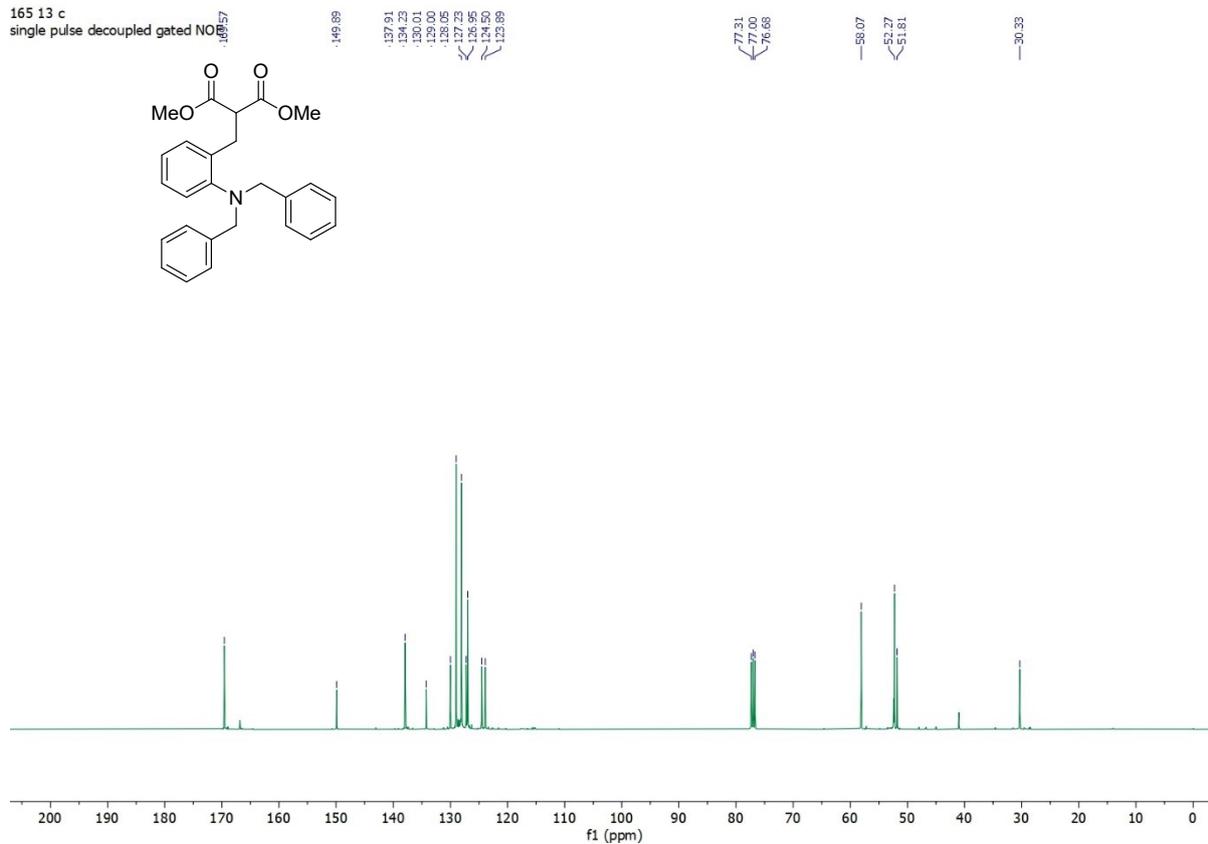
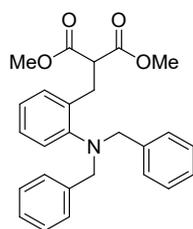
¹³C-NMR spectra of 3f in CDCl₃



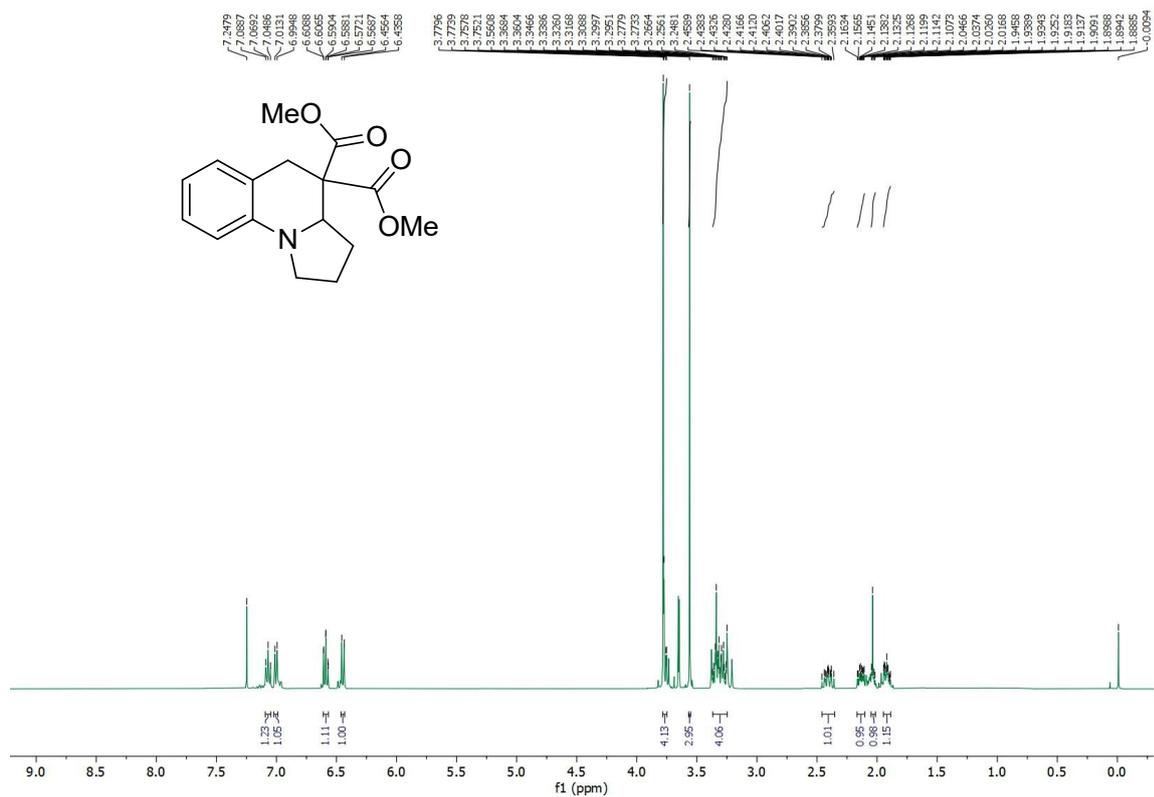
¹H

-NMR spectra of **6** in CDCl₃

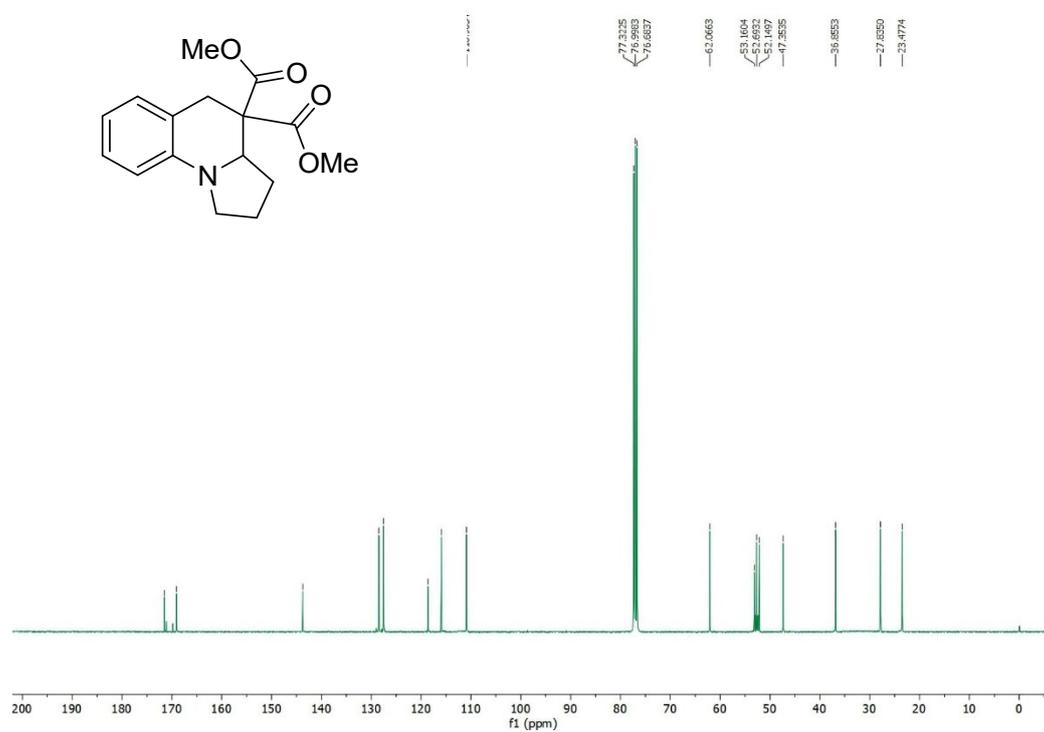
165 13 c
single pulse decoupled gated NOE



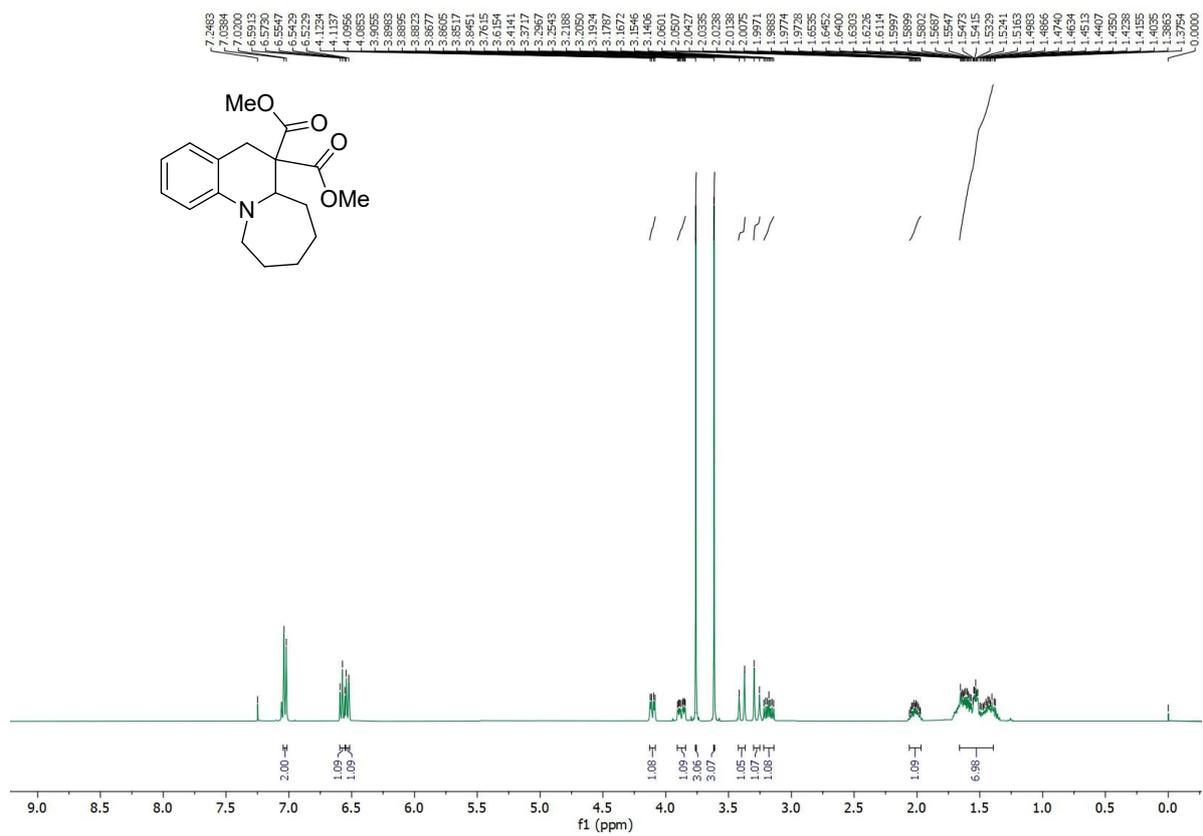
¹³C-NMR spectra of **6** in CDCl₃



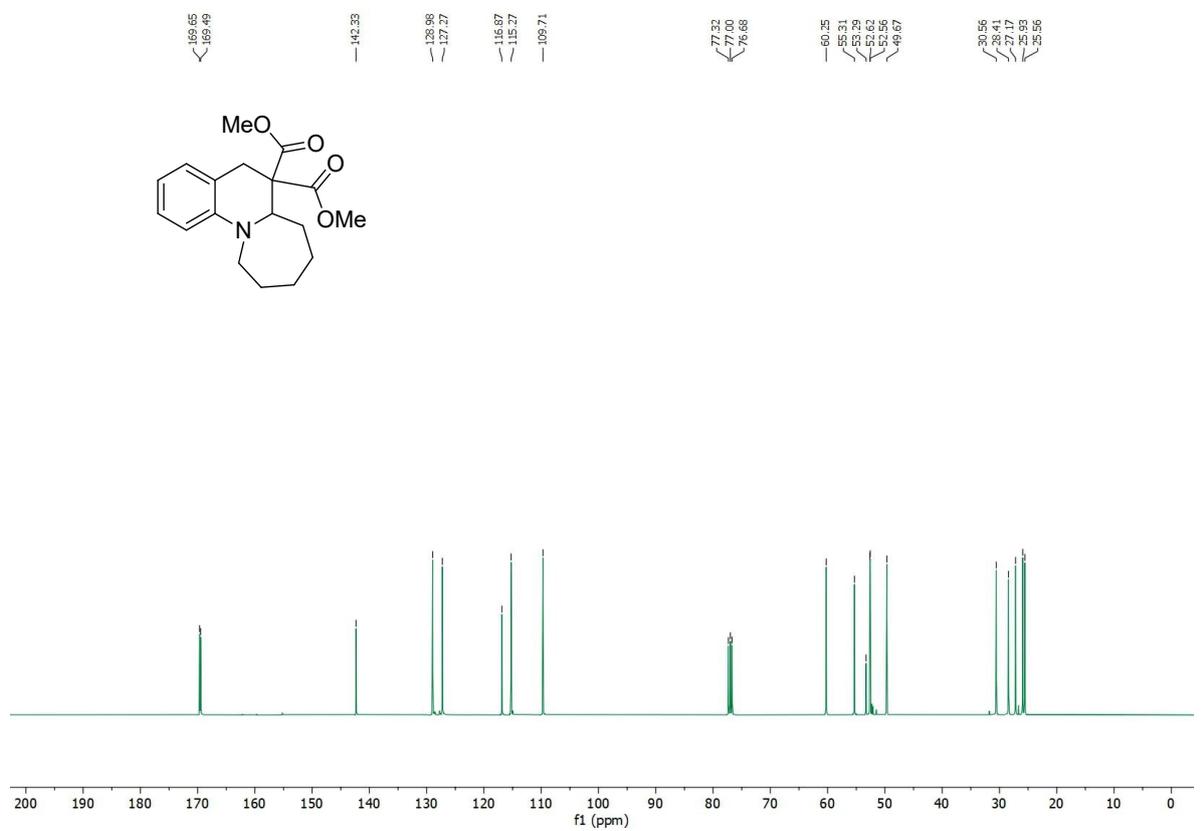
¹H-NMR spectra of **2a** in CDCl₃



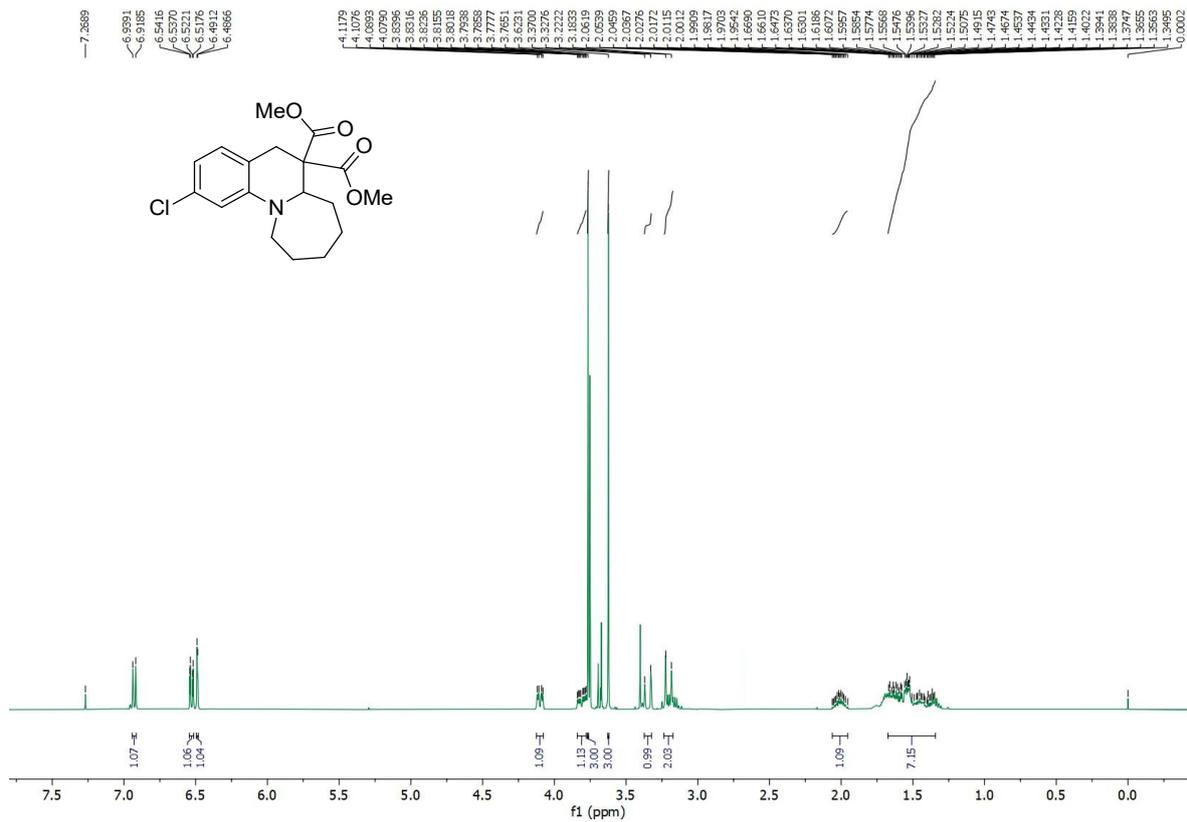
¹³C-NMR spectra of **2a** in CDCl₃



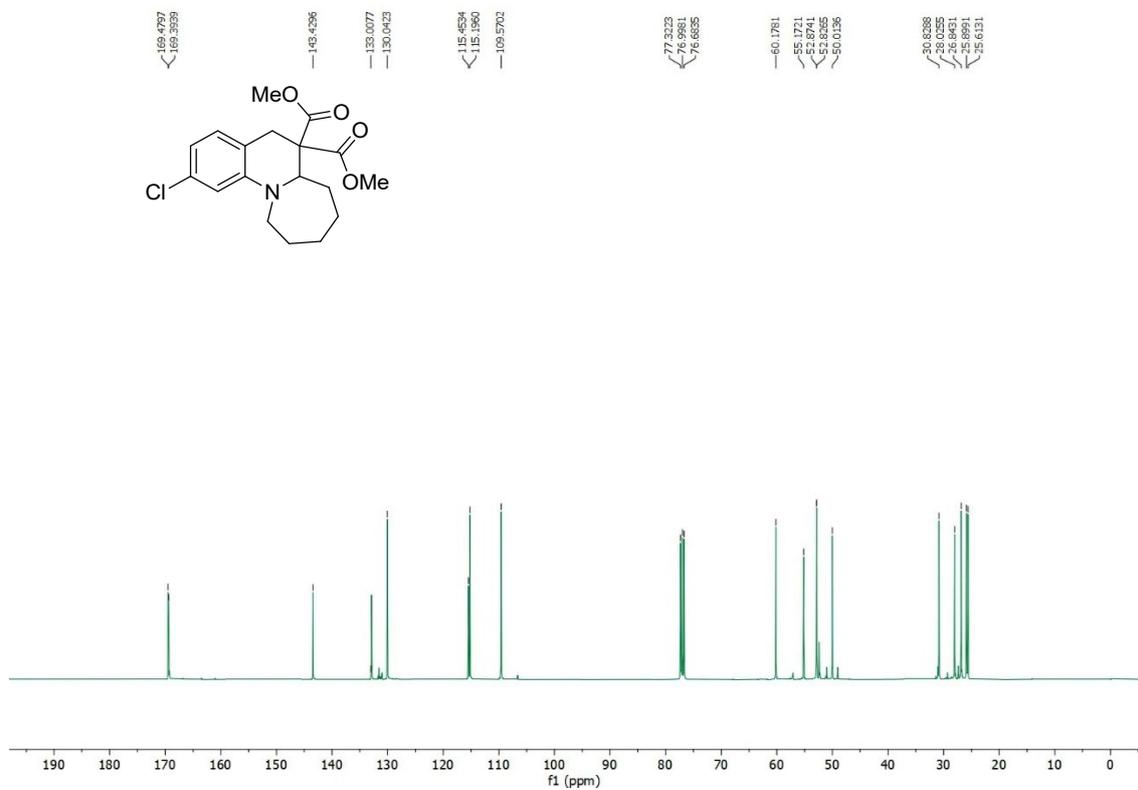
$^1\text{H-NMR}$ spectra of **2b** in CDCl_3



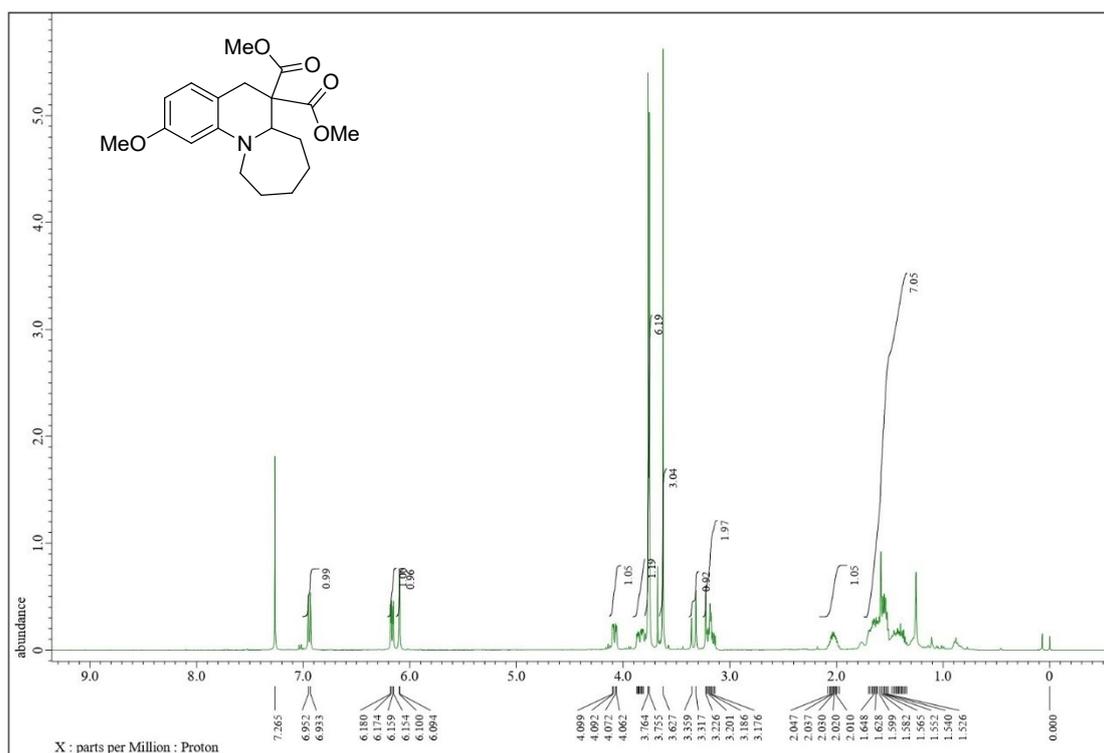
$^{13}\text{C-NMR}$ spectra of **2b** in CDCl_3



¹H-NMR spectra of **2c** in CDCl₃

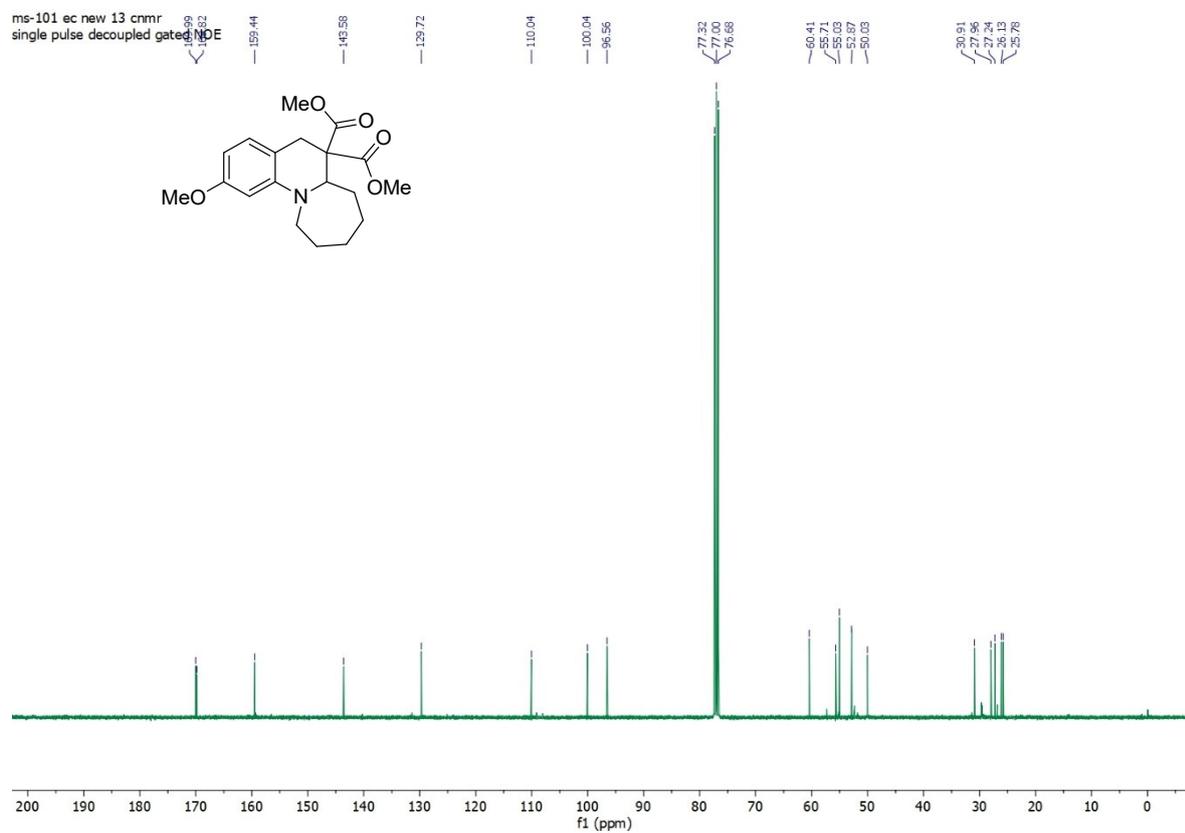


¹³C-NMR spectra of **2c** in CDCl₃

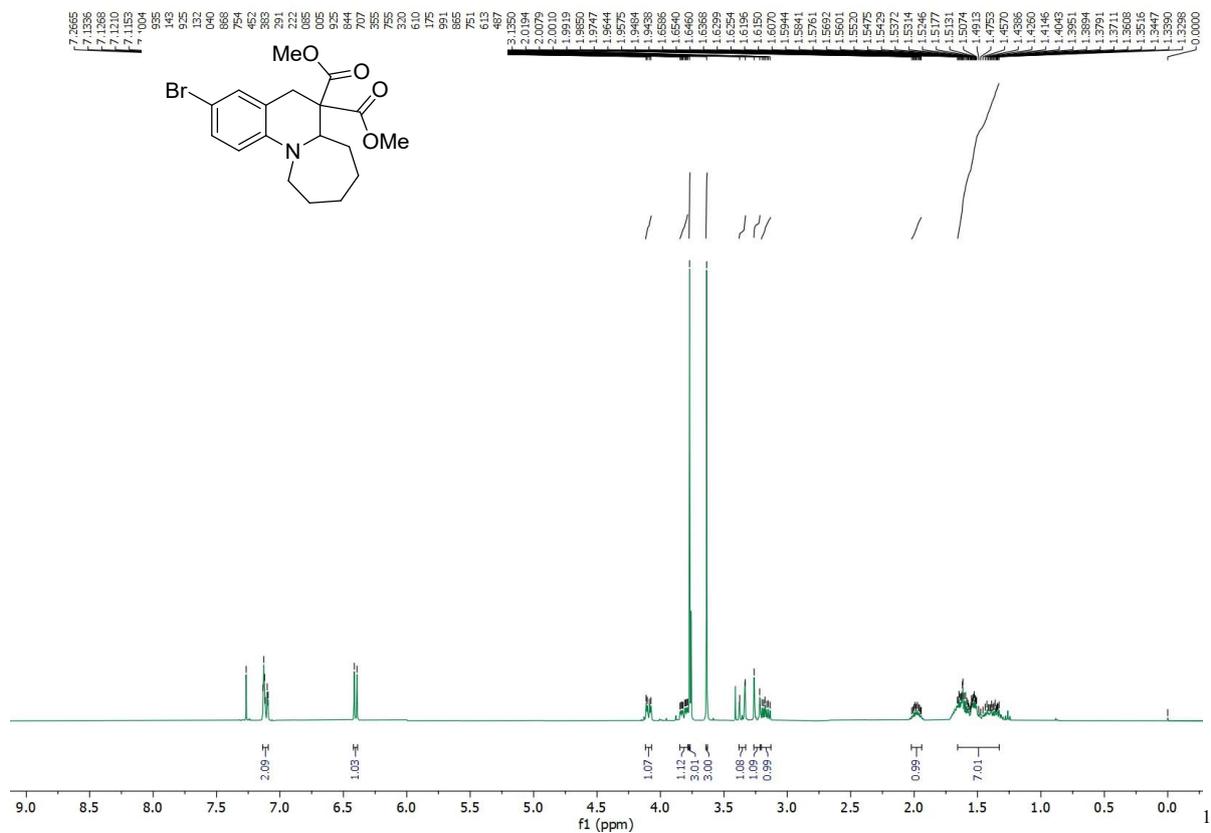


¹H-NMR spectra of **2d** in CDCl₃

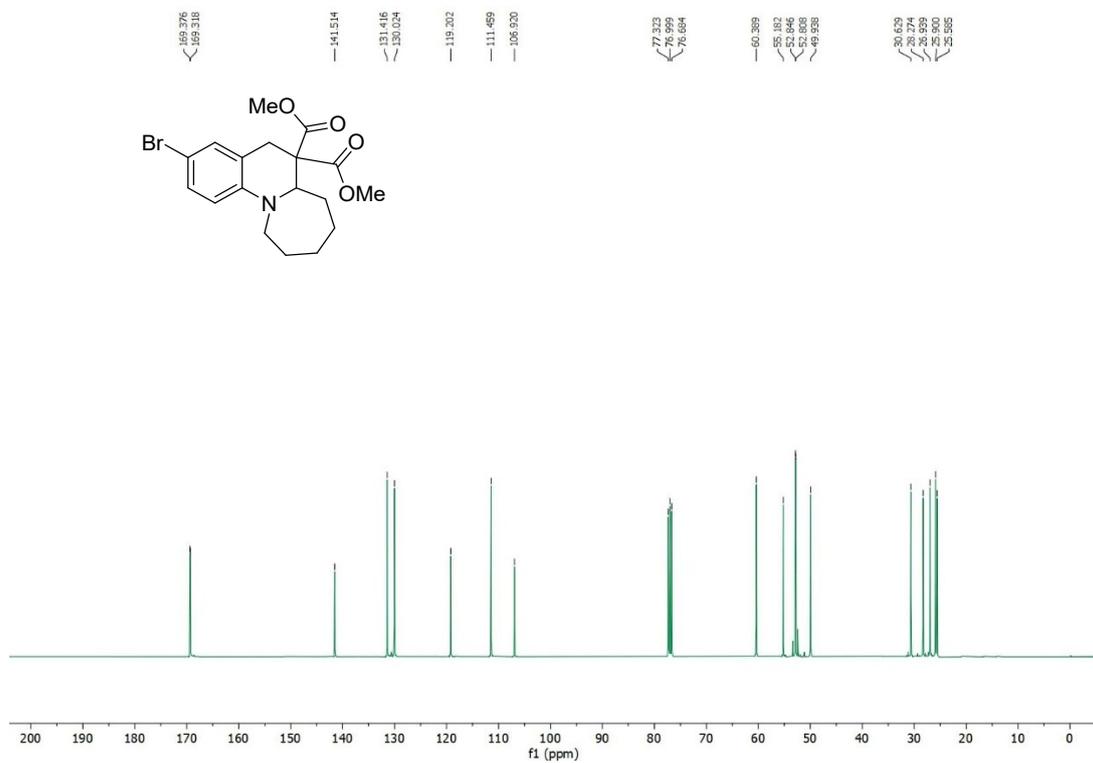
ms-101 ec new 13 cmr
single pulse decoupled gated NDE



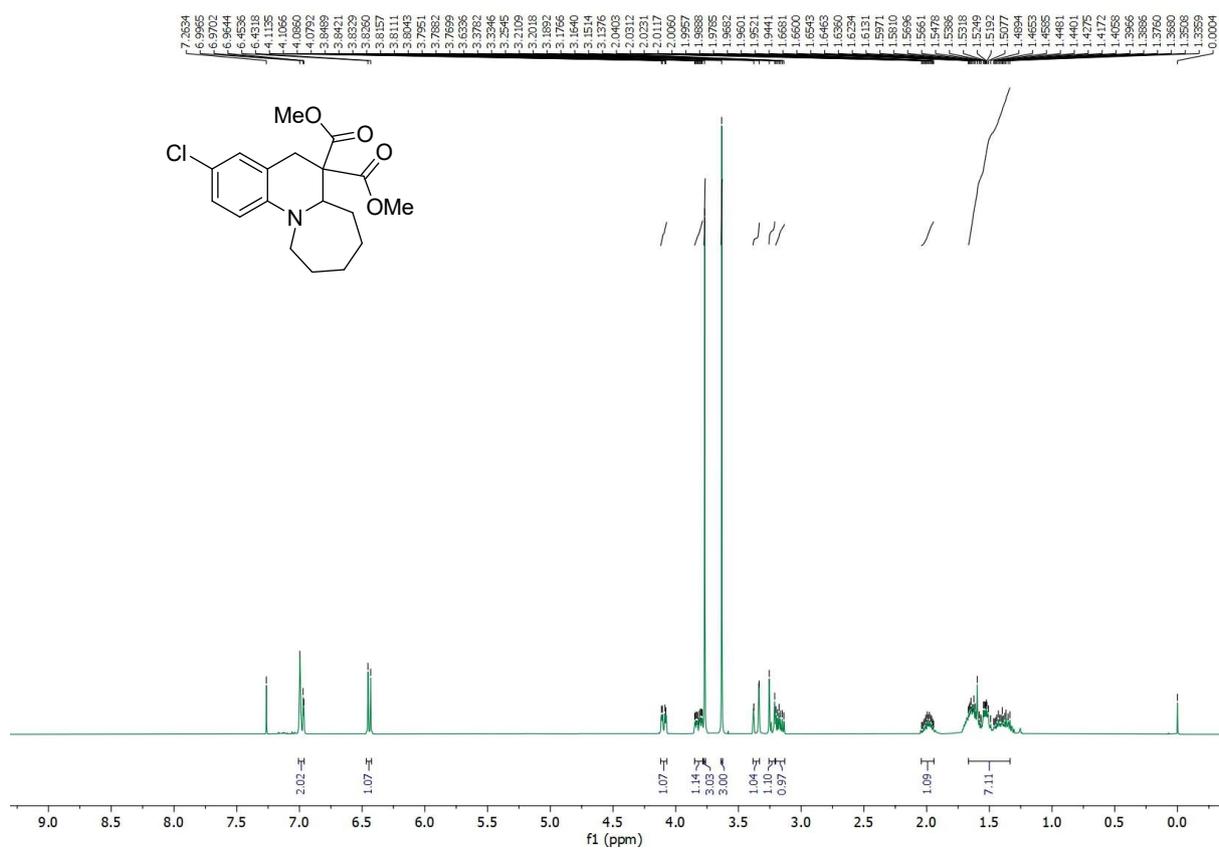
¹³C-NMR spectra of **2d** in CDCl₃



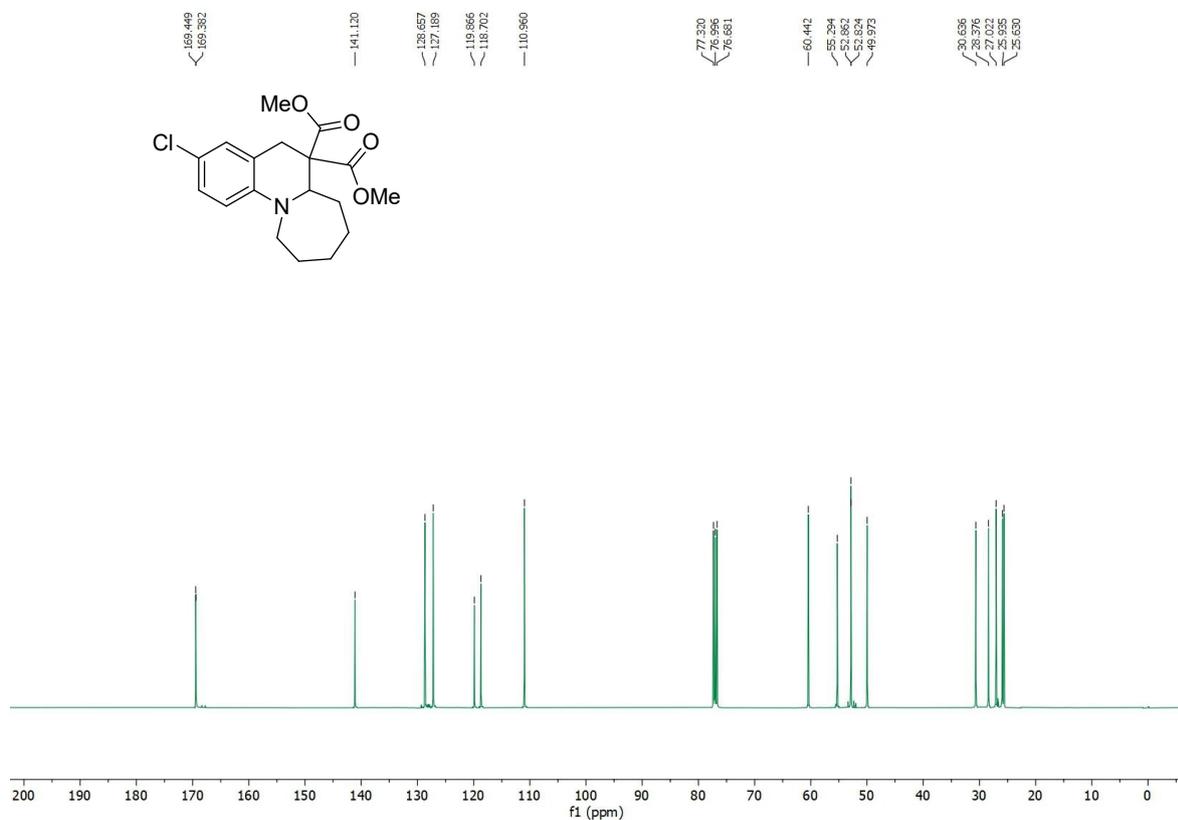
H-NMR spectra of **2e** in CDCl₃



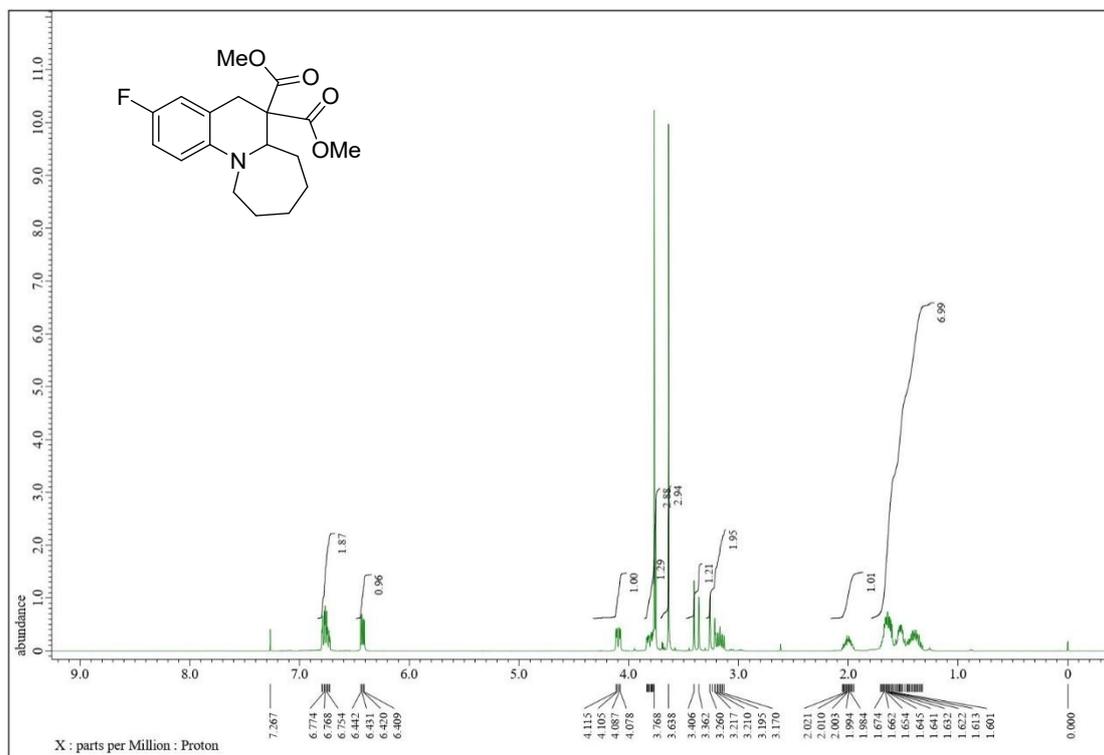
^{13}C -NMR spectra of **2e** in CDCl_3



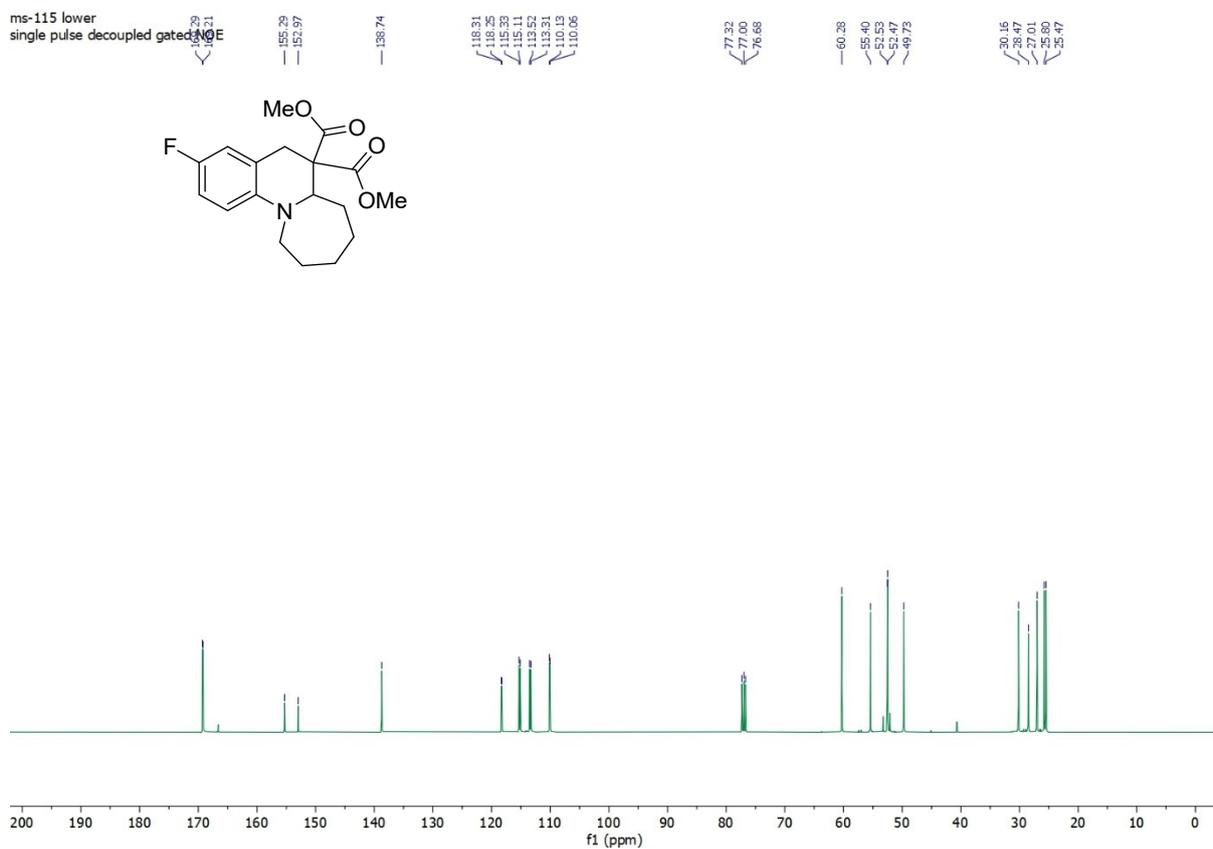
^1H -NMR spectra of **2f** in CDCl_3



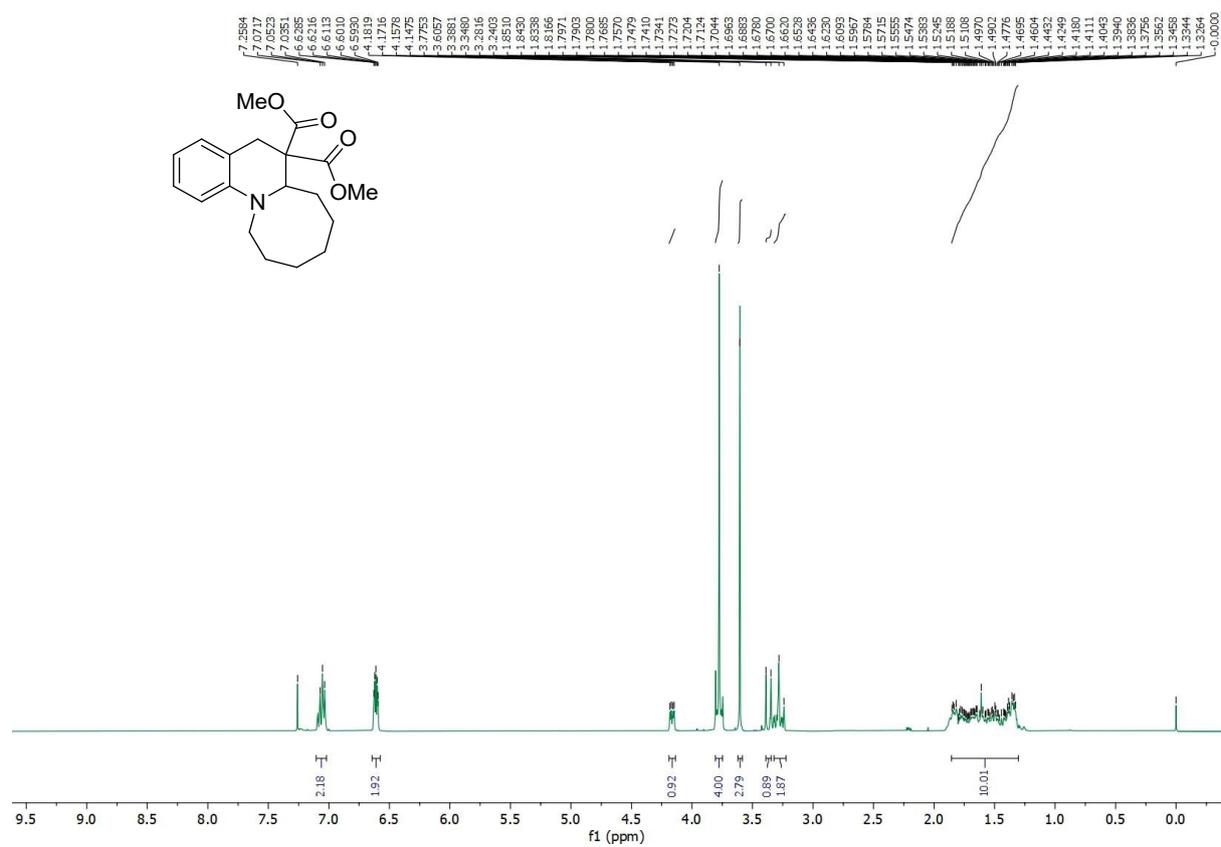
^{13}C -NMR spectra of **2f** in CDCl_3



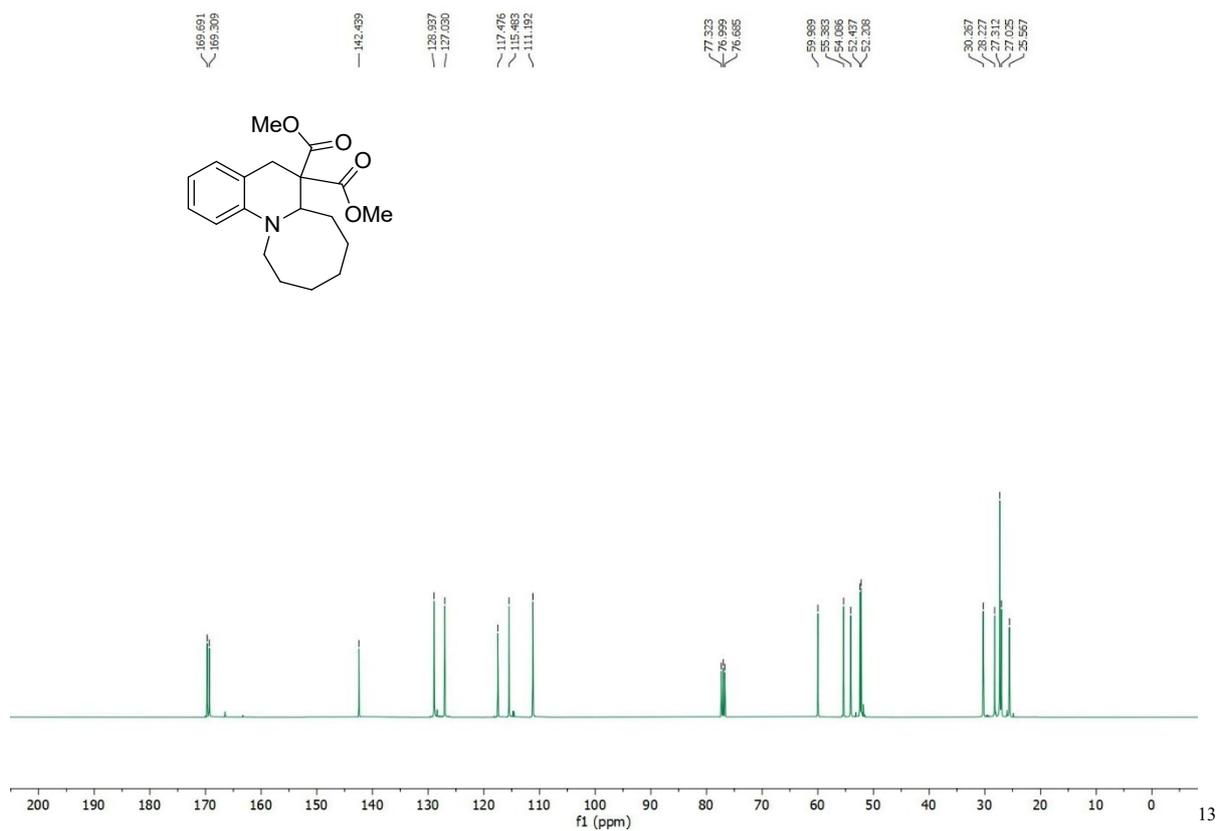
^1H -NMR spectra of **2g** in CDCl_3



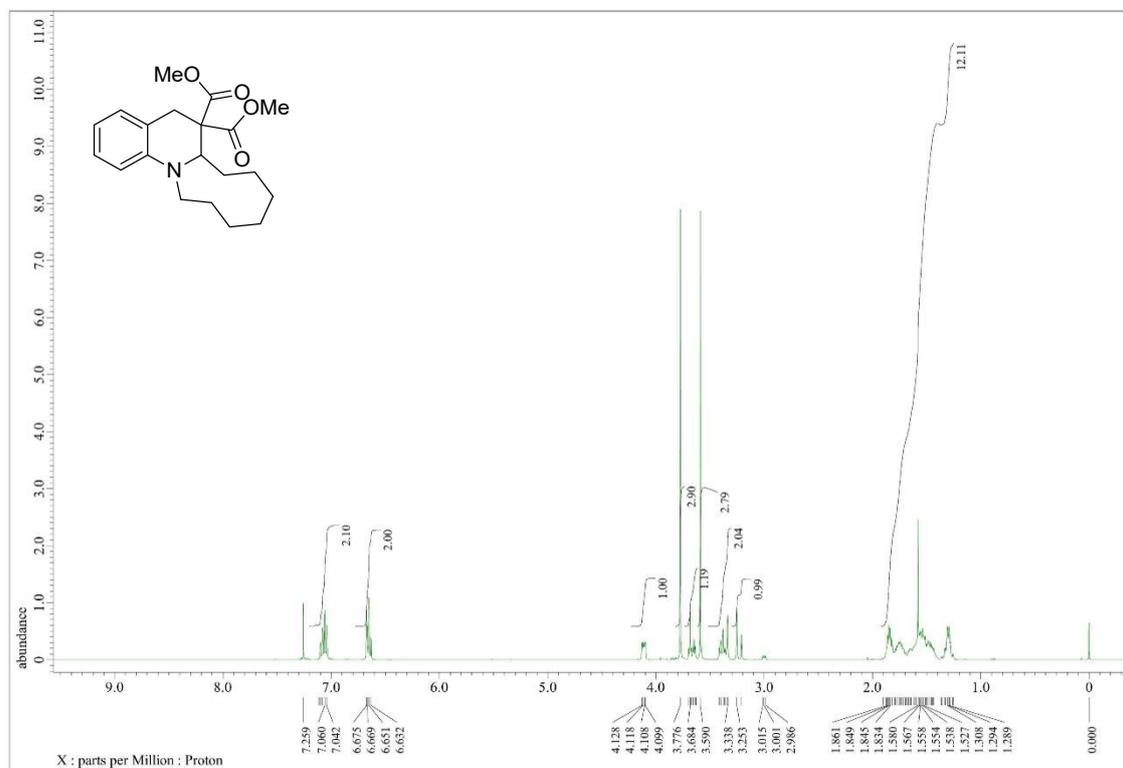
^{13}C -NMR spectra of **2g** in CDCl_3



^1H -NMR spectra of **2h** in CDCl_3

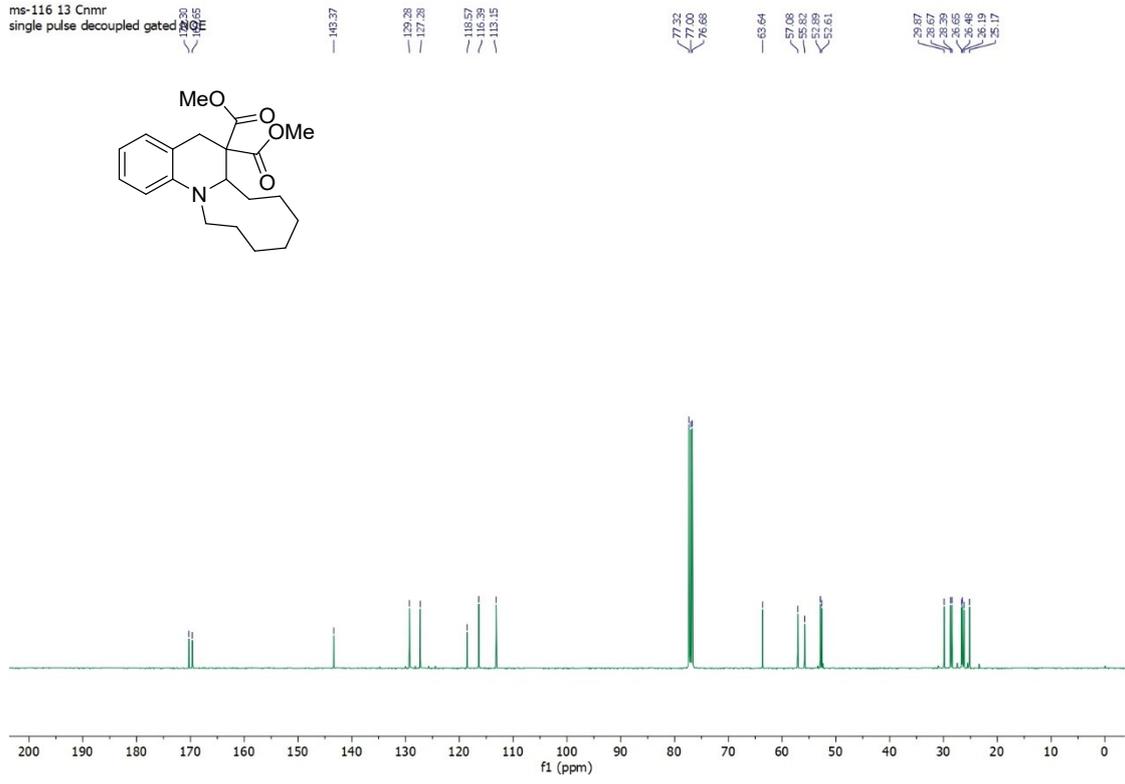
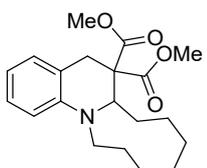


^{13}C -NMR spectra of **2h** in CDCl_3

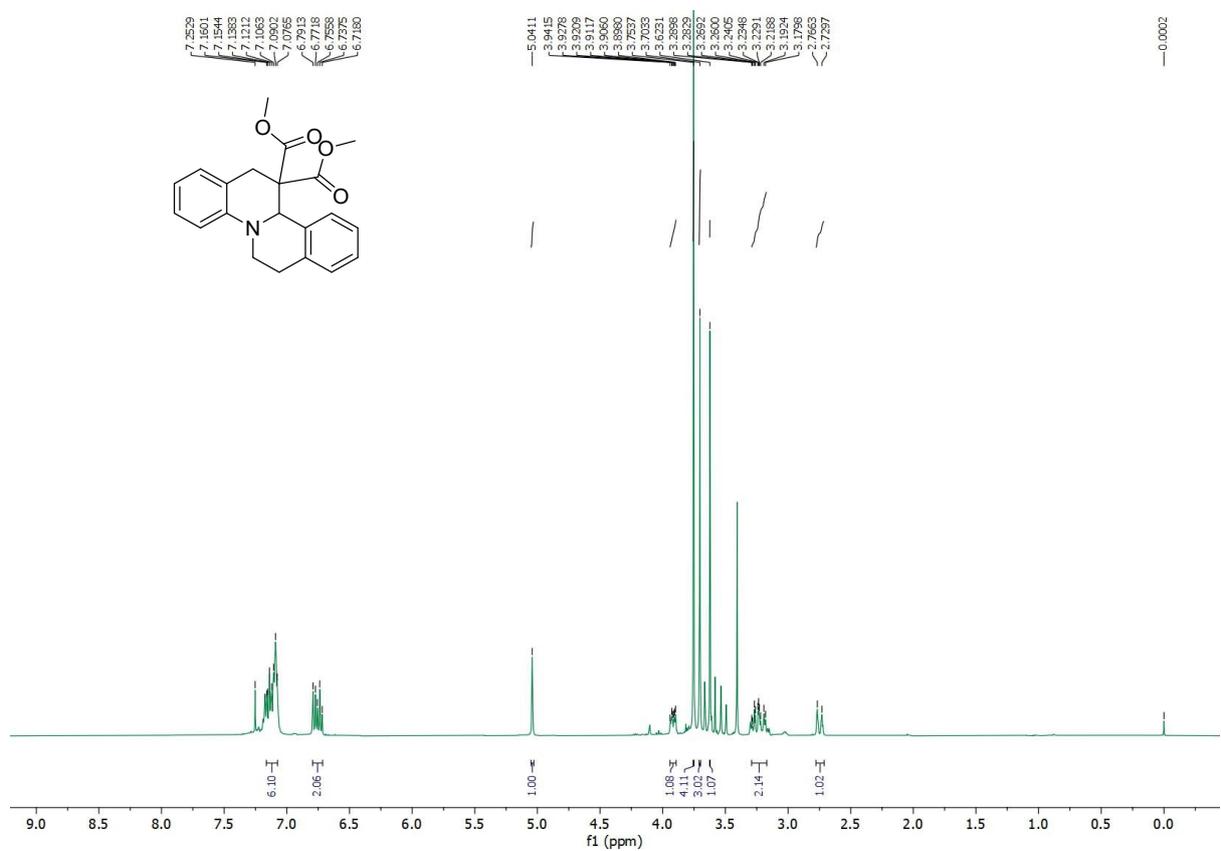
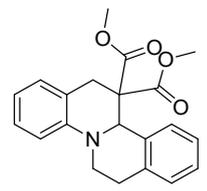


^1H -NMR spectra of **2i** in CDCl_3

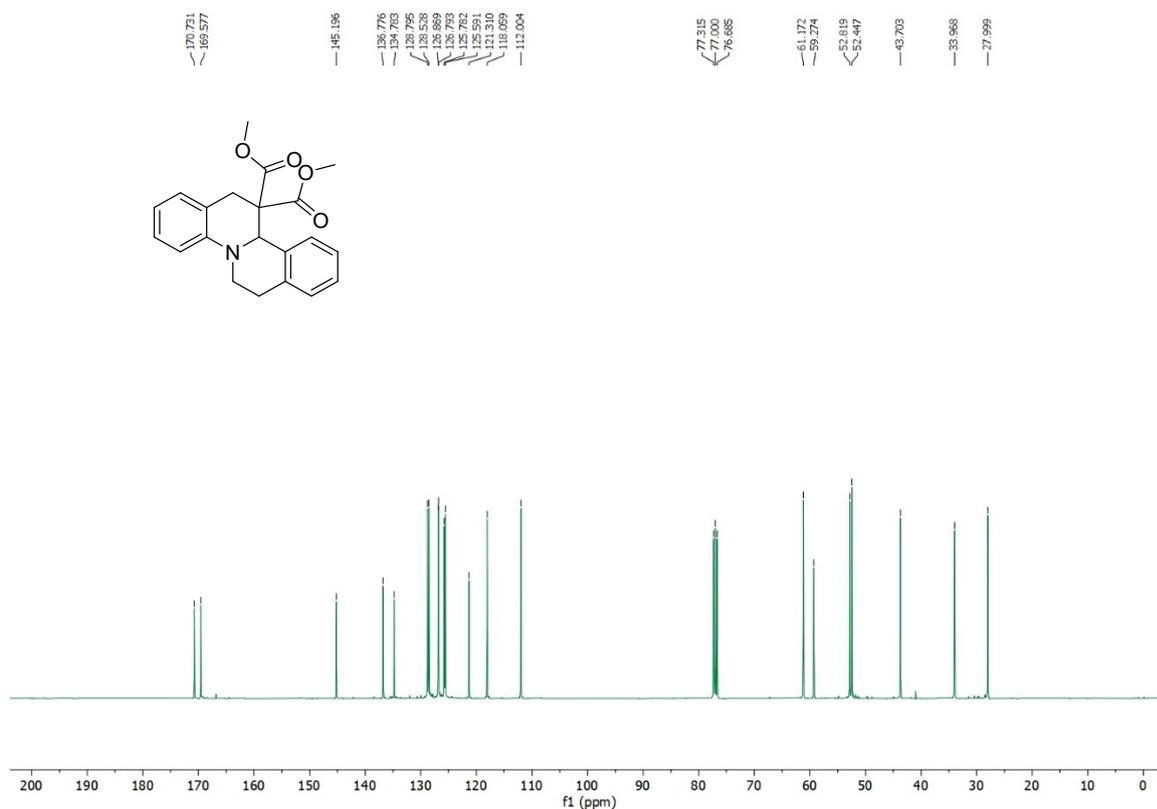
ms-116 13 Cnmr
single pulse decoupled gated NQF



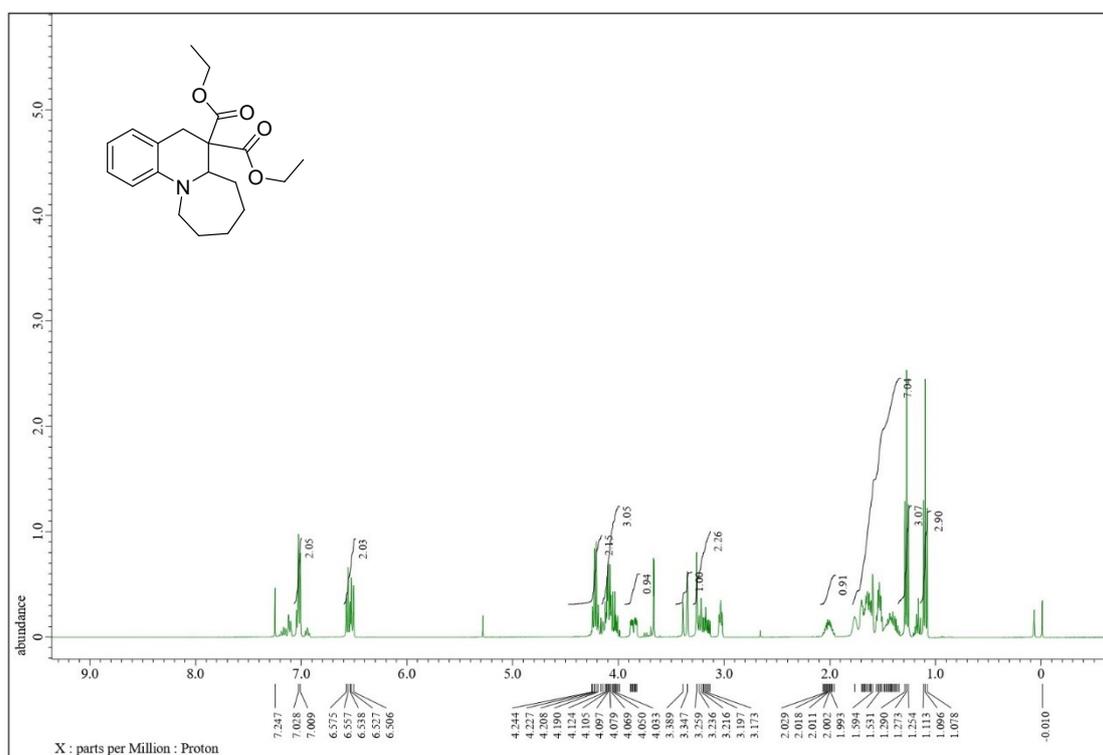
¹³C-NMR spectra of **2i** in CDCl₃



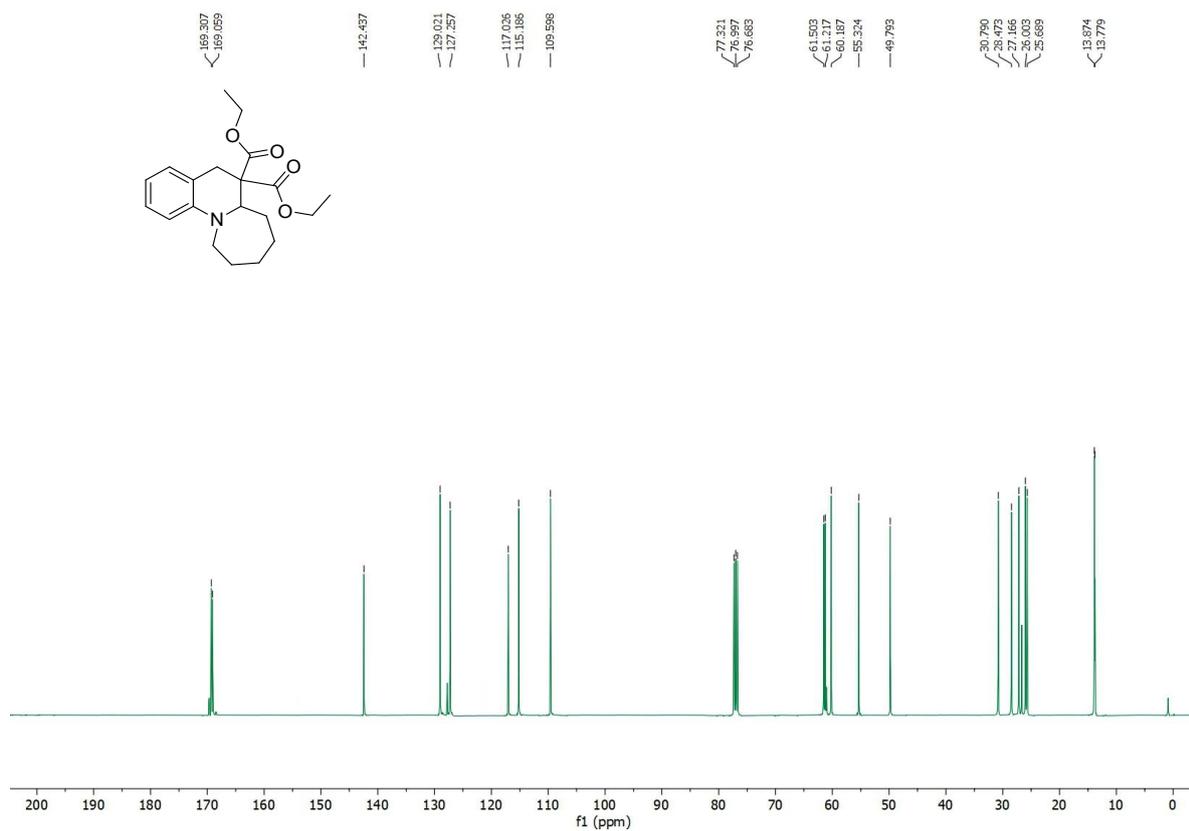
¹H-NMR spectra of **2j** in CDCl₃



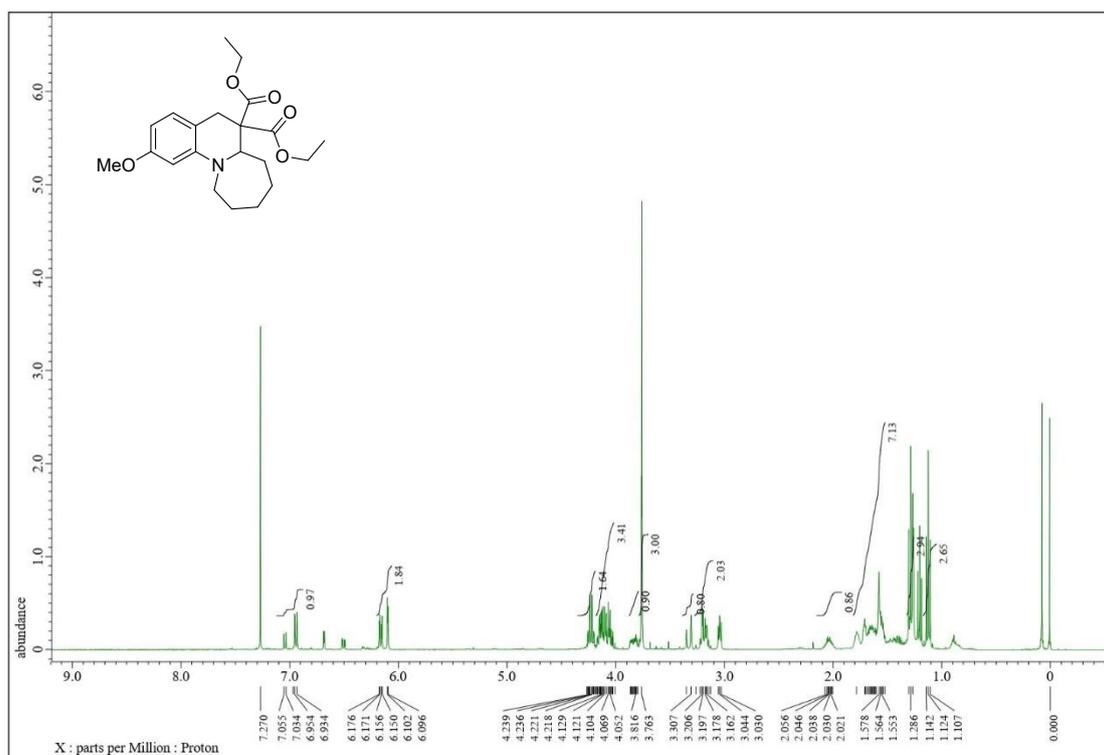
^{13}C -NMR spectra of **2j** in CDCl_3



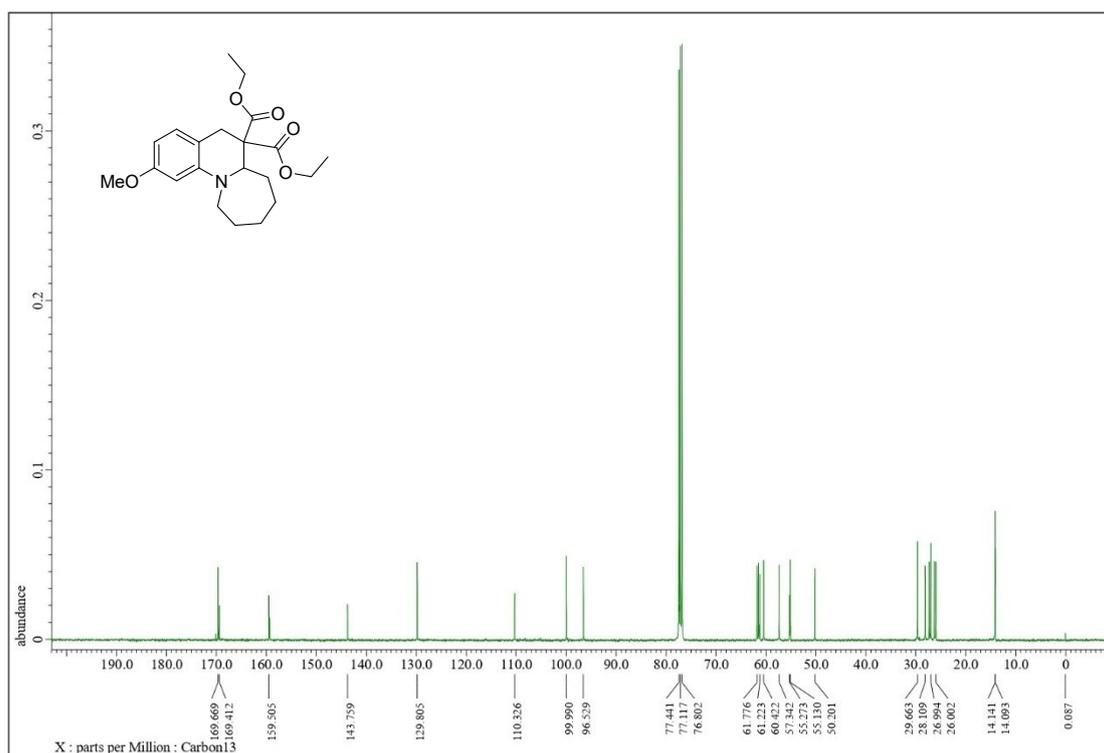
^1H -NMR spectra of **2k** in CDCl_3



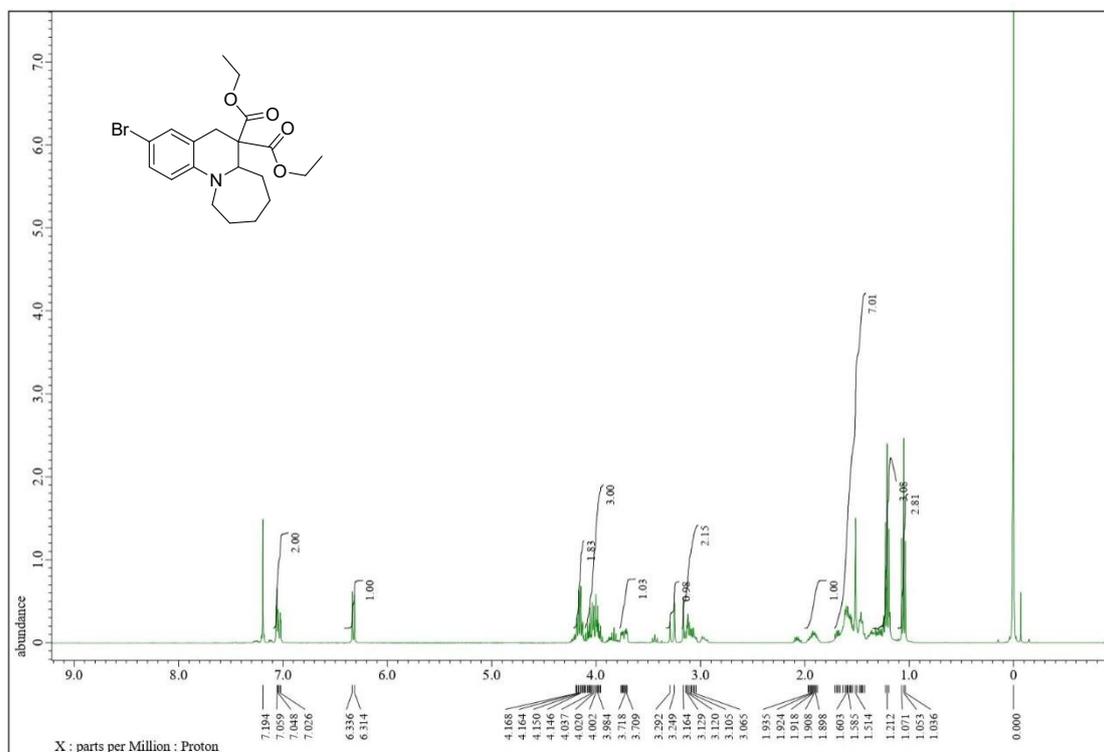
¹³C-NMR spectra of **2k** in CDCl₃



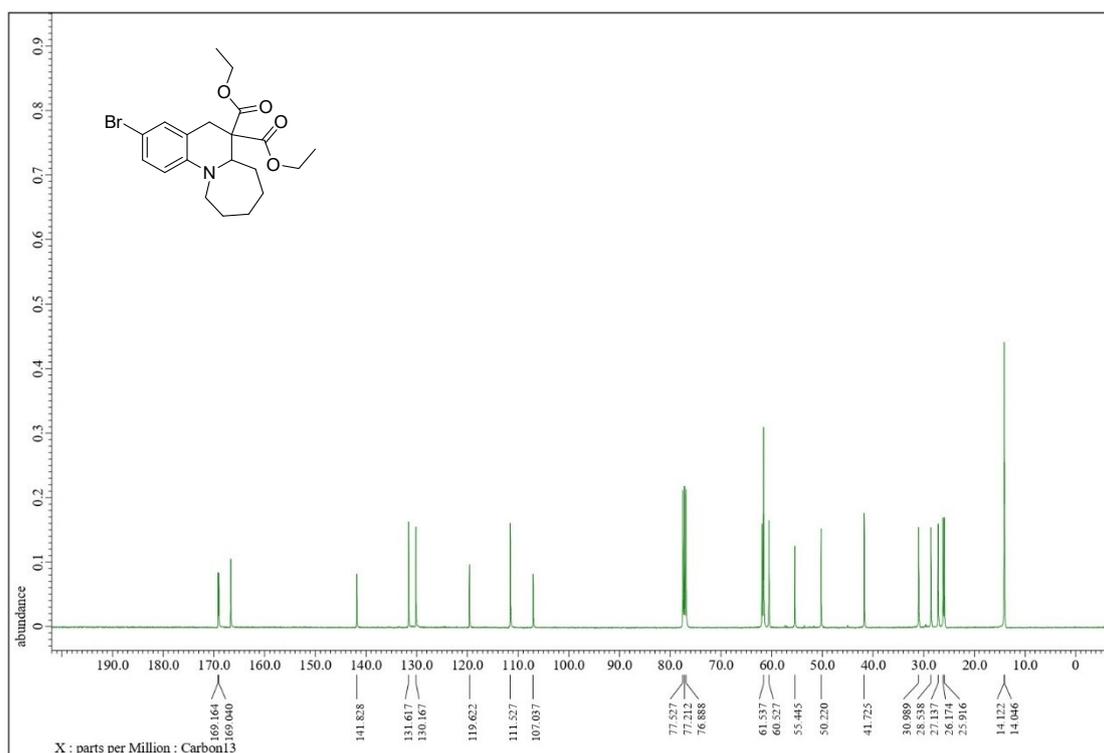
¹H-NMR spectra of **2l** in CDCl₃



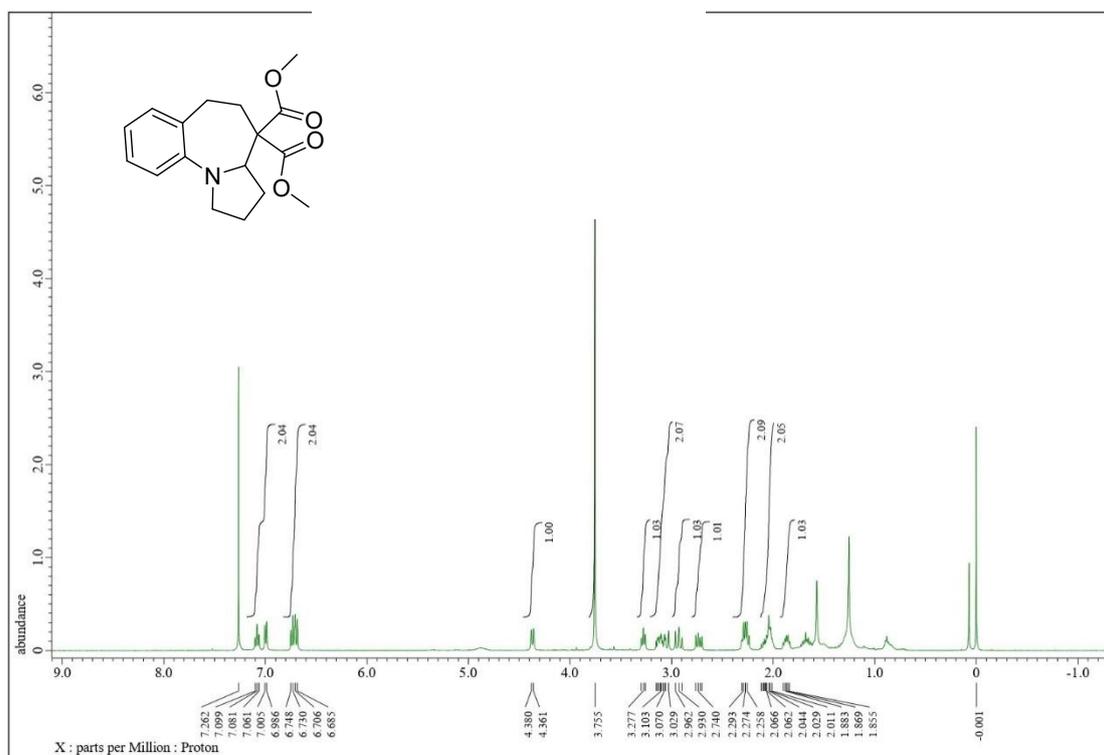
^{13}C -NMR spectra of **2l** in CDCl_3



^1H -NMR spectra of **2m** in CDCl_3

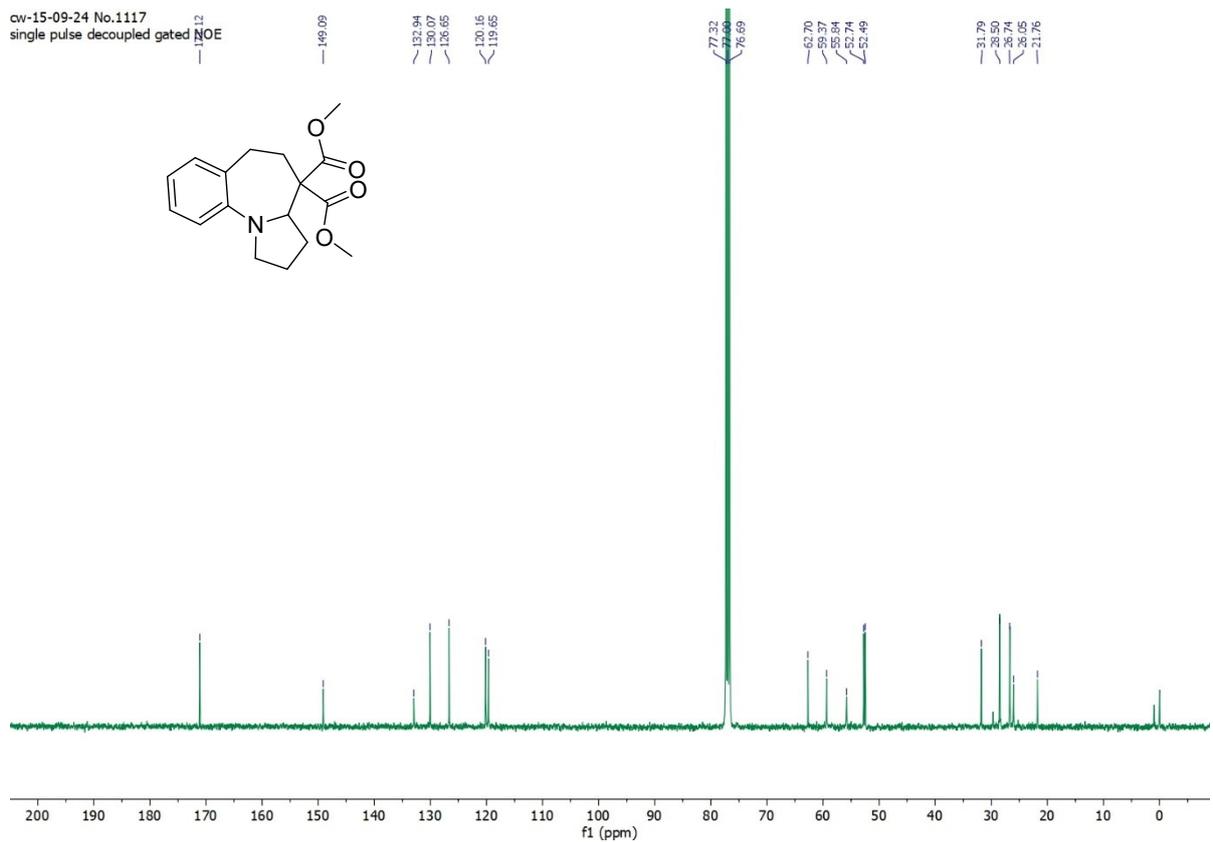


¹³C-NMR of spectra of **2m** in CDCl₃

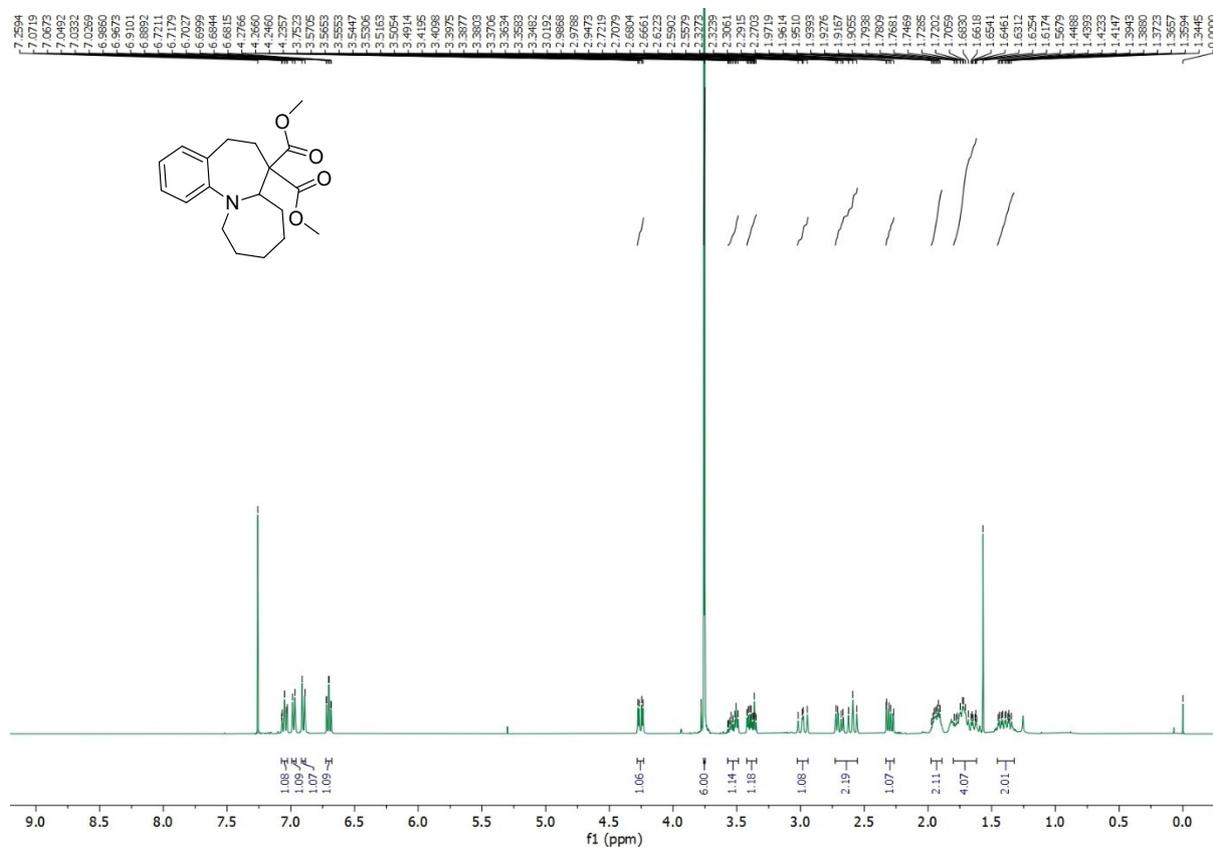


¹H-NMR spectra of **4a** in CDCl₃

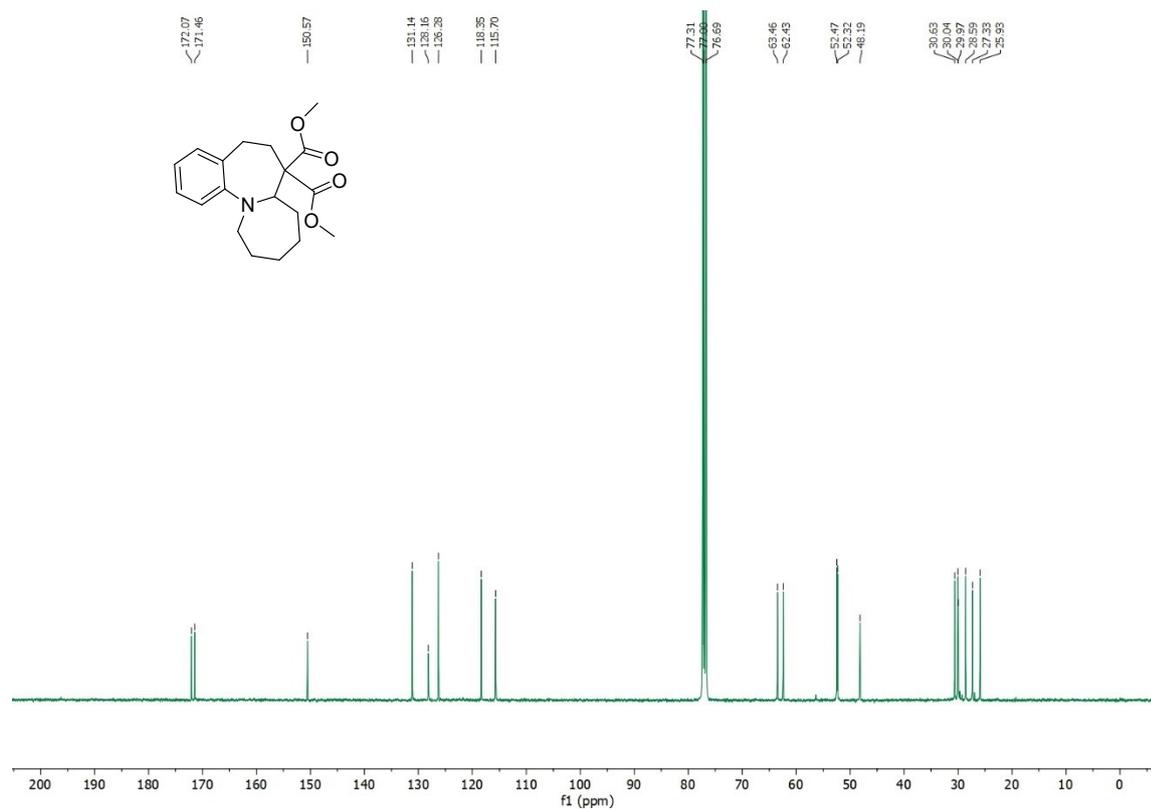
cw-15-09-24 No.1117
single pulse decoupled gated NOE



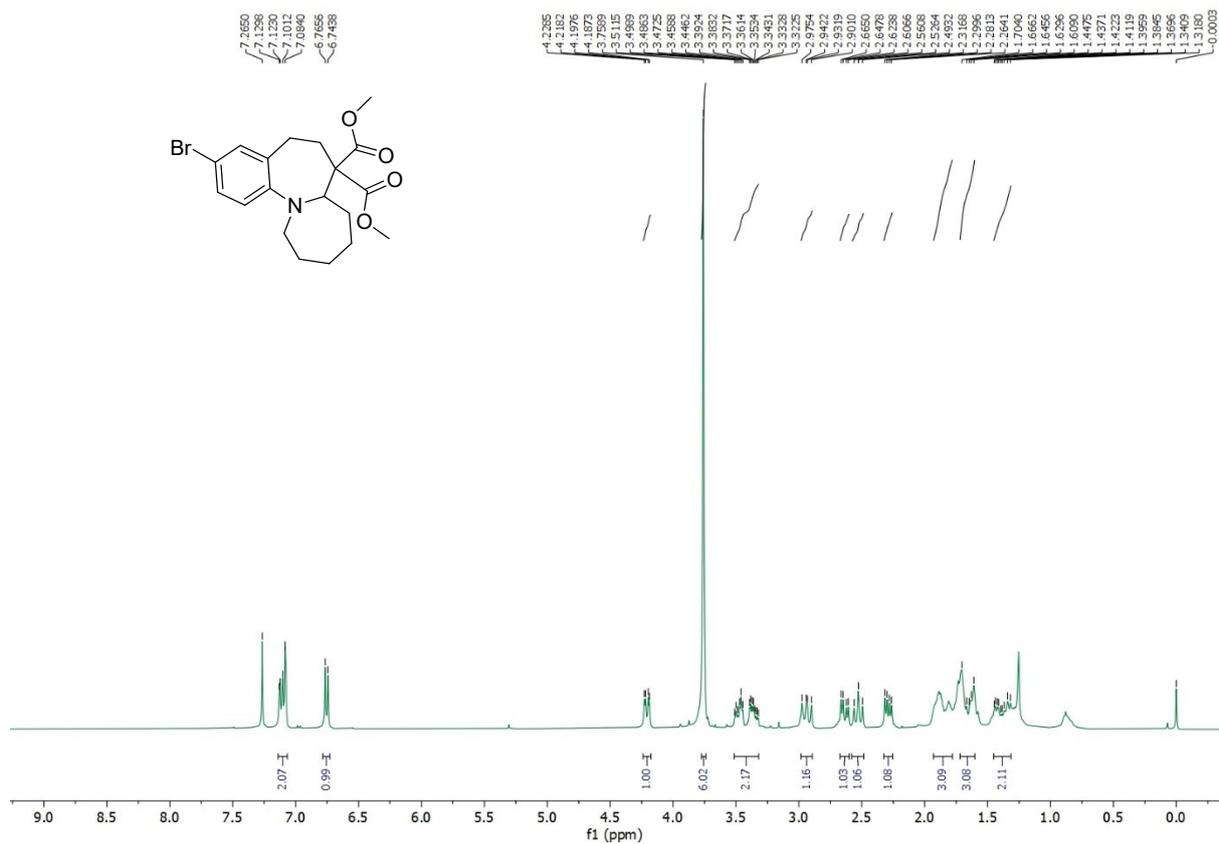
¹³C-NMR spectra of 4a in CDCl₃



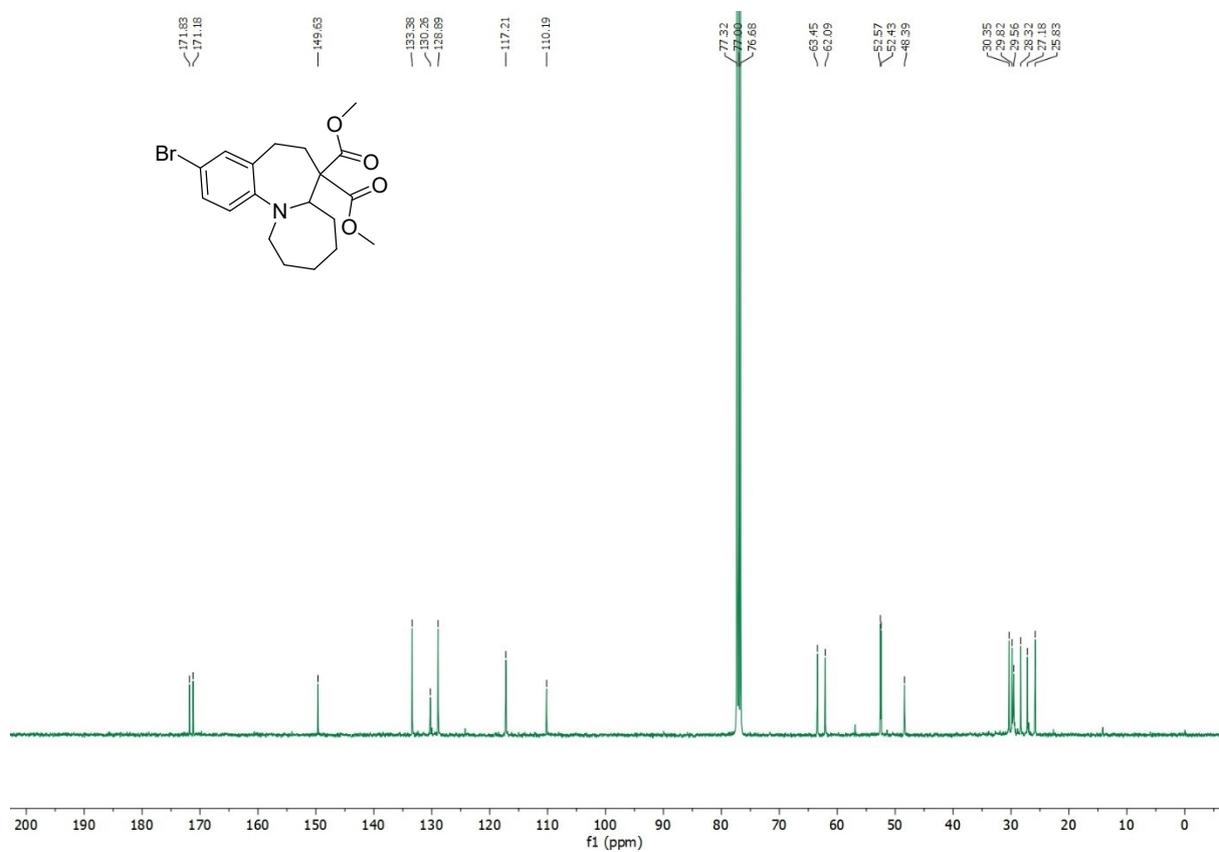
$^1\text{H-NMR}$ spectra of **4b** in CDCl_3



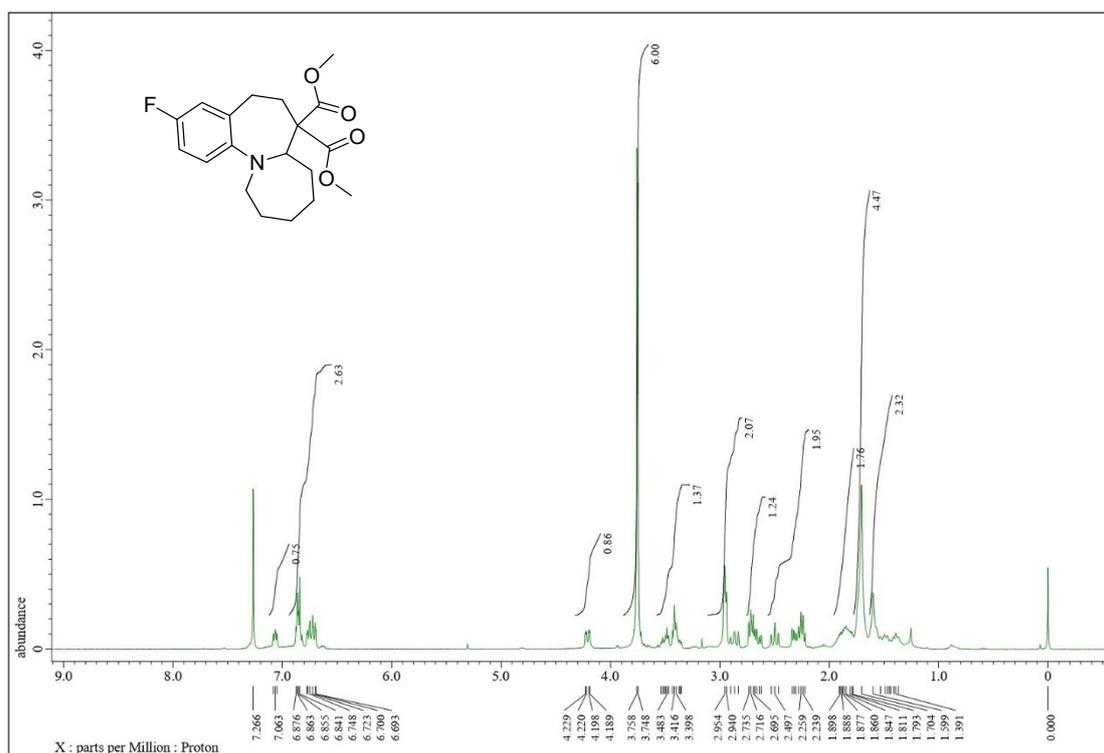
$^{13}\text{C-NMR}$ spectra of **4b** in CDCl_3



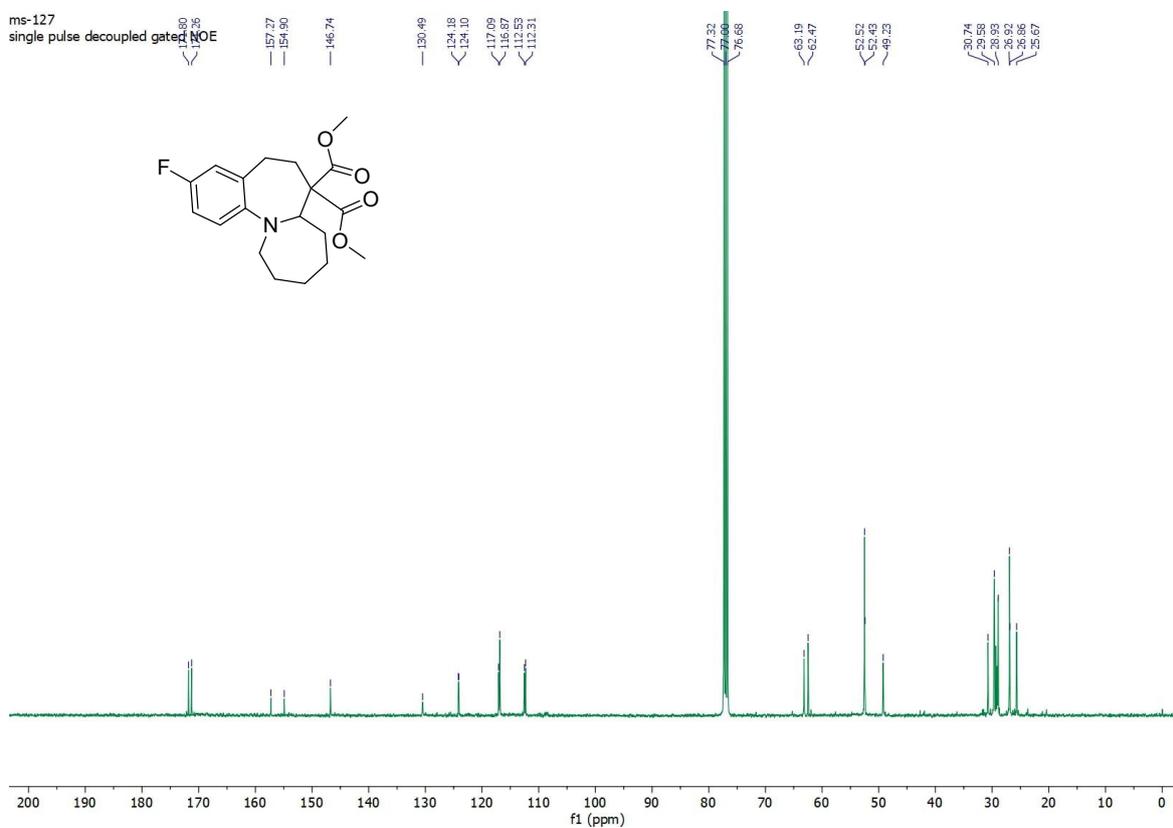
$^1\text{H-NMR}$ of spectra of **4c** in CDCl_3



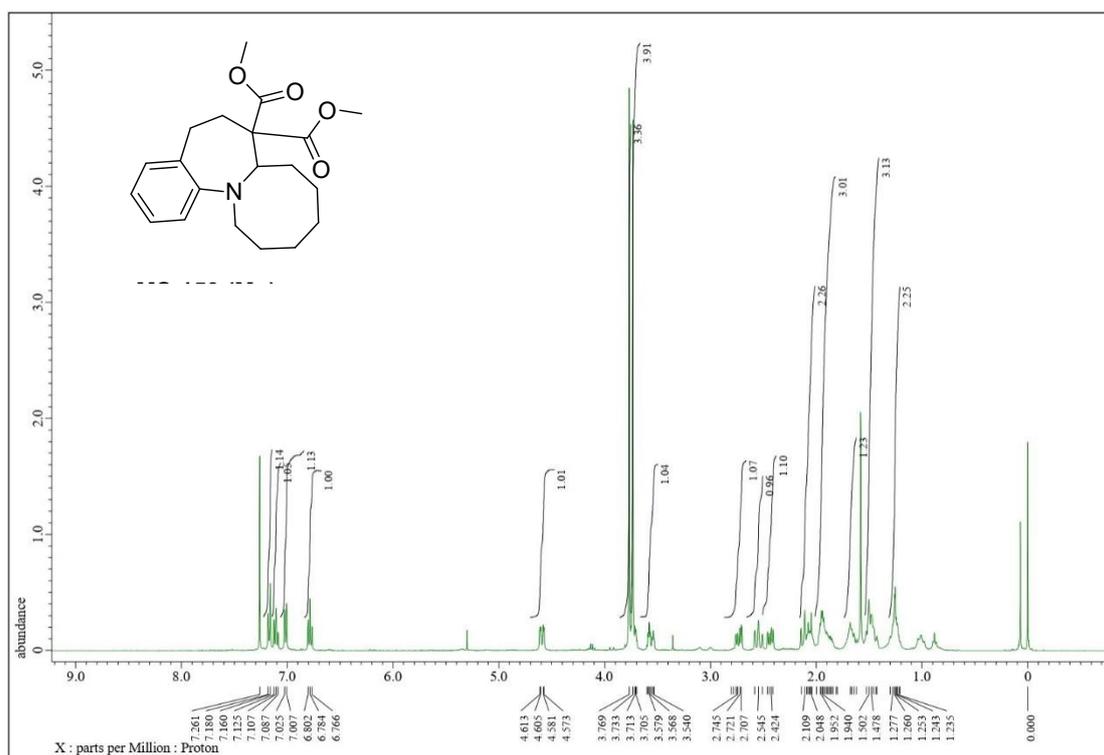
$^{13}\text{C-NMR}$ spectra of **4c** in CDCl_3



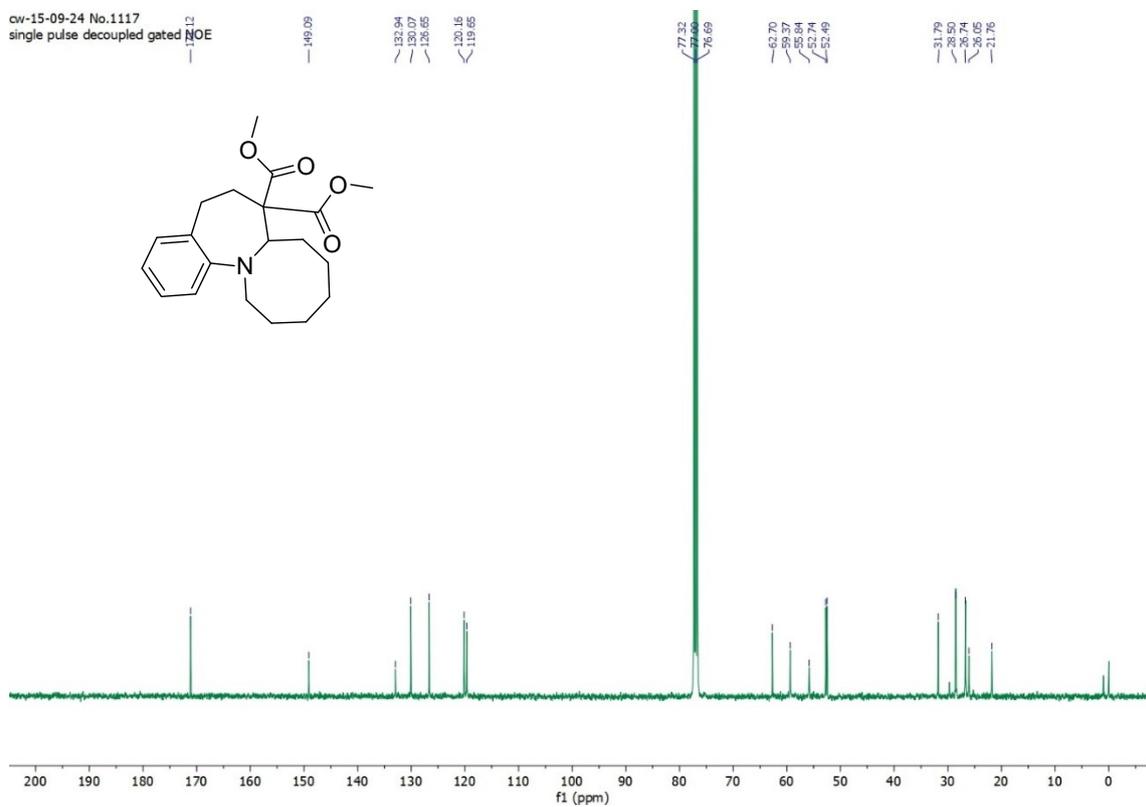
¹H-NMR spectra of **4d** in CDCl₃



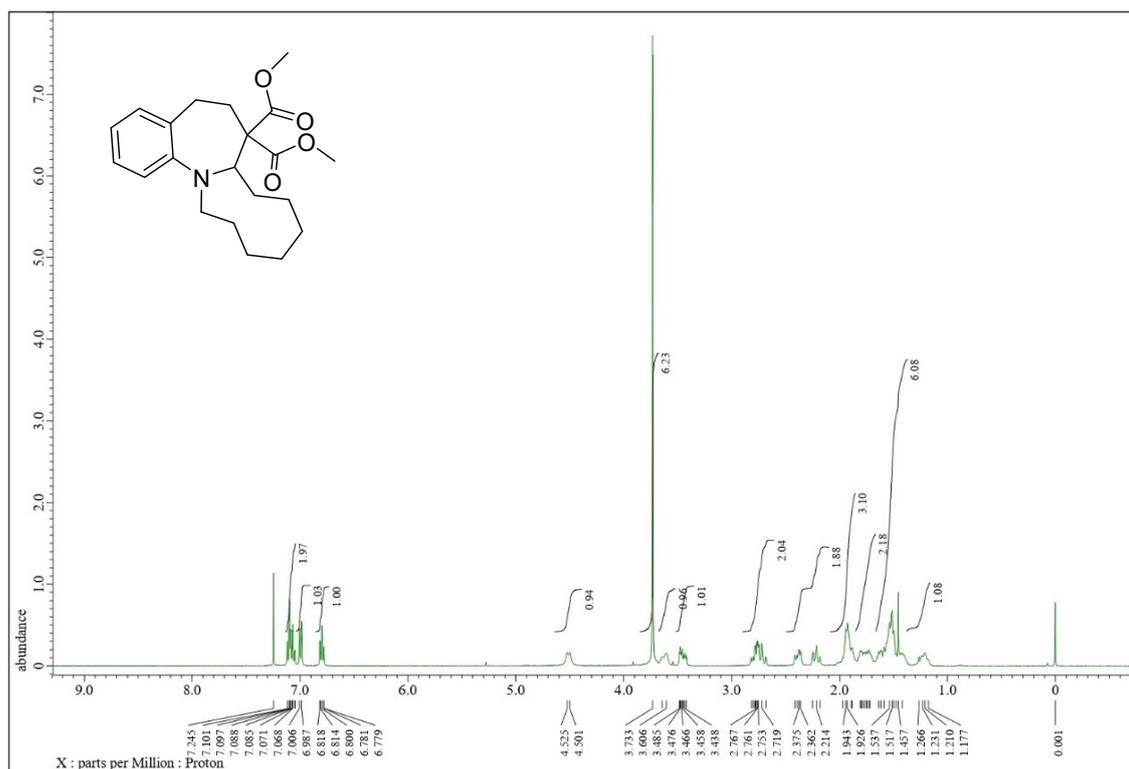
¹³C-NMR spectra of **4d** in CDCl₃



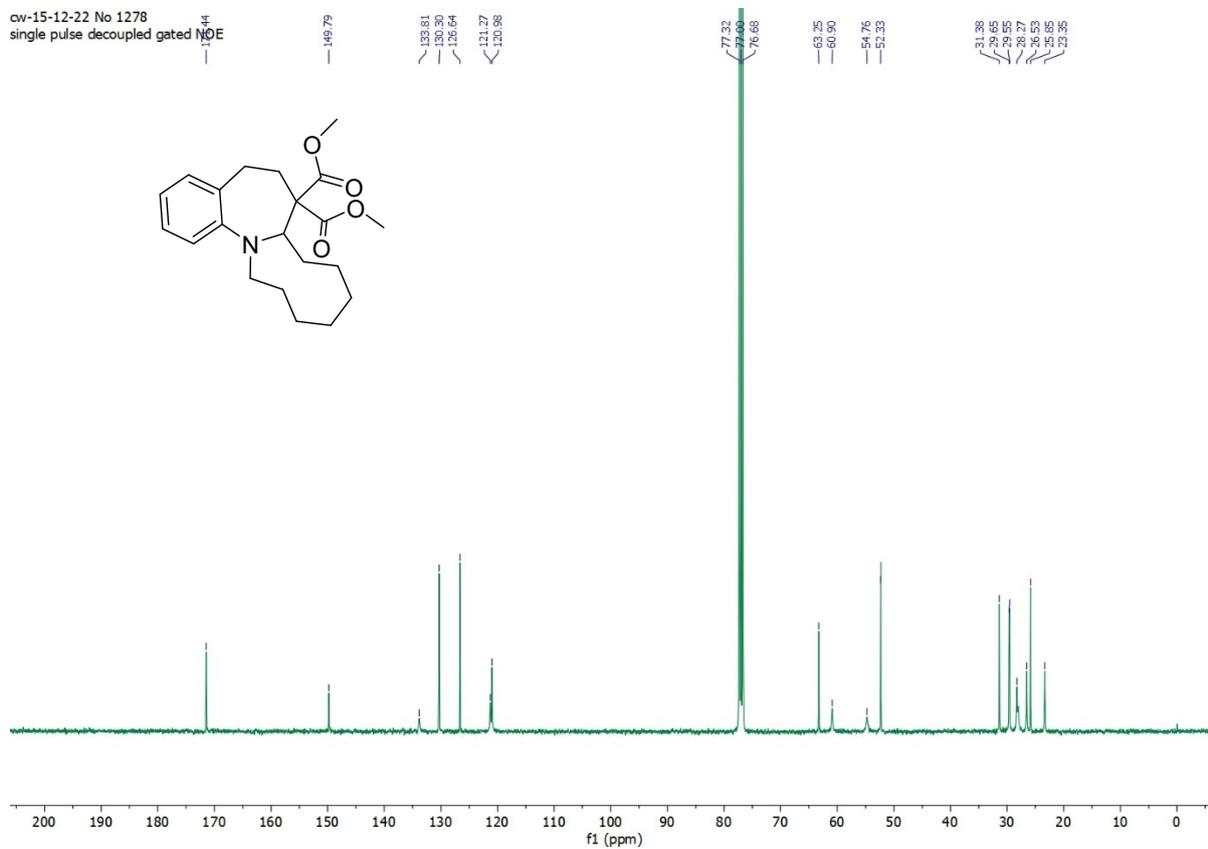
$^1\text{H-NMR}$ spectra of **4e** in CDCl_3



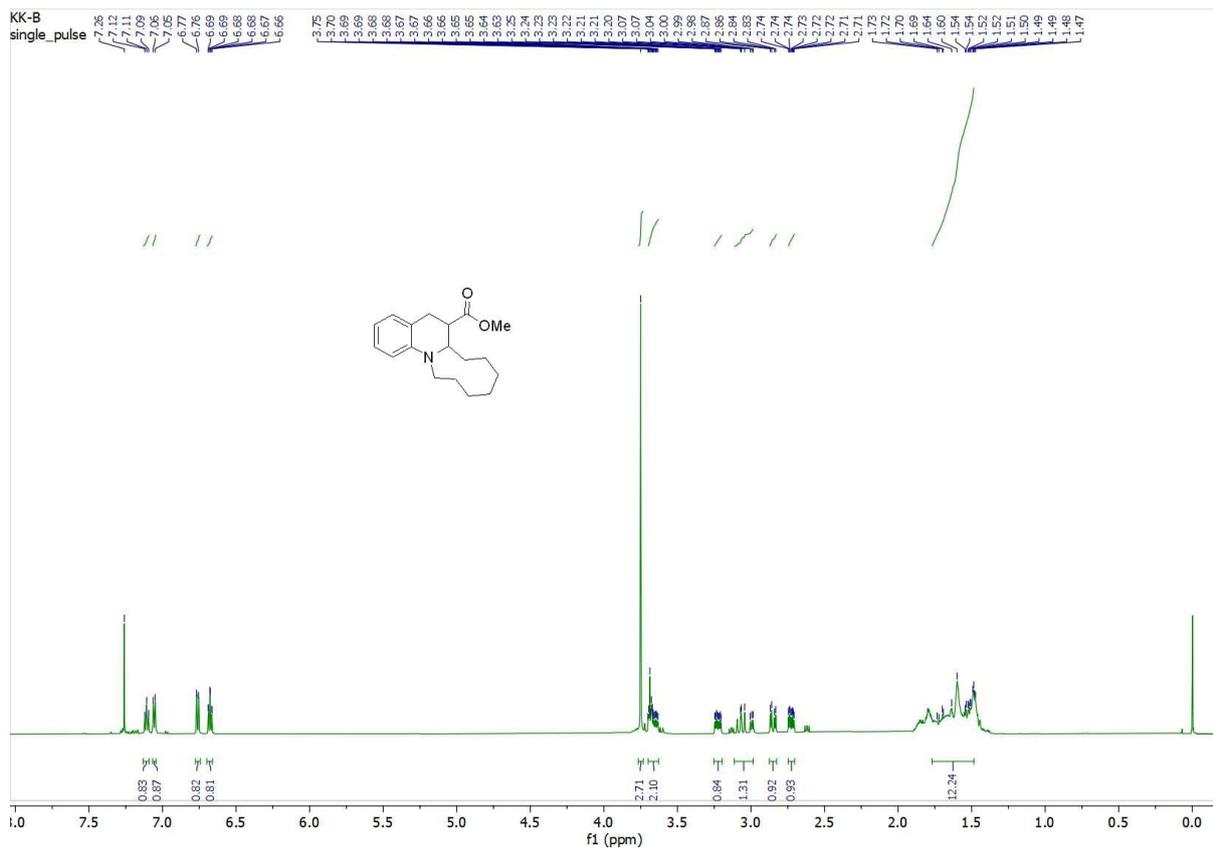
$^{13}\text{C-NMR}$ spectra of **4e** in CDCl_3



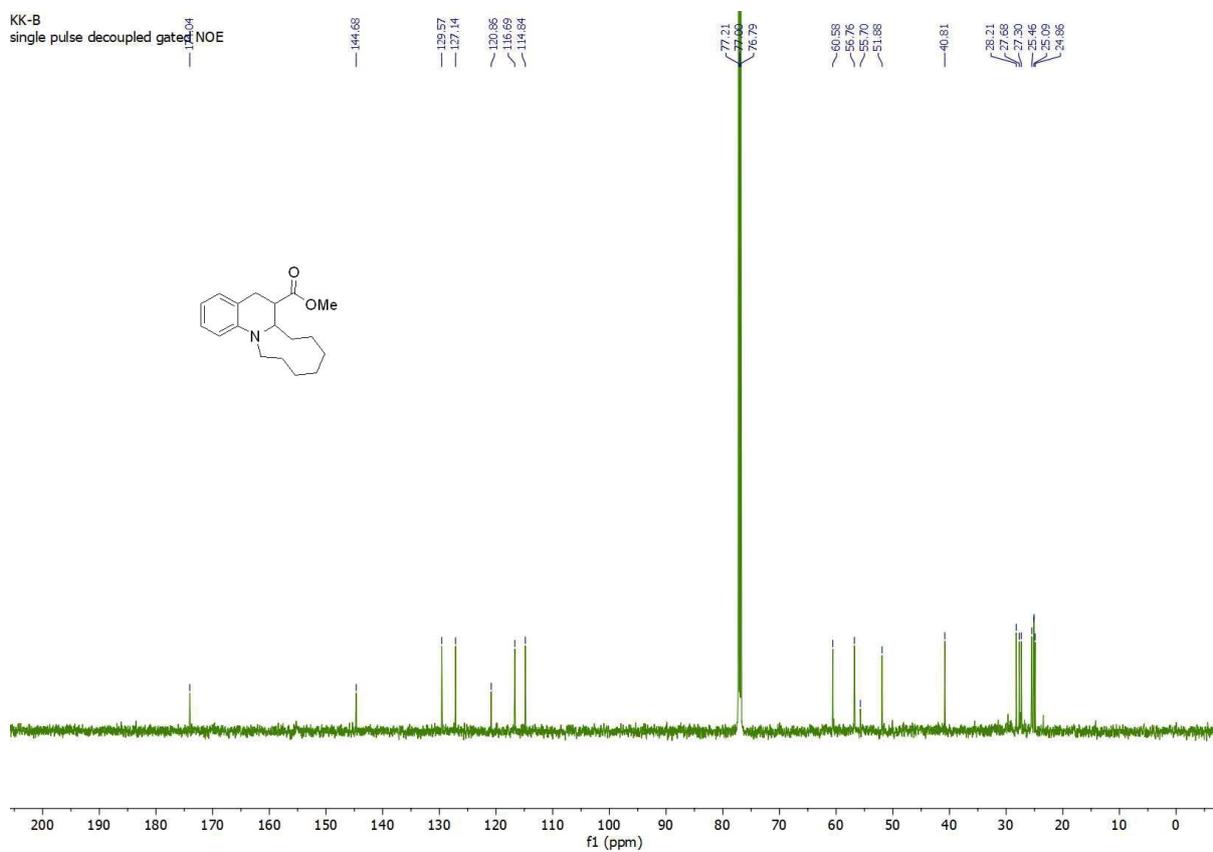
¹H-NMR spectra of **4f** in CDCl₃



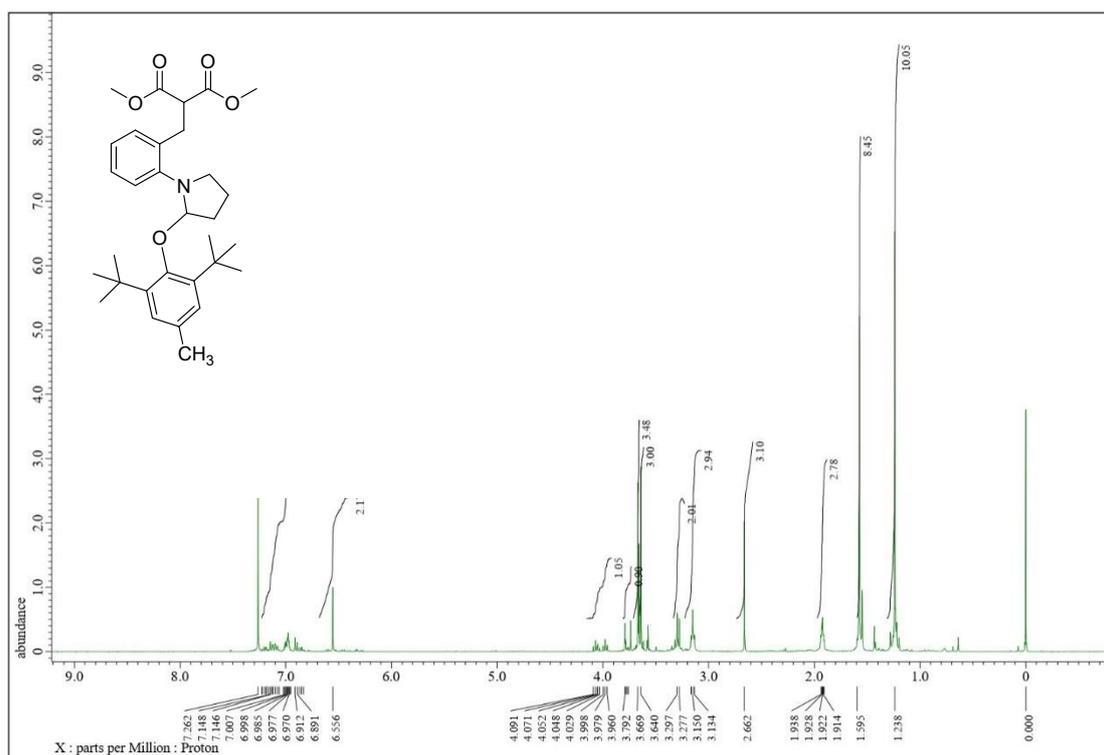
¹³C-NMR spectra of **4f** in CDCl₃



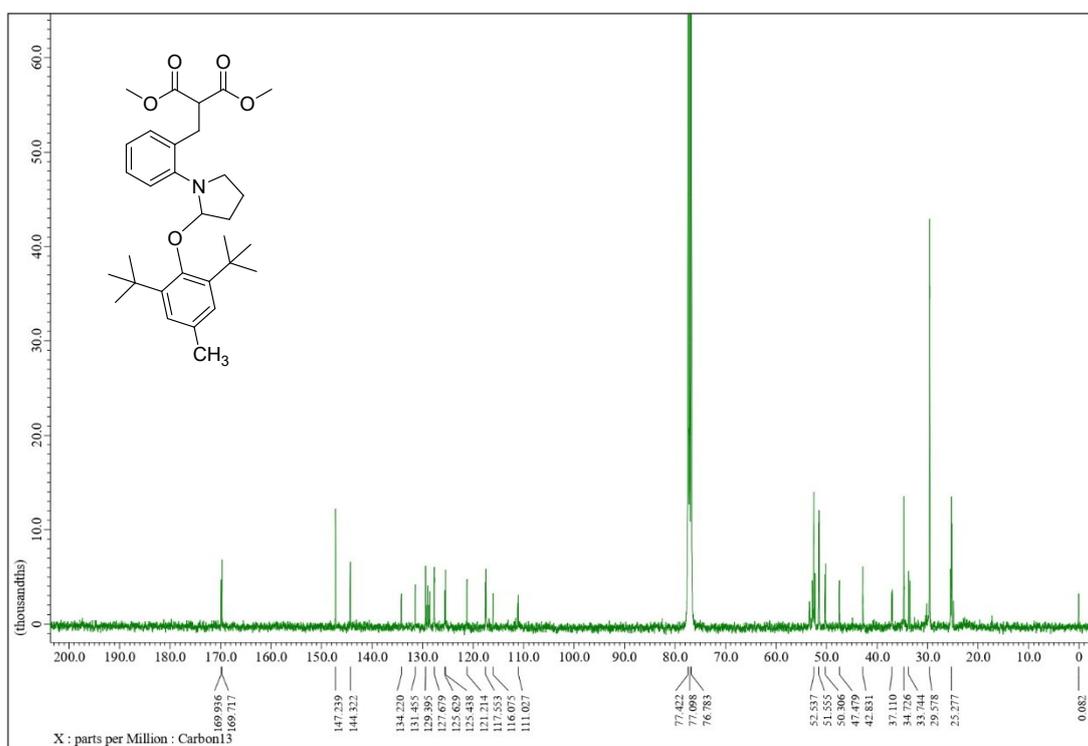
¹H-NMR spectra of **5** in CDCl₃



¹³C-NMR spectra of **5** in CDCl₃



$^1\text{H-NMR}$ spectra of **8** in CDCl_3



$^{13}\text{C-NMR}$ spectra of **8** in CDCl_3