Green Chemistry

Electronic Supporting Information

Base-Selective Access to Highly Functionalized Heterocycles from Multicomponent Ugi Adducts

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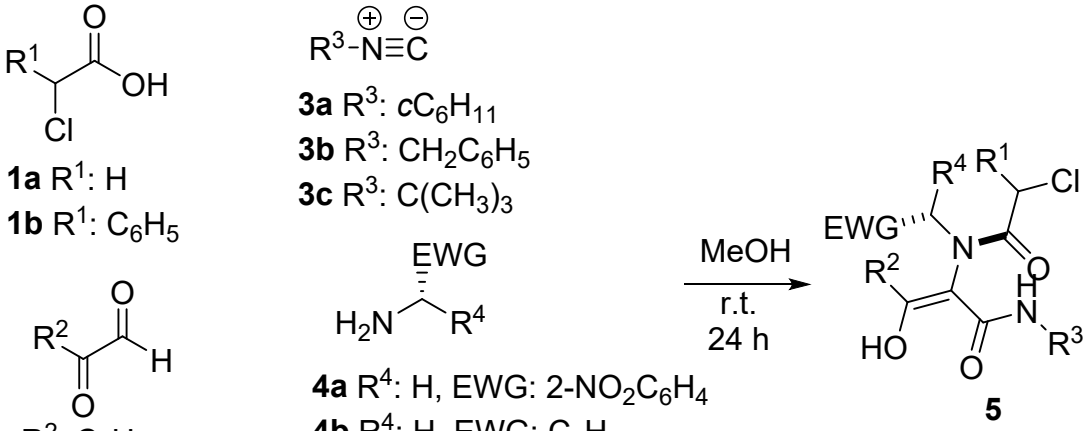
1. General methods

All reagents and solvents were purchased and used without any further purification. Melting points are not corrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Varian Mercury 300 system or a Bruker Avance III HD system, and at 500 and 125 MHz on a BRUKER AVANCE NEO 4500; DEPT-135 experiments were conducted to assign carbon-13 signals. Chemical shifts are reported in parts per million with respect to residual solvent protons and coupling constants in hertz. High resolution mass spectra were recorded on a 6545 Q-TOF Agilent LC-MS mass spectrometer (positive electrospray ionization mode, ESI (+)) and Waters Micromass AutoSpec mass spectrometer (positive ion mode by electronic impact at 70 eV). X-ray diffraction studies were performed on a Bruker D8 VENTURE diffractometer.

2. Synthetic procedures and characterization data:

2.1. Synthesis of Ugi adducts 5

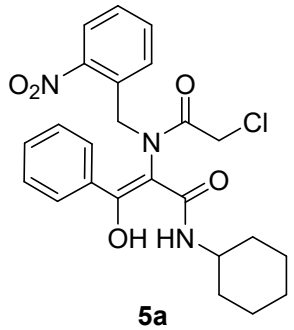


When commercial amines are in the form of hydrochlorides (**4a,4c-g**): Initially, to a solution of the corresponding hydrochloride (1.1 mmol) in methanol (5 mL), powdered sodium hydroxide (1.0 mmol) was added, and the mixture was sonicated for 10 min.

Glyoxal **2a-g** (1.0 mmol) was added to a solution of the corresponding amine **4a-g** (1.0 mmol) in methanol and the mixture was stirred for 15 min. Then, chloroacetic acid **1a-b** (1.0 mmol) and isocyanide **3a-c** (1.0 mmol) were added to the preformed imine. The reaction mixture was stirred at room temperature for 24 h. The solid (formed in most cases) was filtered out, washed with methanol and recrystallized from a diisopropyl ether/isopropanol mixture to give the corresponding Ugi adduct.

If a precipitate was not formed, the solvent was evaporated to dryness, the residue was redissolved in dichloromethane and washed successively with a 10% HCl aqueous solution, a saturated $NaHCO_3$ aqueous solution and a 10% $NaHSO_3$ aqueous solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness, and the residue was crystallized from a chloroform/diisopropyl ether mixture to give the corresponding Ugi adduct.

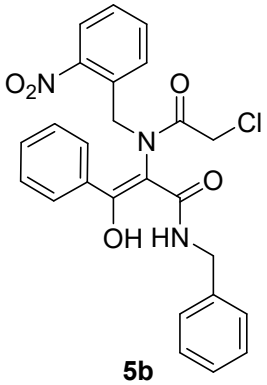
(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-hydroxy-3-phenylacrylamide (5a)



5a

White solid. **M. p.:** 156-157 °C (as a 96:4 rotamers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major rotamer) 15.46 (s, 1H, OH), 7.83 (dt, J = 8.1, 1.8 Hz, 1H), 7.59-7.44 (m, 7H), 7.29 (dt, J = 7.5, 2.0 Hz, 1H), 5.84 (d, J = 8.2 Hz, 1H, NH), 5.48 (d, J = 13.9 Hz, 1H), 4.33 (d, J = 13.9 Hz, 1H), 4.23 (d, J = 13.9 Hz, 1H), 3.73 (d, J = 13.9 Hz, 1H), 3.57-3.44 (m, 1H), 1.82-0.37 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major rotamer) 170.4 (Cq), 169.5 (Cq), 169.1 (Cq), 150.2 (Cq), 133.9 (CH_{Ar}), 133.6 (CH_{Ar}), 133.1 (Cq), 131.4 (CH_{Ar}), 129.8 (CH_{Ar}), 129.6 (Cq), 129.3 (CH_{Ar}), 127.2 (CH_{Ar}), 124.8 (CH_{Ar}), 105.1 (Cq), 48.4 (CH), 46.8 (CH_2), 41.9 (CH_2), 33.0 (CH_2), 32.2 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2). **MS (EI):** *m*/*z* (%): 471 ([M]$^+$, 0.3), 136 (15), 120 (12), 105 (100), 83 (15), 78 (39), 77 (90). **HRMS (EI):** *m*/*z* calculated for $[C_{24}H_{26}ClN_3O_5]^+$ 471.1561, *m*/*z* found for $[M]^+$ 471.1567.

(*E*)-*N*-Benzyl-2-(2-chloro-*N*-(2-nitrobenzyl)acetamido)-3-hydroxy-3-phenylacrylamide (5b)

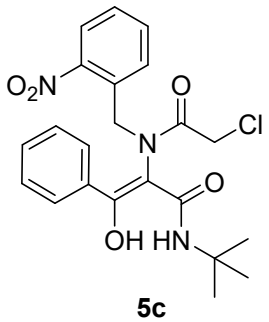


5b

Pink solid. **M. p.:** 142-145 °C (as a 95:5 rotamers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major rotamer) 15.33 (s, 1H, OH), 7.58-6.95 (m, 14H), 6.39-6.35 (m, 1H, NH), 5.41 (d, J = 13.9 Hz, 1H), 4.37 (dd, J = 14.3, 6.7 Hz, 1H), 4.35 (d, J = 14.3 Hz, 1H), 4.25 (d, J = 14.0 Hz, 1H), 4.01 (dd, J = 14.3, 4.8 Hz, 1H), 3.75 (d, J = 13.9 Hz, 1H). **^{13}C NMR**

(75 MHz, $CDCl_3$): δ (major rotamer) 170.6 (Cq), 170.3 (Cq), 169.0 (Cq), 149.7 (Cq), 136.9 (Cq), 133.5 (CH_{Ar}), 133.2 (CH_{Ar}), 133.0 (Cq), 131.5 (CH_{Ar}), 129.6 (CH_{Ar}), 129.3 (CH_{Ar}), 129.1 (Cq), 129.0 (CH_{Ar}), 128.2 (CH_{Ar}), 127.9 (CH_{Ar}), 127.3 (CH_{Ar}), 124.7 (CH_{Ar}), 105.1 (Cq), 46.9 (CH_2), 43.4 (CH_2), 42.2 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{25}H_{22}ClN_3O_5H]^+$ 480.1321, *m*/*z* found for $[M+H]^+$ 480.1334.

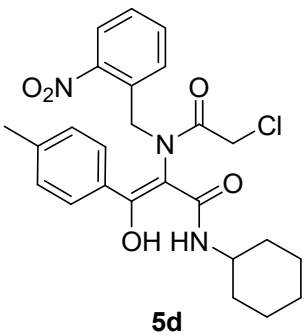
(*E*)-*N*-(*tert*-Butyl)-2-(2-chloro-*N*-(2-nitrobenzyl)acetamido)-3-hydroxy-3-phenylacrylamide (5c)



5c

Pink solid. **M. p.:** 160-162 °C (as a 95:5 rotamers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major rotamer) 15.57 (s, 1H, OH), 7.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.61-7.46 (m, 7H), 7.38 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.65 (bs, 1H, NH), 5.49 (d, *J* = 13.9 Hz, 1H), 4.30 (d, *J* = 13.6 Hz, 1H), 4.25 (d, *J* = 13.6 Hz, 1H), 3.68 (d, *J* = 13.9 Hz, 1H), 1.03 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major rotamer) 170.5 (Cq), 170.4 (Cq), 169.1 (Cq), 150.2 (Cq), 134.0 (CH_{Ar}), 133.7 (CH_{Ar}), 133.4 (Cq), 131.3 (CH_{Ar}), 130.0 (Cq), 129.8 (CH_{Ar}), 129.2 (CH_{Ar}), 127.2 (CH_{Ar}), 124.7 (CH_{Ar}), 105.7 (Cq), 51.9 (Cq), 46.9 (CH_2), 41.6 (CH_2), 28.3 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{22}H_{24}ClN_3O_5H]^+$ 446.1477, *m*/*z* found for $[M+H]^+$ 446.1499.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-hydroxy-3-(*p*-tolyl)acrylamide (5d)

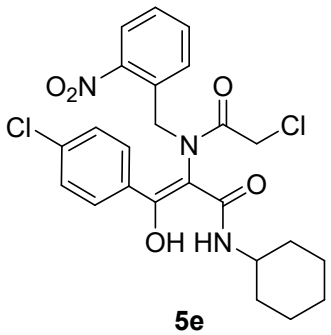


5d

White solid. **M. p.:** 159-160 °C (as a 95:5 rotamers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major rotamer) 15.44 (s, 1H, OH), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.58-7.45

(m, 4H), 7.30-7.27 (m, 3H), 5.84 (d, J = 8.3 Hz, 1H), 5.52 (d, J = 13.9 Hz, 1H), 4.31 (d, J = 13.9 Hz, 1H), 4.22 (d, J = 13.9 Hz, 1H), 3.75 (d, J = 13.9 Hz, 1H), 3.56-3.43 (m, 1H), 2.40 (s, 3H), 1.81-1.52 (m, 4H), 1.32-0.85 (m, 5H), 0.43 (qd, J = 13.0, 12.5, 4.3 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major rotamer) 170.4 (Cq), 169.6 (Cq), 169.1 (Cq), 150.2 (Cq), 142.0 (Cq), 134.0 (CH_{Ar}), 133.5 (CH_{Ar}), 130.2 (Cq), 130.0 (CH_{Ar}), 129.8 (CH_{Ar}), 129.7 (Cq), 127.2 (CH_{Ar}), 124.7 (CH_{Ar}), 104.6 (Cq), 48.3 (CH), 46.7 (CH_2), 42.0 (CH_2), 33.0 (CH_2), 32.2 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 21.6 (CH_3). **HRMS (+ESI):** m/z calculated for $[C_{25}H_{28}ClN_3O_5H]^+$, 486.1790, m/z found for $[M+H]^+$ 486.1808.

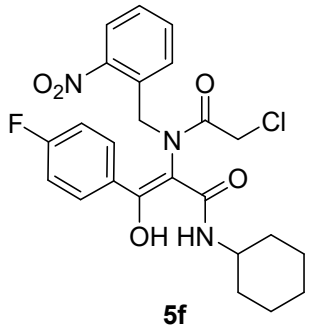
(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-3-(4-chlorophenyl)-*N*-cyclohexyl-3-hydroxyacrylamide (5e)



5e

White solid. **M. p.:** 163-165 °C (as a 94:6 rotamers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major rotamer) 15.55 (s, 1H, OH), 7.83 (dd, J = 8.0, 1.3 Hz, 1H), 7.59-7.42 (m, 6H), 7.34-7.30 (m, 1H), 5.77 (d, J = 8.3 Hz, 1H), 5.49 (d, J = 13.8 Hz, 1H), 4.29 (d, J = 13.8 Hz, 1H), 4.20 (d, J = 13.8 Hz, 1H), 3.83 (d, J = 13.9 Hz, 1H), 3.57-3.45 (m, 1H), 1.81-1.54 (m, 4H), 1.29-0.85 (m, 5H), 0.51-0.38 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major rotamer) 169.2 (Cq), 169.1 (Cq), 150.2 (Cq), 137.7 (Cq), 133.9 (CH_{Ar}), 133.7 (CH_{Ar}), 131.5 (Cq), 129.9 (CH_{Ar}), 129.6 (CH_{Ar}), 128.8 (CH_{Ar}), 124.9 (CH_{Ar}), 105.3 (Cq), 48.5 (CH), 46.8 (CH_2), 41.7 (CH_2), 33.0 (CH_2), 32.3 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{24}H_{25}Cl_2N_3O_5H]^+$, 506.1244, m/z found for $[M+H]^+$ 506.1262.

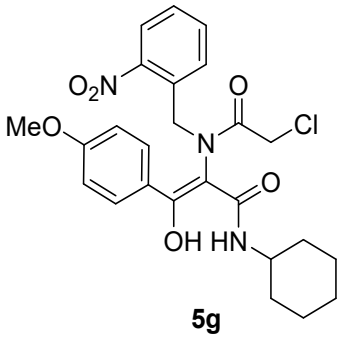
(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-(4-fluorophenyl)-3-hydroxyacrylamide (5f)



5f

White solid. **M. p.:** 156-157 °C (as a 96:4 rotamers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major rotamer) 15.57 (s, 1H, OH), 7.84 (dd, J = 7.9, 1.4 Hz, 1H), 7.62-7.46 (m, 4H), 7.31 (dd, J = 7.6, 1.5 Hz, 1H), 7.16 (dd, J = 9.0, 8.3 Hz, 2H), 5.77 (d, J = 8.3 Hz, 1H, NH), 5.50 (d, J = 13.9 Hz, 1H), 4.30 (d, J = 13.8 Hz, 1H), 4.20 (d, J = 13.8 Hz, 1H), 3.82 (d, J = 13.9 Hz, 1H), 3.58-3.45 (m, 1H), 1.81-1.53 (m, 4H), 1.29-0.85 (m, 5H), 0.51-0.37 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major rotamer) 169.5 (Cq), 169.3 (Cq), 169.1 (Cq), 164.3 (d, ^1J = 253.6 Hz, Cq), 150.2 (Cq), 133.9 (CH_{Ar}), 133.6 (CH_{Ar}), 129.9 (CH_{Ar}), 129.8 (d, ^3J = 8.8 Hz, CH_{Ar}), 129.6 (Cq), 124.8 (CH_{Ar}), 116.6 (d, ^2J = 21.8 Hz, CH_{Ar}), 104.9 (Cq), 48.5 (CH), 46.7 (CH_2), 41.7 (CH_2), 33.0 (CH_2), 32.2 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{24}H_{25}ClFN_3O_5H]^+$ 490.1540, m/z found for $[M+H]^+$ 490.1545.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-(4-methoxyphenyl)-3-hydroxyacrylamide (5g)

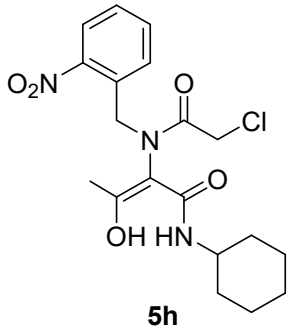


5g

Pink solid. **M. p.:** 170-171 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 15.52 (s, 1H, OH), 7.88 (d, J = 9.0 Hz, 1H), 7.83 (dd, J = 8.0, 1.4 Hz, 1H), 7.57 (d, J = 9.0 Hz, 2H), 7.53-7.45 (m, 2H), 7.29 (dd, J = 7.4, 1.7 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 5.80 (d, J = 8.7 Hz, 1H, NH), 5.55 (d, J = 13.8 Hz, 1H), 4.31 (d, J = 13.9 Hz, 1H), 4.22 (d, J = 14.0 Hz, 1H), 3.86 (s, 3H), 3.88-3.81 (m, 1H), 3.63-3.43 (m, 1H), 1.82-0.38 (m, 10H). **^{13}C NMR (75 MHz,**

$CDCl_3$) (enol form)**:** δ 169.9 (Cq), 169.8 (Cq), 169.3 (Cq), 162.0 (Cq), 134.1 (CH_{Ar}), 133.5 (CH_{Ar}), 129.8 (CH_{Ar}), 129.7 (Cq), 129.3 (CH_{Ar}), 125.2 (Cq), 124.8 (CH_{Ar}), 114.6 (CH_{Ar}), 103.9 (Cq), 55.6 (CH_3), 51.0 (CH), 48.4 (CH), 46.6 (CH_2), 42.0 (CH_2), 33.1 (CH_2), 32.3 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{25}H_{28}ClN_3O_6H]^+$ 502.1739, *m*/*z* found for $[M+H]^+$ 502.1747.

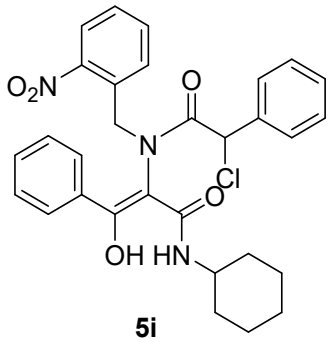
(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-hydroxybut-2-enamide (5h)



5h

Pink solid. **M. p.:** 166-169 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 14.78 (s, 1H, OH), 7.88 (d, *J* = 8.0 Hz, 1H), 7.65-7.49 (m, 3H), 5.59 (d, *J* = 7.8 Hz, 1H, NH), 5.46 (d, *J* = 13.9 Hz, 1H), 4.47 (d, *J* = 13.9 Hz, 1H), 4.01 (s, 2H), 3.58-3.46 (m, 1H), 1.80 (s, 3H), 1.76-1.50 (m, 4H), 1.42-0.87 (m, 5H), 0.60 (qd, *J* = 12.0, 3.5 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 174.4 (Cq), 168.9 (Cq), 168.5 (Cq), 134.0 (CH_{Ar}), 133.6 (CH_{Ar}), 129.9 (CH_{Ar}), 129.7 (Cq), 124.9 (CH_{Ar}), 105.6 (Cq), 48.2 (CH), 47.4 (CH_2), 41.6 (CH_2), 33.1 (CH_2), 32.5 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 18.2 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{19}H_{24}ClN_3O_5H]^+$, 410.1477, *m*/*z* found for $[M+H]^+$ 410.1497.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)-2-phenylacetamido)-*N*-cyclohexyl-3-hydroxy-3-phenylacrylamide (5i)

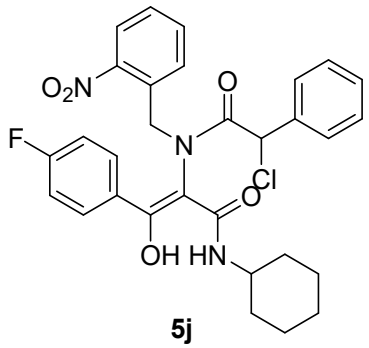


5i

White solid. **M. p.:** 128-130 °C (as a 94:6 isomers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major isomer) 15.65 (s, 1H, OH), 7.85-7.07 (m, 14H), 6.01 (d, *J* = 8.8 Hz,

1H, NH), 5.68 (s, 1H), 5.50 (d, J = 13.9 Hz, 1H), 3.64 (d, J = 13.9 Hz, 1H), 3.63-3.51 (m, 1H), 1.96-0.94 (m, 9H), 0.48 (qd, J = 11.9, 3.4 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major isomer) 170.3 (Cq), 170.0 (Cq), 169.6 (Cq), 150.2 (Cq), 134.9 (Cq), 133.8 (CH_{Ar}), 133.3 (CH_{Ar}), 132.6 (Cq), 130.9 (CH_{Ar}), 129.6 (CH_{Ar}), 129.5 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 127.2 (CH_{Ar}), 124.6 (CH_{Ar}), 104.6 (Cq), 56.7 (CH), 48.6 (CH), 46.3 (CH_2), 32.7 (CH_2), 32.3 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 24.8 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{30}H_{30}ClN_3O_5H]^+$ 548.1947, m/z found for $[M+H]^+$ 548.1961.

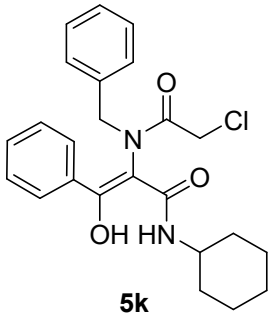
(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)-2-phenylacetamido)-*N*-cyclohexyl-3-(4-fluorophenyl)-3-hydroxyacrylamide (5j)



5j

White solid. **M. p.:** 145-147 °C (as a 93:7 isomers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major isomer) 15.73 (s, 1H, OH), 7.85-6.77 (m, 13H), 5.93 (d, J = 6.7 Hz, 1H, NH), 5.64 (s, 1H), 5.50 (d, J = 13.5 Hz, 1H), 3.71 (d, J = 13.7 Hz, 1H), 3.65-3.48 (m, 1H), 2.20-0.31 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major isomer) 170.5 (Cq), 169.7 (Cq), 169.0 (Cq), 150.4 (Cq), 134.9 (Cq), 133.9 (CH_{Ar}), 133.5 (CH_{Ar}), 129.9 (d, ^3J = 3.1 Hz, CH_{Ar}), 129.8 (CH_{Ar}), 129.7 (Cq), 129.0 (CH_{Ar}), 124.9 (CH_{Ar}), 115.8 (d, ^2J = 21.8 Hz, CH_{Ar}), 104.5 (Cq), 57.0 (CH), 48.8 (CH), 46.4 (CH_2), 32.8 (CH_2), 32.4 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{30}H_{29}ClFN_3O_5H]^+$ 566.1853, m/z found for $[M+H]^+$ 566.1865.

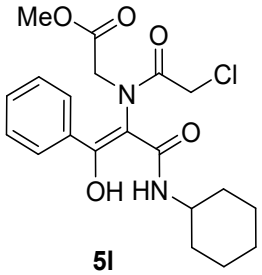
(*E*)-2-(*N*-Benzyl-2-chloroacetamido)-*N*-cyclohexyl-3-hydroxy-3-phenylacrylamide (5k)



5k

Pink solid. **M. p.:** 135-137 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 15.48 (s, 1H, OH), 7.61-7.57 (m, 2H), 7.50-7.45 (m, 3H), 7.38-7.31 (m, 5H), 5.48 (d, J = 13.7 Hz, 1H), 5.00 (d, J = 7.7 Hz, 1H, NH), 4.17 (d, J = 14.1 Hz, 1H), 4.11 (d, J = 14.1 Hz, 1H), 3.52-3.39 (m, 1H), 3.44 (d, J = 13.6 Hz, 1H), 1.71-1.47 (m, 5H), 1.32-0.70 (m, 4H), 0.30 (qd, J = 11.9, 3.5 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 169.9 (Cq), 169.6 (Cq), 169.1 (Cq), 137.1 (Cq), 133.0 (Cq), 131.3 (CH_{Ar}), 129.7 (CH_{Ar}), 129.5 (CH_{Ar}), 129.1 (CH_{Ar}), 128.7 (CH_{Ar}), 127.3 (CH_{Ar}), 54.3 (CH_2), 48.5 (CH), 42.3 (CH_2), 32.7 (CH_2), 31.8 (CH_2), 25.4 (CH_2), 24.8 (CH_2), 24.7 (CH_2). **MS (EI):** *m*/*z* (%): 429 (M^+, 1.2), 265 (17), 259 (31), 105 (54), 91 (100), 77 (17). **HRMS (EI):** *m*/*z* calculated for $[C_{24}H_{27}ClN_2O_3]^+$ 426.1710, *m*/*z* found for $[M]^+$ 426.1701.

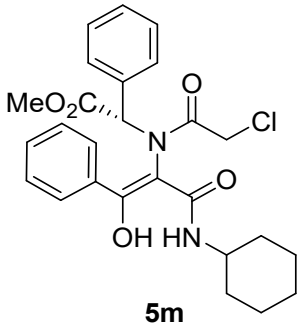
Methyl (*E*)-2-(2-chloro-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)acetate (5l)



5l

Pink solid. **M. p.:** 139-141 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 15.61 (s, 1H, OH), 8.31 (d, J = 7.3 Hz, 1H, NH), 7.47-7.39 (m, 5H), 4.45 (d, J = 16.7 Hz, 1H), 4.12 (d, J = 14.1 Hz, 1H), 4.04 (d, J = 14.1 Hz, 1H), 3.88-3.74 (m, 1H), 3.79 (s, 3H), 3.40 (d, J = 16.7 Hz, 1H), 2.00-1.13 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 171.1 (Cq), 170.5 (Cq), 169.4 (Cq), 168.7 (Cq), 131.0 (CH_{Ar}), 129.0 (CH_{Ar}), 126.9 (CH_{Ar}), 107.7 (Cq), 53.8 (CH_2), 53.0 (CH_3), 48.9 (CH), 41.2 (CH_2), 32.9 (CH_2), 32.4 (CH_2), 25.3 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{20}H_{25}ClN_2O_5H]^+$ 409.1525, *m*/*z* found for $[M+H]^+$ 409.1530.

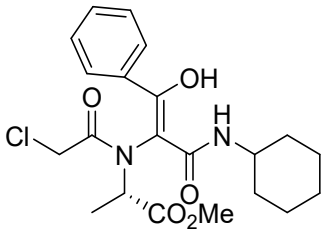
Methyl (*S*,*E*)-2-(2-chloro-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)-2-phenylacetate (5m)



5m

Pink solid. **M. p.:** 153-155 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 15.55 (s, 1H, OH), 8.62 (d, J = 7.9 Hz, 1H, NH), 7.40-6.96 (m, 8H), 6.48 (d, J = 7.4 Hz, 2H), 5.26 (s, 1H), 4.35 (d, J = 14.7 Hz, 1H), 4.20 (d, J = 14.7 Hz, 1H), 3.90-3.75 (m, 1H), 3.64 (s, 3H), 2.08-0.96 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.1 (Cq), 170.5 (Cq), 170.5 (Cq), 169.6 (Cq), 133.5 (Cq), 130.8 (CH_{Ar}), 129.5 (CH_{Ar}), 129.5 (Cq), 129.3 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 127.5 (CH_{Ar}), 103.0 (Cq), 77.4 (Cq), 65.6 (CH), 53.1 (CH_3), 48.7 (CH), 42.3 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 25.3 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{26}H_{29}ClN_2O_5H]^+$ 485.1838, *m*/*z* found for $[M+H]^+$ 485.1852.

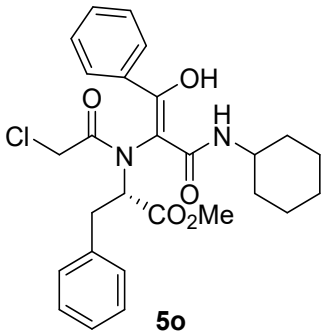
Methyl (*S*,*E*)-2-(2-chloro-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)propanoate (5n)



5n

Orange oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 16.07 (s, 1H, OH), 8.56 (d, J = 7.6 Hz, 1H, NH), 7.50-7.34 (m, 5H), 4.35 (q, J = 7.6 Hz, 1H), 4.06 (d, J = 14.3 Hz, 1H), 3.97 (d, J = 14.3 Hz, 1H), 3.89-3.67 (m, 1H), 3.81 (s, 3H), 1.98-1.12 (m, 10H), 1.20 (d, J = 7.6 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 175.5 (Cq), 170.8 (Cq), 170.4 (Cq), 168.8 (Cq), 132.9 (Cq), 131.0 (CH_{Ar}), 128.9 (CH_{Ar}), 126.6 (CH_{Ar}), 102.2 (Cq), 56.4 (CH), 52.9 (CH_3), 48.6 (CH), 42.0 (CH_2), 32.5 (CH_2), 32.3 (CH_2), 25.1 (CH_2), 24.7 (CH_2), 13.9 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{21}H_{27}ClN_2O_5H]^+$ 423.1681, *m*/*z* found for $[M+H]^+$ 423.1691.

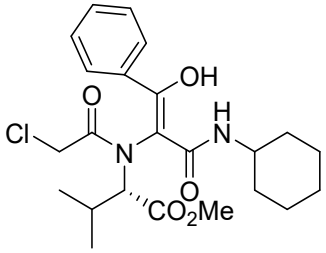
Methyl (*S*,*E*)-2-(2-chloro-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)-3-phenylpropanoate (5o)



5o

Pink solid. **M. p.:** 137-139 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 16.14 (s, 1H, OH), 8.68 (d, J = 7.6 Hz, 1H, NH), 7.51-7.45 (m, 5H), 7.21-7.19 (m, 3H), 6.85-6.83 (m, 2H), 4.41 (dd, J = 11.1, 5.7 Hz, 1H), 4.09 (d, J = 14.4 Hz, 1H), 4.03 (d, J = 14.4 Hz, 1H), 3.93-3.79 (m, 1H), 3.50 (s, 3H), 2.91 (dd, J = 13.2, 5.7 Hz, 1H), 2.62 (dd, J = 13.3, 11.1 Hz, 1H), 1.99-1.59 (m, 5H), 1.48-1.22 (m, 5H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 175.1 (Cq), 171.1 (Cq), 170.7 (Cq), 169.3 (Cq), 134.8 (Cq), 131.4 (CH_{Ar}), 129.2 (CH_{Ar}), 128.9 (CH_{Ar}), 128.7 (CH_{Ar}), 127.4 (CH_{Ar}), 127.1 (CH_{Ar}), 102.9 (Cq), 63.0 (CH), 52.6 (CH_3), 49.1 (CH), 42.4 (CH_2), 35.3 (CH_2), 33.0 (CH_2), 32.8 (CH_2), 25.5 (CH_2), 25.2 (CH_2), 25.1 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{27}H_{31}ClN_2O_5H]^+$ 499.1994, *m*/*z* found for $[M+H]^+$ 499.2003.

Methyl (S,*E*)-2-(2-chloroacetyl)-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)-3-methylbutanoate (5p)

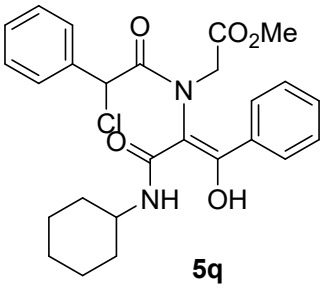


5p

Yellowish-orange oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 16.22 (s, 1H, OH), 8.67 (d, J = 7.8 Hz, 1H, NH), 7.47-7.35 (m, 5H), 4.22 (d, J = 2.4 Hz, 1H), 4.08 (d, J = 14.7 Hz, 1H), 4.03 (d, J = 14.7 Hz, 1H), 3.85-3.69 (m, 1H), 3.77 (s, 3H), 1.95-1.07 (m, 10H), 0.84 (d, J = 7.1 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 173.5 (Cq), 170.7 (Cq), 170.7 (Cq), 169.3 (Cq), 133.0 (Cq), 131.2 (CH_{Ar}), 129.0 (CH_{Ar}), 127.0 (CH_{Ar}), 102.2 (Cq), 66.4 (CH_3), 52.6 (CH), 48.8 (CH), 42.4 (CH_2), 32.8 (CH_2), 32.2 (CH_2), 26.4 (CH),

25.3 (CH_2), 24.9 (CH_2), 24.9 (CH_2), 22.2 (CH_3), 18.4 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{23}H_{31}ClN_2O_5H]^+$ 451.1994, *m*/*z* found for $[M+H]^+$ 451.2000.

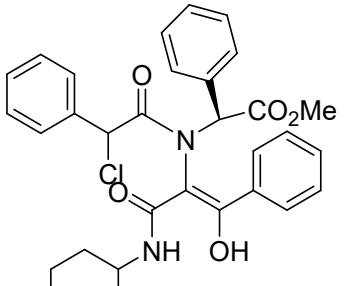
Methyl 2-(2-chloro-*N*-((*E*)-3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2-phenylacetamido)acetate (5q)



5q

Pink solid. **M. p.:** 123-126 °C (as a 95:5 isomers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major isomer) 15.73 (s, 1H, OH), 7.61-7.20 (m, 11H), 5.75 (s, 1H), 4.47 (d, *J* = 16.5 Hz, 1H), 3.77 (s, 3H), 3.39 (d, *J* = 16.5 Hz, 1H), 3.38-3.25 (m, 1H), 1.81-0.49 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major isomer) 171.1 (Cq), 170.9 (Cq), 169.9 (Cq), 169.2 (Cq), 135.8 (Cq), 133.2 (Cq), 131.1 (CH_{Ar}), 129.4 (CH_{Ar}), 129.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.6 (CH_{Ar}), 127.3 (CH_{Ar}), 108.1 (Cq), 56.9 (CH), 54.2 (CH_2), 53.0 (CH_3), 49.1 (CH), 32.5 (CH_2), 31.7 (CH_2), 25.4 (CH_2), 24.9 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{26}H_{29}ClN_2O_5H]^+$ 485.1838, *m*/*z* found for $[M+H]^+$ 485.1852.

Methyl (2*S*)-2-(2-chloro-*N*-((*E*)-3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2-phenylacetamido)-2-phenylacetate (5r)

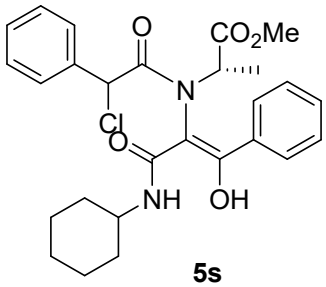


5r

Orange oil (as a 48:44:5:3 isomers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major isomers) 15.82 (s, 0.48H, OH), 15.69 (s, 0.52H, OH), 8.75 (d, *J* = 8.1 Hz, 0.48H), 8.05 (d, *J* = 7.1 Hz, 0.52H), 7.55-6.48 (m, 10H), 6.04 (s, 0.48H), 5.75 (s, 0.52H), 5.38 (s, 0.48H), 5.24 (s, 0.52H), 4.05-3.90 (m, 0.48H), 3.75 (s, 1.56H), 3.71 (s, 1.44H), 3.36-3.23 (m, 0.52H), 2.17-0.54 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major isomers) 173.1 (Cq), 173.0 (Cq), 171.2 (Cq), 171.0 (Cq), 170.9 (Cq), 170.7 (Cq), 170.6 (Cq), 170.3 (Cq),

135.8 (Cq), 134.9 (Cq), 133.8 (Cq), 133.1 (Cq), 130.9 (CH_{Ar}), 130.5 (CH_{Ar}), 129.8 (CH_{Ar}), 129.7 (Cq), 129.6 (CH_{Ar}), 129.5 (Cq), 129.5 (CH_{Ar}), 129.3 (CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.3 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.6 (CH_{Ar}), 103.4 (Cq), 103.0 (Cq), 66.0 (CH), 65.7 (CH), 57.2 (CH), 53.3 (CH_3), 53.2 (CH_3), 49.3 (CH), 49.1 (CH), 32.9 (CH_2), 32.9 (CH_2), 32.5 (CH_2), 31.3 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{32}H_{33}ClN_2O_5H]^+$ 561.2151, *m*/*z* found for $[M+H]^+$ 561.2165.

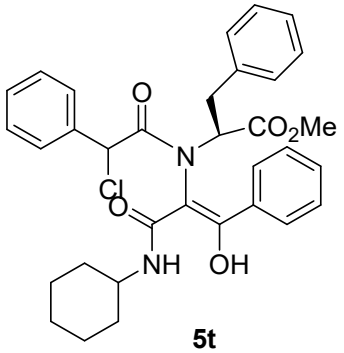
Methyl (2*S*)-2-(2-chloro-*N*-((*E*)-3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2-phenylacetamido)propanoate (5s)



5s

Pink solid. **M. p.:** 181-183 °C (as a 92:8 isomers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major isomer) 16.28 (s, 1H, OH), 8.68 (d, *J* = 7.9 Hz, 1H, NH), 7.26-7.05 (m, 10H), 5.56 (s, 1H), 4.34 (q, *J* = 7.6 Hz, 1H), 3.99-3.82 (m, 1H), 3.85 (s, 3H), 2.16-1.14 (m, 10H), 1.18 (d, *J* = 7.6 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major isomer) 175.5 (Cq), 170.7 (Cq), 134.9 (Cq), 132.9 (Cq), 130.9 (CH_{Ar}), 129.1 (CH_{Ar}), 128.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.5 (CH_{Ar}), 127.1 (CH_{Ar}), 102.5 (Cq), 56.8 (CH), 56.4 (CH), 53.2 (CH_3), 49.2 (CH), 32.8 (CH_2), 25.5 (CH_2), 25.1 (CH_2), 14.4 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{27}H_{31}ClN_2O_5H]^+$ 499.1994, *m*/*z* found for $[M+H]^+$ 499.2004.

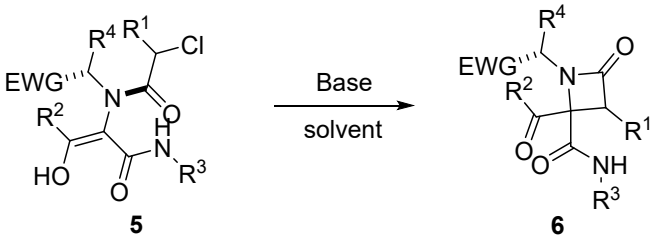
Methyl (2*S*)-2-(2-chloro-*N*-((*E*)-3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2-phenylacetamido)-3-phenylpropanoate (5t)



5t

Yellow oil (as a 50:42:5:3 isomers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major isomers) 16.34 (s, 1H, OH), 8.79 (d, J = 7.9 Hz, 0.54H), 8.05 (d, J = 7.1 Hz, 0.46H), 7.65-6.76 (m, 15H), 5.78 (s, 0.54H), 5.61 (s, 0.46H), 4.46-4.36 (m, 1H), 4.04-3.90 (m, 0.46H), 3.51 (s, 1.38H), 3.47 (s, 1.62H), 3.42-3.29 (m, 0.54H), 2.86 (td, J = 14.0, 5.7 Hz, 1H), 2.64-2.56 (m, 1H), 2.13-0.61 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ (major isomers) 174.8 (Cq), 174.7 (Cq), 171.3 (Cq), 170.7 (Cq), 170.6 (Cq), 170.6 (Cq), 170.4 (Cq), 170.3 (Cq), 135.5 (Cq), 134.8 (Cq), 134.7 (Cq), 134.7 (Cq), 133.2 (Cq), 132.6 (Cq), 131.1 (CH_{Ar}), 130.8 (CH_{Ar}), 129.2 (CH_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 127.2 (CH_{Ar}), 127.2 (CH_{Ar}), 127.1 (CH_{Ar}), 127.0 (CH_{Ar}), 103.0 (Cq), 102.6 (Cq), 63.1 (CH), 62.8 (CH), 58.0 (CH), 56.4 (CH), 52.4 (CH_3), 52.3 (CH_3), 49.1 (CH), 49.0 (CH), 35.2 (CH_2), 35.1 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 31.4 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 24.7 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{33}H_{35}ClN_2O_5H]^+$ 575.2307, m/z found for $[M+H]^+$ 575.2313.

2.2. Synthesis of the azetidin-2-ones 6a-u

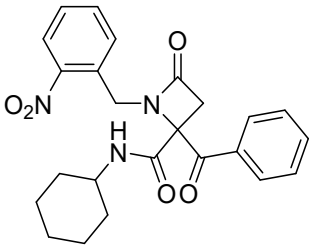


Method A: To a 0.05 M solution of Ugi adduct **5a-h, 5m-p** (1 mmol) in acetonitrile, cesium carbonate (1 mmol) and lithium iodide (2 mmol; for the synthesis of **6m** 10 mmol were used) were added, and the reaction mixture was stirred at reflux for 12 h. The solvent was removed under reduced pressure, and the residue was redissolved in dichloromethane and washed successively with a 10% HCl aqueous solution and water. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness, and the residue was crystallized from a diisopropyl ether/isopropanol mixture to give the corresponding azetidin-2-one **6**.

Method B: To a 0.05 M solution of Ugi adduct **5i-j, 5q-t** (1 mmol) in methanol thiethylamine (3 mmol) was added, and the reaction mixture was ultrasonicated for 2 h. The solvent was removed under reduced pressure, and the residue was redissolved in chloroform and washed successively with a 10% HCl aqueous solution and water. The

organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness, and the residue was purified by column chromatography using a 7:1 hexane:ethyl acetate mixture as eluent and SiO_2 as stationary phase. Diastereomers **6q-t** were separated by column chromatography as well, using the same stationary phase and a 20:1 hexane:ethyl acetate mixture as eluent.

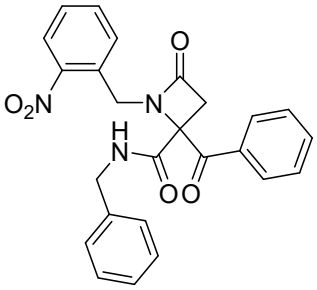
4-Benzoyl-4-cyclohexylcarbamoyl-1-(2-nitrobenzyl)azetidin-2-one (6a)



6a

White solid. **M. p.:** 173-176 °C. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.00 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.65-7.57 (m, 3H), 7.47-7.42 (m, 3H), 5.74 (d, J = 7.8 Hz, 1H, NH), 5.15 (d, J = 17.0 Hz, 1H), 5.10 (d, J = 17.0 Hz, 1H), 4.13 (d, J = 14.6 Hz, 1H), 3.58-3.48 (m, 1H), 3.25 (d, J = 14.6 Hz, 1H), 1.66-1.33 (m, 4H), 1.21-1.10 (m, 3H), 1.03-0.91 (m, 1H), 0.81-0.71 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.9 (Cq), 166.6 (Cq), 164.4 (Cq), 148.1 (Cq), 134.6 (CH_{Ar}), 134.0 (CH_{Ar}), 133.3 (Cq), 132.0 (Cq), 131.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 124.9 (CH_{Ar}), 69.5 (Cq), 49.6 (CH), 46.4 (CH_2), 42.3 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 25.2 (CH_2), 24.7 (CH_2), 24.6 (CH_2). **HRMS (+ESI):** *m/z* calculated for $[C_{24}H_{25}N_3O_5H]^+$ 436.1872, *m/z* found for $[M+H]^+$ 436.1856.

4-Benzoyl-4-benzylcarbamoyl-1-(2-nitrobenzyl)azetidin-2-one (6b)

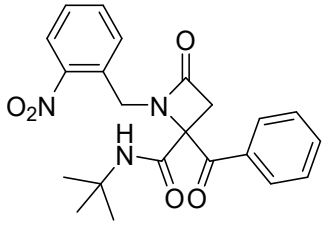


6b

Brown oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.91 (d, J = 8.1 Hz, 1H), 7.79-7.75 (m, 2H), 7.62-7.53 (m, 3H), 7.44-7.38 (m, 3H), 7.15-7.05 (m, 3H), 6.82-6.79 (m, 2H), 6.62 (t, J =

5.6 Hz, 1H, NH), 5.13 (d, J = 17.5 Hz, 1H), 5.06 (d, J = 17.5 Hz, 1H), 4.23 (dd, J = 14.7, 6.1 Hz, 1H), 4.09 (d, J = 14.6 Hz, 1H), 3.96 (dd, J = 14.7, 5.3 Hz, 1H), 3.23 (d, J = 14.6 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 195.3 (Cq), 166.5 (Cq), 165.5 (Cq), 147.9 (Cq), 136.7 (Cq), 134.6 (CH_{Ar}), 133.9 (CH_{Ar}), 133.3 (Cq), 131.6 (Cq), 130.7 (CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 127.7 (CH_{Ar}), 127.5 (CH_{Ar}), 124.9 (CH_{Ar}), 69.1 (Cq), 46.3 (CH_2), 44.2 (CH_2), 42.7 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{25}H_{21}N_3O_5H]^+$ 444.1559, m/z found for $[M+H]^+$ 444.1557.

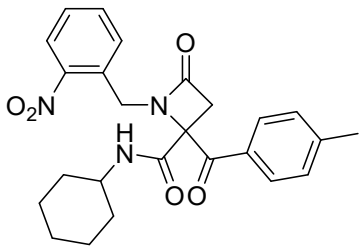
4-Benzoyl-4-(*tert*-butylcarbamoyl)-1-(2-nitrobenzyl)azetidin-2-one (6c)



6c

Pale yellowish oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.98 (dd, J = 8.1, 1.1 Hz, 1H), 7.84-7.80 (m, 2H), 7.69-7.57 (m, 3H), 7.48-7.42 (m, 3H), 5.57 (s, 1H, NH), 5.15 (d, J = 17.2 Hz, 1H), 5.09 (d, J = 17.2 Hz, 1H), 4.10 (d, J = 14.5 Hz, 1H), 3.21 (d, J = 14.5 Hz, 1H), 1.00 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.1 (Cq), 166.6 (Cq), 164.3 (Cq), 134.6 (CH_{Ar}), 134.0 (CH_{Ar}), 133.4 (Cq), 132.0 (Cq), 131.5 (CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 124.8 (CH_{Ar}), 70.1 (Cq), 52.7 (Cq), 46.3 (CH_2), 41.9 (CH_2), 28.0 (CH_3). **HRMS (+ESI):** m/z calculated for $[C_{22}H_{23}N_3O_5H]^+$ 410.1716, m/z found for $[M+H]^+$ 410.1713.

4-Cyclohexylcarbamoyl-4-(4-methylbenzoyl)-1-(2-nitrobenzyl)azetidin-2-one (6d)

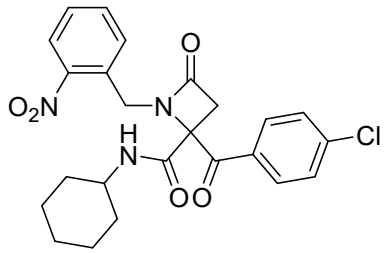


6d

White solid. **M. p.:** 198-200 ^{o}C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.99 (d, J = 8.1 Hz, 1H), 7.71-7.61 (m, 4H), 7.47-7.39 (m, 1H), 7.22 (d, J = 8.3 Hz, 2H), 5.70 (d, J = 7.7 Hz, 1H, NH), 5.16 (d, J = 17.6 Hz, 1H), 5.10 (d, J = 17.6 Hz, 1H), 4.12 (d, J = 14.5 Hz, 1H), 3.59-3.47 (m, 1H), 3.23 (d, J = 14.5 Hz, 1H), 2.40 (s, 3H), 1.57-0.67 (m, 10H). **^{13}C NMR (75**

MHz, $CDCl_3$): δ 195.4 (Cq), 166.7 (Cq), 164.5 (Cq), 145.9 (Cq), 134.0 (CH_{Ar}), 132.1 (Cq), 131.1 (CH_{Ar}), 130.8 (Cq), 129.8 (CH_{Ar}), 129.0 (CH_{Ar}), 128.5 (CH_{Ar}), 124.9 (CH_{Ar}), 69.5 (Cq), 49.5 (CH), 46.3 (CH_2), 42.3 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 25.2 (CH_2), 24.7 (CH_2), 24.6 (CH_2), 22.0 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{25}H_{27}N_3O_5H]^+$ 450.2029, *m*/*z* found for $[M+H]^+$ 450.2029.

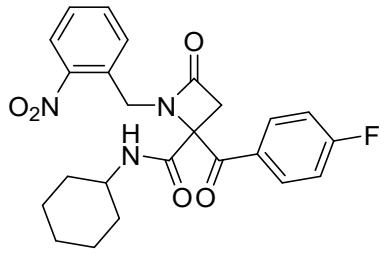
4-(4-Chlorobenzoyl)-4-cyclohexylcarbamoyl-1-(2-nitrobenzyl)azetidin-2-one (6e)



6e

White solid. **M. p.:** 190-193 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.00 (d, J = 7.8 Hz, 1H), 7.79-7.63 (m, 4H), 7.50-7.39 (m, 3H), 5.74 (d, J = 8.0 Hz, 1H, NH), 5.14 (d, J = 16.9 Hz, 1H), 5.08 (d, J = 16.9 Hz, 1H), 4.09 (d, J = 14.5 Hz, 1H), 3.61-3.49 (m, 1H), 3.22 (d, J = 14.5 Hz, 1H), 1.61-0.72 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.6 (Cq), 166.3 (Cq), 164.3 (Cq), 148.1 (Cq), 141.2 (Cq), 134.0 (CH_{Ar}), 131.8 (Cq), 131.6 (Cq), 131.2 (CH_{Ar}), 130.2 (CH_{Ar}), 129.4 (CH_{Ar}), 128.7 (CH_{Ar}), 124.9 (CH_{Ar}), 69.3 (Cq), 49.6 (CH), 46.3 (CH_2), 42.4 (CH_2), 32.2 (CH_2), 32.0 (CH_2), 25.2 (CH_2), 24.7 (CH_2), 24.7 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{24}H_{24}ClN_3O_5H]^+$ 470.1483, *m*/*z* found for $[M+H]^+$ 470.1484.

4-Cyclohexylcarbamoyl-4-(4-fluorobenzoyl)-1-(2-nitrobenzyl)azetidin-2-one (6f)

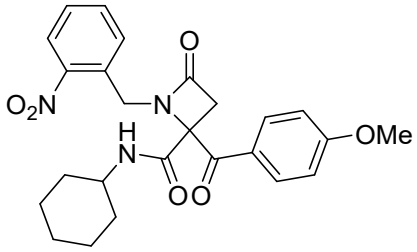


6f

White solid. **M. p.:** 197-200 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.00 (d, J = 8.0 Hz, 1H), 7.88-7.84 (m, 2H), 7.63 (d, J = 3.9 Hz, 2H), 7.49-7.42 (m, 1H), 7.14-7.09 (m, 2H), 5.85 (d, J = 7.9 Hz, 1H, NH), 5.15 (d, J = 17.1 Hz, 1H), 5.09 (d, J = 17.1 Hz, 1H), 4.12 (d, J = 14.5 Hz, 1H), 3.60-3.46 (m, 1H), 3.22 (d, J = 14.5 Hz, 1H), 1.51-0.68 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.1 (Cq), 166.2 (Cq), 164.2 (Cq), 148.0 (Cq), 133.9 (CH_{Ar}),

131.8 (Cq), 131.6 (d, ^{3}J = 9.6 Hz, CH_{Ar}), 131.2 (CH_{Ar}), 129.8 (d, ^{4}J = 3.1 Hz, Cq), 128.6 (CH_{Ar}), 124.8 (CH_{Ar}), 116.3 (d, ^{2}J = 22.1 Hz, CH_{Ar}), 69.3 (Cq), 49.5 (CH), 46.2 (CH_2), 42.1 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 25.0 (CH_2), 24.6 (CH_2), 24.5 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{24}H_{24}FN_3O_5H]^+$ 454.1778, *m*/*z* found for $[M+H]^+$ 454.1774.

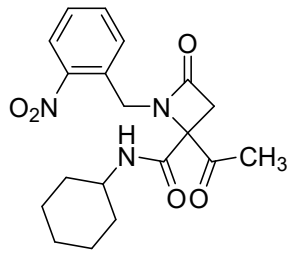
4-Cyclohexylcarbamoyl-4-(4-methoxybenzoyl)-1-(2-nitrobenzyl)azetidin-2-one (6g)



6g

Dark brown solid. **M. p.:** 198-201 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.02-7.98 (m, 1H), 7.79 (d, *J* = 9.0 Hz, 2H), 7.64-7.62 (m, 2H), 7.46-7.39 (m, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.60 (d, *J* = 8.5 Hz, 1H, NH), 5.14 (s, 2H), 4.13 (d, *J* = 14.5 Hz, 1H), 3.87 (s, 3H), 3.60-3.46 (m, 1H), 3.23 (d, *J* = 14.4 Hz, 1H), 1.57-0.68 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.1 (Cq), 166.8 (Cq), 164.7 (Cq), 164.6 (Cq), 148.1 (Cq), 134.0 (CH_{Ar}), 132.2 (Cq), 131.4 (CH_{Ar}), 131.0 (CH_{Ar}), 128.5 (CH_{Ar}), 126.1 (Cq), 124.9 (CH_{Ar}), 114.3 (CH_{Ar}), 69.4 (Cq), 55.8 (CH_3), 49.5 (CH), 46.3 (CH_2), 42.3 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 29.8 (CH_2), 25.2 (CH_2), 24.7 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{25}H_{27}N_3O_6H]^+$ 466.1978, *m*/*z* found for $[M+H]^+$ 466.1975.

4-Acetyl-4-cyclohexylcarbamoyl-1-(2-nitrobenzyl)azetidin-2-one (6h)

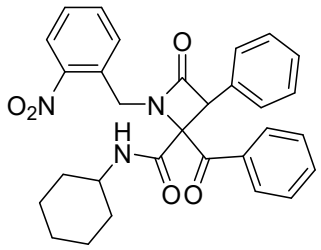


6h

Yellow-orange solid. **M. p.:** 175-178 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.98 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.72-7.63 (m, 2H), 7.49 (ddd, *J* = 8.1, 7.2, 1.7 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H, NH), 4.87 (d, *J* = 15.5 Hz, 1H), 4.81 (d, *J* = 15.5 Hz, 1H), 3.70-3.57 (m, 1H), 3.38 (d, *J* = 14.8 Hz, 1H), 3.10 (d, *J* = 14.8 Hz, 1H), 2.18 (s, 3H), 1.76-1.54 (m, 5H), 1.38-0.92 (m, 5H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 206.3 (Cq), 166.6 (Cq), 165.3 (Cq),

148.7 (Cq), 134.2 (CH_{Ar}), 132.9 (CH_{Ar}), 130.9 (Cq), 129.4 (CH_{Ar}), 124.8 (CH_{Ar}), 67.8 (Cq), 48.9 (CH), 48.4 (CH_2), 43.1 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 27.1 (CH_3), 25.5 (CH_2), 24.8 (CH_2), 24.7 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{19}H_{23}N_3O_5H]^+$ 374.1716, *m*/*z* found for $[M+H]^+$ 374.1720.

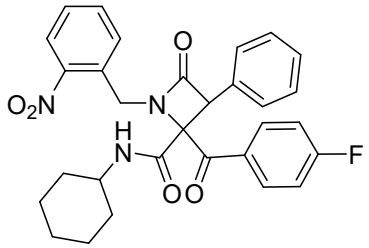
4-Benzoyl-4-cyclohexylcarbamoyl-3-phenyl-1-(2-nitrobenzyl)azetidin-2-one (6i)



6i

Yellow-orange oil (as a 87:13 mixture of diastereomers). **^{1}H NMR (300 MHz, $CDCl_3$):** δ ((3*R**,4*R**) diastereomer) 7.98 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.66 (td, *J* = 7.7, 1.4 Hz, 1H), 7.51 (d, *J* = 7.0 Hz, 2H), 7.41 (td, *J* = 7.7, 1.6 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 2H), 6.99-6.87 (m, 5H), 5.90 (d, *J* = 7.9 Hz, 1H), 5.64 (s, 1H), 5.31 (d, *J* = 17.6 Hz, 1H), 5.16 (d, *J* = 17.6 Hz, 1H), 3.48-3.33 (m, 1H), 1.46-0.36 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ ((3*R**,4*R**) diastereomer) 168.8 (Cq), 164.4 (Cq), 147.8 (Cq), 134.0 (CH_{Ar}), 133.8 (CH_{Ar}), 133.6 (Cq), 132.3 (Cq), 130.9 (Cq), 130.5 (CH_{Ar}), 129.5 (CH_{Ar}), 128.7 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 124.8 (CH_{Ar}), 77.0 (Cq), 63.1 (CH), 49.5 (CH), 42.2 (CH_2), 31.6 (CH_2), 31.5 (CH_2), 24.9 (CH_2), 24.6 (CH_2), 24.5 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{30}H_{29}N_3O_5H]^+$ 512.2180, *m*/*z* found for $[M+H]^+$ 512.2190.

4-Cyclohexylcarbamoyl-4-fluorobenzoyl-3-phenyl-1-(2-nitrobenzyl)azetidin-2-one (6j)

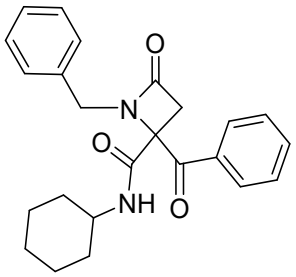


6j

Yellow-orange oil (as a 86:14 mixture of diastereomers). **^{1}H NMR (300 MHz, $CDCl_3$):** δ ((3*R**,4*R**) diastereomer) 7.98 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.74 (dd, *J* = 7.9, 1.6 Hz, 1H),

7.66 (td, J = 7.6, 1.4 Hz, 1H), 7.58-7.54 (m, 2H), 7.41 (td, J = 8.5, 1.5 Hz, 1H), 6.94 (m, 5H), 6.81 (t, J = 8.6 Hz, 2H), 6.07 (d, J = 7.9 Hz, 1H), 5.62 (s, 1H), 5.32 (d, J = 17.6 Hz, 1H), 5.17 (d, J = 17.6 Hz, 1H), 3.47-3.34 (m, 1H), 1.47-0.38 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ ((3*R**,4*R**) diastereomer) 192.7 (Cq), 168.6 (Cq), 165.7 (d, ^1J = 257.3 Hz, Cq), 164.3 (Cq), 147.8 (Cq), 134.0 (CH_{Ar}), 132.2 (Cq), 131.5 (d, ^3J = 9.4 Hz, CH_{Ar}), 130.8 (Cq), 130.4 (CH_{Ar}), 130.1 (d, ^4J = 2.9 Hz, Cq), 129.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 124.9 (CH_{Ar}), 115.4 (d, ^2J = 22.0 Hz, CH_{Ar}), 76.8 (Cq), 63.0 (CH), 49.6 (CH), 42.2 (CH_2), 31.6 (CH_2), 31.4 (CH_2), 24.9 (CH_2), 24.6 (CH_2), 24.5 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{30}H_{28}FN_3O_5H]^+$, 530.2086 *m*/*z* found for $[M+H]^+$ 530.2102.

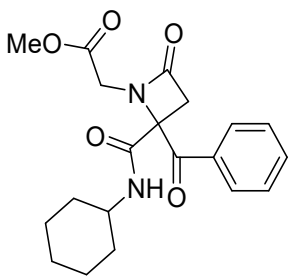
1-Benzyl-4-benzoyl-4-cyclohexylcarbamoylazetidin-2-one (6k)



6k

White solid. **M. p.:** 163-164 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.87 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.47 (d, J = 7.7 Hz, 2H), 7.40-7.24 (m, 5H), 5.36 (d, J = 7.5 Hz, 1H), 5.02 (d, J = 16.0 Hz, 1H), 4.55 (d, J = 16.0 Hz, 1H), 3.80 (d, J = 14.6 Hz, 1H), 3.44 (d, J = 14.6 Hz, 1H), 3.39-3.29 (m, 1H), 1.56-0.83 (m, 8H), 0.60-0.48 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.1 (Cq), 166.7 (Cq), 165.7 (Cq), 136.6 (Cq), 134.4 (CH_{Ar}), 134.1 (Cq), 129.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.9 (CH_{Ar}), 128.2 (CH_{Ar}), 128.0 (CH_{Ar}), 68.6 (Cq), 49.1 (CH), 47.0 (CH_2), 46.0 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 24.6 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{24}H_{26}N_2O_3H]^+$ 391.2016, *m*/*z* found for $[M+H]^+$ 391.2016.

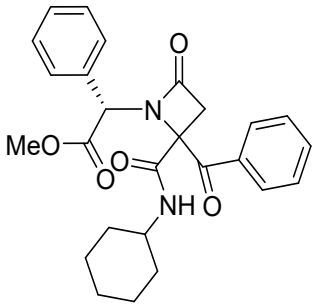
4-Benzoyl-4-cyclohexylcarbamoyl-1-(methoxycarbonylmethyl)azetidin-2-one (6l)



6l

Yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.95-7.90 (m, 2H), 7.87 (d, J = 7.9 Hz, 1H, NH), 7.63-7.56 (m, 1H), 7.50-7.43 (m, 2H), 4.39 (d, J = 18.3 Hz, 1H), 4.32 (d, J = 18.3 Hz, 1H), 3.81 (s, 3H), 3.82-3.67 (m, 1H), 3.63 (d, J = 15.0 Hz, 1H), 3.55 (d, J = 15.0 Hz, 1H), 1.96-1.09 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 170.5, 166.8, 166.5, 134.8, 134.1, 129.9, 128.7, 68.0, 53.1, 49.3, 48.4, 43.8, 32.7, 32.6, 25.5, 25.0. **HRMS (+ESI):** m/z calculated for $[C_{20}H_{24}N_2O_5H]^+$ 373.1758, m/z found for $[M+H]^+$ 373.1762.

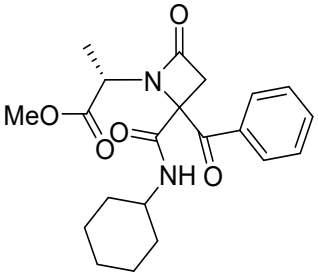
(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-1'-phenylmethyl)-azetidin-2-one (6m)



6m

Pale yellowish oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.86-7.80 (m, 2H), 7.60-7.29 (m, 8H), 6.13 (d, J = 7.8 Hz, 1H, NH), 5.56 (s, 1H), 3.76 (s, 3H), 3.65-3.51 (m, 1H), 3.60 (d, J = 14.9 Hz, 1H), 3.51 (d, J = 14.8 Hz, 1H), 1.75-0.71 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.2 (Cq), 169.1 (Cq), 166.3 (Cq), 165.3 (Cq), 134.8 (Cq), 134.4 (Cq), 133.9 (CH_{Ar}), 129.3 (CH_{Ar}), 129.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 67.6 (Cq), 62.2 (CH), 53.1 (CH_3), 49.1 (CH), 47.3 (CH_2), 32.2 (CH_2), 32.1 (CH_2), 25.2 (CH_2), 24.7 (CH_2), 24.7 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{26}H_{28}N_2O_5H]^+$ 449.2076, m/z found for $[M+H]^+$ 449.2070.

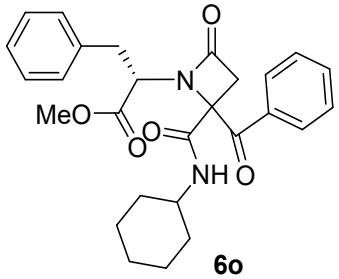
(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonylethyl)-azetidin-2-one (6n)



6n

Yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.84 (d, J = 8.3 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 6.86 (d, J = 7.8 Hz, 1H), 4.40 (q, J = 7.4 Hz, 1H), 3.81-3.72 (m, 1H), 3.77 (s, 3H), 3.67 (d, J = 14.6 Hz, 1H), 3.34 (d, J = 14.6 Hz, 1H), 1.63 (d, J = 7.5 Hz, 3H), 1.92-1.01 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 195.8 (Cq), 172.4 (Cq), 166.6 (Cq), 165.3 (Cq), 134.4 (Cq), 134.0 (CH_{Ar}), 129.4 (CH_{Ar}), 128.7 (CH_{Ar}), 68.8 (Cq), 53.6 (CH), 52.9 (CH_3), 49.3 (CH), 47.6 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 25.4 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 16.0 (CH_3). **HRMS (+ESI):** m/z calculated for $[C_{21}H_{26}N_2O_5H]^+$ 387.1914, m/z found for $[M+H]^+$ 387.1918.

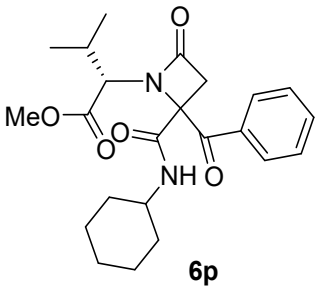
(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-2'-phenylethyl)-azetidin-2-one (6o)



6o

Orange oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.82-7.79 (m, 2H), 7.59-7.53 (m, 1H), 7.46-7.31 (m, 7H), 5.42 (d, J = 8.3 Hz, 1H, NH), 4.30 (dd, J = 11.6, 4.5 Hz, 1H), 3.82-3.71 (m, 1H), 3.75 (s, 3H), 3.55 (d, J = 15.0 Hz, 1H), 3.50 (d, J = 15.0 Hz, 1H), 3.48-3.33 (m, 1H), 3.21 (dd, J = 13.6, 4.5 Hz, 1H), 1.66-0.54 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.3 (Cq), 170.8 (Cq), 167.6 (Cq), 166.3 (Cq), 137.5 (Cq), 134.7 (Cq), 133.9 (CH_{Ar}), 129.5 (CH_{Ar}), 129.4 (CH_{Ar}), 129.3 (CH_{Ar}), 128.7 (CH_{Ar}), 127.6 (CH_{Ar}), 67.3 (Cq), 62.3 (CH), 52.8 (CH_3), 48.8 (CH), 47.2 (CH_2), 36.4 (CH_2), 32.1 (CH_2), 32.1 (CH_2), 25.2 (CH_2), 25.1 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{27}H_{30}N_2O_5H]^+$ 463.2227, m/z found for $[M+H]^+$ 463.2230.

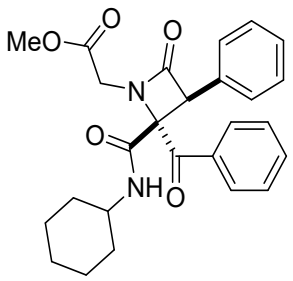
(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-2'-methylpropyl)-azetidin-2-one (6p)



6p

Yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.80 (d, J = 8.1 Hz, 2H), 7.59 (t, J = 7.0 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 5.67 (d, J = 7.1 Hz, 1H), 4.00 (d, J = 14.5 Hz, 1H), 3.81 (s, 3H), 3.86-3.69 (m, 1H), 3.52 (d, J = 10.3 Hz, 1H), 3.13 (d, J = 14.4 Hz, 1H), 2.87-2.75 (m, 1H), 1.88-0.82 (m, 10H), 1.02 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.0 (Cq), 170.9 (Cq), 164.8 (Cq), 164.5 (Cq), 134.6 (CH_{Ar}), 133.0 (Cq), 129.0 (CH_{Ar}), 128.8 (CH_{Ar}), 69.0 (Cq), 67.1 (CH), 52.2 (CH_3), 49.6 (CH), 45.1 (CH_2), 32.8 (CH_2), 32.3 (CH_2), 28.8 (CH), 25.2 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 20.8 (CH_3), 19.7 (CH_3). **HRMS (+ESI):** m/z calculated for $[C_{23}H_{30}N_2O_5H]^+$ 415.2227, m/z found for $[M+H]^+$ 415.2232.

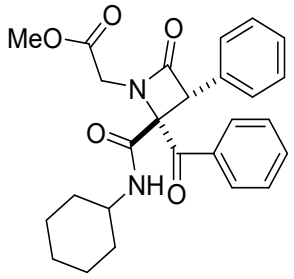
(3*R,4*S**)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(methoxycarbonylmethyl)-3-phenylazetidin-2-one ($6q_{diast1}$)**



$6q_{diast1}$

Orange oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.03 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 7.9 Hz, 1H), 7.63-7.57 (m, 1H), 7.54-7.43 (m, 2H), 7.44-7.32 (m, 5H), 5.11 (s, 1H), 4.46 (d, J = 18.5 Hz, 1H), 4.34 (d, J = 18.5 Hz, 1H), 3.77 (s, 3H), 3.51-3.35 (m, 1H), 1.81-0.81 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.2 (Cq), 171.0 (Cq), 168.5 (Cq), 164.6 (Cq), 135.5 (Cq), 133.8 (CH_{Ar}), 130.9 (Cq), 130.1 (CH_{Ar}), 129.6 (CH_{Ar}), 128.9 (CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 75.6 (Cq), 64.0 (CH), 53.1 (CH_3), 48.9 (CH), 43.7 (CH_2), 32.4 (CH_2), 32.3 (CH_2), 25.4 (CH_2), 24.9 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** m/z calculated for $[C_{26}H_{28}N_2O_5Na]^+$ 471.1890, m/z found for $[M+Na]^+$ 471.1900.

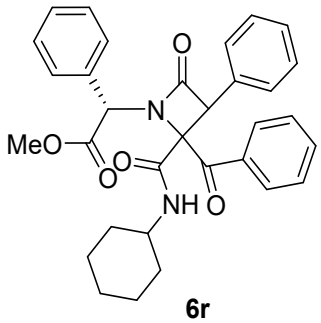
(3*R,4*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(methoxycarbonylmethyl)-3-phenylazetidin-2-one ($6q_{diast2}$)**



$6q_{diast2}$

Orange oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.60-7.51 (m, 2H), 7.35-7.30 (m, 1H), 7.18-7.12 (m, 2H), 7.09-6.95 (m, 5H), 6.39 (d, J = 7.3 Hz, 1H), 5.41 (s, 1H), 4.46 (d, J = 16.1 Hz, 1H), 4.40 (d, J = 16.1 Hz, 1H), 3.82 (s, 3H), 3.78-3.66 (m, 1H), 1.84-0.77 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 195.3 (Cq), 169.0 (Cq), 167.8 (Cq), 164.6 (Cq), 134.0 (Cq), 133.7 (CH_{Ar}), 131.3 (Cq), 129.5 (CH_{Ar}), 129.2 (CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 127.9 (CH_{Ar}), 64.3 (CH), 52.8 (CH_3), 49.6 (CH), 43.6 (CH_2), 32.5 (CH_2), 32.2 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 24.7 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{26}H_{28}N_2O_5H]^+$ 449.2077, *m*/*z* found for $[M+H]^+$ 449.2071.

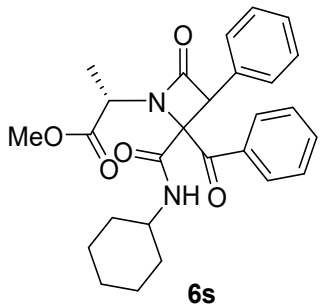
(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-1'-phenylmethyl)-3-phenylazetidin-2-one (6r)



6r

Yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.60-7.00 (m, 15H), 6.08 (s, 1H), 5.78 (s, 1H), 3.94 (s, 3H), 3.56-3.42 (m, 1H), 1.96-0.64 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.4 (Cq), 171.5 (Cq), 168.1 (Cq), 165.2 (Cq), 135.2 (Cq), 134.6 (Cq), 133.4 (CH_{Ar}), 130.8 (Cq), 130.0 (CH_{Ar}), 128.8 (CH_{Ar}), 128.8 (CH_{Ar}), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 127.9 (CH_{Ar}), 127.0 (CH_{Ar}), 78.3 (Cq), 63.6 (CH), 59.4 (CH), 53.5 (CH_3), 49.1 (CH), 31.7 (CH_2), 31.2 (CH_2), 25.3 (CH_2), 24.4 (CH_2), 24.2 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{32}H_{32}N_2O_5H]^+$ 525.2393, *m*/*z* found for $[M+H]^+$ 525.2384.

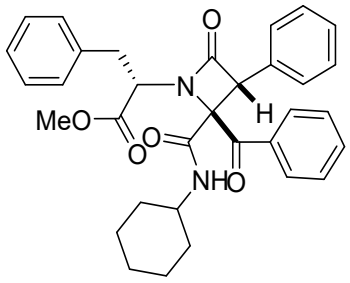
(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonylethyl)-3-phenylazetidin-2-one (6s)



6s

Pale yellowish oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.92 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.35 (s, 5H), 6.50 (d, J = 8.0 Hz, 1H, NH), 5.00 (s, 1H), 4.54 (q, J = 7.4 Hz, 1H), 3.59 (s, 3H), 3.48-3.37 (m, 1H), 1.76 (d, J = 7.5 Hz, 3H), 1.64-0.66 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.8 (Cq), 172.5 (Cq), 167.6 (Cq), 164.8 (Cq), 136.2 (Cq), 133.5 (CH_{Ar}), 131.3 (Cq), 129.7 (CH_{Ar}), 129.5 (CH_{Ar}), 129.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 76.6 (Cq), 63.9 (CH), 53.7 (CH), 52.7 (CH_3), 48.9 (CH), 32.3 (CH_2), 32.1 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 16.5 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{27}H_{30}N_2O_5H]^+$ 463.2227, *m*/*z* found for $[M+H]^+$ 463.2238.

(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-2'-phenylethyl)-3-phenylazetidin-2-one (6t)

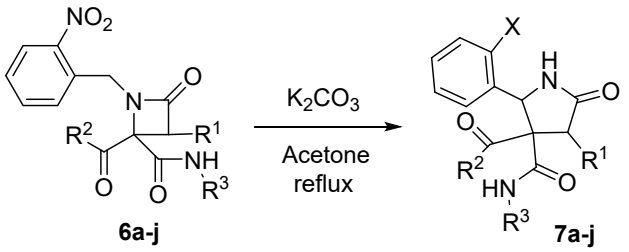


6t

White solid. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.48-7.42 (m, 2H), 7.36-7.24 (m, 6H), 7.17-7.07 (m, 4H), 7.04-6.93 (m, 3H), 5.35 (s, 1H), 5.07 (d, J = 7.5 Hz, 1H), 4.20 (dd, J = 10.6, 4.8 Hz, 1H), 3.97 (s, 3H), 3.82 (dd, J = 13.5, 10.7 Hz, 1H), 3.28 (dd, J = 13.6, 4.8 Hz, 1H), 3.22-3.12 (m, 1H), 1.60-0.49 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.0 (Cq), 170.9 (Cq), 168.0 (Cq), 163.8 (Cq), 137.2 (Cq), 133.9 (CH_{Ar}), 133.6 (Cq), 132.0 (Cq), 129.7 (CH_{Ar}), 129.4 (CH_{Ar}), 128.9 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.2 (CH_{Ar}), 128.0 (CH_{Ar}), 127.2 (CH_{Ar}), 76.5 (Cq), 62.8 (CH), 62.2 (CH), 52.9 (CH_3), 49.6 (CH),

36.5 (CH_2), 32.1 (CH_2), 31.8 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 24.4 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{33}H_{34}N_2O_5H]^+$ 539.2540, *m*/*z* found for $[M+H]^+$ 539.2550.

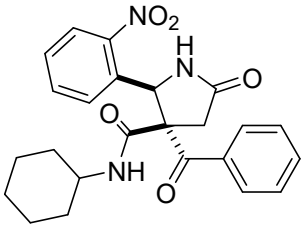
2.3. Synthesis of pyrrolidin-2-ones 7a-j derived from 2-nitrobenzylamine



6a-j **7a-j**

To a 0.05 M solution of azetidin-2-one **6a-j** (1 mmol) in acetone potassium carbonate (1 eq) was added, and the reaction mixture was stirred at reflux for 12 h. The solvent was evaporated under reduced pressure, and the residue was redissolved in dichloromethane and washed with a 10% HCl aqueous solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness, and the residue (crude mixture of diastereoisomers) was crystallized from methanol to give pyrrolidin-2-one **7a-h** as a single diastereoisomer. For derivatives **7i-j**, diastereomers were isolated by column chromatography using SiO_2 as stationary phase and hexane/ethyl acetate mixtures as eluent.

(4*R,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (7a)**

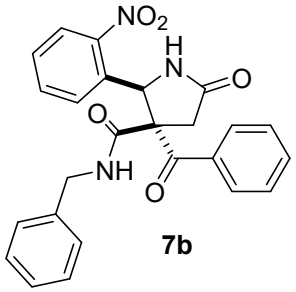


7a

Pale brown solid. **M. p.:** 162-164 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.91 (dd, *J* = 7.2, 1.3 Hz, 2H), 7.81 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.69 (td, *J* = 8.1, 1.0 Hz, 1H), 7.57 (td, *J* = 7.4, 1.2 Hz, 2H), 7.51-7.38 (m, 3H), 6.55 (s, 1H), 6.31 (s, 1H), 5.77 (d, *J* = 8.1 Hz, 1H, NH), 4.29 (d, *J* = 18.3 Hz, 1H), 3.23-3.11 (m, 1H), 2.76 (d, *J* = 18.2 Hz, 1H), 1.42-0.25 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.3 (Cq), 174.3 (Cq), 165.2 (Cq), 149.7 (Cq), 134.0 (CH_{Ar}), 134.0 (Cq), 133.9 (CH_{Ar}), 133.2 (Cq), 130.7 (CH_{Ar}), 129.7 (CH_{Ar}), 129.5 (CH_{Ar}), 129.0 (CH_{Ar}), 124.3 (CH_{Ar}), 65.8 (Cq), 54.2 (CH), 49.1 (CH), 37.5 (CH_2), 31.9

(CH_2), 31.5 (CH_2), 25.1 (CH_2), 24.5 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{24}H_{25}N_3O_5Na]^+$ 458.1692, *m*/*z* found for $[M+Na]^+$ 458.1683.

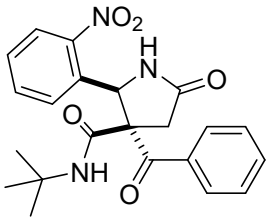
(4*R,5*R**)-4-Benzoyl-4-benzylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (7b)**



7b

Dark brown oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.92 (d, *J* = 7.5 Hz, 2H), 7.66-7.31 (m, 6H), 7.23-7.02 (m, 3H), 6.62 (d, *J* = 7.3 Hz, 2H), 6.58 (s, 1H), 6.32 (t, *J* = 5.6 Hz, 1H, NH), 6.00 (s, 1H, NH), 4.29 (d, *J* = 18.2 Hz, 1H), 3.87 (dd, *J* = 12.5, 3.4 Hz, 1H), 3.80 (dd, *J* = 12.5, 5.9 Hz, 1H), 2.84 (d, *J* = 18.2 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.0 (Cq), 174.4 (Cq), 166.2 (Cq), 149.0 (Cq), 136.5 (Cq), 134.1 (CH_{Ar}), 133.6 (CH_{Ar}), 133.4 (Cq), 133.1 (Cq), 130.2 (CH_{Ar}), 129.6 (CH_{Ar}), 129.0 (CH_{Ar}), 128.7 (CH_{Ar}), 127.9 (CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (CH_{Ar}), 124.6 (CH_{Ar}), 65.7 (Cq), 54.2 (CH), 44.2 (CH_2), 37.6 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{25}H_{21}N_3O_5H]^+$ 444.1559, *m*/*z* found for $[M+H]^+$ 444.1561.

(4*R,5*R**)-4-Benzoyl-4-(*tert*-butylcarbamoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (7c)**

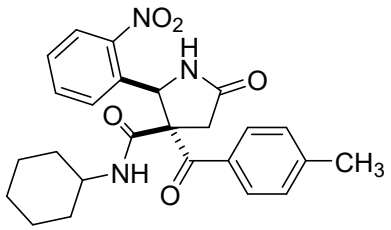


7c

Pale brown solid. **M. p.:** 173-175 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.95-7.91 (m, 2H), 7.82 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.71-7.65 (m, 1H), 7.61-7.41 (m, 5H), 6.54 (s, 1H), 6.29 (s, 1H, NH), 5.78 (s, 1H, NH), 4.25 (d, *J* = 18.3 Hz, 1H), 2.74 (d, *J* = 18.3 Hz, 1H), 0.68 (s, 9H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.4 (Cq), 174.4 (Cq), 164.8 (Cq), 149.7 (Cq), 134.1 (Cq), 134.0 (CH_{Ar}), 133.8 (CH_{Ar}), 133.3 (Cq), 131.0 (CH_{Ar}), 129.7 (CH_{Ar}), 129.5 (CH_{Ar}), 128.9 (CH_{Ar}), 124.2 (CH_{Ar}), 66.4 (Cq), 54.1 (CH), 51.9 (Cq), 37.3 (CH_2), 27.5

(CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{22}H_{23}N_3O_5H]^+$ 410.1716, *m*/*z* found for $[M+H]^+$ 410.1713.

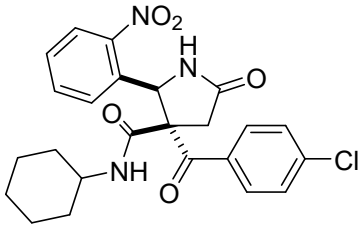
(4*R,5*R**)-4-Cyclohexylcarbamoyl-4-(4-methylbenzoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (7d)**



7d

Pale brown solid. **Decomposition** > 250 °C (as a 89:11 diastereomers mixture). **^{1}H NMR (300 MHz, $CDCl_3$):** δ (major diastereomer) 7.81 (d, *J* = 8.3 Hz, 2H), 7.68 (td, *J* = 7.9, 1.2 Hz, 1H), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.48 (td, *J* = 8.1, 1.3 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.57 (s, 1H), 6.11 (s, 1H, NH), 5.75 (d, *J* = 7.9 Hz, 1H), 4.28 (d, *J* = 18.2 Hz, 1H), 3.24-3.11 (m, 1H), 2.76 (d, *J* = 18.2 Hz, 1H), 2.40 (s, 3H), 1.82-0.26 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 193.8 (Cq), 165.4 (Cq), 149.6 (Cq), 145.0 (Cq), 134.0 (Cq), 133.8 (CH_{Ar}), 130.7 (CH_{Ar}), 130.5 (Cq), 129.6 (CH_{Ar}), 129.6 (CH_{Ar}), 124.2 (CH_{Ar}), 65.6 (Cq), 54.4 (CH), 49.1 (CH), 37.8 (CH_2), 31.9 (CH_2), 31.5 (CH_2), 25.1 (CH_2), 24.5 (CH_2), 24.4 (CH_2), 21.8 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{25}H_{27}N_3O_5H]^+$ 450.2029, *m*/*z* found for $[M+H]^+$ 450.2027.

(4*R,5*R**)-4-(4-Chlorobenzoyl)-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (7e)**

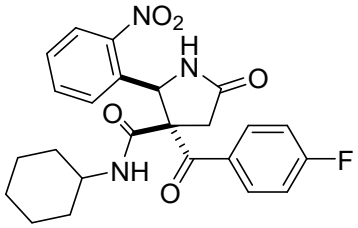


7e

Pale brown solid. **M. p.:** 235-237 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.90 (d, *J* = 8.8 Hz, 2H), 7.83 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.54 (s, 1H), 5.83 (d, *J* = 7.7 Hz, 1H), 5.69 (s, 1H, NH), 4.32 (d, *J* = 18.1 Hz, 1H), 3.25-3.12 (m, 1H), 2.74 (d, *J* = 18.1 Hz, 1H), 1.41-0.27 (m, 10H). **^{13}C NMR (75 MHz, DMSO-d_6):** δ 193.2, 173.7, 166.2, 149.7, 138.9, 133.6, 133.4, 132.3, 130.9, 130.3, 129.8, 129.2, 124.9, 65.5, 54.5, 48.6, 37.1, 31.2, 25.2,

24.8. **HRMS (+ESI):** *m*/*z* calculated for $[C_{24}H_{24}ClN_3O_5H]^+$ 470.1483, *m*/*z* found for $[M+H]^+$ 470.1475.

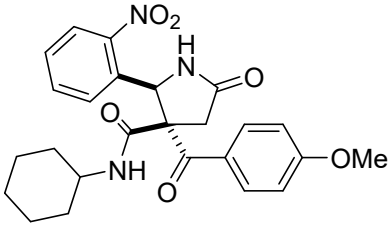
(4*R,5*R**)-4-Cyclohexylcarbamoyl-4-(4-fluorobenzoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (7f)**



7f

Pale brown solid. **Decomposition** at 235 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.99 (dd, *J* = 9.0, 5.3 Hz, 2H), 7.83 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 8.6 Hz, 2H), 6.55 (s, 1H), 5.84 (s, 1H, NH), 5.82 (d, *J* = 8.3 Hz, 1H, NH), 4.32 (d, *J* = 18.3 Hz, 1H), 3.25-3.13 (m, 1H), 2.76 (d, *J* = 18.3 Hz, 1H), 1.44-0.26 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 192.5, 173.9, 165.1, 164.3, 162.8 (d, ^1J = 244.8 Hz), 149.7, 134.0, 133.9, 132.4 (d, ^3J = 9.4 Hz), 130.7, 129.9, 124.3, 116.3 (d, ^2J = 21.9 Hz), 65.8, 54.0, 49.2, 37.4, 32.0, 31.6, 25.1, 24.5, 24.5. **HRMS (+ESI):** *m*/*z* calculated for $[C_{24}H_{24}FN_3O_5H]^+$ 454.1778, *m*/*z* found for $[M+H]^+$ 454.1776.

(4*R,5*R**)-4-Cyclohexylcarbamoyl-4-(4-methoxybenzoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (7g)**

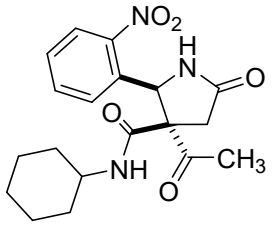


7g

Pale brown solid. **M. p.:** 232-235 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.91 (d, *J* = 9.0 Hz, 2H), 7.80 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.70-7.65 (m, 1H), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.50-7.45 (m, 1H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.58 (s, 1H), 6.11 (s, 1H), 5.76 (d, *J* = 8.0 Hz, 1H), 4.28 (d, *J* = 18.2 Hz, 1H), 3.87 (s, 3H), 3.24-3.11 (m, 1H), 2.76 (d, *J* = 18.2 Hz, 1H), 1.44-0.27 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 192.6 (Cq), 174.4 (Cq), 165.6 (Cq), 164.1 (Cq), 149.7 (Cq), 134.1 (CH_{Ar}), 133.8 (Cq), 132.0 (CH_{Ar}), 130.7 (CH_{Ar}), 129.6 (CH_{Ar}), 125.8 (Cq), 124.2 (CH_{Ar}), 114.1 (CH_{Ar}), 65.6 (Cq), 55.7 (CH), 54.1 (CH_3),

49.1 (CH), 37.8 (CH_2), 32.0 (CH_2), 31.6 (CH_2), 25.1 (CH_2), 24.6 (CH_2), 24.5 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{25}H_{27}N_3O_6H]^+$ 466.1978, *m*/*z* found for $[M+H]^+$ 466.1975.

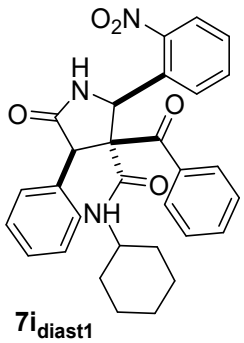
(4*R,5*R**)-4-Acetyl-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (7h)**



7h

Pale brown solid. **M. p.:** 199-202 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.81 (d, J = 8.1 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.52-7.44 (m, 2H), 6.38 (s, 1H, NH), 6.14 (s, 1H), 6.08 (d, J = 8.0 Hz, 1H, NH), 3.97 (d, J = 18.5 Hz, 1H), 3.36-3.23 (m, 1H), 2.52 (d, J = 18.5 Hz, 1H), 2.28 (s, 3H), 1.69-0.77 (m, 9H), 0.31 (qd, J = 12.0, 3.7 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 201.3 (Cq), 174.0 (Cq), 164.0 (Cq), 149.5 (Cq), 134.2 (Cq), 134.1 (CH_{Ar}), 130.0 (CH_{Ar}), 129.7 (CH_{Ar}), 124.4 (CH_{Ar}), 68.2 (Cq), 53.1 (CH), 49.2 (CH), 35.4 (CH_2), 32.5 (CH_2), 31.8 (CH_2), 25.3 (CH_3), 25.2 (CH_2), 24.8 (CH_2), 24.7 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{19}H_{23}N_3O_5H]^+$ 374.1716, *m*/*z* found for $[M+H]^+$ 374.1715.

(3*R,4*R**,5*S**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)-3-phenylpyrrolidin-2-one ($7i_{diast1}$)**

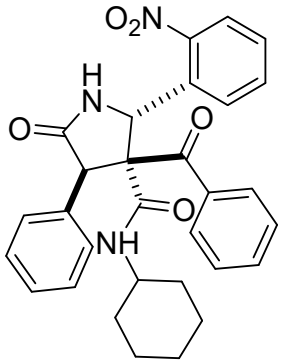


$7i_{diast1}$

Brown oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.48-7.15 (m, 15H), 6.70 (s, 1H), 6.48 (s, 1H), 5.35 (s, 1H), 4.12-4.09 (m, 1H), 3.26-3.15 (m, 1H), 1.77-0.09 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 195.7 (Cq), 174.5 (Cq), 165.5 (Cq), 149.5 (Cq), 135.5 (Cq), 135.1 (Cq), 133.6 (Cq), 133.5 (CH_{Ar}), 133.1 (CH_{Ar}), 130.6 (CH_{Ar}), 129.6 (CH_{Ar}), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 124.4 (CH_{Ar}), 72.6 (Cq), 54.5 (CH), 52.7 (CH), 49.1 (CH), 31.4 (CH_2), 30.8 (CH_2), 25.1 (CH_2), 24.3 (CH_2), 24.0 (CH_2).

HRMS (+ESI): *m*/*z* calculated for $[C_{30}H_{29}N_3O_5H]^+$ 512.2180, *m*/*z* found for $[M+H]^+$ 512.2190.

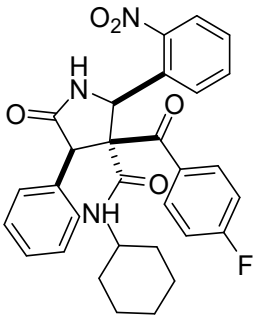
(3*R,4*R**,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)-3-phenylpyrrolidin-2-one ($7i_{diast2}$)**



$7i_{diast2}$

Pale brown oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.81-7.63 (m, 2H), 7.52-7.28 (m, 6H), 7.13-6.97 (m, 6H), 6.91 (s, 1H), 6.45 (s, 1H), 5.48 (s, 1H), 5.34 (d, J = 7.8 Hz, 1H), 3.23-3.10 (m, 1H), 1.89-0.11 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 196.2 (Cq), 176.3 (Cq), 166.5 (Cq), 150.0 (Cq), 135.9 (Cq), 134.4 (Cq), 133.8 (Cq), 133.7 (CH_{Ar}), 132.8 (CH_{Ar}), 130.9 (CH_{Ar}), 130.1 (CH_{Ar}), 129.6 (CH_{Ar}), 129.0 (CH_{Ar}), 128.5 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 124.4 (CH_{Ar}), 71.5 (Cq), 55.8 (CH), 54.2 (CH), 49.0 (CH), 31.5 (CH_2), 31.3 (CH_2), 25.0 (CH_2), 24.4 (CH_2), 24.3 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{30}H_{29}N_3O_5H]^+$ 512.2180, *m*/*z* found for $[M+H]^+$ 512.2195.

(3*R,4*R**,5*S**)-4-Cyclohexylcarbamoyl-4-(4-fluorobenzoyl)-5-(2-nitrophenyl)-3-phenylpyrrolidin-2-one ($7j_{diast1}$)**

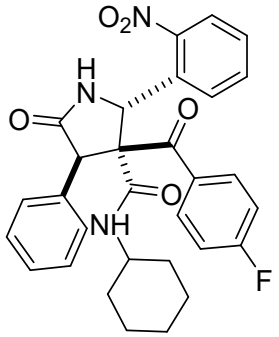


$7j_{diast1}$

Pale brown solid. **M. p.:** 157-160 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.46-7.17 (m, 11H), 7.15-7.08 (m, 1H), 6.83 (t, J = 8.5 Hz, 2H), 6.70 (s, 1H), 5.29 (s, 1H), 4.19 (d, J = 6.9 Hz, 1H), 3.22-3.10 (m, 1H), 1.43-0.08 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.0 (Cq),

174.3 (Cq), 165.6 (d, ^{1}J = 257.7 Hz, Cq), 165.5 (Cq), 149.8 (Cq), 135.4 (Cq), 133.5 (Cq), 133.1 (CH_{Ar}), 131.6 (d, ^{4}J = 3.2 Hz, Cq), 130.8 (d, ^{3}J = 9.5 Hz, CH_{Ar}), 130.6 (CH_{Ar}), 129.7 (CH_{Ar}), 129.4 (CH_{Ar}), 128.9 (CH_{Ar}), 128.2 (CH_{Ar}), 124.5 (CH_{Ar}), 116.0 (d, ^{2}J = 22.0 Hz, CH_{Ar}), 72.5 (Cq), 54.4 (CH), 52.7 (CH), 49.2 (CH), 31.5 (CH_2), 30.9 (CH_2), 25.1 (CH_2), 24.3 (CH_2), 24.1 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{30}H_{28}FN_3O_5H]^+$ 530.2086, *m*/*z* found for $[M+H]^+$ 530.2090.

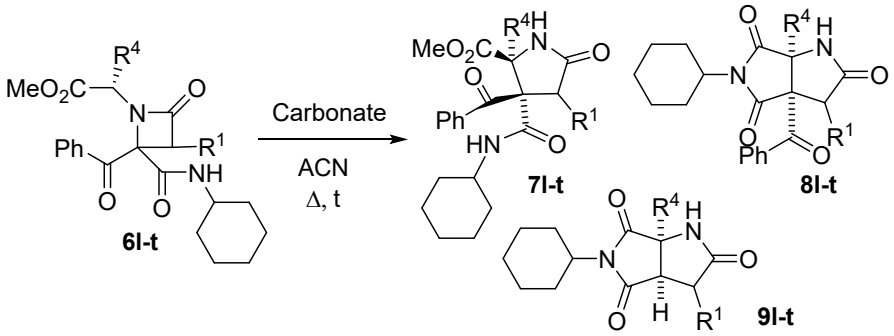
(3*R,4*R**,5*R**)-4-Cyclohexylcarbamoyl-4-(4-fluorobenzoyl)-5-(2-nitrophenyl)-3-phenylpyrrolidin-2-one ($7j_{diast2}$)**



$7j_{diast2}$

Brown solid. **M. p.:** 145-148 °C **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 4.1 Hz, 2H), 7.52-7.44 (m, 3H), 7.16 (s, 1H), 7.09-6.97 (m, 5H), 6.75 (t, *J* = 8.6 Hz, 2H), 6.43 (s, 1H), 5.50 (d, *J* = 8.0 Hz, 1H), 5.49 (s, 1H), 3.22-3.10 (m, 1H), 1.48-0.09 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.1 (Cq), 176.0 (Cq), 166.5 (Cq), 166.3 (d, ^{1}J = 257.5 Hz, Cq), 150.0 (Cq), 134.3 (Cq), 134.0 (Cq), 133.9 (CH_{Ar}), 133.1 (Cq), 131.9 (d, ^{3}J = 9.5 Hz, CH_{Ar}), 131.0 (CH_{Ar}), 130.2 (CH_{Ar}), 129.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.1 (CH_{Ar}), 124.5 (CH_{Ar}), 114.9 (d, ^{2}J = 22.0 Hz, CH_{Ar}), 71.3 (Cq), 55.4 (CH), 53.9 (CH), 49.1 (CH), 31.5 (CH_2), 29.8 (CH_2), 25.1 (CH_2), 24.5 (CH_2), 24.4 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{30}H_{28}FN_3O_5H]^+$ 530.2086, *m*/*z* found for $[M+H]^+$ 530.2096.

2.4. Synthesis of pyrrolidin-2-ones 7, 8 and 9, derived from α-aminoesters

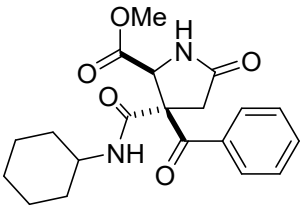


Method A. To a 0.05 M solution of azetidin-2-one **6m-t** (1 mmol) in acetonitrile cesium carbonate (1.2 eq) was added, and the reaction mixture was stirred at reflux for 1 h. The solvent was evaporated under reduced pressure, and the residue was redissolved in dichloromethane and washed with a 10% HCl aqueous solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. Pyrrolidinones were purified by column chromatography column, using hexane/ethyl acetate mixtures as eluent and SiO_2 as stationary phase.

Method B. To a 0.05 M solution of azetidin-2-one **6m-t** (1 mmol) in acetonitrile potassium carbonate (1.2 eq) was added, and the reaction mixture was stirred at reflux for 12 h. The solvent was evaporated under reduced pressure, and the residue was redissolved in dichloromethane and washed with a 10% HCl aqueous solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The different expansion compounds were purified by column chromatography, using hexane/ethyl acetate mixtures as eluent and SiO_2 as stationary phase.

2.4.1. Chloroacetic acid (R^1: H) and glycine (R^4: H) derivatives

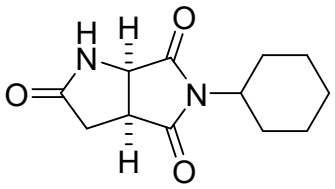
(4*R,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-(methoxycarbonyl)pyrrolidin-2-one (7l)**



7l

White solid. **M. p.:** 175-177 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.89 (d, J = 7.4 Hz, 2H), 7.59-7.54 (m, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.23 (d, J = 7.7 Hz, 1H, NH), 6.66 (s, 1H, NH), 4.49 (s, 1H), 3.87 (s, 3H), 3.86 (d, J = 17.7 Hz, 1H), 3.79-3.67 (m, 1H), 2.84 (d, J = 17.7 Hz, 1H), 1.80-0.77 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.4, 173.0, 172.0, 166.7, 134.1, 133.2, 129.2, 128.9, 65.5, 60.6, 53.4, 49.2, 38.6, 32.1, 32.0, 25.4, 24.4, 24.2. **HRMS (+ESI):** *m/z* calculated for $[C_{20}H_{24}N_2O_5H]^+$ 373.1763, *m/z* found for $[M+H]^+$ 373.1760.

(3a*R,6a*S**)-5-Cyclohexyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9l)**

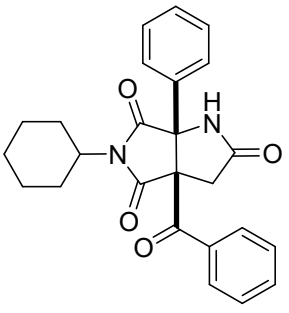


9l

Pale yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.50 (s, 1H), 4.36 (d, J = 8.0 Hz, 1H), 3.95 (tt, J = 12.2, 3.9 Hz, 1H), 3.49 (ddd, J = 12.0, 8.1, 4.0 Hz, 1H), 2.81 (dd, J = 18.3, 11.6 Hz, 1H), 2.64 (dd, J = 18.3, 4.0 Hz, 1H), 2.14-1.11 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 176.7 (Cq), 174.7 (Cq), 174.7 (Cq), 55.4 (CH), 52.4 (CH), 38.8 (CH), 31.9 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 25.0 (CH_2). **HRMS (+ESI):** *m/z* calculated for $[C_{12}H_{16}N_2O_3H]^+$ 237.1234, *m/z* found for $[M+H]^+$ 237.1237.

2.4.2. Chloroacetic acid (R^1: H) and phenylglycine (R^4: C_6H_5) derivatives

(3a*R,6a*S**)-3a-Benzoyl-5-cyclohexyl-6a-phenyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8m)**

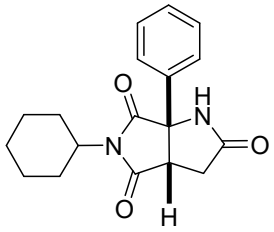


8m

Crystalline white solid. **M. p.:** 166-168 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.43-7.37 (m, 1H), 7.24-7.08 (m, 9H), 6.43 (s, 1H), 4.24 (tt, J = 12.4, 3.9 Hz, 1H), 3.82 (d, J = 18.5 Hz, 1H), 3.00 (d, J = 18.5 Hz, 1H), 2.34-2.21 (m, 1H), 1.96-1.72 (m, 4H), 1.49-1.23 (m,

5H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 193.6 (Cq), 175.3 (Cq), 175.2 (Cq), 173.0 (Cq), 136.0 (Cq), 133.2 (Cq), 132.9 (CH_{Ar}), 129.4 (CH_{Ar}), 128.6 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (CH_{Ar}), 70.9 (Cq), 66.2 (Cq), 53.5 (CH), 37.5 (CH_2), 29.8 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 25.9 (CH_2), 25.0 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{25}H_{24}N_2O_4H]^+$ 417.1814, *m*/*z* found for $[M+H]^+$ 417.1809.

(3a*R,6a*S**)-5-Cyclohexyl-6a-phenyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9m)**

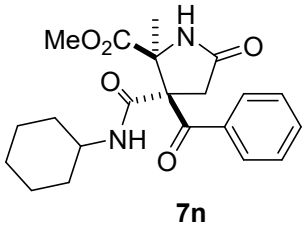


9m

Crystalline white solid. **M. p.:** 156-159 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.44-7.22 (m, 6H, NH), 4.06 (tt, *J* = 12.3, 3.7 Hz, 1H), 3.30 (ddd, *J* = 11.3, 3.4, 0.7 Hz, 1H), 2.90 (ddd, *J* = 18.2, 11.3, 0.7 Hz, 1H), 2.71 (ddd, *J* = 18.3, 3.5, 0.8 Hz, 1H), 2.23-2.11 (m, 2H), 1.89-1.84 (m, 2H), 1.70-1.67 (m, 2H), 1.42-1.20 (m, 3H), 0.91-0.82 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 176.0 (Cq), 175.9 (Cq), 174.4 (Cq), 137.7 (Cq), 129.3 (CH_{Ar}), 129.0 (CH_{Ar}), 124.8 (CH_{Ar}), 67.4 (Cq), 52.7 (CH), 48.4 (CH), 32.1 (CH_2), 29.7 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 25.7 (CH_2), 24.9 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{18}H_{20}N_2O_3H]^+$ 313.1547, *m*/*z* found for $[M+H]^+$ 313.1545.

2.4.3. Chloroacetic acid (R^1: H) and alanine (R^4: CH_3) derivatives

(4*R,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-5-methylpyrrolidin-2-one (7n)**

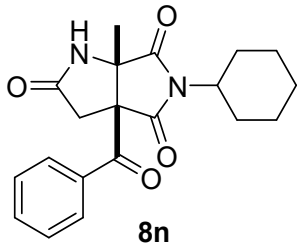


7n

White solid. **M. p.:** 139-141 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 6.66 (s, 1H), 3.97 (d, *J* = 18.0 Hz, 1H), 3.93 (s, 3H), 3.82-3.68 (m, 1H), 2.73 (d, *J* = 18.0 Hz, 1H), 2.18-0.68 (m, 10H), 1.52 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.3 (Cq), 175.4 (Cq),

171.4 (Cq), 165.5 (Cq), 134.0 (CH_{Ar}), 133.1 (Cq), 129.2 (CH_{Ar}), 128.8 (CH_{Ar}), 69.1 (Cq), 64.7 (Cq), 53.6 (CH_3), 49.0 (CH), 38.0 (CH_2), 32.1 (CH_2), 31.9 (CH_2), 25.8 (CH_2), 25.4 (CH_2), 24.5 (CH_3), 24.2 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{21}H_{26}N_2O_5H]^+$ 387.1914, *m*/*z* found for $[M+H]^+$ 387.1913.

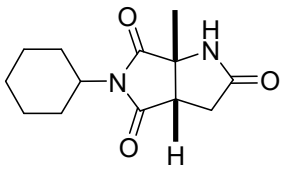
(3a*R,6a*S**)-3a-Benzoyl-5-cyclohexyl-6a-methyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8n)**



8n

Yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.70-7.64 (m, 2H), 7.63-7.57 (m, 1H), 7.49-7.43 (m, 2H), 6.49 (s, 1H), 4.06 (tt, *J* = 12.0, 3.8 Hz, 1H), 3.57 (d, *J* = 18.3 Hz, 1H), 2.98 (d, *J* = 18.3 Hz, 1H), 2.20-2.06 (m, 2H), 1.98-1.64 (m, 6H), 1.46 (s, 3H), 1.44-1.17 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 194.2 (Cq), 176.2 (Cq), 175.3 (Cq), 172.4 (Cq), 136.1 (Cq), 133.8 (CH_{Ar}), 129.0 (CH_{Ar}), 128.5 (CH_{Ar}), 64.7 (Cq), 63.7 (Cq), 53.1 (CH), 38.0 (CH_2), 28.7 (CH_2), 28.3 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 25.0 (CH_2), 18.7 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{20}H_{22}N_2O_4H]^+$ 355.1652, *m*/*z* found for $[M+H]^+$ 355.1667.

(3a*R,6a*S**)-5-Cyclohexyl-6a-methyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9n)**

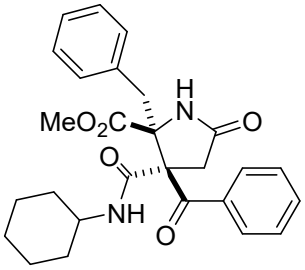


9n

White solid. **M. p.:** 209-212 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.00 (s, 1H), 3.93 (tt, *J* = 12.3, 3.8 Hz, 1H), 3.06 (dd, *J* = 11.4, 3.3 Hz, 1H), 2.87 (dd, *J* = 18.0, 11.3 Hz, 1H), 2.66 (dd, *J* = 18.1, 3.3 Hz, 1H), 2.13-1.12 (m, 10H), 1.55 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 177.1 (Cq), 176.1 (Cq), 174.1 (Cq), 61.6 (Cq), 52.3 (CH), 45.4 (CH), 32.6 (CH_2), 28.8 (CH_2), 28.7 (CH_2), 25.8 (CH_2), 25.0 (CH_2), 21.7 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{13}H_{18}N_2O_3H]^+$ 251.1390, *m*/*z* found for $[M+H]^+$ 251.1394.

2.4.4. Chloroacetic acid (R^1: H) and phenylalanine (R^4: $C_6H_5CH_2$) derivatives

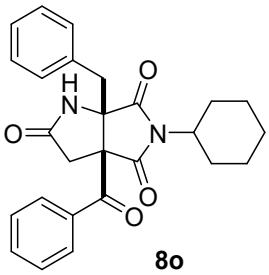
(4*R,5*R**)-4-Benzoyl-5-benzyl-4-cyclohexylcarbamoyl-5-(methoxycarbonyl)pyrrolidin-2-one (7o)**



7o

Yellowish oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.95 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.9 Hz, 2H), 7.33-7.28 (m, 3H), 7.06-7.03 (m, 2H), 5.91 (s, 1H), 4.08 (d, J = 18.0 Hz, 1H), 3.90-3.77 (m, 1H), 3.68 (s, 3H), 3.17 (d, J = 12.9 Hz, 1H), 2.97 (d, J = 12.9 Hz, 1H), 2.83 (d, J = 18.0 Hz, 1H), 1.97-0.80 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 193.9, 174.5, 171.1, 165.4, 134.1, 133.2, 132.9, 130.1, 129.2, 128.8, 128.8, 128.0, 69.6, 68.3, 52.9, 49.2, 42.7, 38.1, 32.1, 31.9, 25.5, 24.5, 24.2. **HRMS (+ESI):** *m*/*z* calculated for $[C_{27}H_{30}N_2O_5H]^+$ 463.2233, *m*/*z* found for $[M+H]^+$ 463.2232.

(3a*R,6a*S**)-3a-Benzoyl-6a-benzyl-5-cyclohexyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8o)**

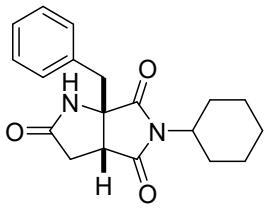


8o

Yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.83 (d, J = 7.2 Hz, 2H), 7.58-7.52 (m, 1H), 7.48-7.40 (m, 3H), 7.11 (s, 5H), 4.01 (tt, J = 12.2, 3.7 Hz, 1H), 3.51 (d, J = 14.7 Hz, 1H), 3.37 (d, J = 14.7 Hz, 1H), 3.12 (d, J = 17.3 Hz, 1H), 2.18-2.00 (m, 2H), 1.94 (d, J = 17.3 Hz, 1H), 1.88-1.57 (m, 5H), 1.40-1.15 (m, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 195.5 (Cq), 175.7 (Cq), 173.7 (Cq), 173.5 (Cq), 136.0 (Cq), 133.4 (Cq), 133.4 (CH_{Ar}), 130.9 (CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 127.7 (CH_{Ar}), 70.1 (Cq), 65.5 (Cq), 53.1 (CH), 36.9 (CH_2), 35.5 (CH_2), 28.9 (CH_2), 28.1 (CH_2), 25.8 (CH_2), 25.7 (CH_2), 25.0

(CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{26}H_{26}N_2O_4H]$+ 431.1965, *m*/*z* found for $[M+H]^+$ 431.1977.

(3a*R,6a*S**)-6a-Benzyl-5-cyclohexyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9o)**

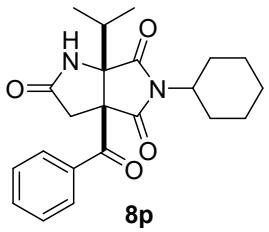


9o

Pale yellowish solid. **M. p.:** 95-97 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.34-7.14 (m, 5H), 7.08 (s, 1H), 3.86 (tt, *J* = 12.3, 3.7 Hz, 1H), 3.23 (d, *J* = 13.7 Hz, 1H), 3.19 (dd, *J* = 11.2, 3.8 Hz, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.53 (dd, *J* = 18.2, 3.8 Hz, 1H), 2.41 (dd, *J* = 18.2, 11.2 Hz, 1H), 2.08-1-15 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 176.8 (Cq), 176.1 (Cq), 174.3 (Cq), 133.2 (Cq), 130.1 (CH_{Ar}), 129.1 (CH_{Ar}), 128.0 (CH_{Ar}), 65.4 (Cq), 52.3 (CH), 42.2 (CH), 40.1 (CH_2), 32.4 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 25.0 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{19}H_{22}N_2O_3H]^+$ 327.1703, *m*/*z* found for $[M+H]^+$ 327.1700.

2.4.5. Chloroacetic acid (R^1: H) and valine (R^4: $CH(CH_3)_2$) derivatives

(3a*R,6a*S**)-3a-Benzoyl-6a-isopropyl-5-cyclohexyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8p)**

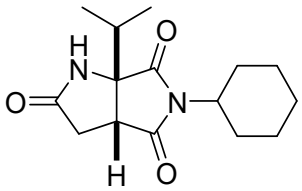


8p

Yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 2H), 6.67 (s, 1H), 3.98 (tt, *J* = 12.6, 4.5 Hz, 1H), 3.34 (d, *J* = 17.6 Hz, 1H), 2.93 (d, *J* = 17.5 Hz, 1H), 2.62 (h, *J* = 6.7 Hz, 1H), 2.15-1.04 (m, 10H), 1.28 (d, *J* = 6.7 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 195.7 (Cq), 175.4 (Cq), 173.7 (Cq), 173.4 (Cq), 136.1 (Cq), 133.4 (CH_{Ar}), 128.9 (CH_{Ar}), 128.7 (CH_{Ar}), 71.3 (Cq), 66.2 (Cq), 52.9 (CH), 37.4 (CH_2), 29.6 (CH), 28.8 (CH_2), 28.1 (CH_2),

25.9 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 18.2 (CH_3), 17.0 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{22}H_{26}N_2O_4H]^+$ 383.1965, *m*/*z* found for $[M+H]^+$ 383.1983.

(3a*R,6a*S**)-5-Cyclohexyl-6a-isopropyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9p)**

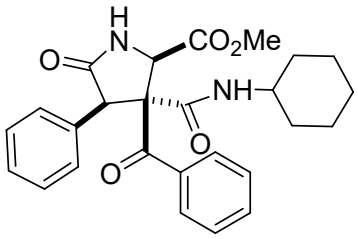


9p

Pale yellowish solid. **M. p.:** 170-173 °C **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.14 (s, 1H), 3.96 (tt, *J* = 12.4, 4.0 Hz, 1H), 3.10 (dd, *J* = 11.3, 3.8 Hz, 1H), 2.77 (dd, *J* = 18.3, 11.3 Hz, 1H), 2.63 (dd, *J* = 18.3, 3.8 Hz, 1H), 2.31 (h, *J* = 6.7 Hz, 1H), 2.17-1.18 (m, 10H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 177.1 (Cq), 176.6 (Cq), 173.8 (Cq), 68.3 (Cq), 52.4 (CH), 39.7 (CH), 33.0 (CH_2), 31.4 (CH), 29.0 (CH_2), 28.7 (CH_2), 25.8 (CH_2), 25.0 (CH_2), 16.7 (CH_3), 15.8 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{15}H_{22}N_2O_3H]^+$ 279.1703, *m*/*z* found for $[M+H]^+$ 279.1709.

2.4.6. 2-Chloro-2-phenylacetic acid (R^1: C_6H_5) and glycine (R^4: H) derivatives

(3*R,4*R**,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-3-phenylpyrrolidin-2-one ($7q_{diast1}$)**

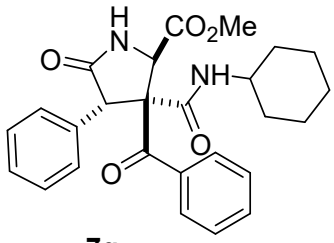


$7q_{diast1}$

Pale yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.32-7.26 (m, 5H), 7.11-6.99 (m, 5H), 6.78 (s, 1H), 5.29 (s, 1H), 4.49 (s, 1H), 3.96 (s, 3H), 3.77-3.63 (m, 1H), 1.78-0.55 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 197.5 (Cq), 174.0 (Cq), 172.7 (Cq), 168.4 (Cq), 136.4 (Cq), 133.3 (Cq), 132.8 (CH_{Ar}), 132.0 (CH_{Ar}), 128.7 (CH_{Ar}), 128.4 (CH_{Ar}), 128.1 (CH_{Ar}), 127.7 (CH_{Ar}), 70.9 (Cq), 60.7 (CH), 54.4 (CH_3), 53.9

(CH), 48.8 (CH), 32.2 (CH_2), 31.4 (CH_2), 25.4 (CH_2), 24.3 (CH_2), 24.0 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{26}H_{28}N_2O_5H]^+$ 449.2071, *m*/*z* found for $[M+H]^+$ 449.2072.

(3*R,4*S**,5*S**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-3-phenylpyrrolidin-2-one ($7q_{diast2}$)**

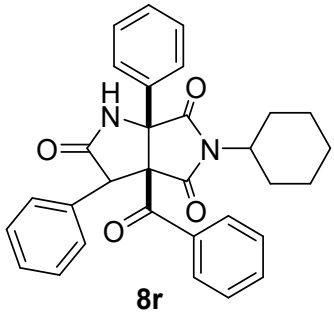


$7q_{diast2}$

Pale yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.79 (d, J = 8.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.40-7.25 (m, 5H), 6.49 (s, 1H), 5.40 (s, 1H), 5.10 (s, 1H), 4.25 (d, J = 6.4 Hz, 1H), 3.29 (s, 3H), 3.34-3.16 (m, 1H), 2.16-0.14 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 195.7, 175.3, 170.3, 164.7, 135.3, 135.3, 134.0, 131.1, 128.9, 128.8, 128.7, 128.2, 70.4, 59.8, 52.7, 52.0, 49.1, 31.7, 30.9, 25.2, 24.3, 24.1. **HRMS (+ESI):** *m*/*z* calculated for $[C_{26}H_{28}N_2O_5H]^+$ 449.2071, *m*/*z* found for $[M+H]^+$ 449.2085.

2.4.7. 2-Chloro-2-phenylacetic acid (R^1: C_6H_5) and phenylglycine (R^4: C_6H_5) derivatives

(3a*R,6a*S**)-3a-Benzoyl-5-cyclohexyl-3,6a-diphenyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8r)**



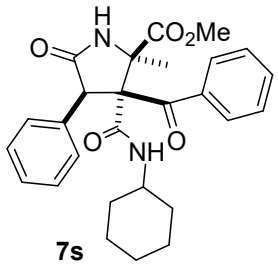
8r

White solid. **M. p.:** 118-120 °C**. ^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.34-7.07 (m, 16H), 5.60 (s, 1H), 4.13-4.03 (m, 1H), 2.24-1.11 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 192.3 (Cq), 175.6 (Cq), 174.6 (Cq), 171.8 (Cq), 135.9 (Cq), 134.0 (Cq), 133.3 (Cq), 132.9 (CH_{Ar}), 130.1 (CH_{Ar}), 129.4 (CH_{Ar}), 128.8 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 128.5

(CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 70.4 (Cq), 70.3 (Cq), 53.5 (CH), 53.2 (CH), 28.6 (CH_2), 28.2 (CH_2), 25.8 (CH_2), 25.8 (CH_2), 24.8 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{31}H_{28}N_2O_4H]^+$ 493.2122, *m*/*z* found for $[M+H]^+$ 493.2132.

2.4.8. 2-Chloro-2-phenylacetic acid (R^1: C_6H_5) and valine (R^4: CH_3) derivatives

(3*R,4*R**,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-5-methyl-3-phenylpyrrolidin-2-one (7s)**

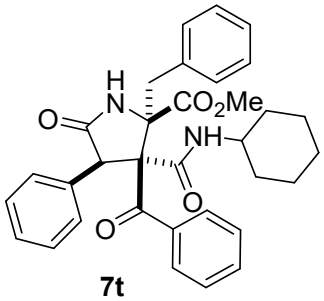


7s

Yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.39 (d, J = 7.7 Hz, 1H), 7.33-6.96 (m, 10H), 5.23 (s, 1H), 3.89 (s, 3H), 3.71-3.60 (m, 1H), 1.92-0.45 (m, 10H), 1.61 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 198.6 (Cq), 176.0 (Cq), 172.8 (Cq), 166.7 (Cq), 137.0 (Cq), 133.2 (Cq), 132.3 (CH_{Ar}), 132.0 (CH_{Ar}), 128.5 (CH_{Ar}), 128.2 (CH_{Ar}), 127.9 (CH_{Ar}), 127.5 (CH_{Ar}), 73.9 (Cq), 65.1 (Cq), 53.7 (CH_3), 53.3 (CH), 48.6 (CH), 32.1 (CH_2), 31.3 (CH_2), 25.3 (CH_2), 24.5 (CH_3), 24.3 (CH_2), 24.1 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{27}H_{30}N_2O_5H]^+$ 463.2227, *m*/*z* found for $[M+H]^+$ 463.2236.

2.4.9. 2-Chloro-2-phenylacetic acid (R^1: C_6H_5) and phenylalanine (R^4: $CH_2C_6H_5$) derivatives

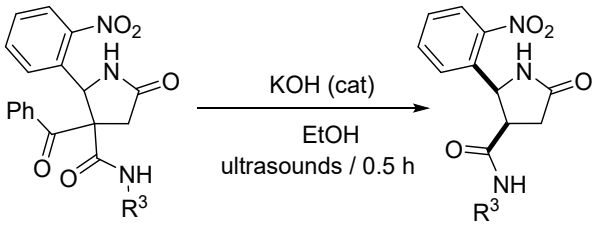
(3*R,4*R**,5*R**)-5-Benzyl-4-benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-3-phenylpyrrolidin-2-one (7t)**



7t

Pale yellow solid. **M. p.:** 100-102 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.38-6.98 (m, 16H), 6.34 (s, 1H), 5.35 (s, 1H), 3.82-3.69 (m, 1H), 3.64 (s, 3H), 3.29 (d, J = 13.0 Hz, 1H), 3.13 (d, J = 12.9 Hz, 1H), 1.95-0.52 (m, 10H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 198.2 (Cq), 172.4 (Cq), 166.6 (Cq), 136.9 (Cq), 133.4 (Cq), 133.0 (Cq), 132.5 (CH_{Ar}), 132.0 (CH_{Ar}), 130.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.5 (CH_{Ar}), 74.7 (Cq), 68.5 (Cq), 53.7 (CH), 53.0 (CH_3), 48.8 (CH), 42.8 (CH_2), 32.2 (CH_2), 31.4 (CH_2), 25.4 (CH_2), 24.4 (CH_2), 24.1 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{33}H_{34}N_2O_5H]^+$ 539.2540, *m*/*z* found for $[M+H]^+$ 539.2553.

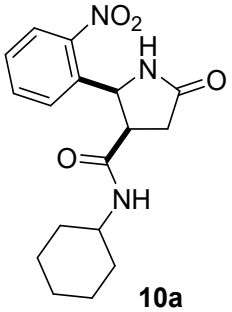
2.5. Deacylation of pyrrolidin-2-ones 7a-c



7a-c **10a-c**

To a 0.05 M solution of pyrrolidin-2-one **7a-c** (1 mmol) in ethanol potassium hydroxide was added (catalytic amount) and the mixture was ultrasonicated at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was redissolved in dichloromethane and washed with a 10% HCl aqueous solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness, and the residue was purified by column chromatography (dichloromethane/ethyl acetate, 90:10, *v*/*v*) to give the corresponding pyrrolidin-2-one **10a-c**.

(4*R,5*S**)-4-Cyclohexylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (10a)**

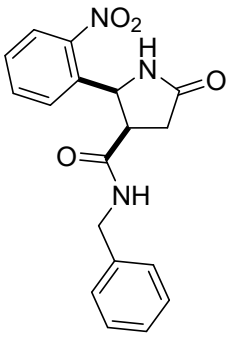


10a

Dark brown solid. **Decomposition** > 184 °C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.93 (d, J = 8.0 Hz, 1H), 7.74-7.66 (m, 2H), 7.50-7.45 (m, 1H), 6.90 (s, 1H), 5.47 (d, J = 8.8 Hz,

2H), 3.70 (td, *J* = 9.3, 4.2 Hz, 1H), 3.33-3.20 (m, 1H), 3.04 (dd, *J* = 17.3, 3.9 Hz, 1H), 2.58 (dd, *J* = 17.4, 9.6 Hz, 1H), 1.70-1.33 (m, 4H), 1.24-0.77 (m, 5H), 0.34-0.22 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 177.8 (Cq), 168.7 (Cq), 148.9 (Cq), 134.4 (Cq), 134.2 (CH_{Ar}), 129.7 (CH_{Ar}), 129.2 (CH_{Ar}), 124.5 (CH_{Ar}), 56.2 (CH), 47.9 (CH), 45.5 (CH), 33.0 (CH_2), 32.9 (CH_2), 32.4 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 24.6 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{17}H_{21}N_3O_4H]^+$ 332.1610, *m*/*z* found for $[M+H]^+$ 332.1608.

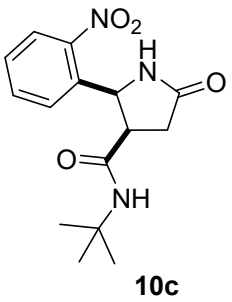
(4*R,5*S**)-4-Benzylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (10b)**



10b

Dark brown oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.03 (d, *J* = 8.0 Hz, 1H, NH), 7.77-6.79 (m, 9H), 5.96 (t, *J* = 5.4 Hz, 1H, NH), 5.47 (d, *J* = 8.8 Hz, 1H), 3.96 (d, *J* = 12.6 Hz, 1H), 3.90 (d, *J* = 12.6 Hz, 1H), 3.78 (td, *J* = 9.6, 4.6 Hz, 1H), 3.07 (dd, *J* = 17.3, 4.3 Hz, 1H), 2.62 (dd, *J* = 17.1, 9.0 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 177.9 (Cq), 169.6 (Cq), 137.4 (Cq), 134.1 (CH_{Ar}), 133.9 (Cq), 133.4 (Cq), 130.1 (CH_{Ar}), 129.3 (CH_{Ar}), 128.8 (CH_{Ar}), 127.9 (CH_{Ar}), 127.6 (CH_{Ar}), 124.6 (CH_{Ar}), 56.1 (CH), 45.4 (CH), 43.7 (CH_2), 33.1 (CH_2). **HRMS (+ESI):** *m*/*z* calculated for $[C_{18}H_{17}N_3O_4H]^+$ 340.1297, *m*/*z* found for $[M+H]^+$ 340.1292.

(4*R,5*S**)-4-(*tert*-Butylcarbamoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (10c)**

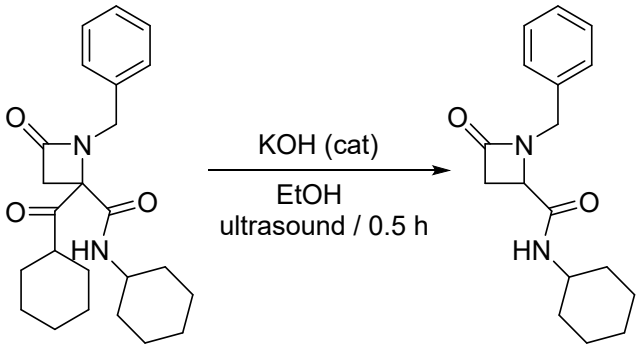


10c

Dark brown oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.98-7.95 (m, 1H), 7.74-7.68 (m, 2H), 7.54-7.46 (m, 1H), 6.16 (s, 1H), 5.47 (d, *J* = 9.4 Hz, 2H), 3.66 (td, *J* = 9.5, 4.6 Hz, 1H), 3.09 (dd, *J* = 17.2, 4.5 Hz, 1H), 2.57 (dd, *J* = 17.7, 9.9 Hz, 1H), 0.86 (s, 9H). **^{13}C NMR**

(75 MHz, $CDCl_3$): δ 177.8 (Cq), 168.7 (Cq), 148.9 (Cq), 134.4 (Cq), 134.3 (CH_{Ar}), 129.9 (CH_{Ar}), 129.3 (CH_{Ar}), 124.4 (CH_{Ar}), 56.0 (CH), 51.0 (Cq), 45.6 (CH), 32.8 (CH_2), 28.2 (CH_3). **HRMS (+ESI):** *m*/*z* calculated for $[C_{15}H_{19}N_3O_4H]^+$ 306.1454, *m*/*z* found for $[M+H]^+$ 306.1447.

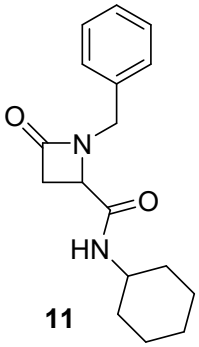
2.6. Treatment of azetidine-2-one 6k with KOH



6k **11**

To a 0.05 M solution of azetidindin-2-one **6k** (1 mmol) in ethanol potassium hydroxide was added (0.4 mmol) and the mixture was ultrasonicated at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was redissolved in dichloromethane and washed with a 10% HCl aqueous solution. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to dryness, and the residue was purified by column chromatography (hexane/ethyl acetate 90:10, *v*/*v*) to give the corresponding azetidine-2-one **11**.

1-Benzyl-4-cyclohexylcarbamoyl-2-azetidinone (11)

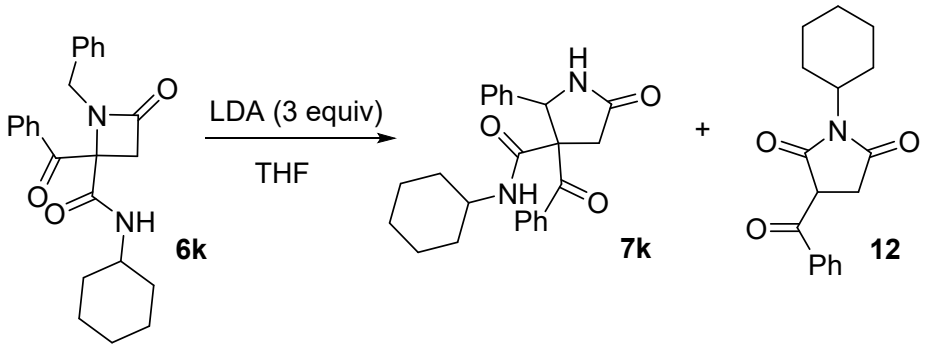


11

Orange oil. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.39-7.24 (m, 5H), 5.56 (d, *J* = 7.8 Hz, 1H), 4.43 (d, *J* = 14.9 Hz, 1H), 4.35 (d, *J* = 14.9 Hz, 1H), 3.85 (dd, *J* = 5.8, 2.7 Hz, 1H), 3.69-

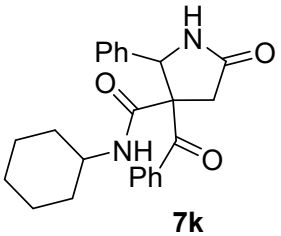
3.56 (m, 1H), 3.25 (dd, J = 14.8, 5.8 Hz, 1H), 2.93 (dd, J = 14.8, 2.7 Hz, 1H), 1.82-1.51 (m, 4H), 1.36-1.19 (m, 4H), 1.12-0.72 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 168.6 (Cq), 167.6 (Cq), 135.5 (Cq), 129.3 (CH_{Ar}), 128.8 (CH_{Ar}), 128.4 (CH_{Ar}), 110.1 (?), 53.2 (CH), 48.3 (CH), 46.7 (CH_2), 43.4 (CH_2), 32.8 (CH_2), 32.7 (CH_2), 25.4 (CH_2), 24.8 (CH_2). **HRMS (+ESI):** *m/z* calculated for $[C_{17}H_{22}N_2O_2H]^+$ 287.1754, m/z found for [M+H]+ 287.1766.

2.7. Treatment of azetidine-2-one 6k with LDA



To compound **6k** (215 mg, 0.551 mmol) placed in a 10 mL Schlenk flask, anhydrous tetrahydrofuran (3.0 mL) was added through a septum *via* a disposable syringe under a nitrogen atmosphere, and to the formed solution a 2.0 M lithium diisopropylamide (LDA) solution in tetrahydrofuran/*n*-heptane/ethylbenzene (0.82 mL, 1.64 mmol, 2.98 equiv.) was added in a similar manner over the period of 1 min. The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 5 h, quenched with a 1.0 M HCl aqueous solution (3 mL) and stirring was continued for a further 5 min. The content of the flask was extracted with ethyl acetate (3 x 3 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (EtOAc/CH_2Cl_2).

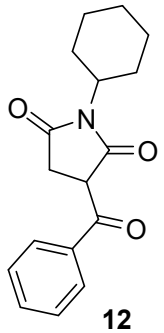
4-Benzoyl-4-cyclohexylcarbamoyl-5-phenylpyrrolidin-2-one (7k)



7k

Yellow oil (as a 62:38 diastereoisomers mixture). **^{1}H NMR (500 MHz, $CDCl_3$):** δ (diastereoisomers mixture) 7.83-6.88 (m, 10H), 6.00 (s, 0.62H), 5.87 (s, 0.38H), 5.84 (s. 0.38H), 5.82 (s, 0.62H), 5.24 (d, J = 7.8 Hz, 0.62H), 4.57 (d, J = 7.3 Hz, 0.38H), 3.95 (d, J = 17.5 Hz, 0.38H), 3.89 (d, J = 17.7 Hz, 0.62H), 3.82-3.74 (m, 0.62H), 3.24-3.17 (m, 0.38H), 2.71 (d, J = 17.5 Hz, 0.38H), 2.64 (d, J = 17.7 Hz, 0.62H), 1.88-0.32 (m, 10H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ (diastereoisomers mixture) 198.2 (Cq), 195.2 (Cq), 174.0 (Cq), 173.7 (Cq), 169.4 (Cq), 165.2 (Cq), 138.1 (Cq),137.4 (Cq), 136.0 (Cq), 134.3 (Cq), 134.0 (CH_{Ar}), 133.4 (CH_{Ar}), 129.3 (CH_{Ar}), 129.0 (CH_{Ar}), 128.9 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.1 (CH_{Ar}), 66.9 (Cq), 66.7 (Cq), 61.6 (CH), 61.1 (CH), 49.5 (CH), 49.1 (CH), 38.9 (CH_2), 38.4 (CH_2), 32.7 (CH_2), 32.3 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 29.8 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 24.8 (CH_2), 24.7 (CH_2), 24.5 (CH_2), 24.3 (CH_2).

3-Benzoyl-1-cyclohexylpyrrolidin-2,5-dione (12)



12

Light brown solid. **M. p.:** 165-167 ^{o}C. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.13-8.09 (m, 2H), 7.72-7.62 (m, 1H), 7.57-7.45 (m, 2H), 4.78 (dd, J = 9.0, 4.1 Hz, 1H), 3.96 (tt, J = 12.3, 3.8 Hz, 1H), 3.32 (dd, J = 18.0, 4.1, 1H), 2.80 (dd, J = 18.0, 9.0 Hz, 1H), 2.22-2.00 (m, 2H), 1.90-1.53 (m, 3H), 1.43-1.08 (m, 4H), 0.91-0.82 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 192.9 (Cq), 175.9 (Cq), 173.0 (Cq), 135.6 (Cq), 134.3 (CH_{Ar}), 129.9 (CH_{Ar}), 128.9 (CH_{Ar}), 52.5 (CH), 48.3 (CH), 31.7 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 26.0 (CH_2), 25.9 (CH_2), 25.1 (CH_2). **HRMS (+ESI):** *m/z* calculated for $[C_{17}H_{19}NO_3H]^+$ 286.1438, *m/z* found for $[M+H]^+$ 286.1448.

3. NMR (^{1}H, ^{13}C and DEPT-135) and HRMS spectra

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-hydroxy-3-phenylacrylamide (5a)

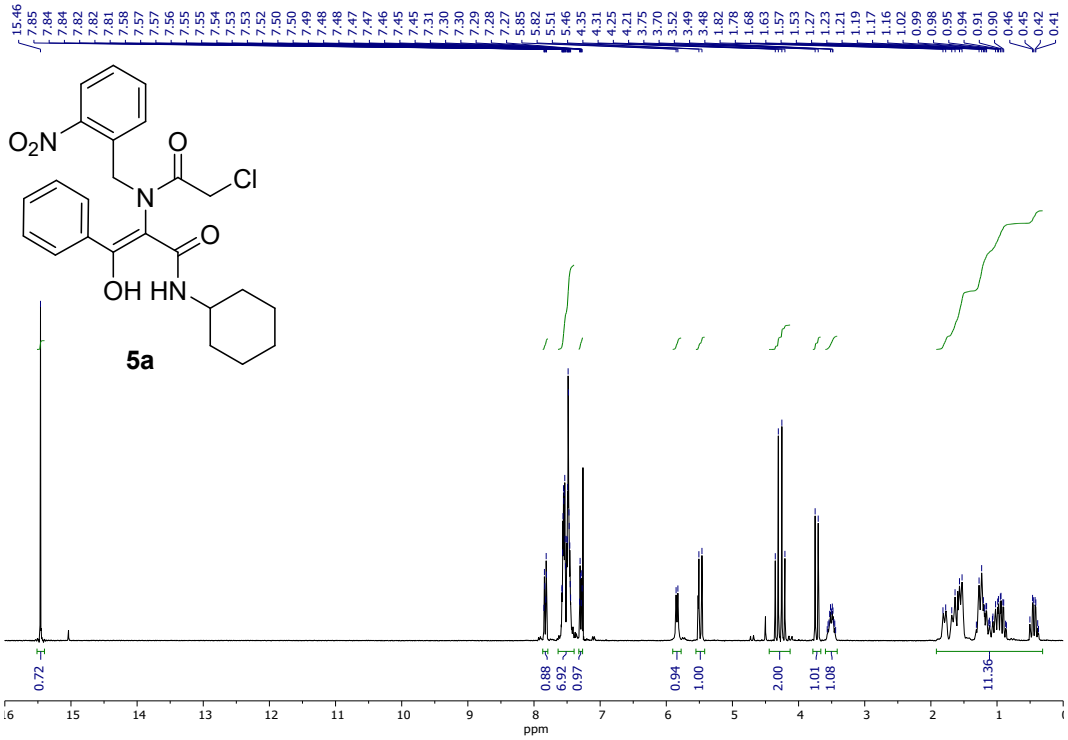


Figure S1. ^{1}H NMR spectrum of **5a** (300 MHz, $CDCl_3$).

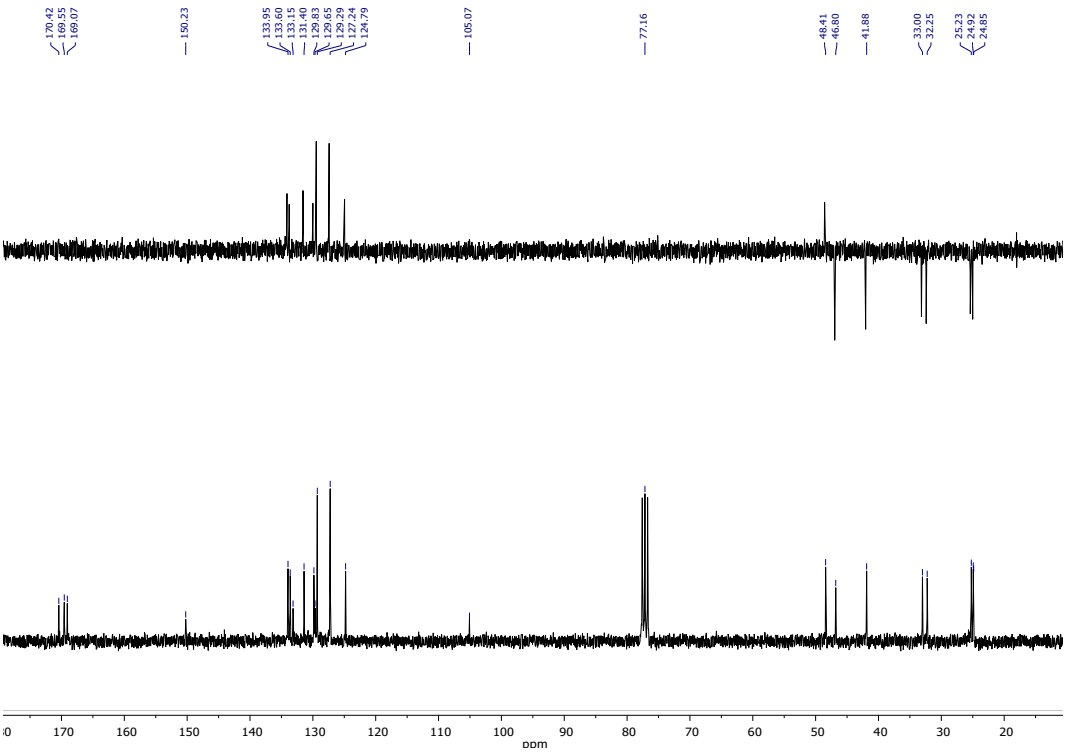


Figure S2. ^{13}C and DEPT-135 NMR spectra of **5a** (75 MHz, $CDCl_3$).

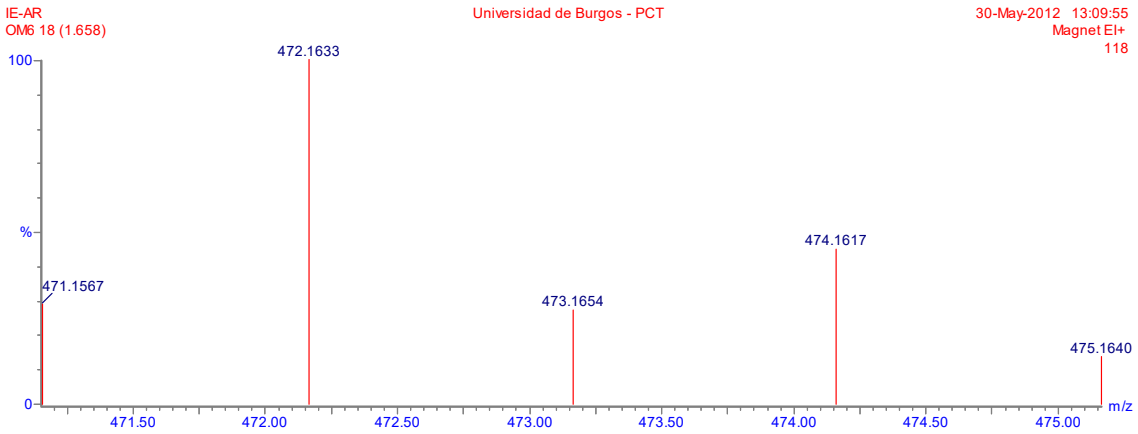


Figure S3. HRMS (EI) spectrum of **5a**.

(*E*)-*N*-Benzyl-2-(2-chloro-*N*-(2-nitrobenzyl)acetamido)-3-hydroxy-3-phenylacrylamide (5b)

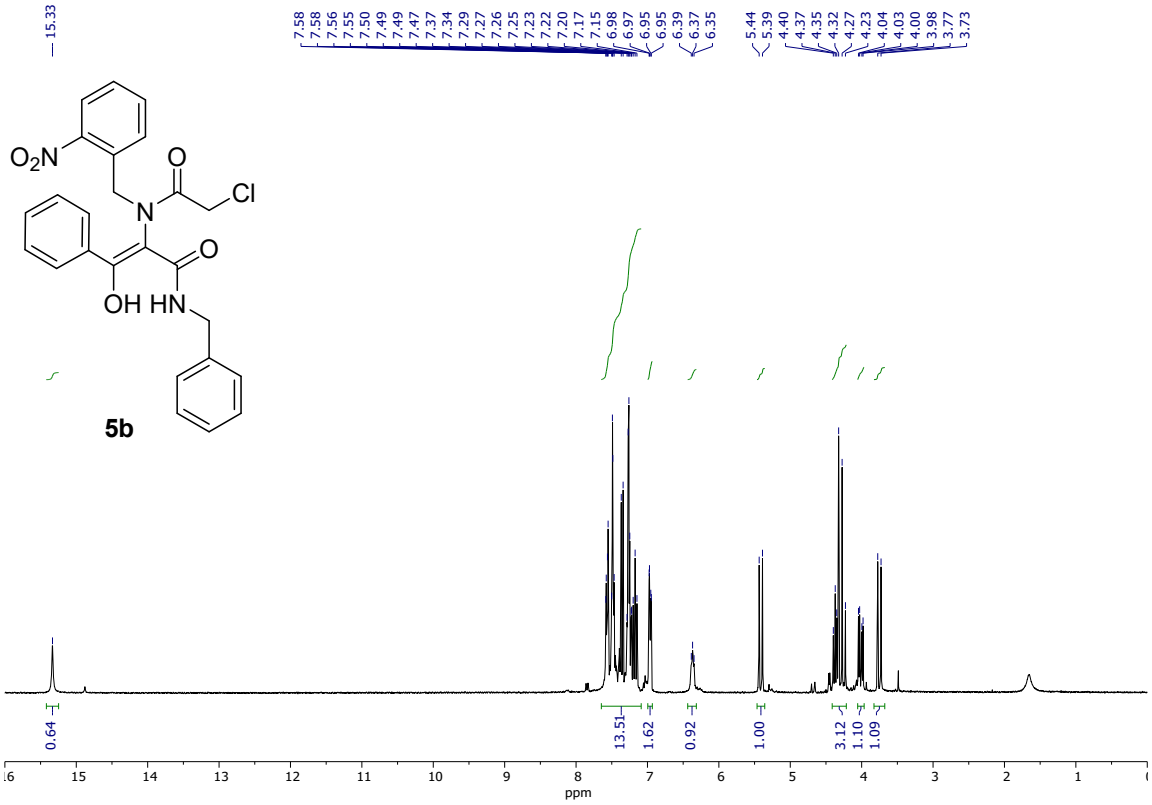


Figure S4. ^{1}H NMR spectrum of **5b** (300 MHz, $CDCl_3$).

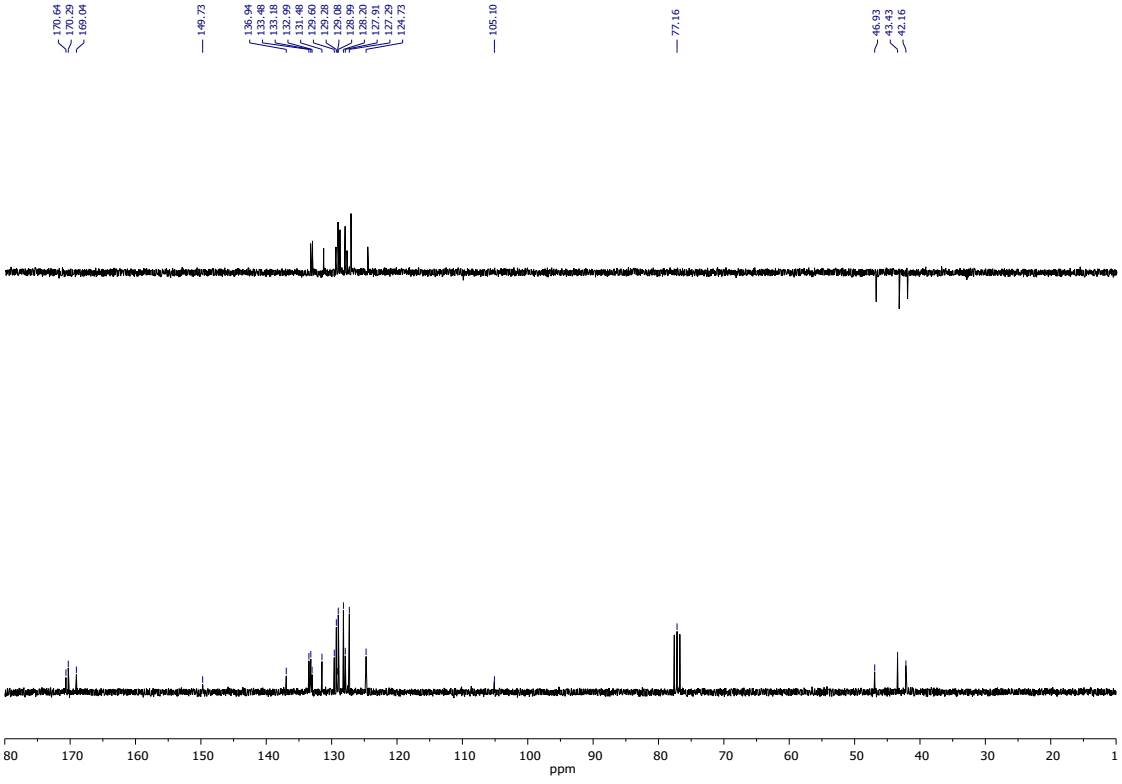


Figure S5. ^{13}C and DEPT-135 NMR spectra of **5b** (75 MHz, $CDCl_3$).

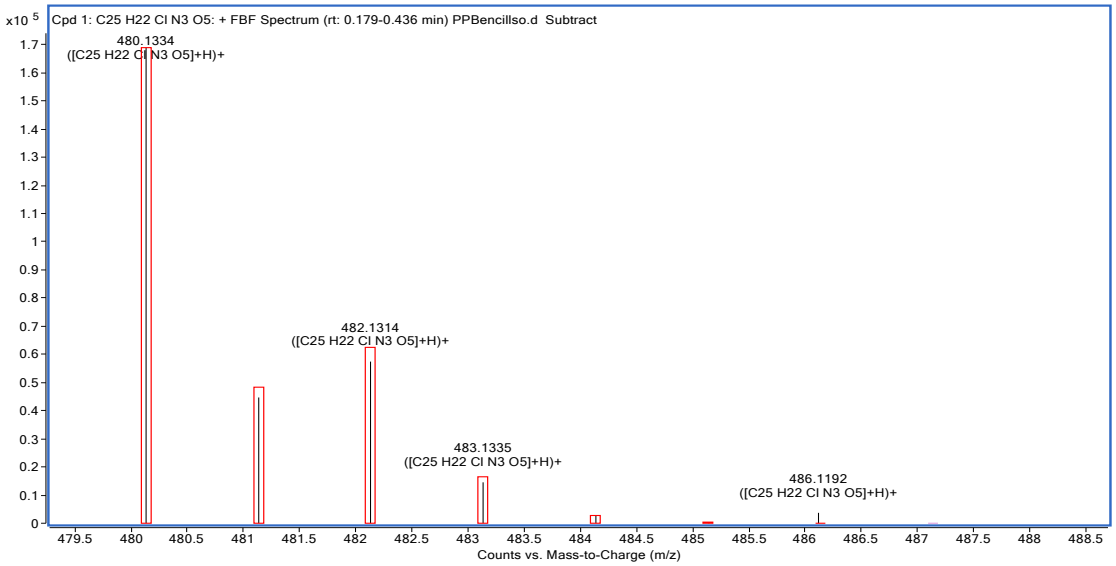


Figure S6. HRMS (+ESI) spectrum of **5b**.

(*E*)-*N*-(*tert*-Butyl)-2-(2-chloro-*N*-(2-nitrobenzyl)acetamido)-3-hydroxy-3-phenylacrylamide (5c)

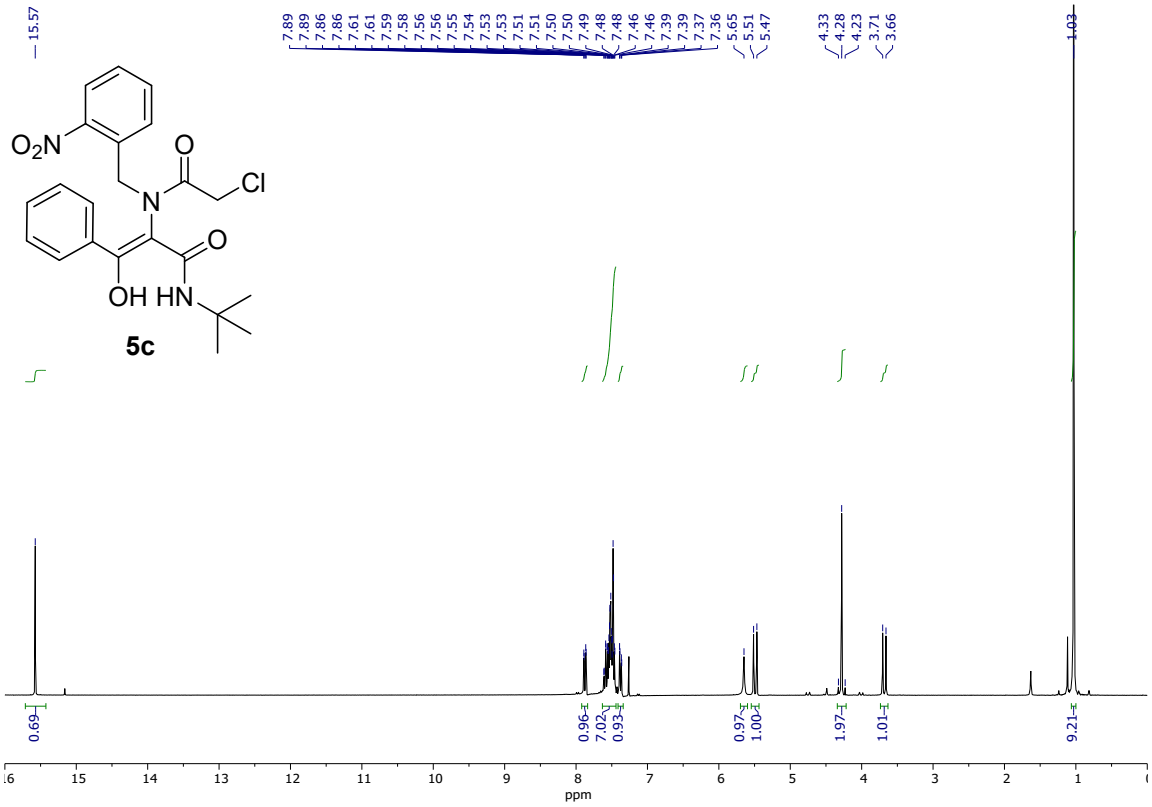


Figure S7. ^{1}H NMR spectrum of **5c** (300 MHz, $CDCl_3$).

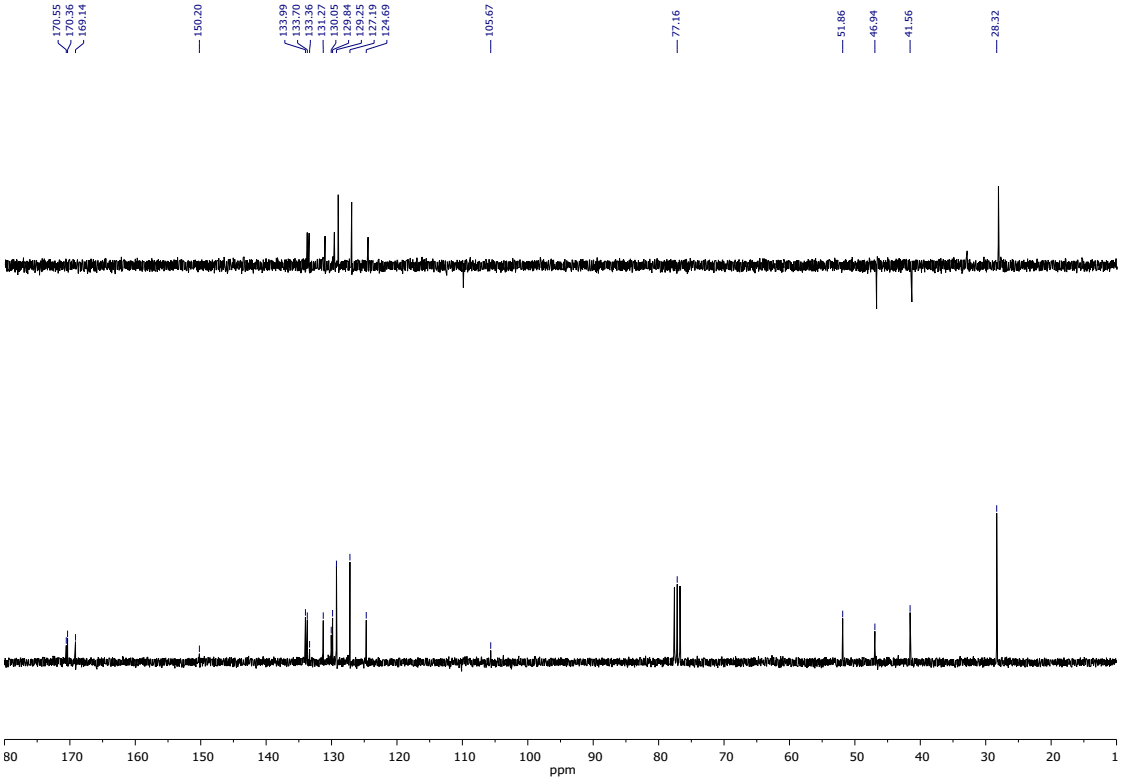


Figure S8. ^{13}C and DEPT-135 NMR spectra of **5c** (75 MHz, $CDCl_3$).

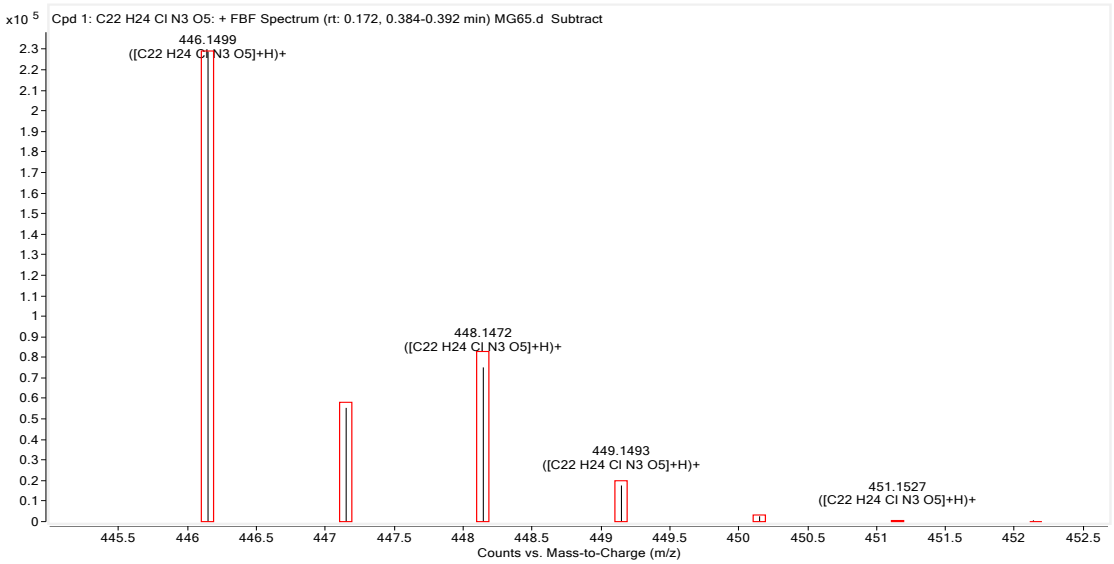


Figure S9. HRMS (+ESI) spectrum of **5c**.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-hydroxy-3-(*p*-tolyl)acrylamide (5d)

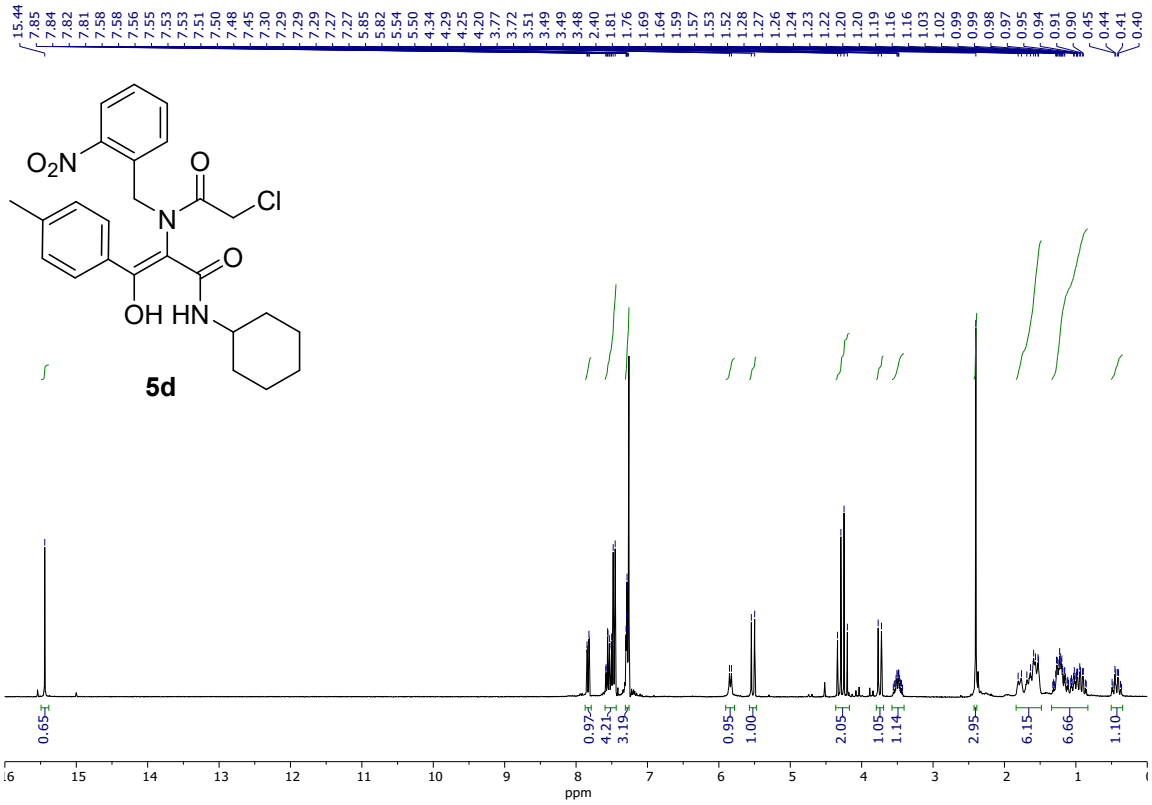


Figure S10. ^{1}H NMR spectrum of **5d** (300 MHz, $CDCl_3$).

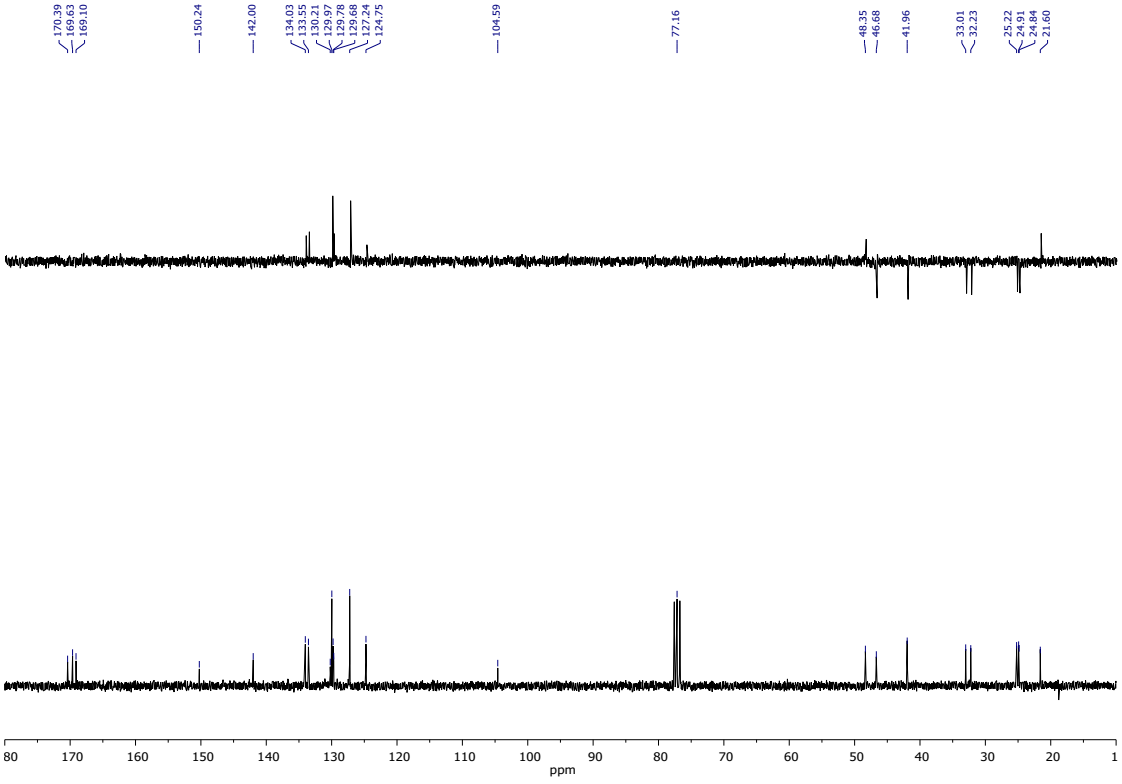


Figure S11. ^{13}C and DEPT-135 NMR spectra of **5d** (75 MHz, $CDCl_3$).

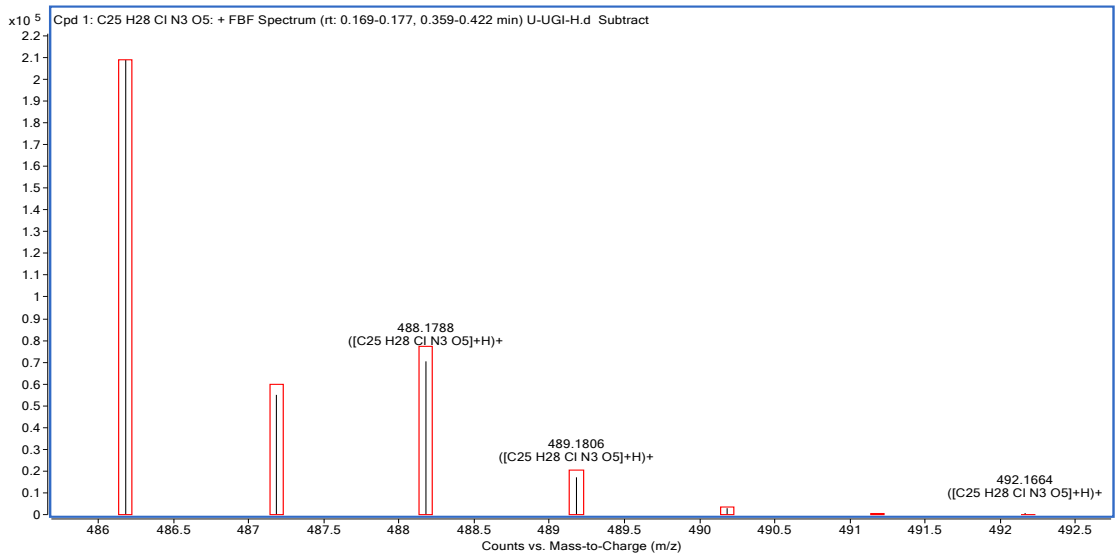


Figure S12. HRMS (+ESI) spectrum of **5d**.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-3-(4-chlorophenyl)-*N*-cyclohexyl-3-hydroxyacrylamide (5e)

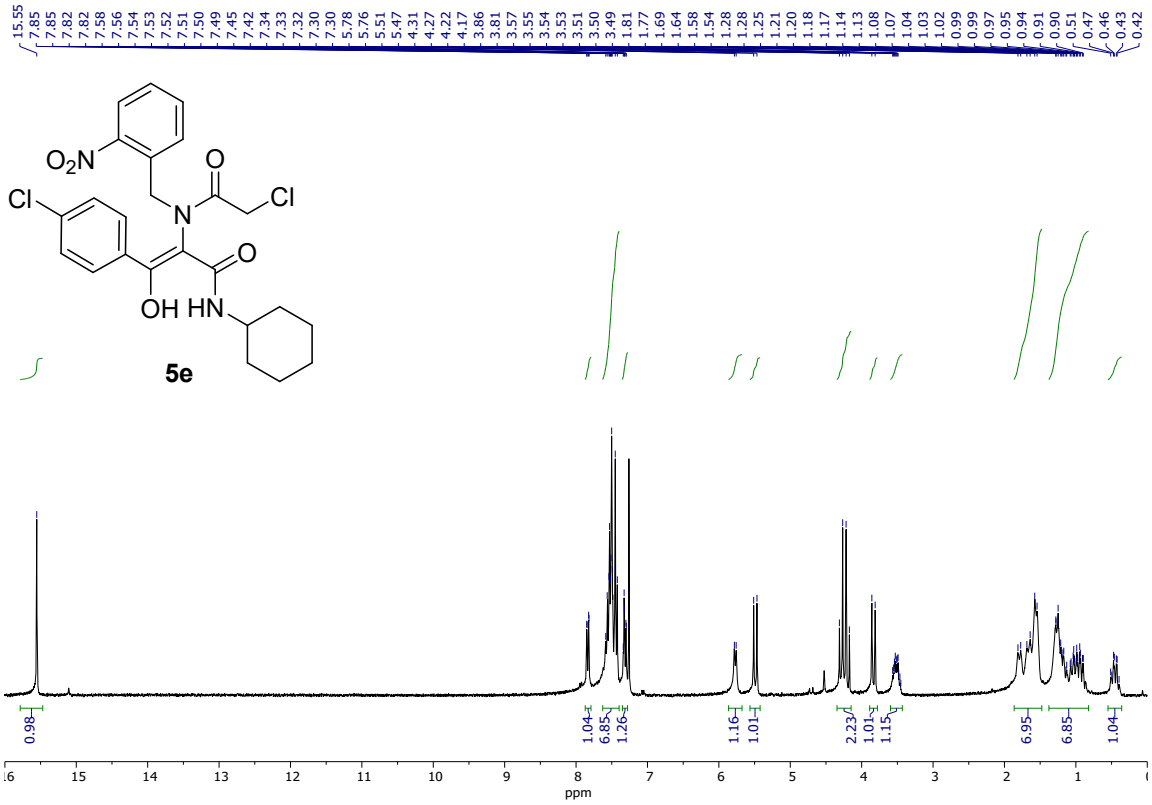


Figure S13. ^{1}H NMR spectrum of **5e** (300 MHz, $CDCl_3$).

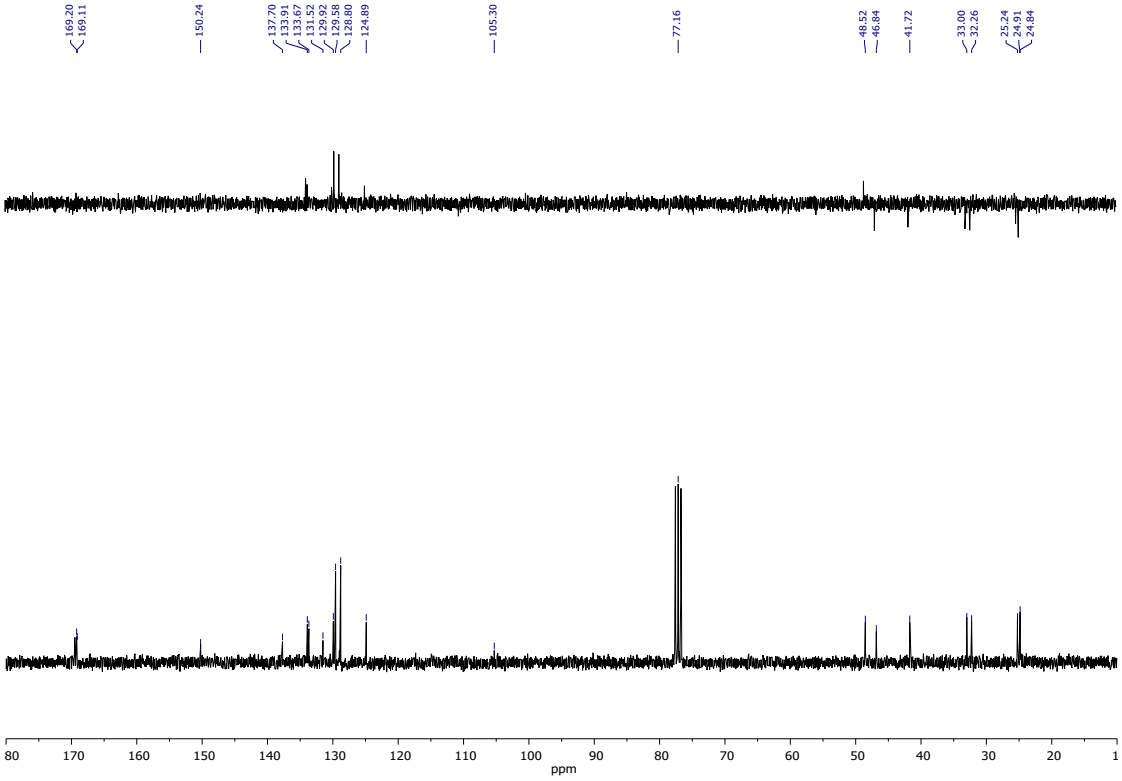


Figure S14. ^{13}C and DEPT-135 NMR spectra of **5e** (75 MHz, $CDCl_3$).

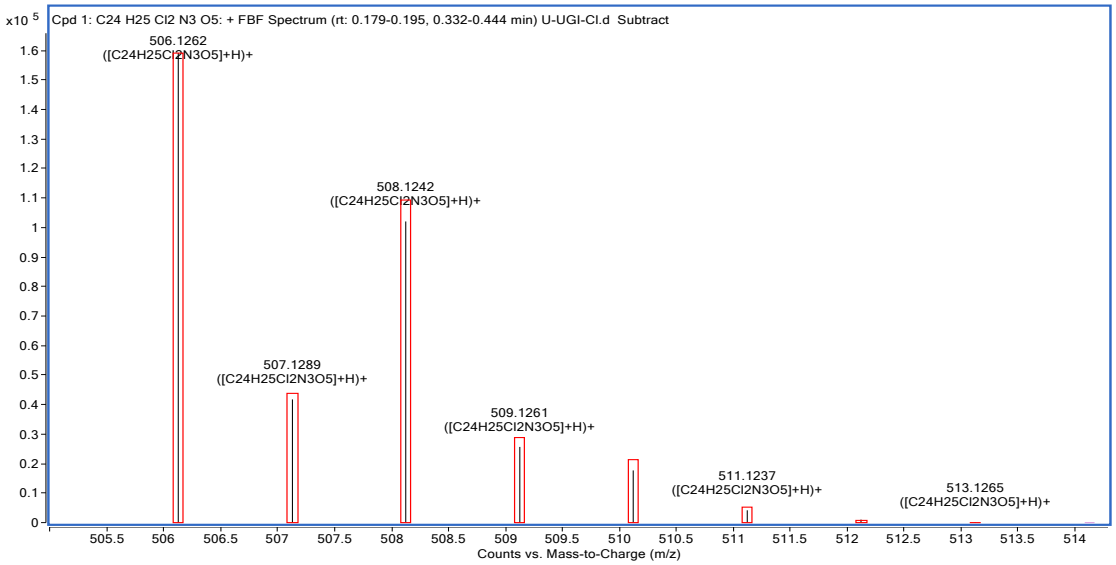


Figure S15. HRMS (+ESI) spectrum of **5e**.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-(4-fluorophenyl)-3-hydroxyacrylamide (5f)

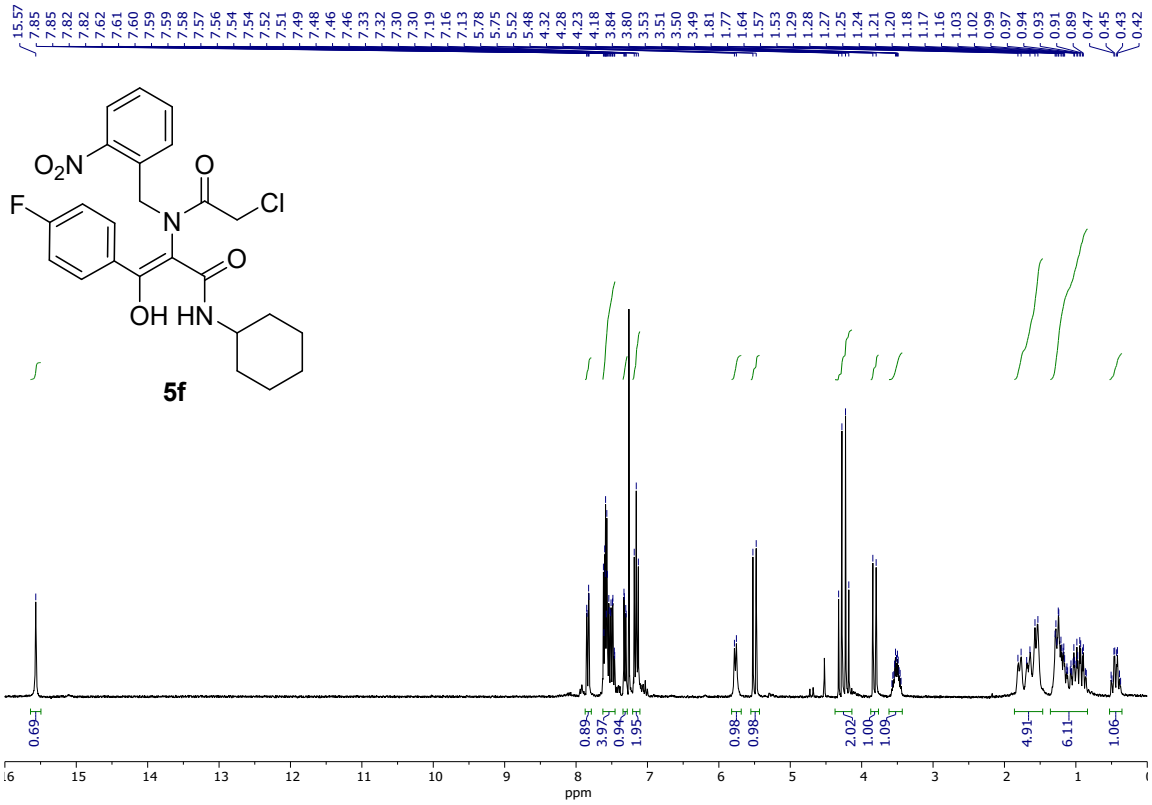


Figure S16. ^{1}H NMR spectrum of **5f** (300 MHz, $CDCl_3$).

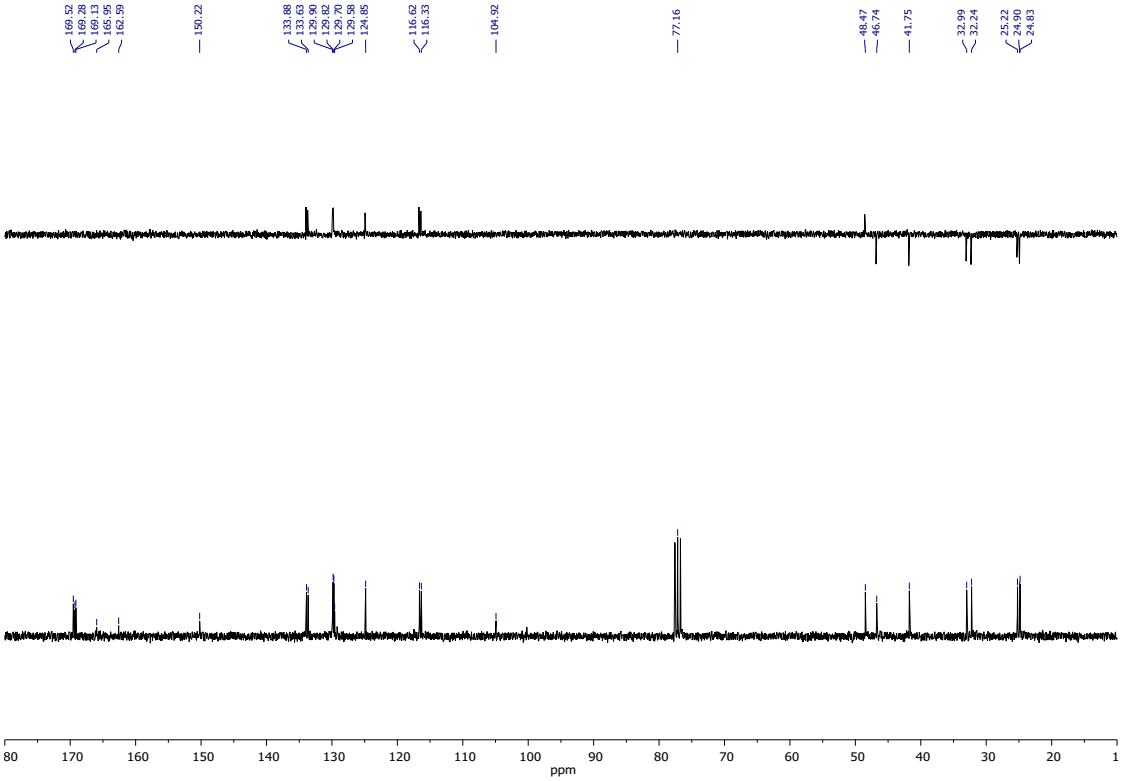


Figure S17. ^{13}C and DEPT-135 NMR spectra of **5f** (75 MHz, $CDCl_3$).

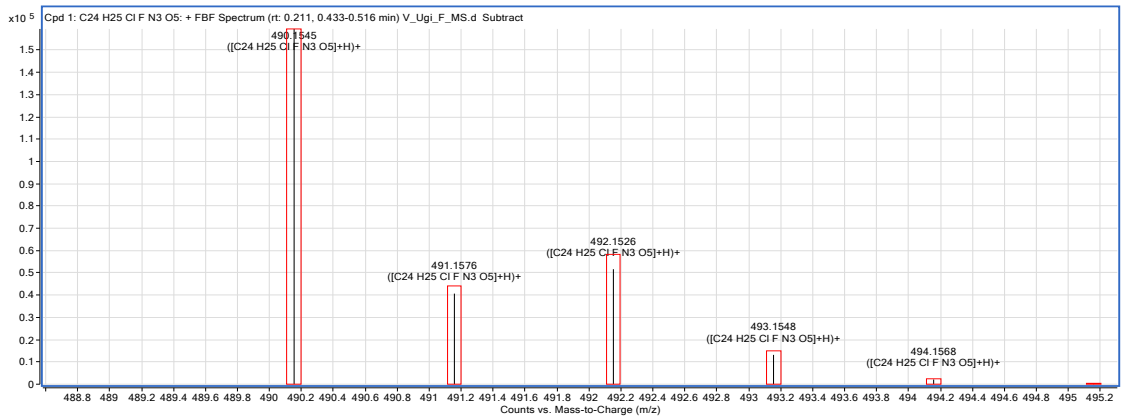


Figure S18. HRMS (+ESI) spectrum of **5f**.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-(4-methoxyphenyl)-3-hydroxyacrylamide (5g)

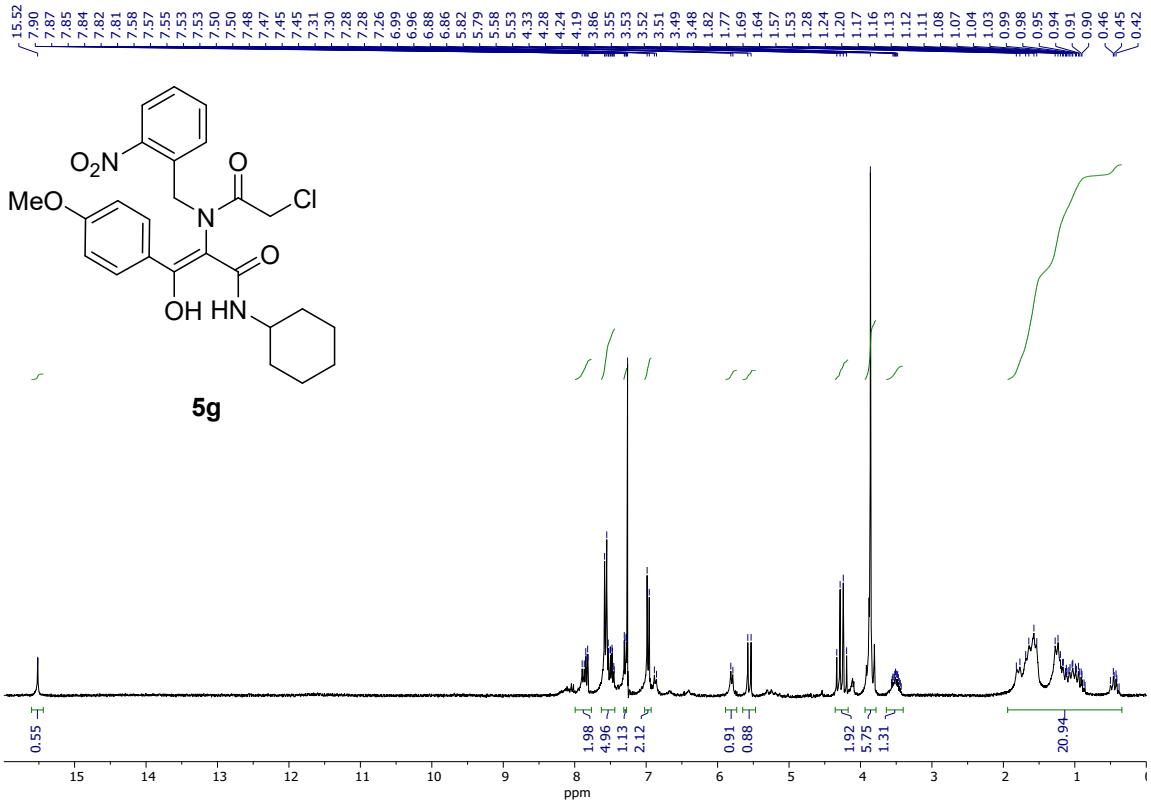


Figure S19. ^{1}H NMR spectrum of **5g** (300 MHz, $CDCl_3$).

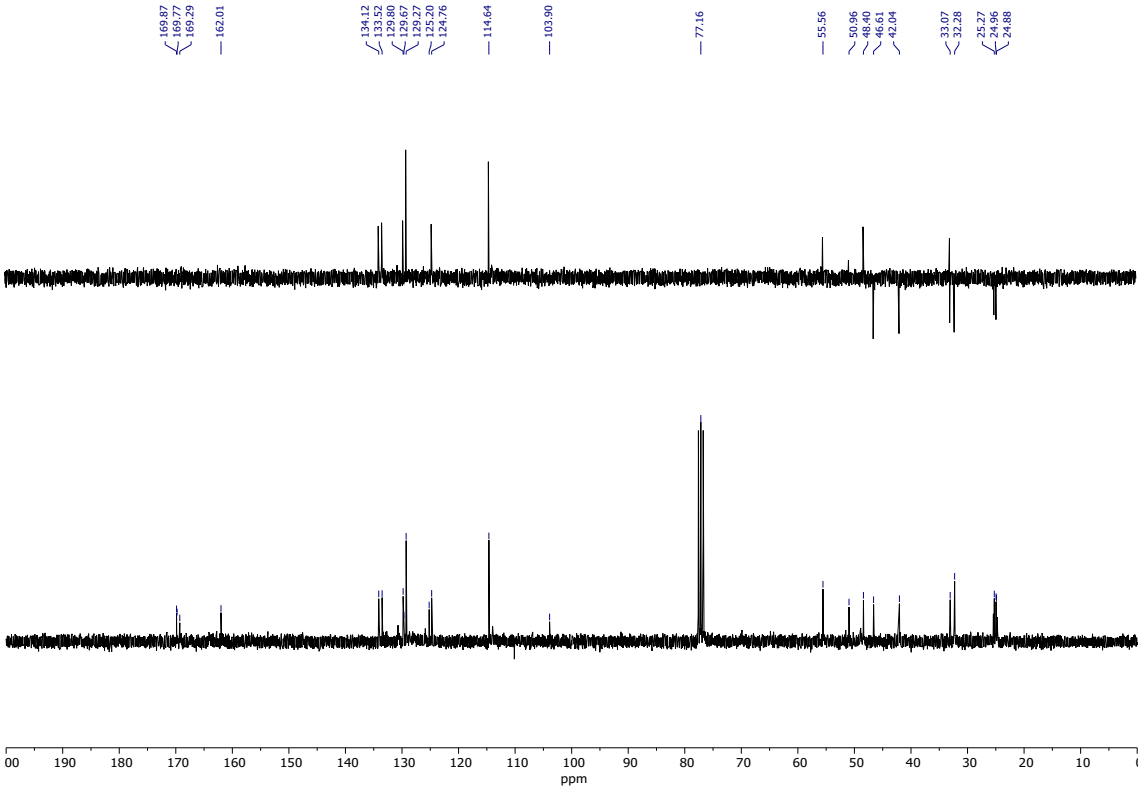


Figure S20. ^{13}C and DEPT-135 NMR spectra of **5g** (75 MHz, $CDCl_3$).

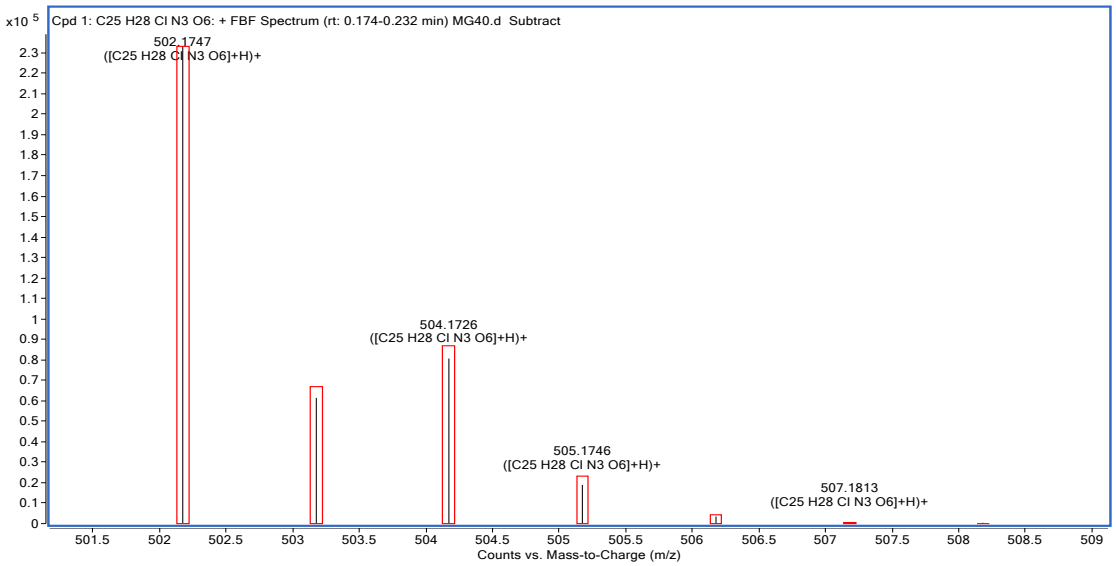


Figure S21. HRMS (+ESI) spectrum of **5g**.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)acetamido)-*N*-cyclohexyl-3-hydroxybut-2-enamide (5h)

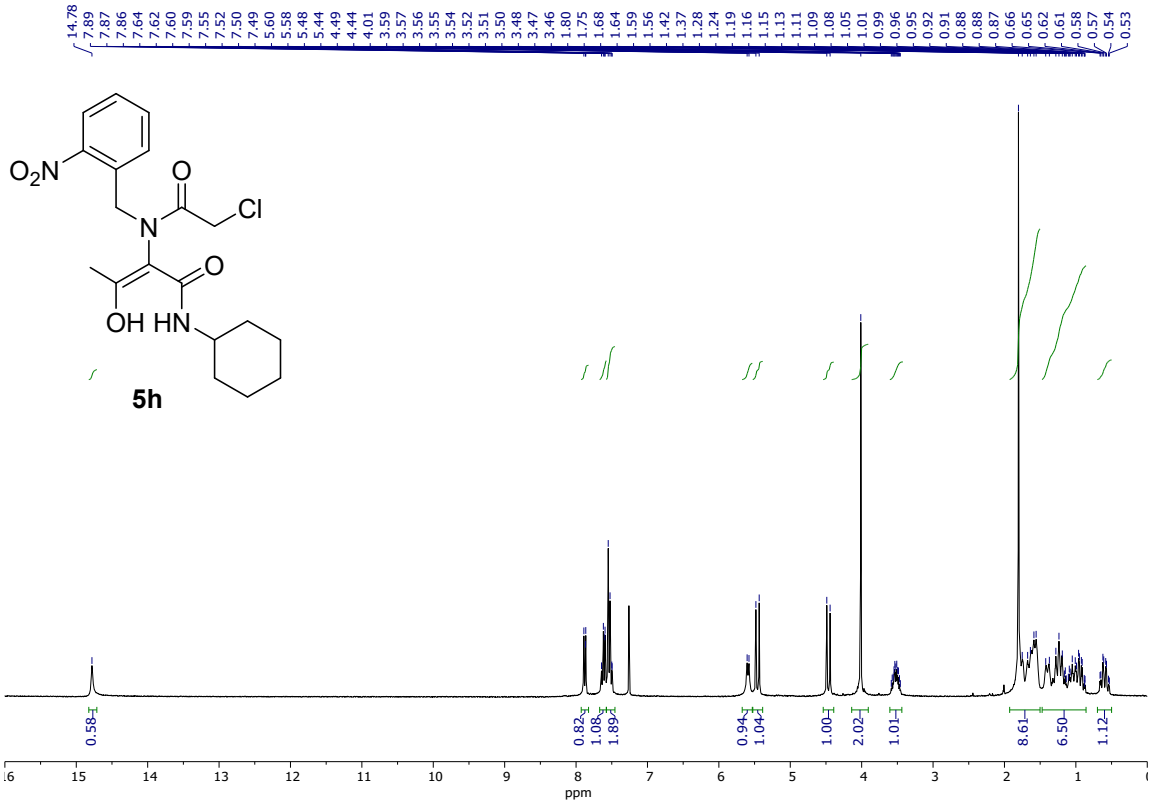


Figure S22. ^{1}H NMR spectrum of **5h** (300 MHz, $CDCl_3$).

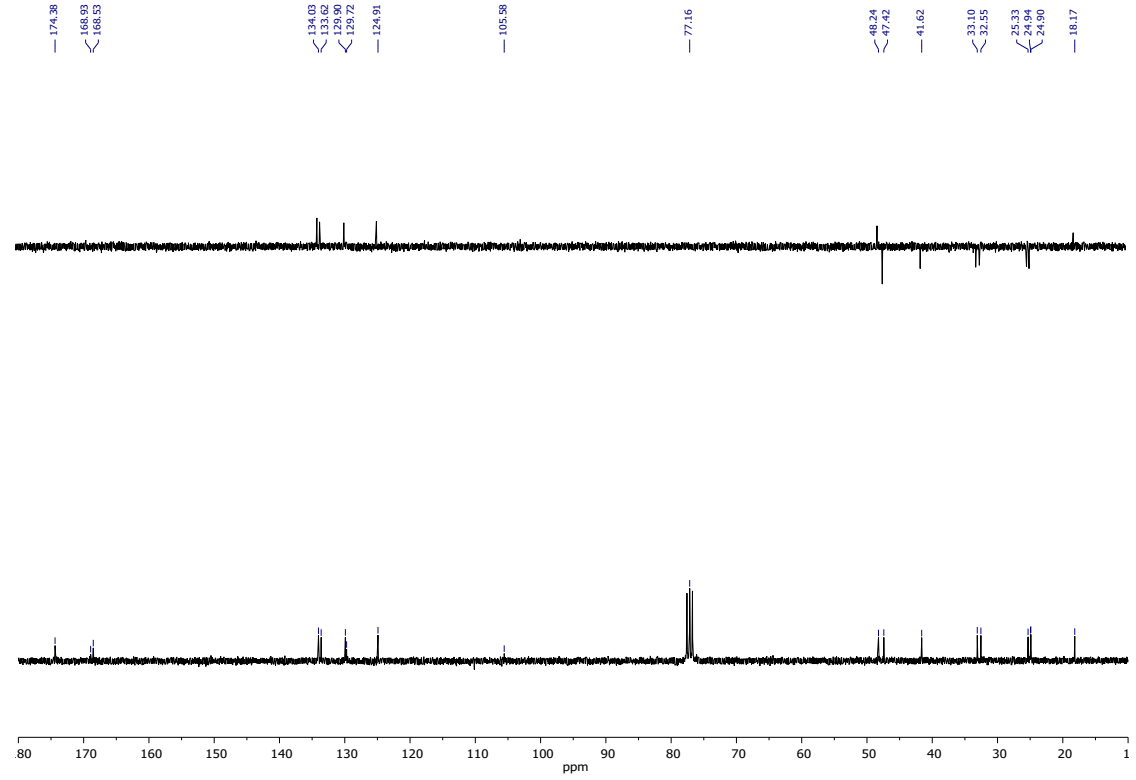


Figure S23. ^{13}C and DEPT-135 NMR spectra of **5h** (75 MHz, $CDCl_3$).

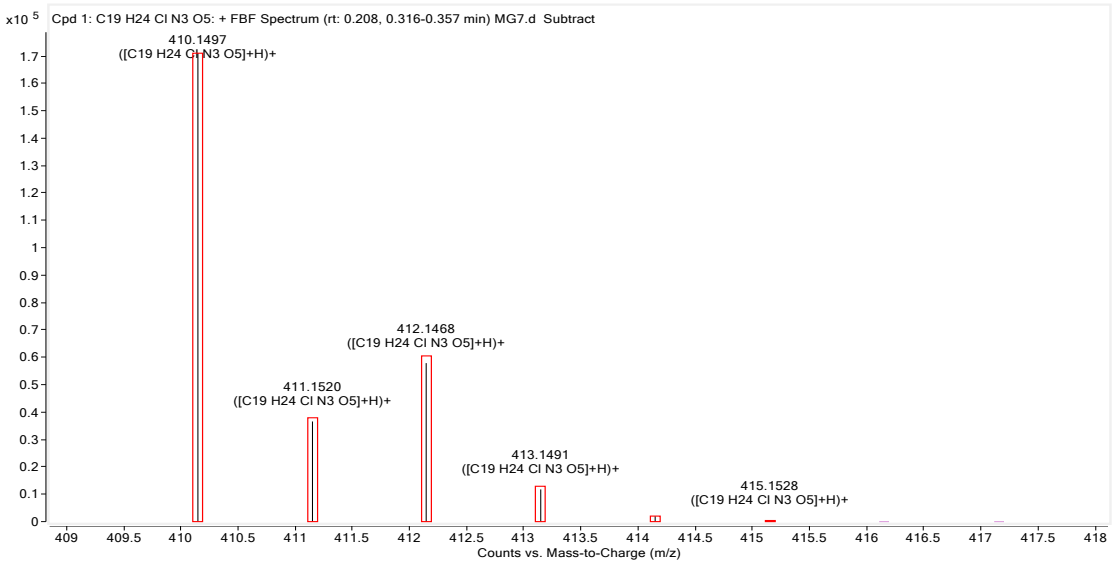


Figure S24. HRMS (+ESI) spectrum of **5h**.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)-2-phenylacetamido)-*N*-cyclohexyl-3-hydroxy-3-phenylacrylamide (5i)

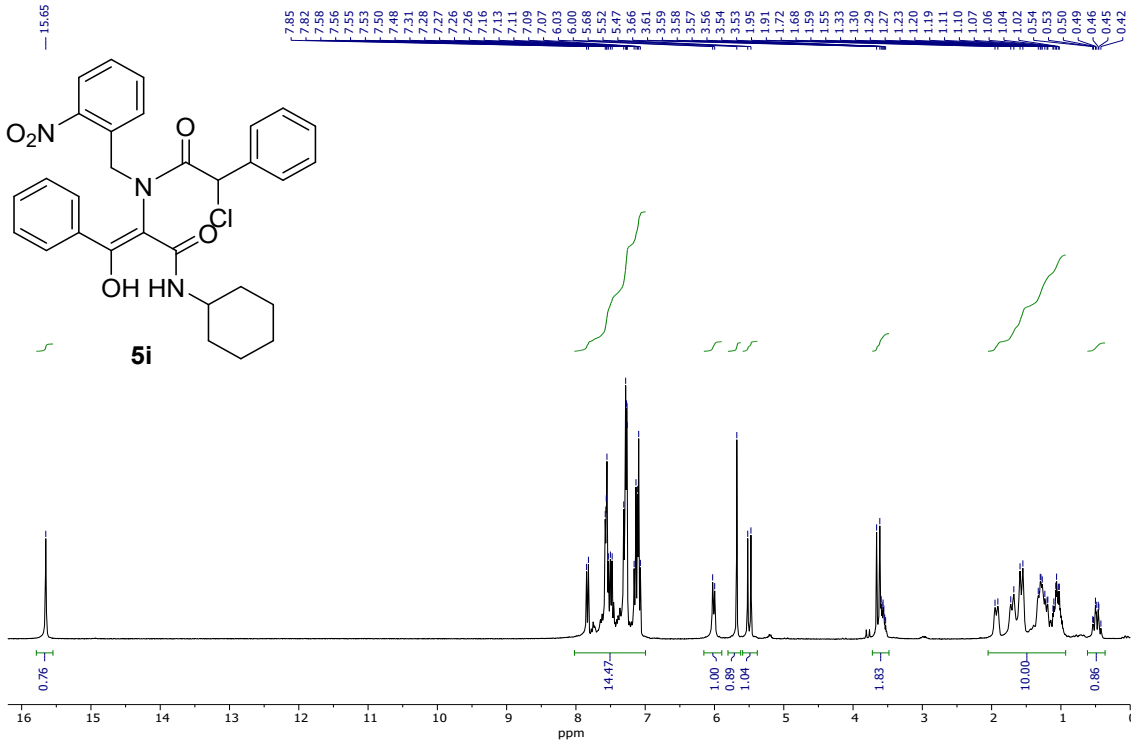


Figure S25. ^{1}H NMR spectrum of **5i** (300 MHz, $CDCl_3$).

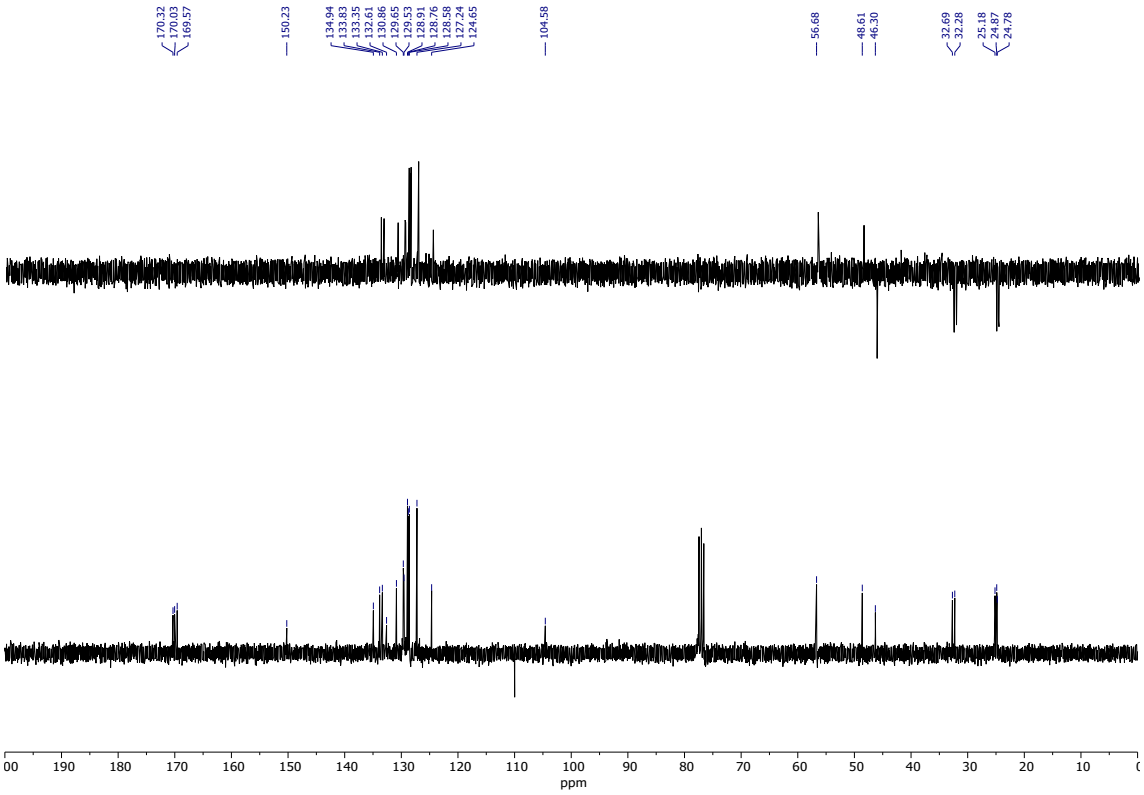


Figure S26. ^{13}C and DEPT-135 NMR spectra of **5i** (75 MHz, $CDCl_3$).

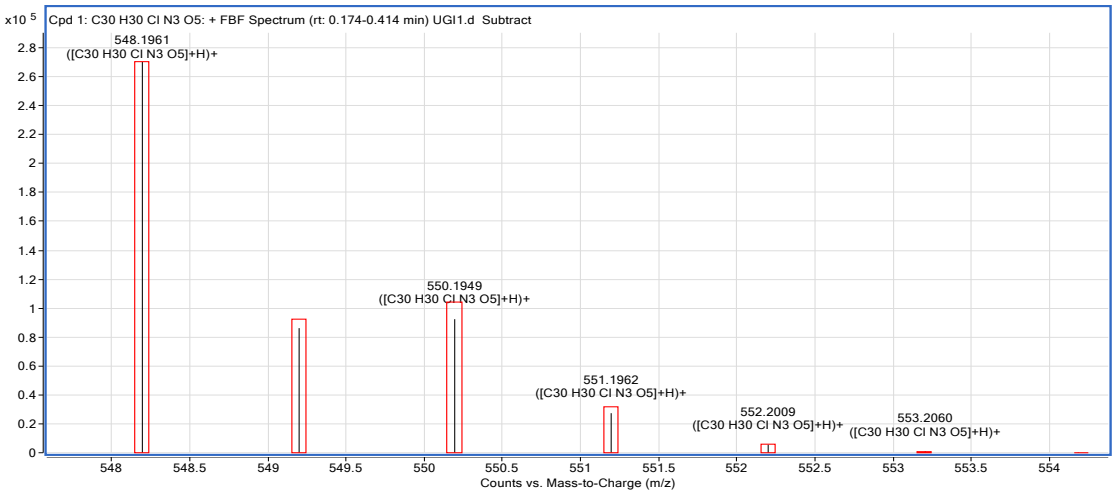


Figure S27. HRMS (+ESI) spectrum of **5i**.

(*E*)-2-(2-Chloro-*N*-(2-nitrobenzyl)-2-phenylacetamido)-*N*-cyclohexyl-3-(4-fluorophenyl)-3-hydroxyacrylamide (5j)

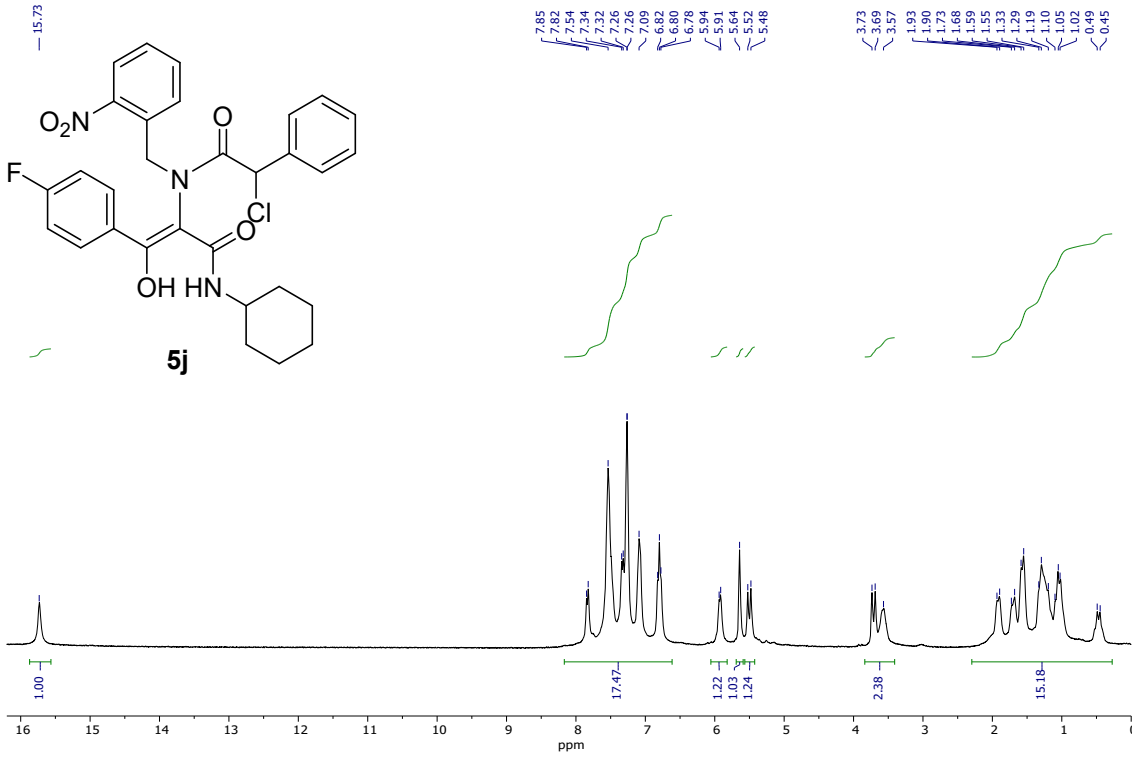


Figure S28. ^{1}H NMR spectrum of **5j** (300 MHz, $CDCl_3$).

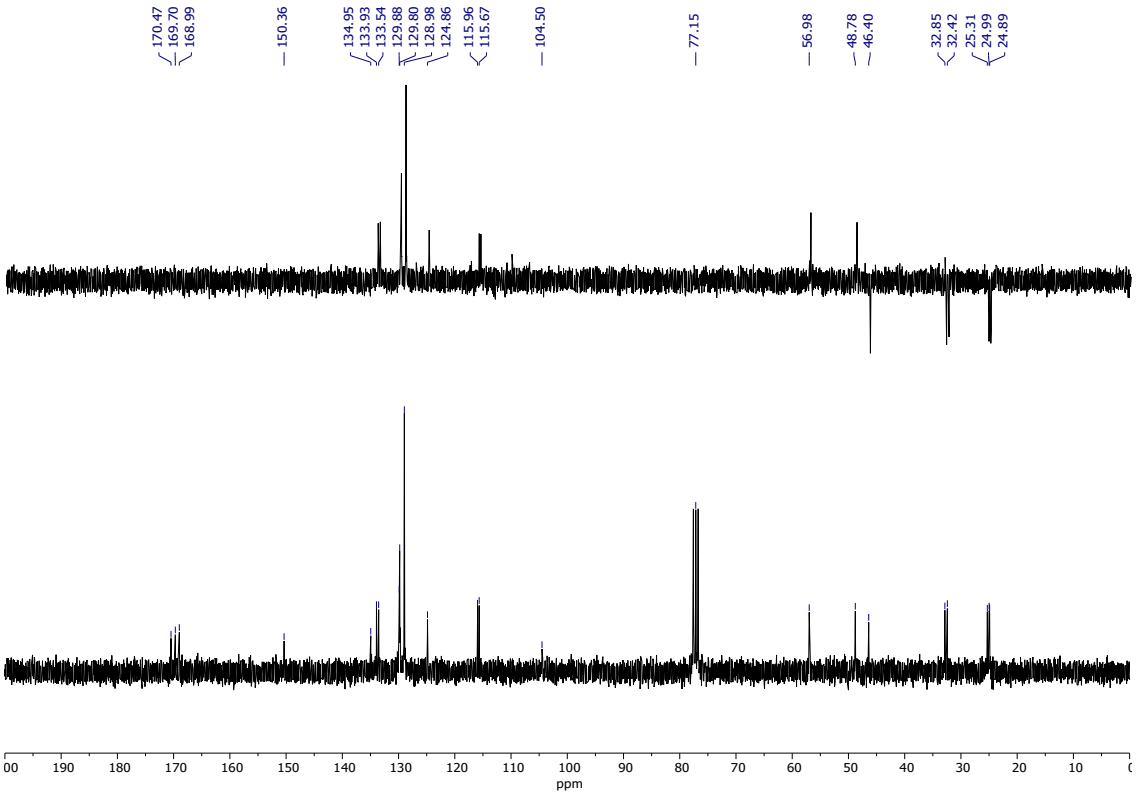


Figure S29. ^{13}C and DEPT-135 NMR spectra of **5j** (75 MHz, $CDCl_3$).

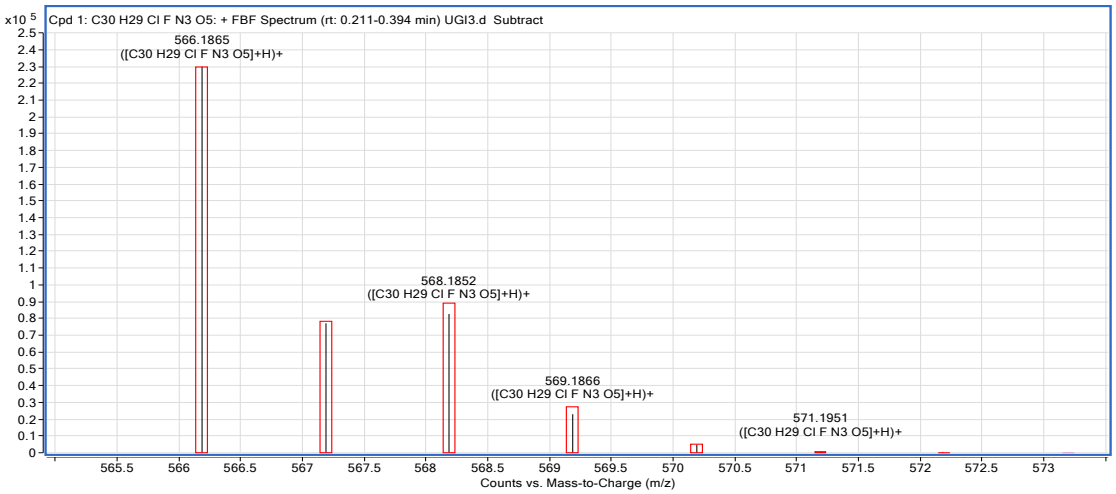


Figure S30. HRMS (+ESI) spectrum of **5j**.

(*E*)-2-(*N*-Benzyl-2-chloroacetamido)-*N*-cyclohexyl-3-hydroxy-3-phenylacrylamide (5k)

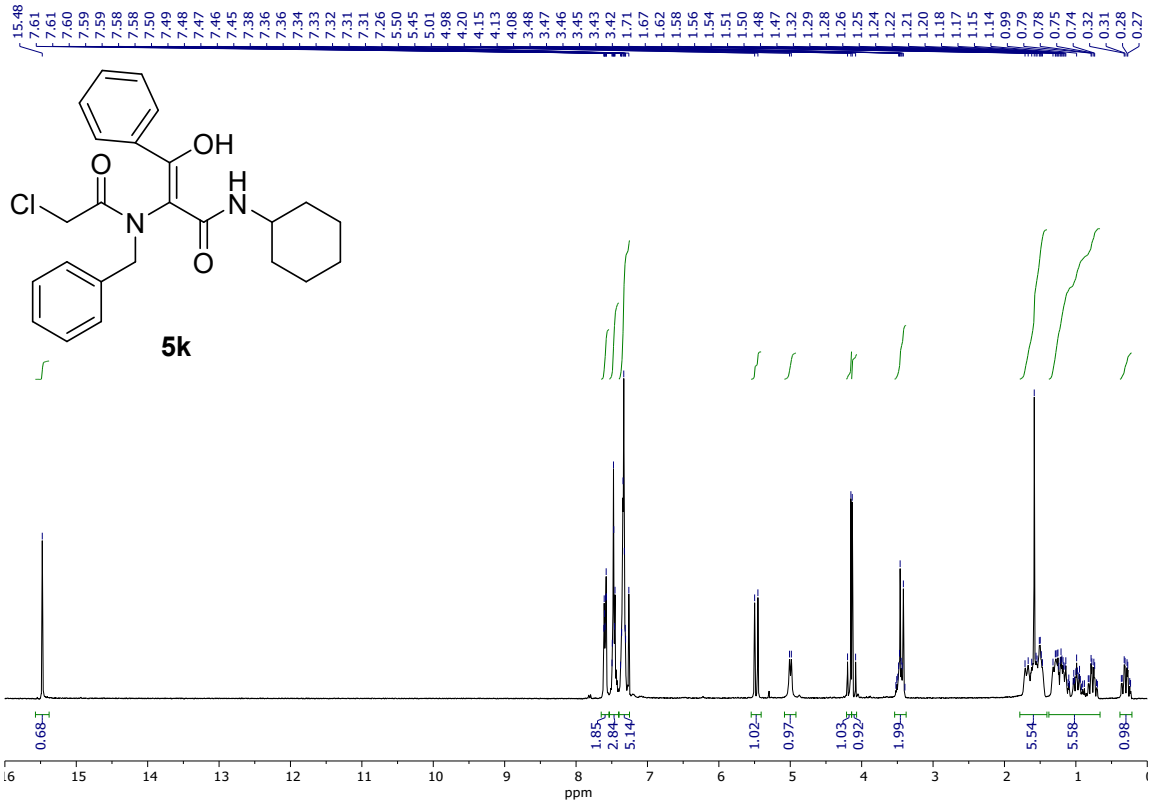


Figure S31. ^{1}H NMR spectrum of **5k** (300 MHz, $CDCl_3$).

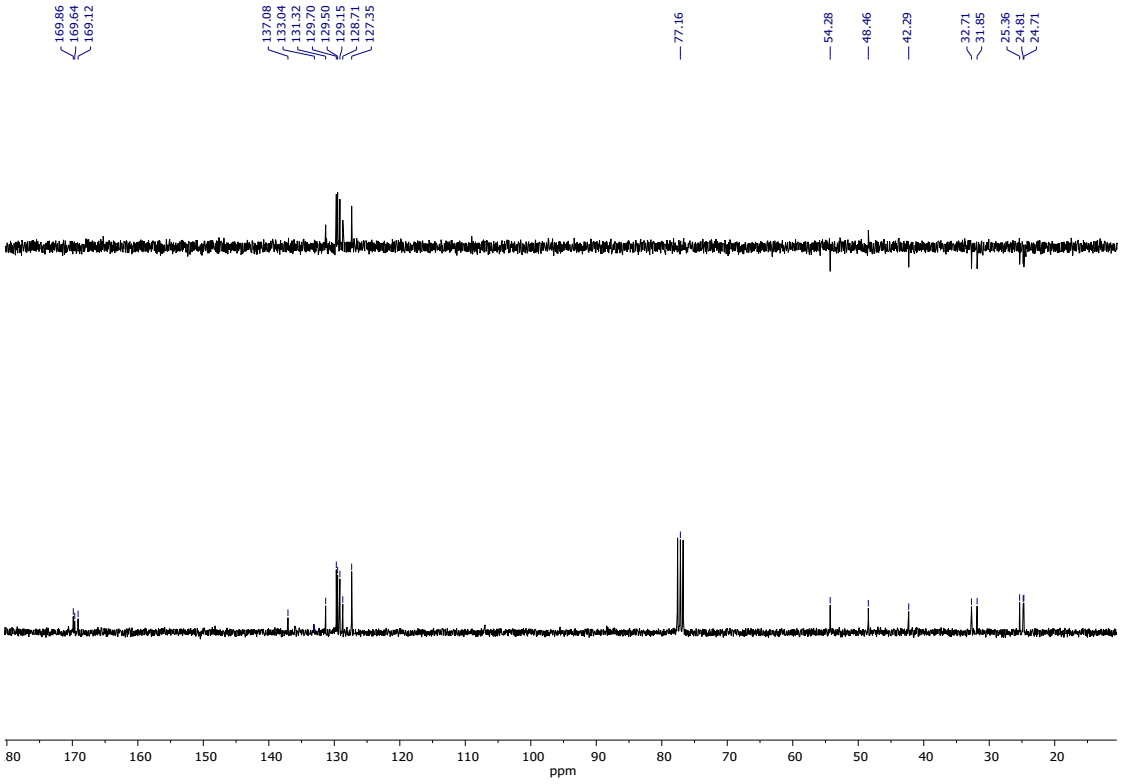


Figure S32. ^{13}C and DEPT-135 NMR spectra of **5k** (75 MHz, $CDCl_3$).

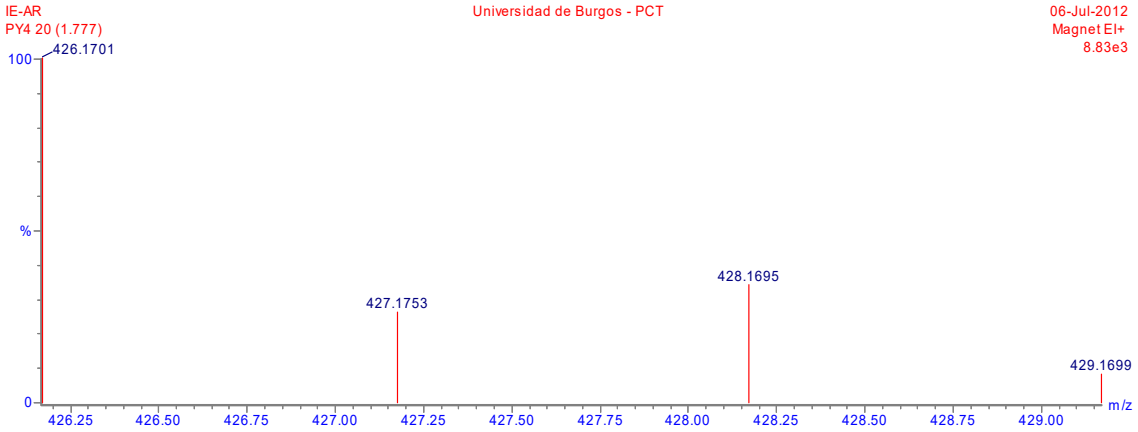


Figure S33. HRMS (EI) spectrum of **5k**.

Methyl (*E*)-2-(2-chloro-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)acetate (5l)

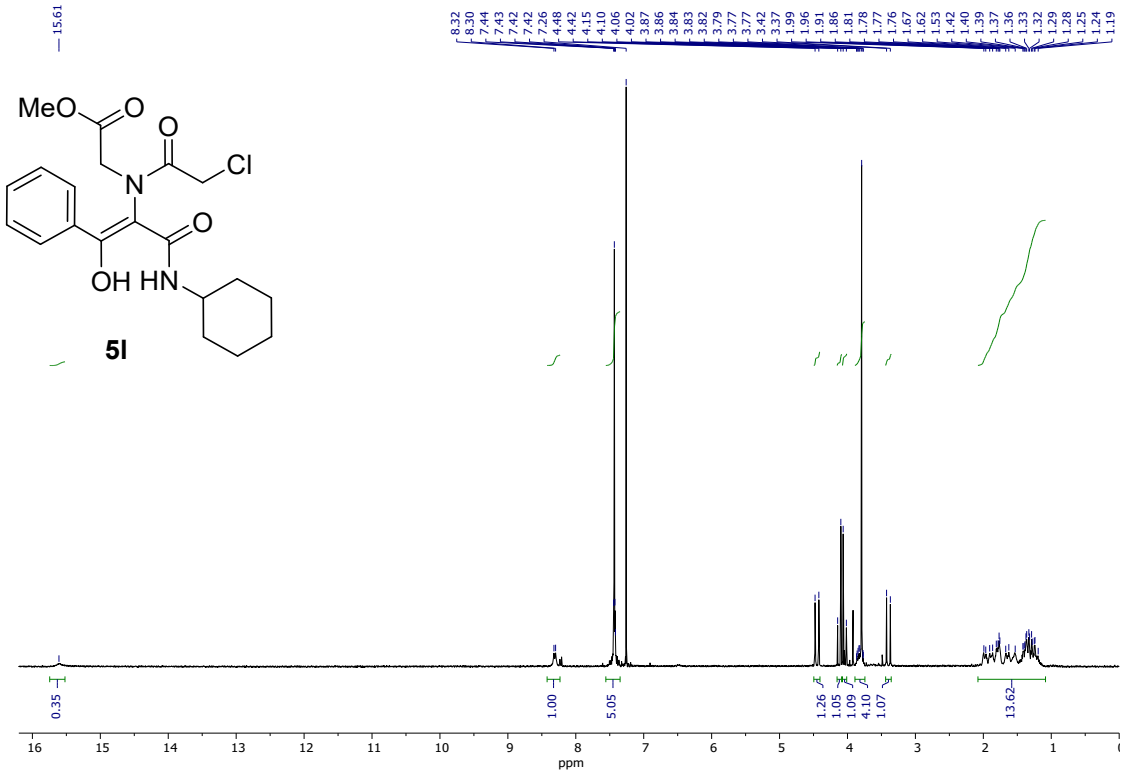


Figure S34. ^{1}H NMR spectrum of **5l** (300 MHz, $CDCl_3$).

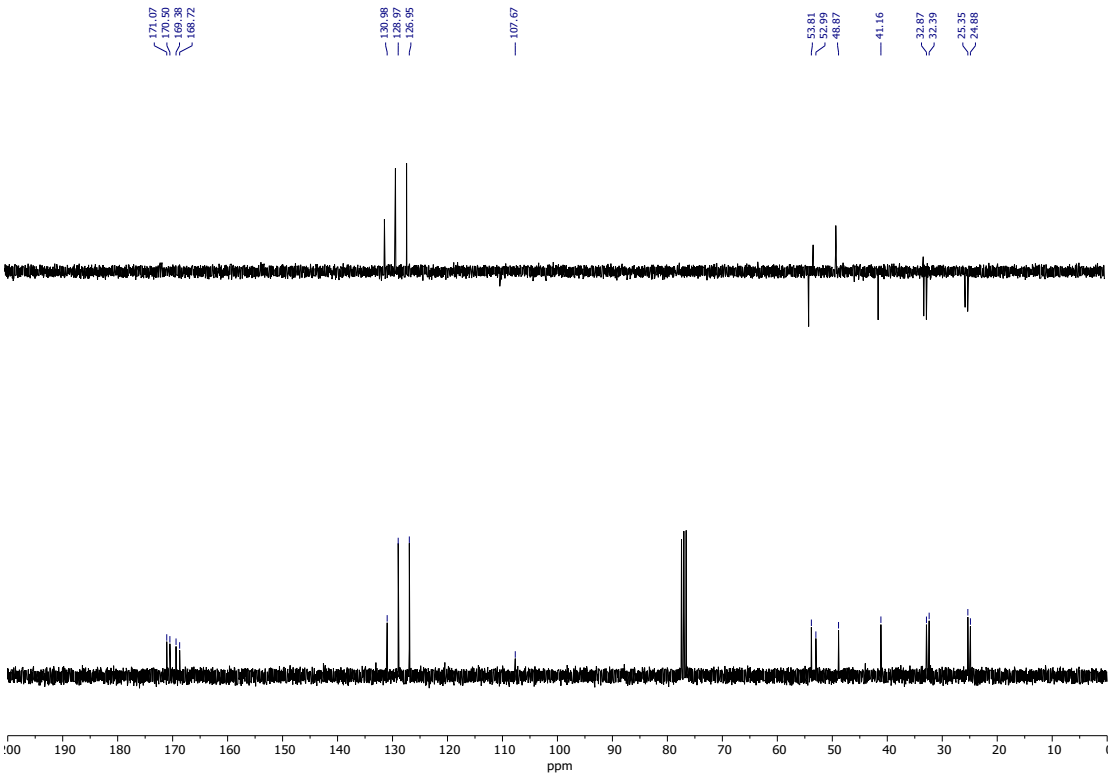


Figure S35. ^{13}C and DEPT-135 NMR spectra of **5l** (75 MHz, $CDCl_3$).

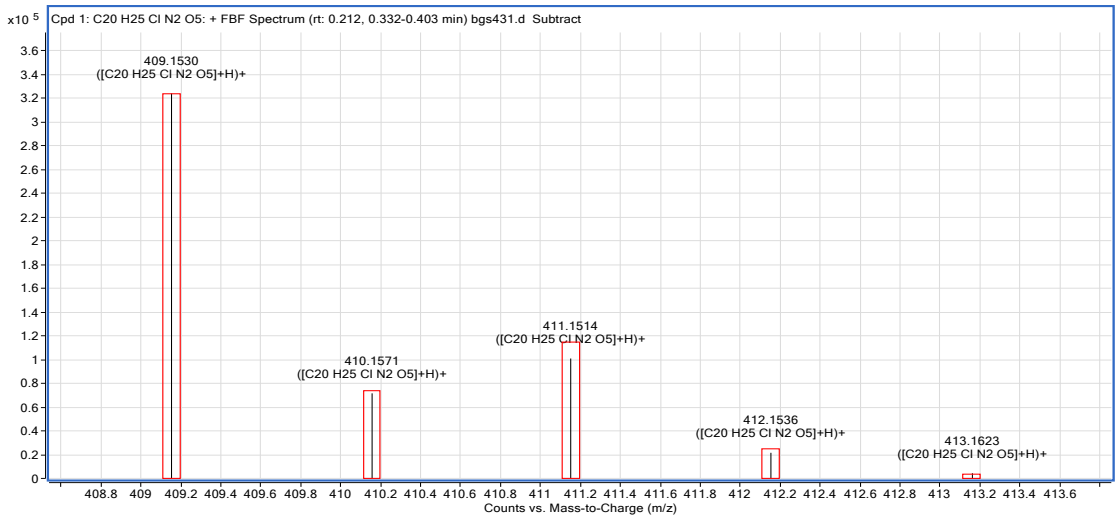


Figure S36. HRMS (+ESI) spectrum of **5l**.

Methyl (*S*,*E*)-2-(2-chloro-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)-2-phenylacetate (5m)

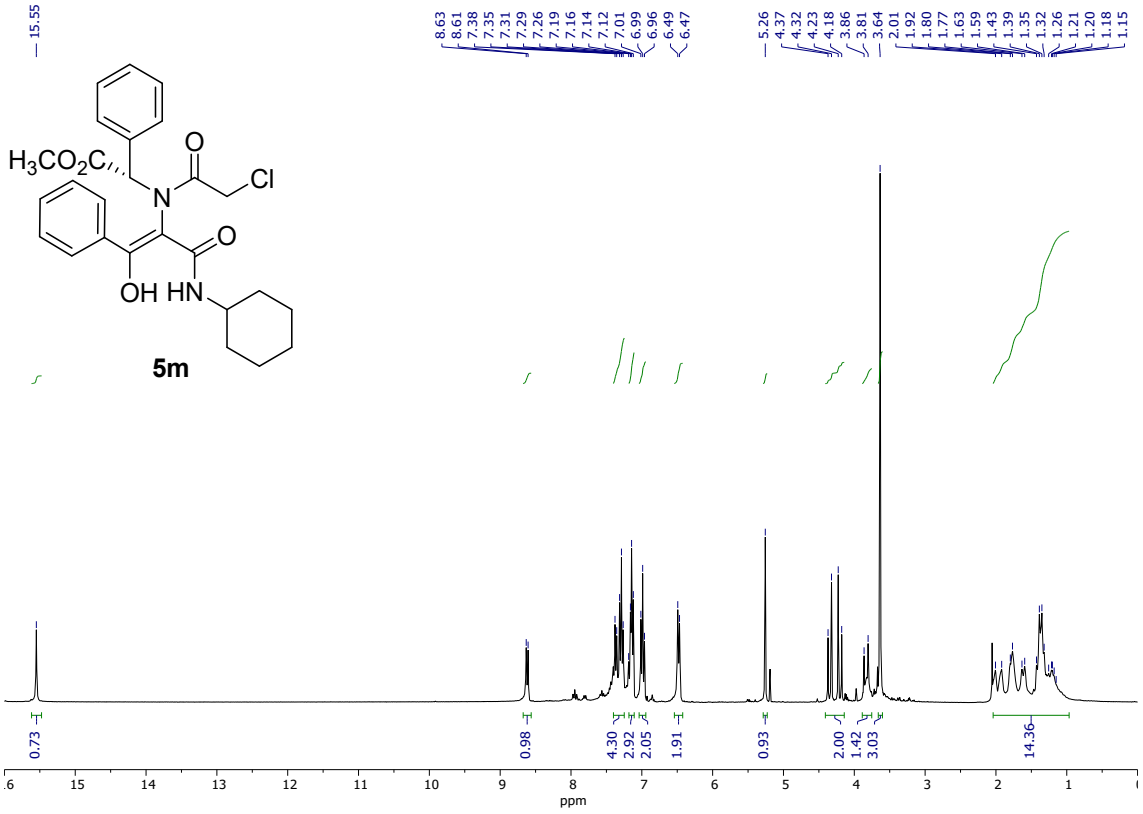


Figure S37. ^{1}H NMR spectrum of **5m** (300 MHz, $CDCl_3$).

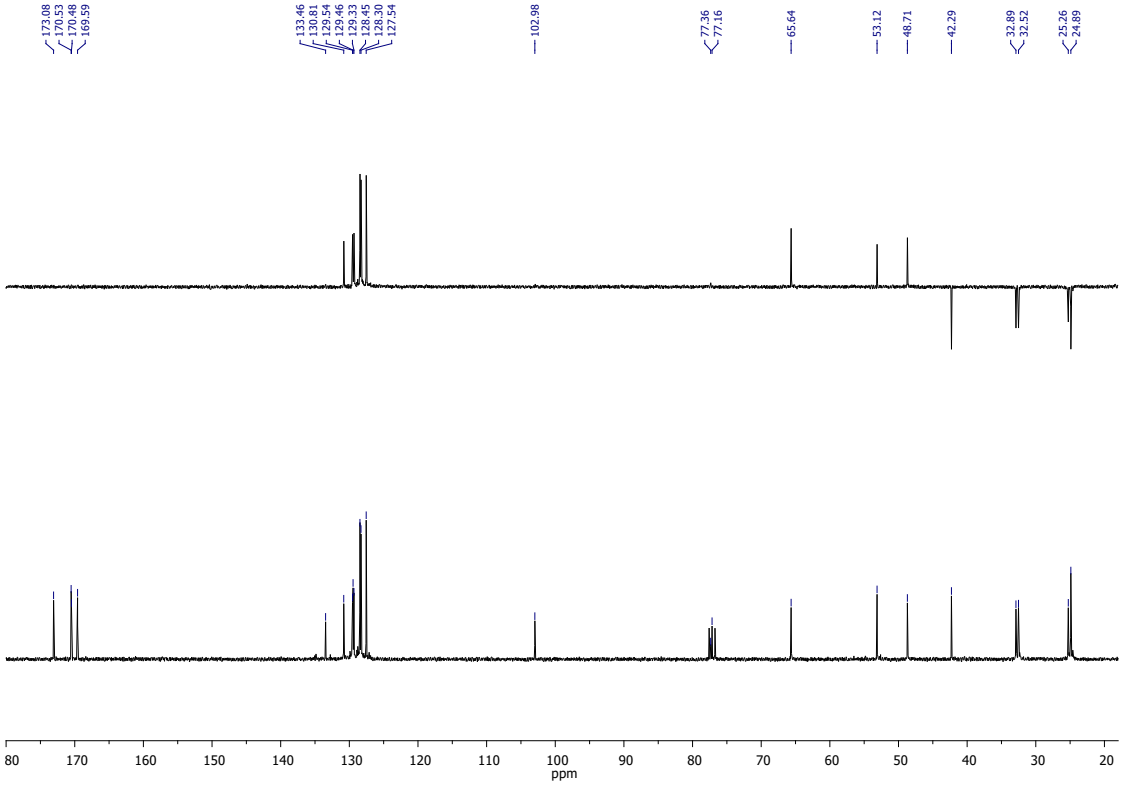


Figure S38. ^{13}C and DEPT-135 NMR spectra of **5m** (75 MHz, $CDCl_3$).

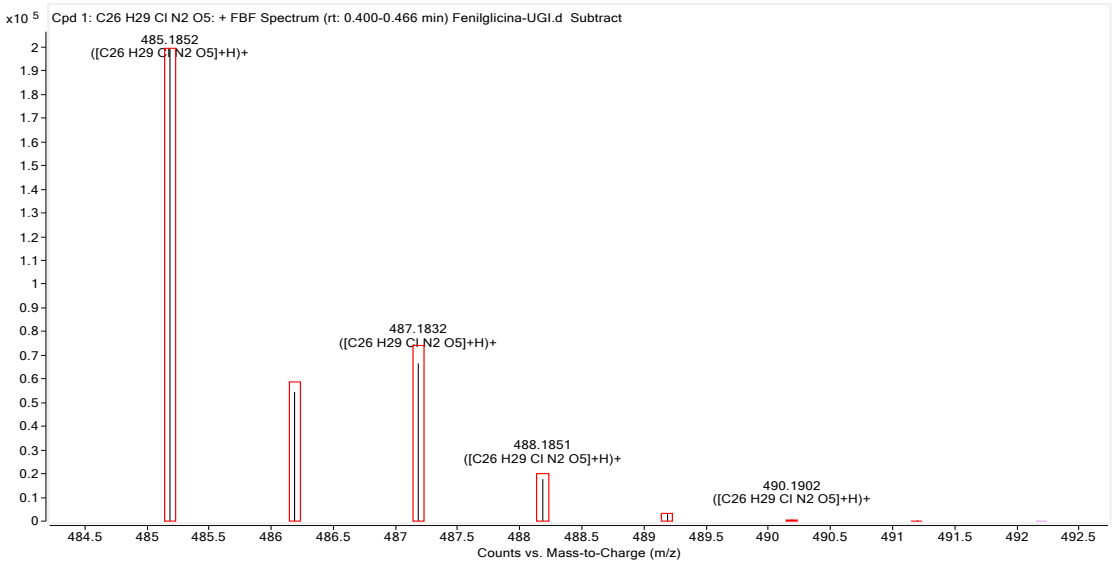


Figure S39. HRMS (+ESI) spectrum of **5m**.

Methyl (*S*,*E*)-2-(2-chloro-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)propanoate (5n)

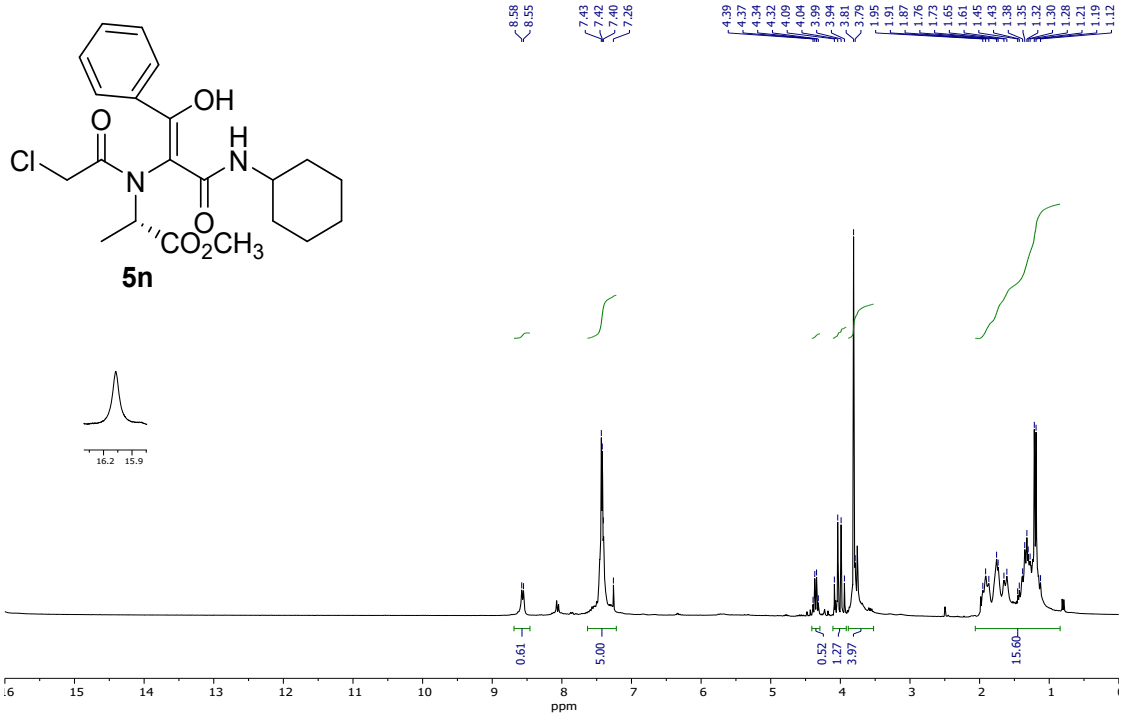


Figure S40. ^{1}H NMR spectrum of **5n** (300 MHz, $CDCl_3$).

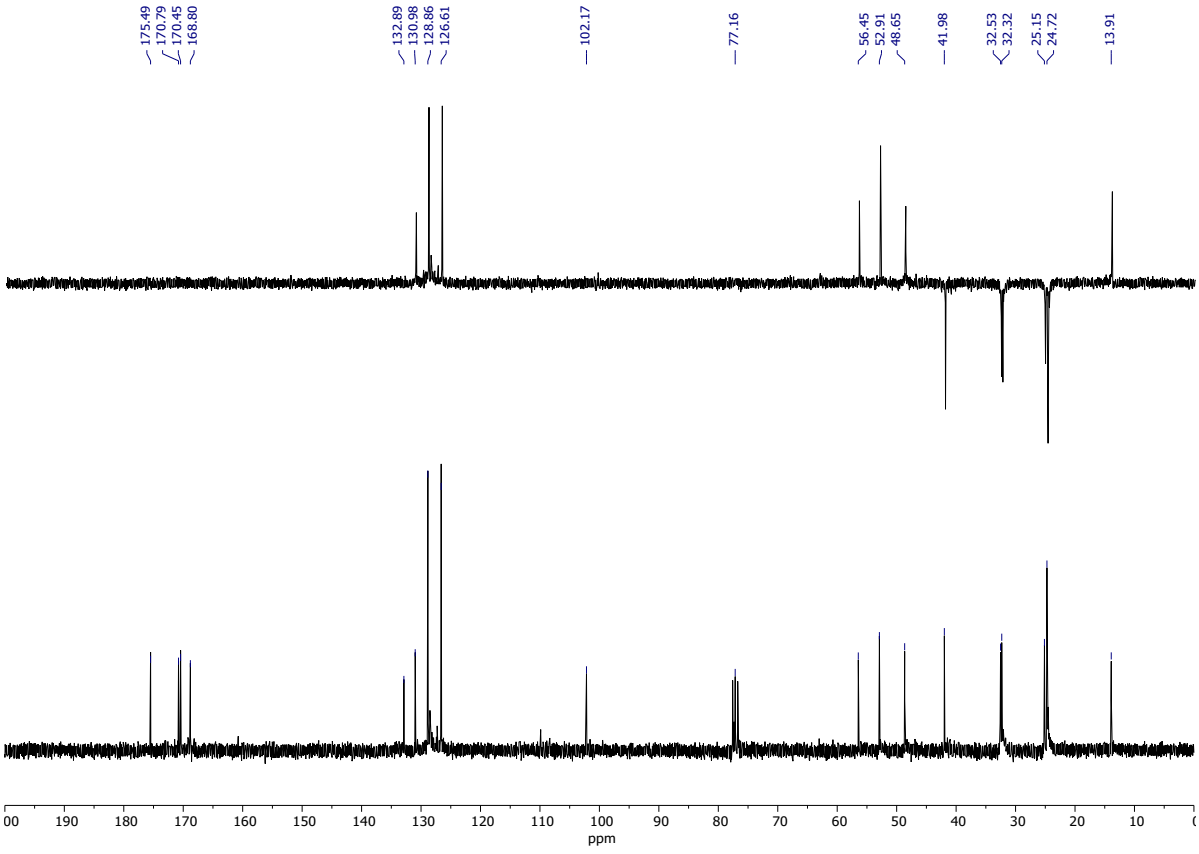


Figure S41. ^{13}C and DEPT-135 NMR spectra of **5n** (75 MHz, $CDCl_3$).

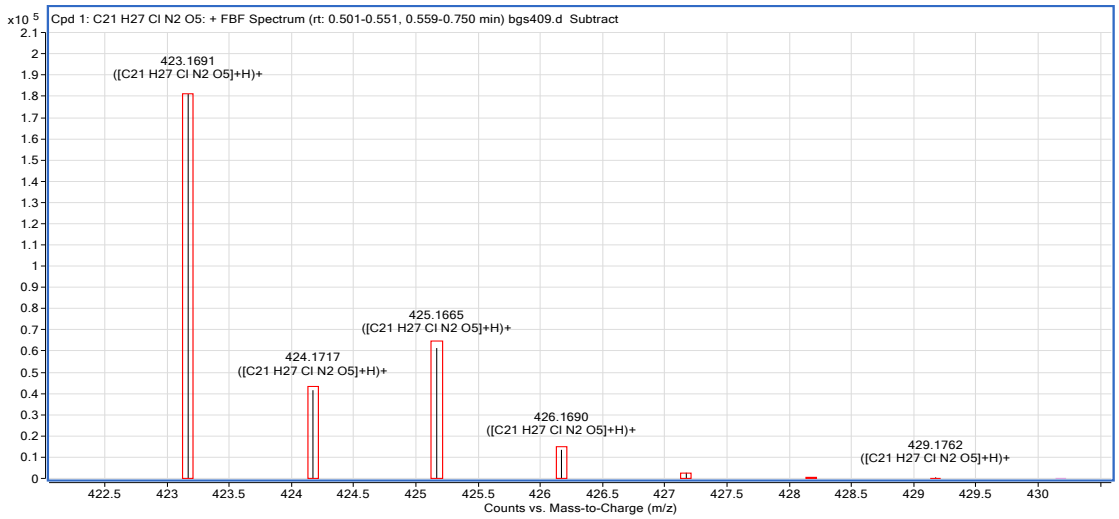


Figure S42. HRMS (+ESI) spectrum of **5n**.

Methyl (*S*,*E*)-2-(2-chloro-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)-3-phenylpropanoate (5o)

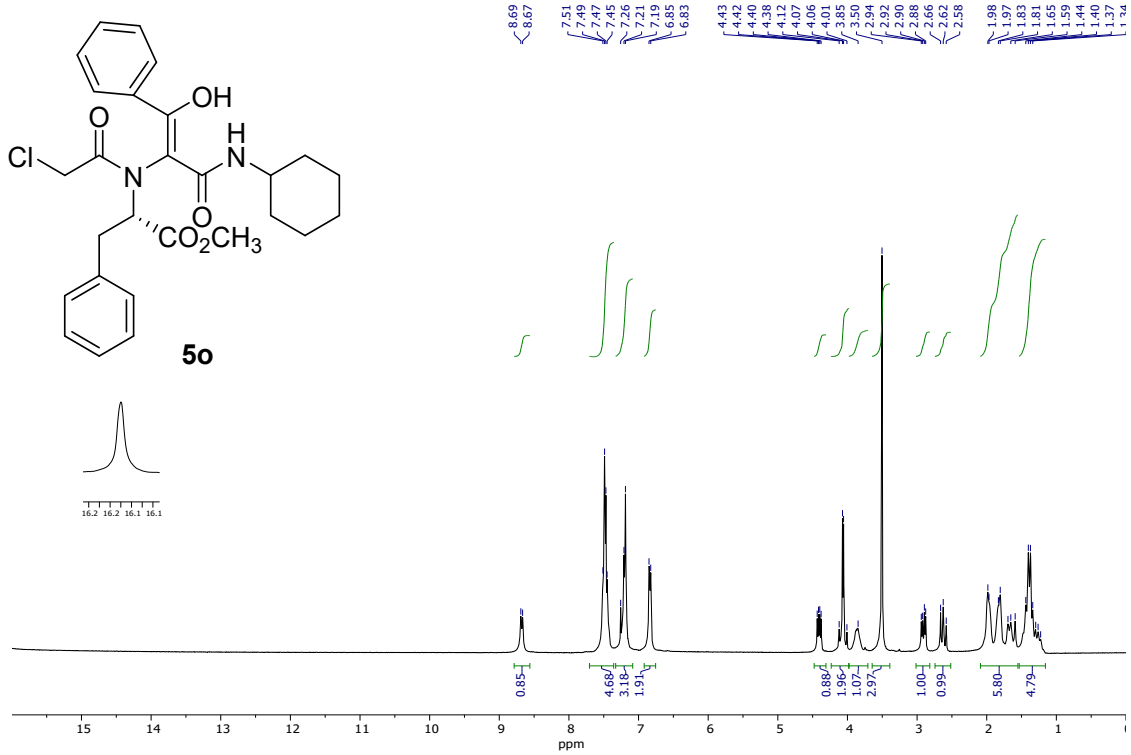


Figure S43. ^{1}H NMR spectrum of **5o** (300 MHz, $CDCl_3$).

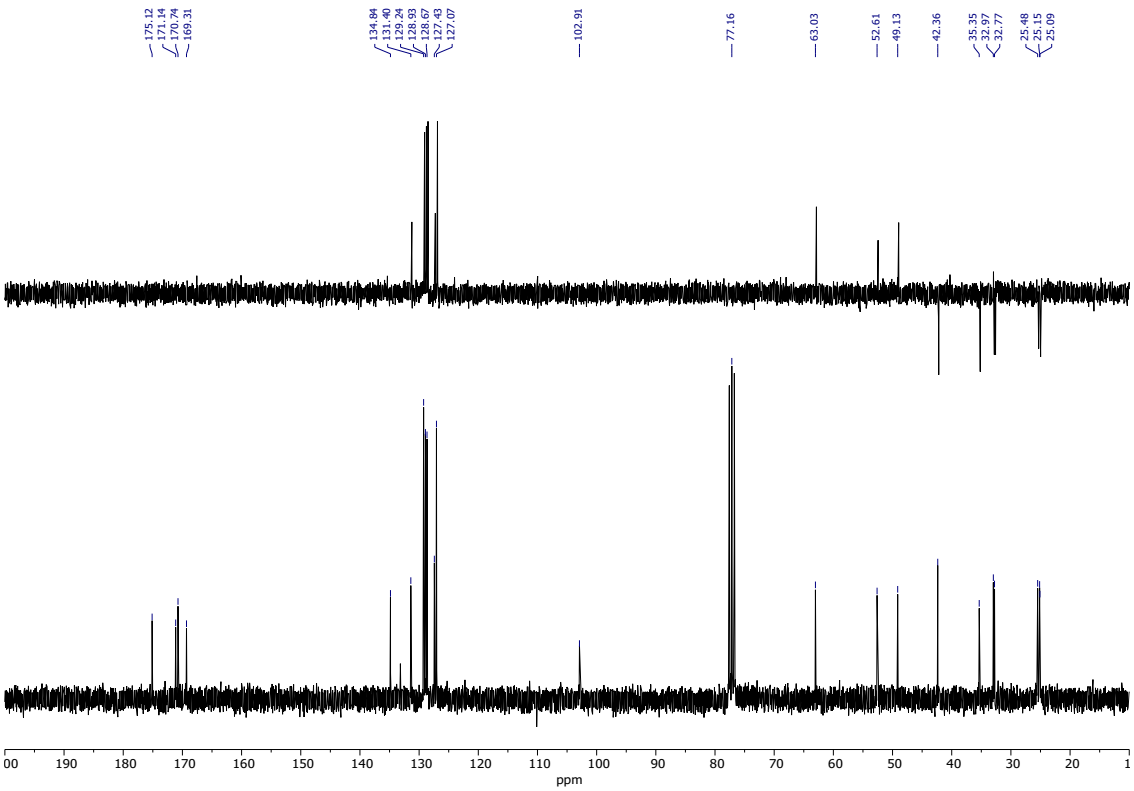


Figure S44. ^{13}C and DEPT-135 NMR spectra of **5o** (75 MHz, $CDCl_3$).

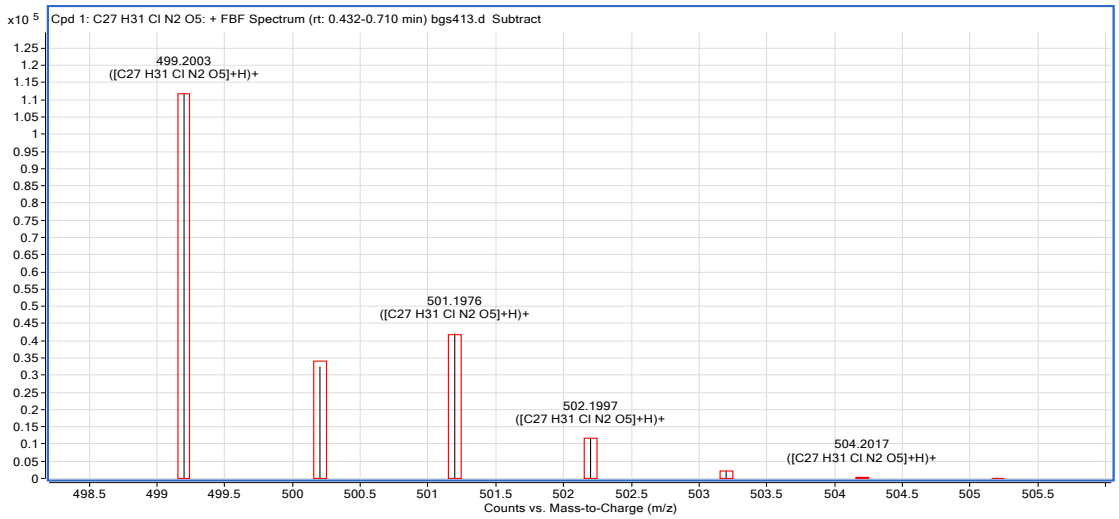


Figure S45. HRMS (+ESI) spectrum of **5o**.

Methyl (S,*E*)-2-(2-chloroacetyl)-*N*-(3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)acetamido)-3-methylbutanoate (5p)

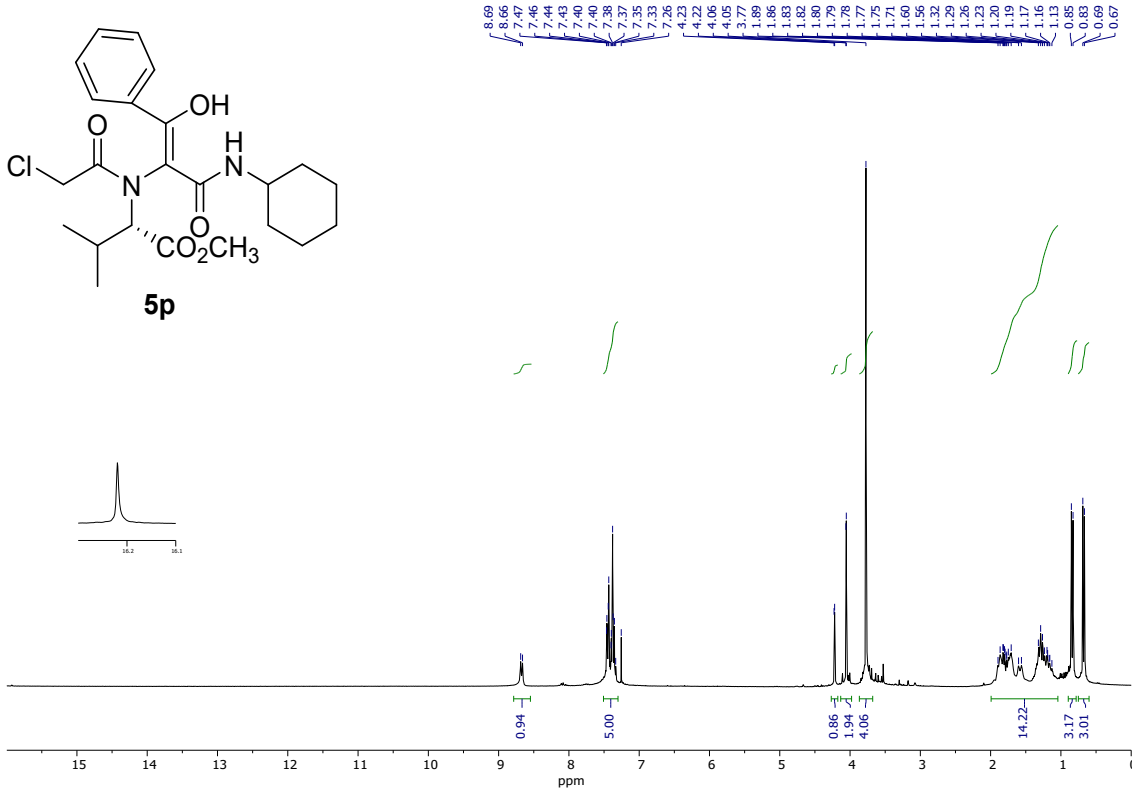


Figure S46. ^{1}H NMR spectrum of **5p** (300 MHz, $CDCl_3$).

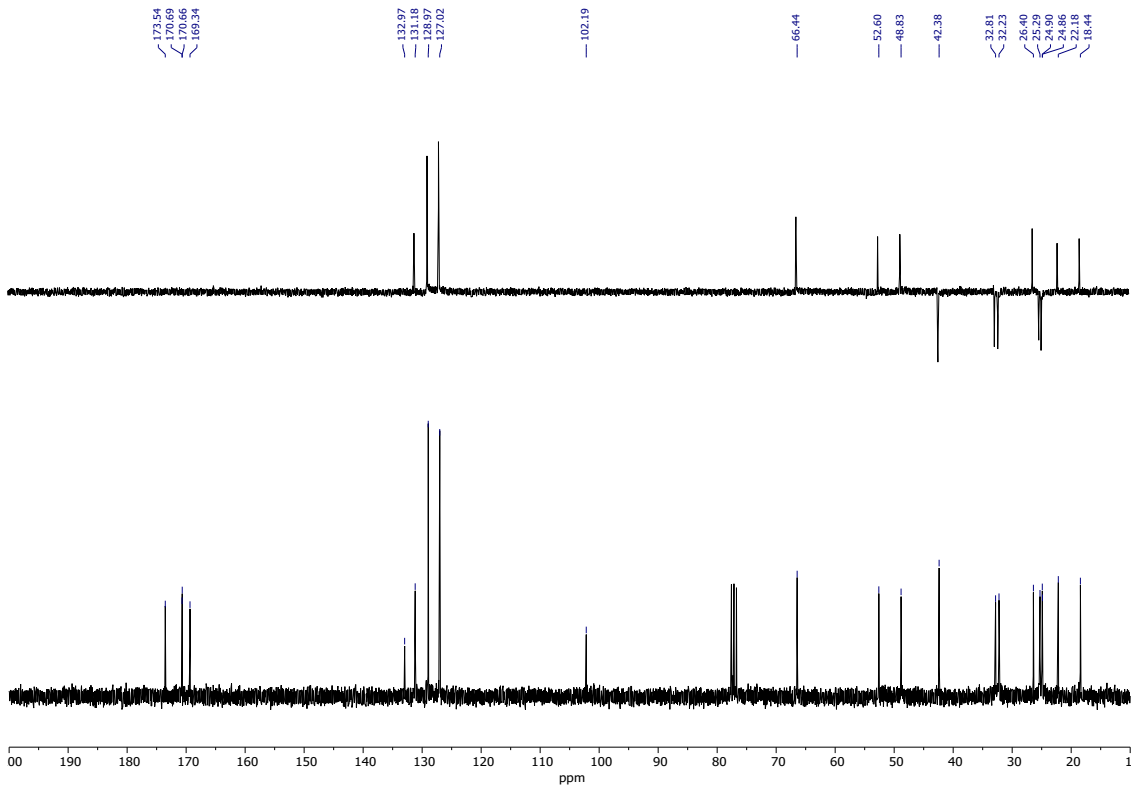


Figure S47. ^{13}C and DEPT-135 NMR spectra of **5p** (75 MHz, $CDCl_3$).

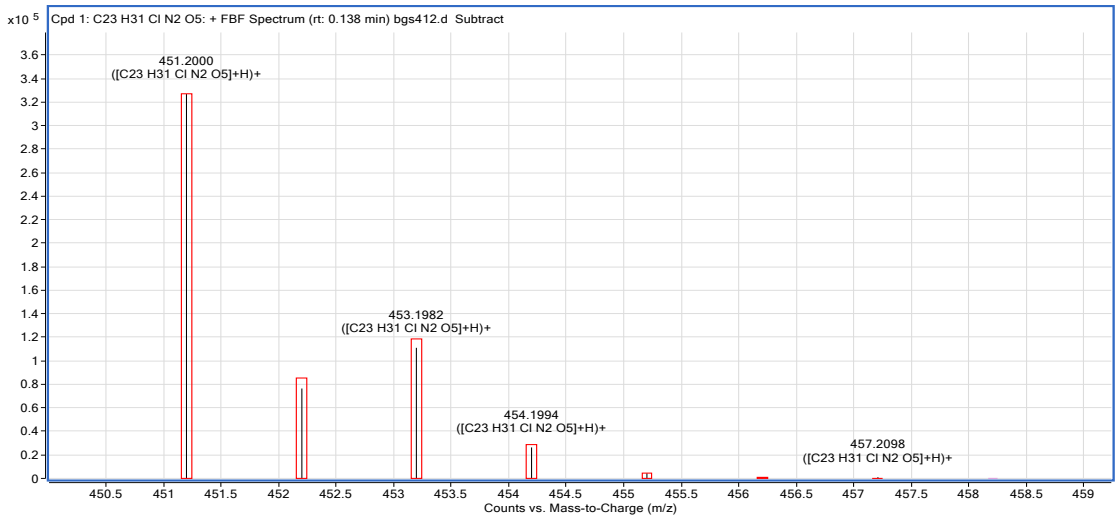


Figure S48. HRMS (+ESI) spectrum of **5p**.

Methyl 2-(2-chloro-*N*-((*E*)-3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2-phenylacetamido)acetate (5q)

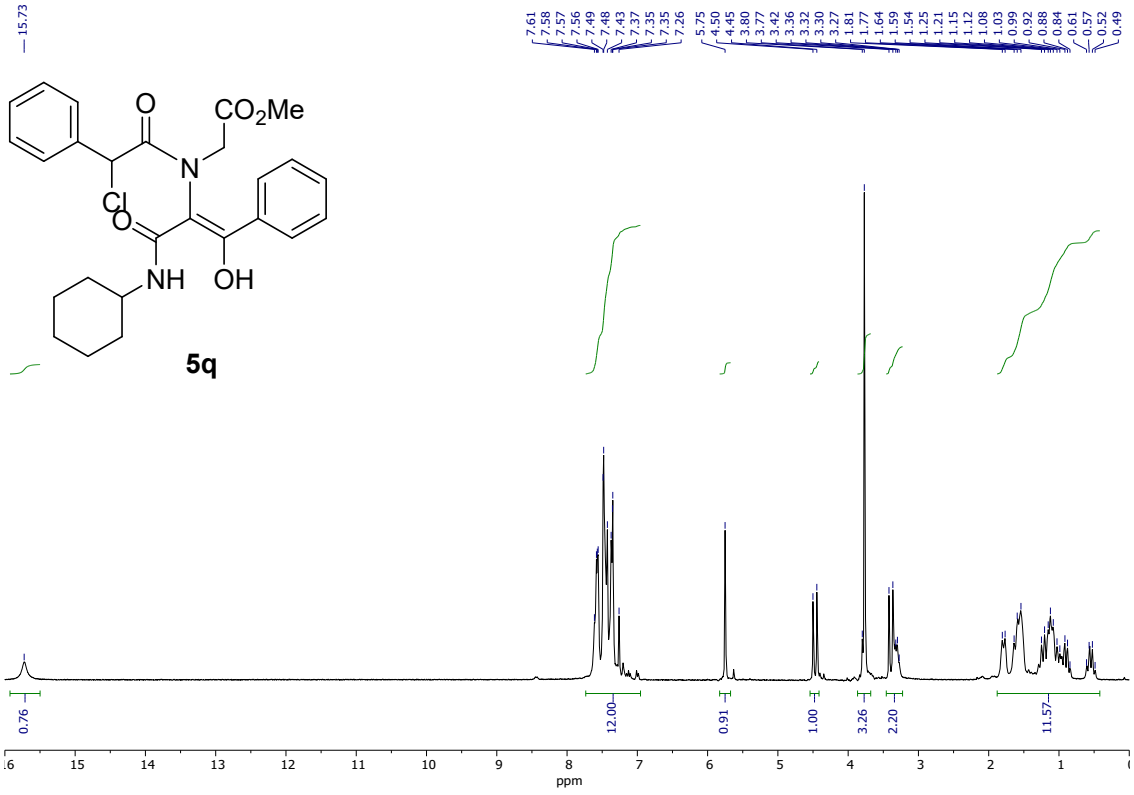


Figure S49. ^{1}H NMR spectrum of **5q** (300 MHz, $CDCl_3$).

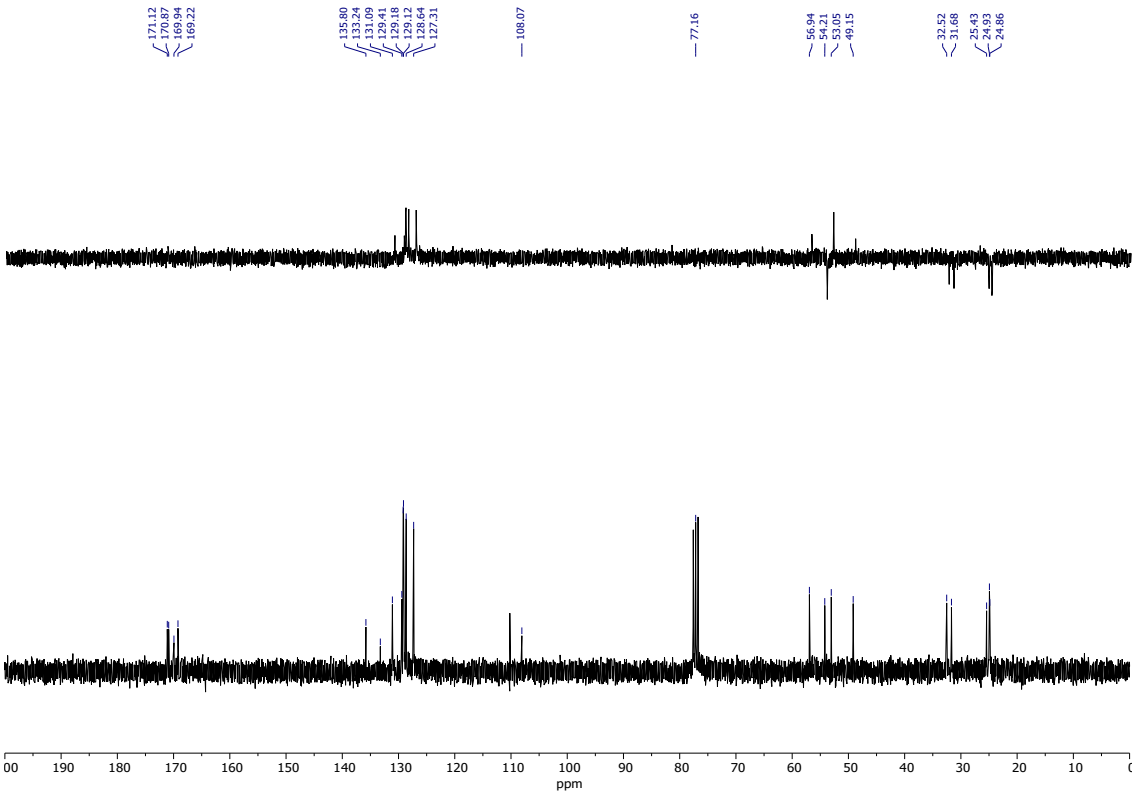


Figure S50. ^{13}C and DEPT-135 NMR spectra of **5q** (75 MHz, $CDCl_3$).

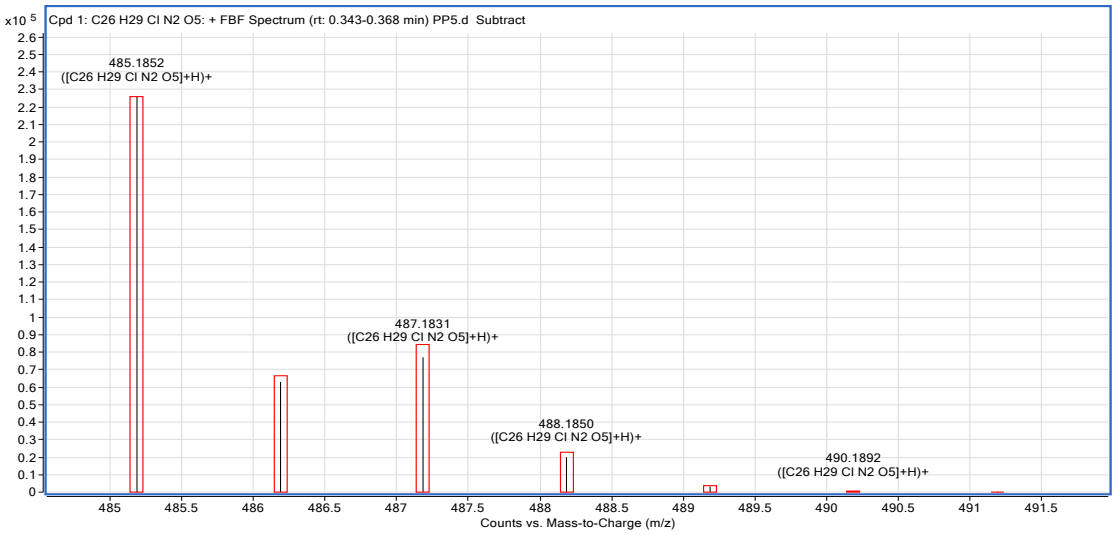


Figure S51. HRMS (+ESI) spectrum of **5q**.

Methyl (2*S*)-2-(2-chloro-*N*-((*E*)-3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2-phenylacetamido)-2-phenylacetate (5r)

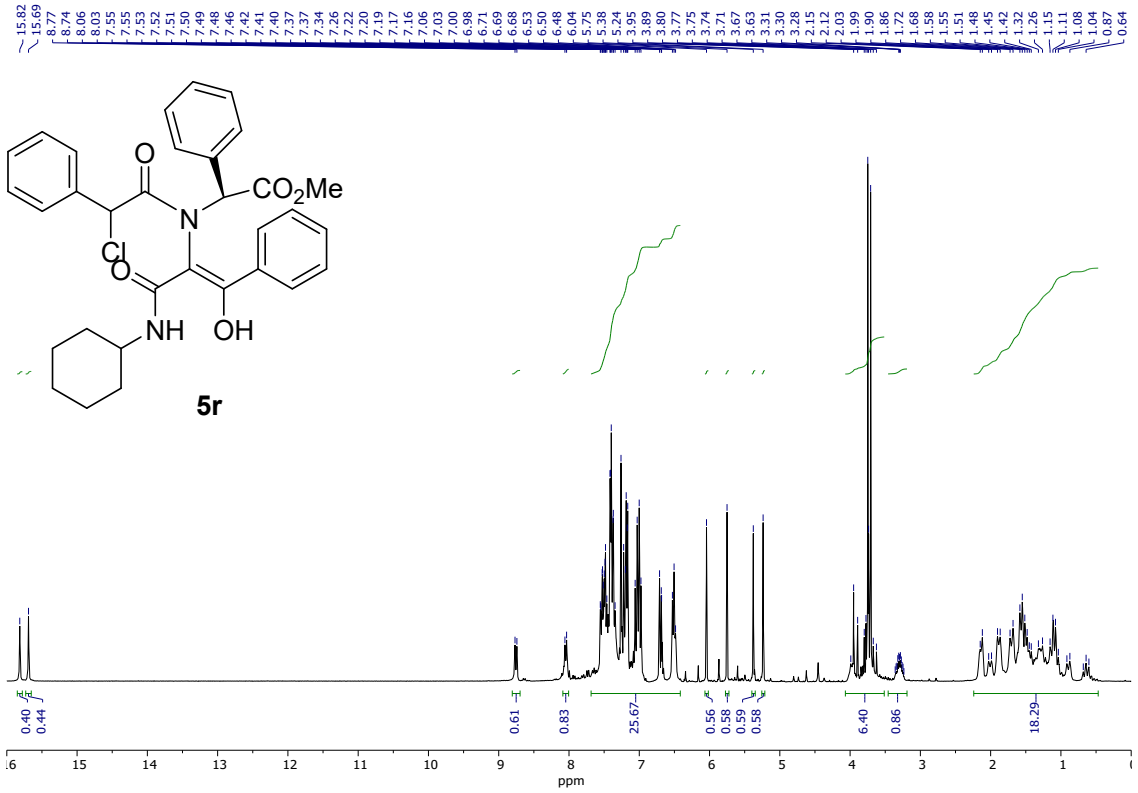


Figure S52. ^{1}H NMR spectrum of **5r** (300 MHz, $CDCl_3$).

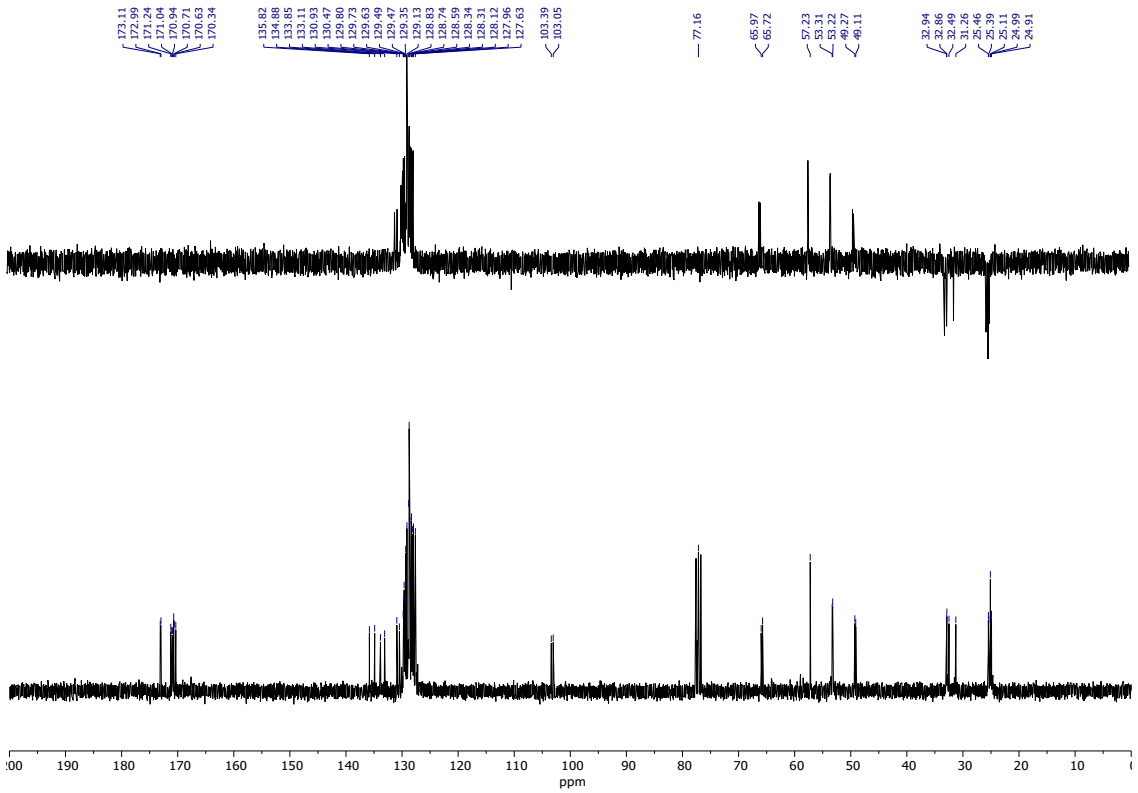


Figure S53. ^{13}C and DEPT-135 NMR spectra of **5r** (75 MHz, $CDCl_3$).

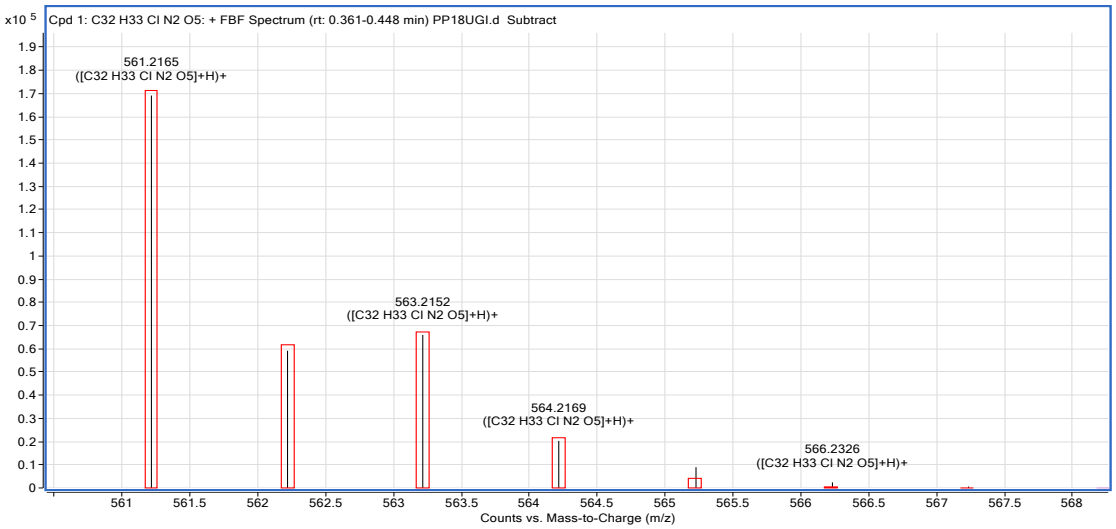


Figure S54. HRMS (+ESI) spectrum of **5r**.

Methyl (2*S*)-2-(2-chloro-*N*-((*E*)-3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2-phenylacetamido)propanoate (5s)

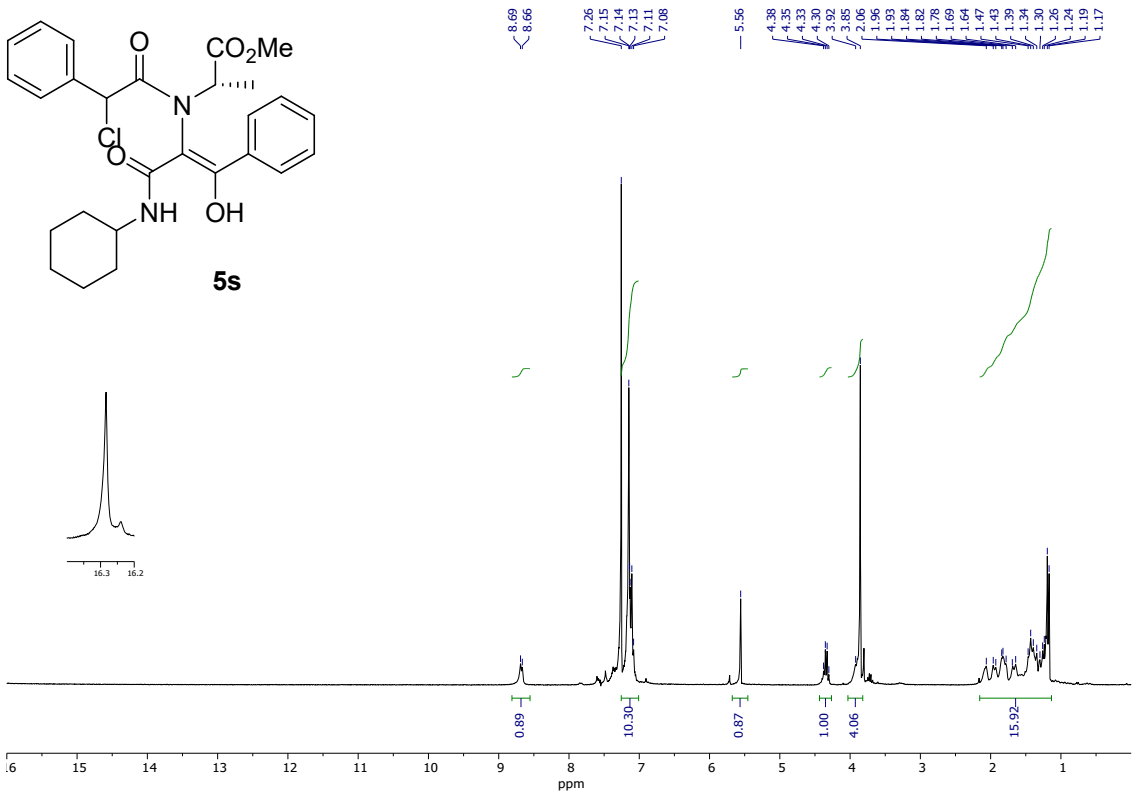


Figure S55. ^{1}H NMR spectrum of **5s** (300 MHz, $CDCl_3$).

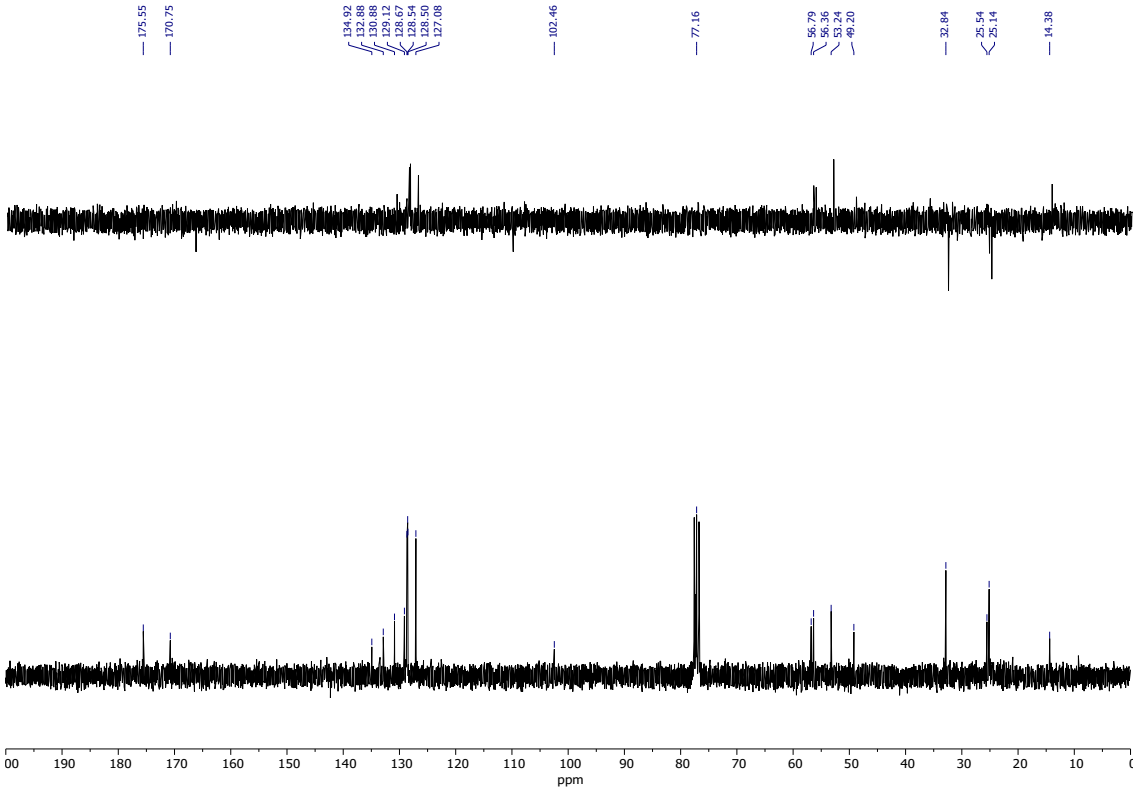


Figure S56. ^{13}C and DEPT-135 NMR spectra of **5s** (75 MHz, $CDCl_3$).

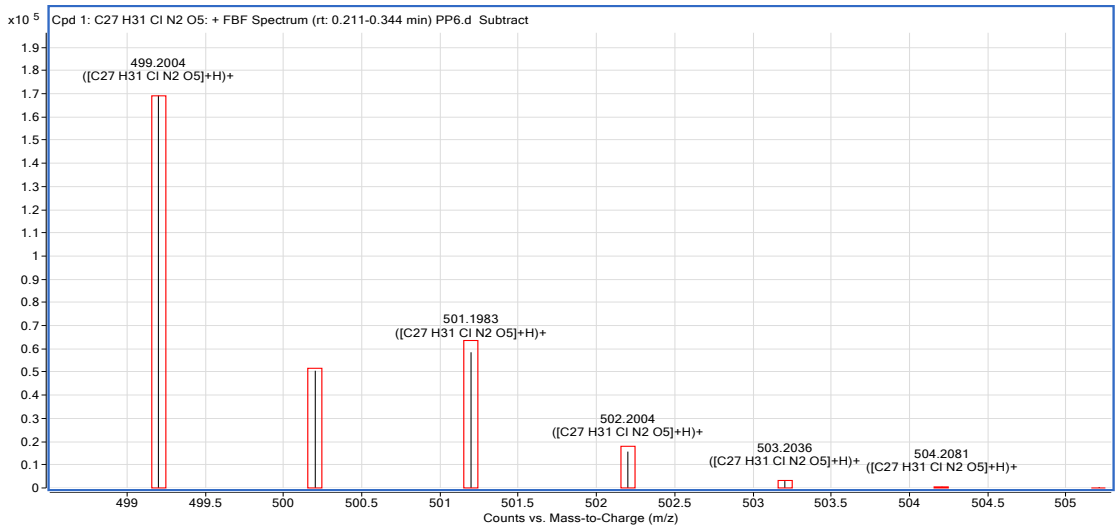


Figure S57. HRMS (+ESI) spectrum of **5s**.

Methyl (2*S*)-2-(2-chloro-*N*-((*E*)-3-(cyclohexylamino)-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2-phenylacetamido)-3-phenylpropanoate (5t)

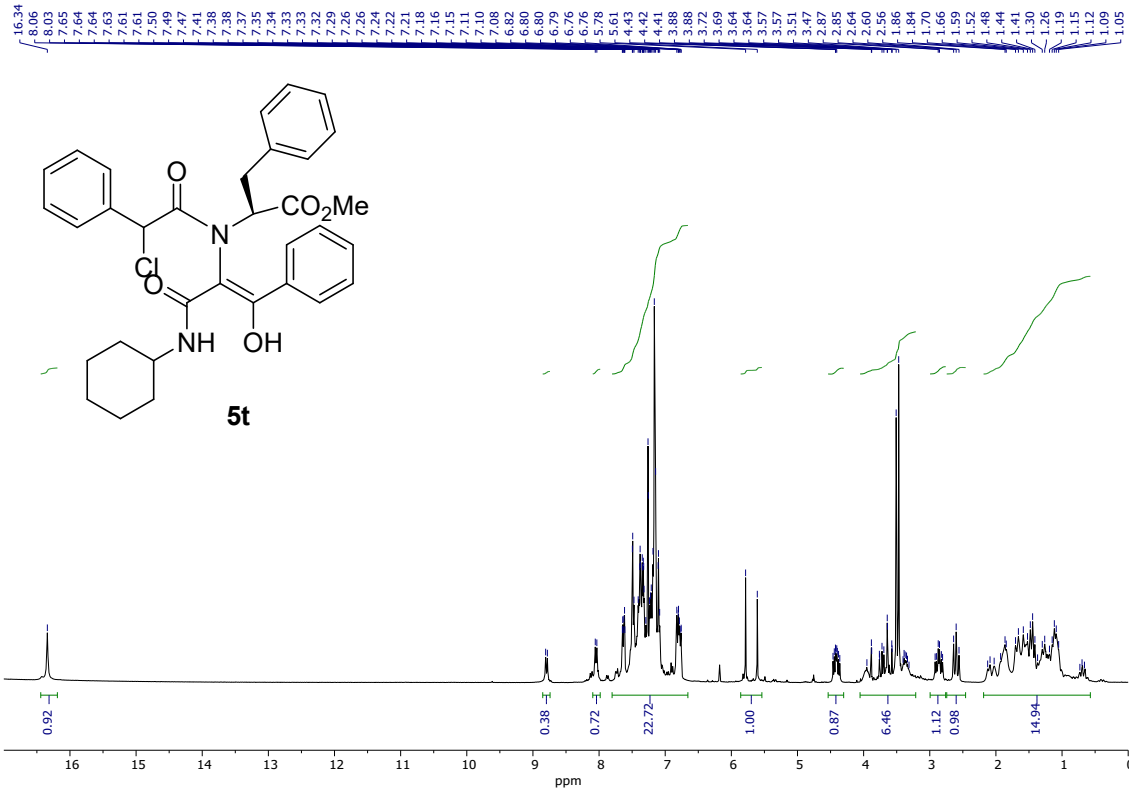


Figure S58. ^{1}H NMR spectrum of **5t** (300 MHz, $CDCl_3$).

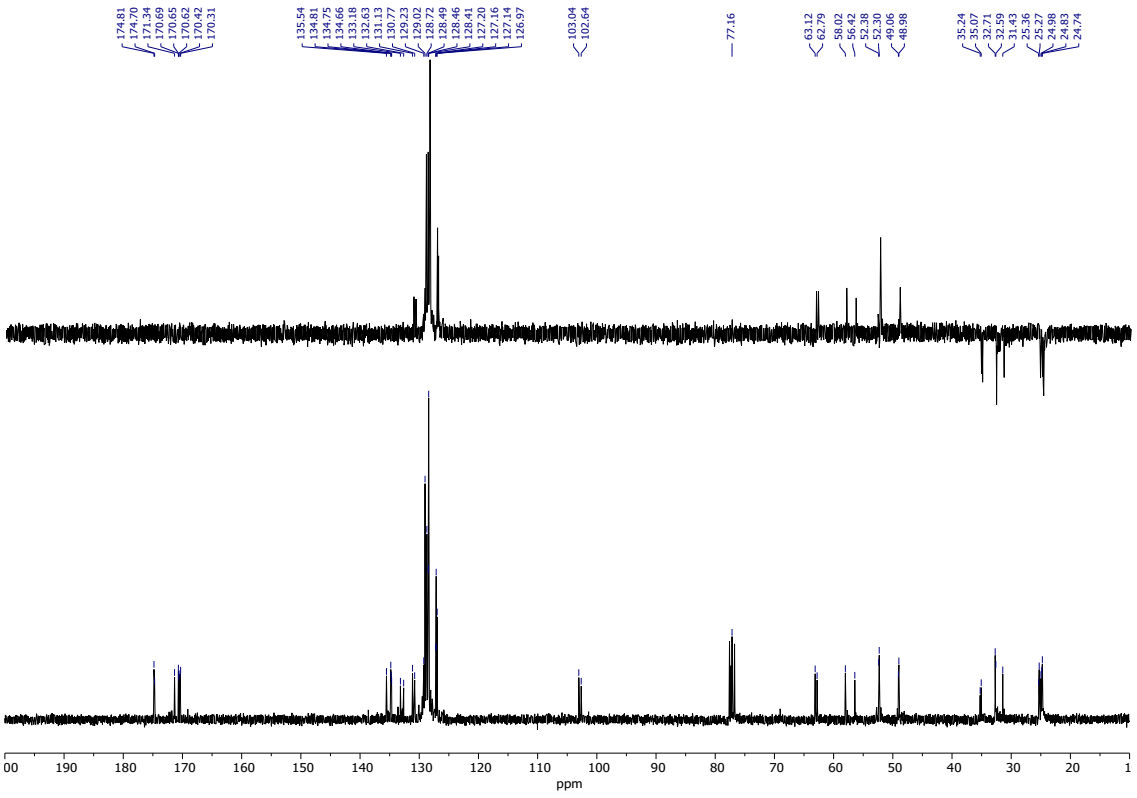


Figure S59. ^{13}C and DEPT-135 NMR spectra of **5t** (75 MHz, $CDCl_3$).

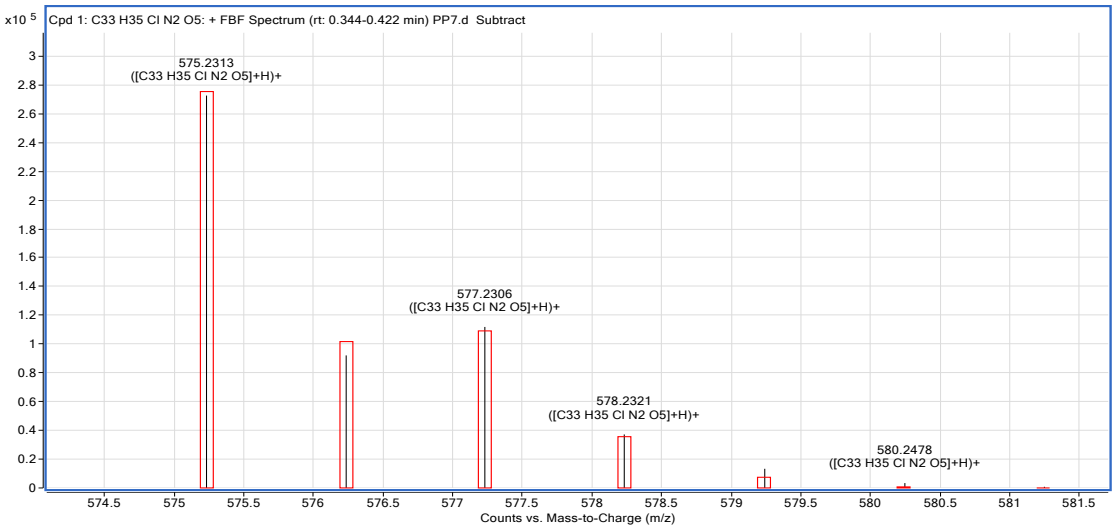


Figure S60. HRMS (+ESI) spectrum of **5t**.

4-Benzoyl-4-cyclohexylcarbamoyl-1-(2-nitrobenzyl)azetidin-2-one (6a)

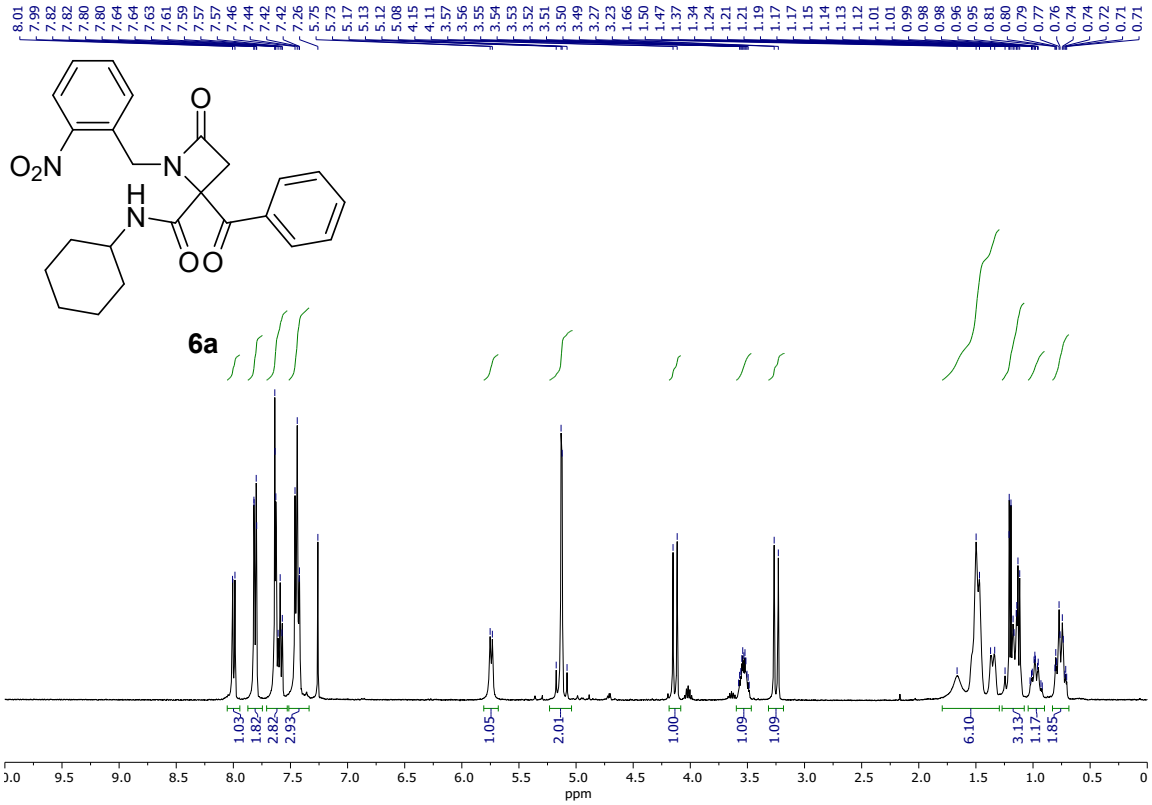


Figure S61. ^{1}H NMR spectrum of **6a** (300 MHz, $CDCl_3$).

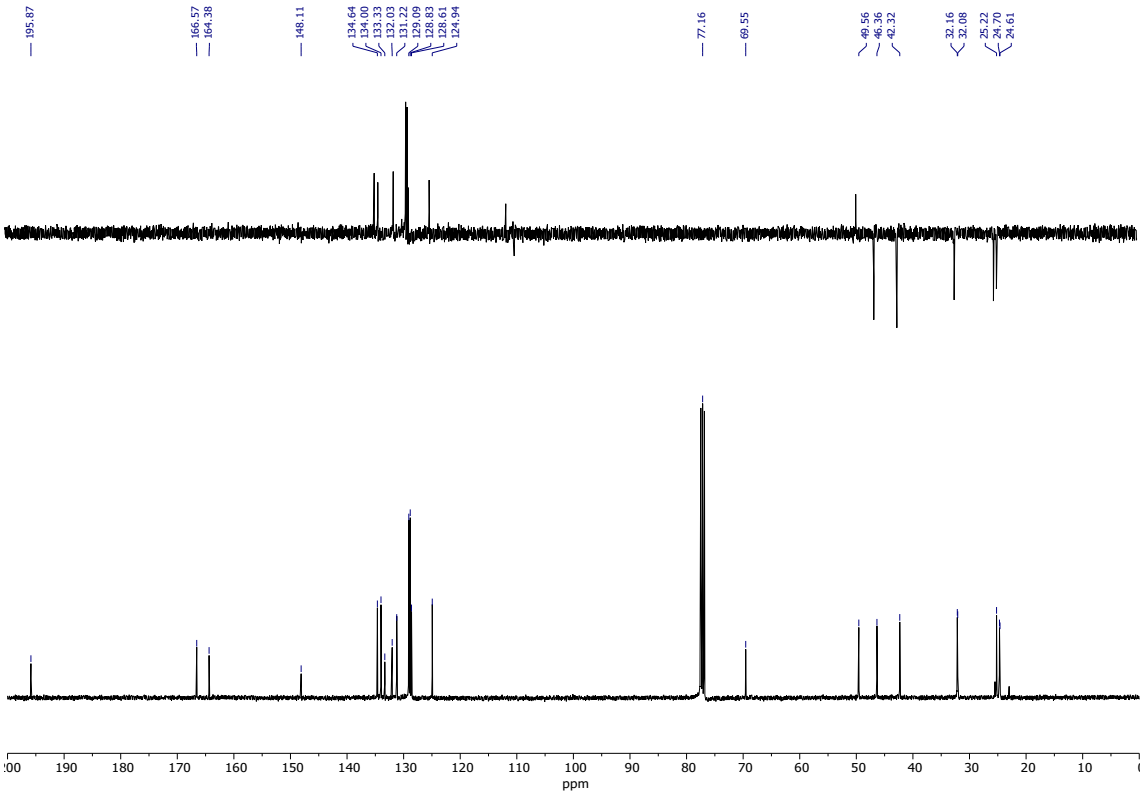


Figure S62. ^{13}C and DEPT-135 NMR spectra of **6a** (75 MHz, $CDCl_3$).

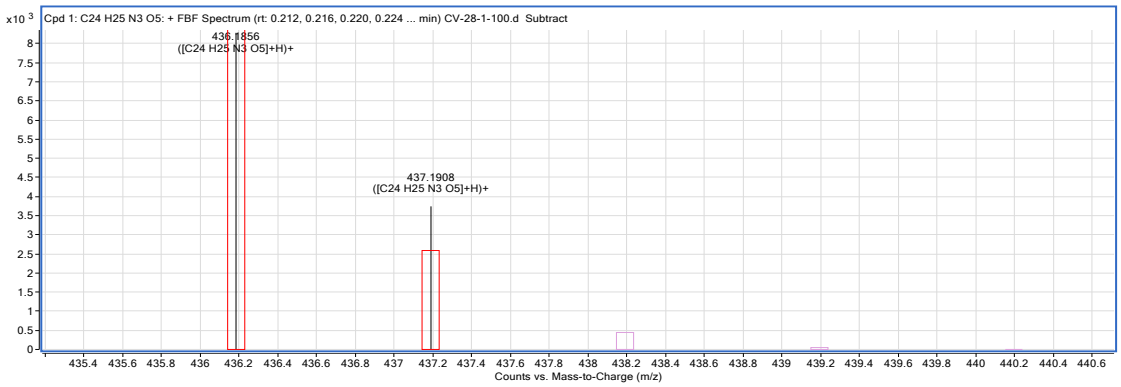


Figure S63. HRMS (+ESI) spectrum of **6a**.

4-Benzoyl-4-benzylcarbamoyl-1-(2-nitrobenzyl)azetidin-2-one (6b)

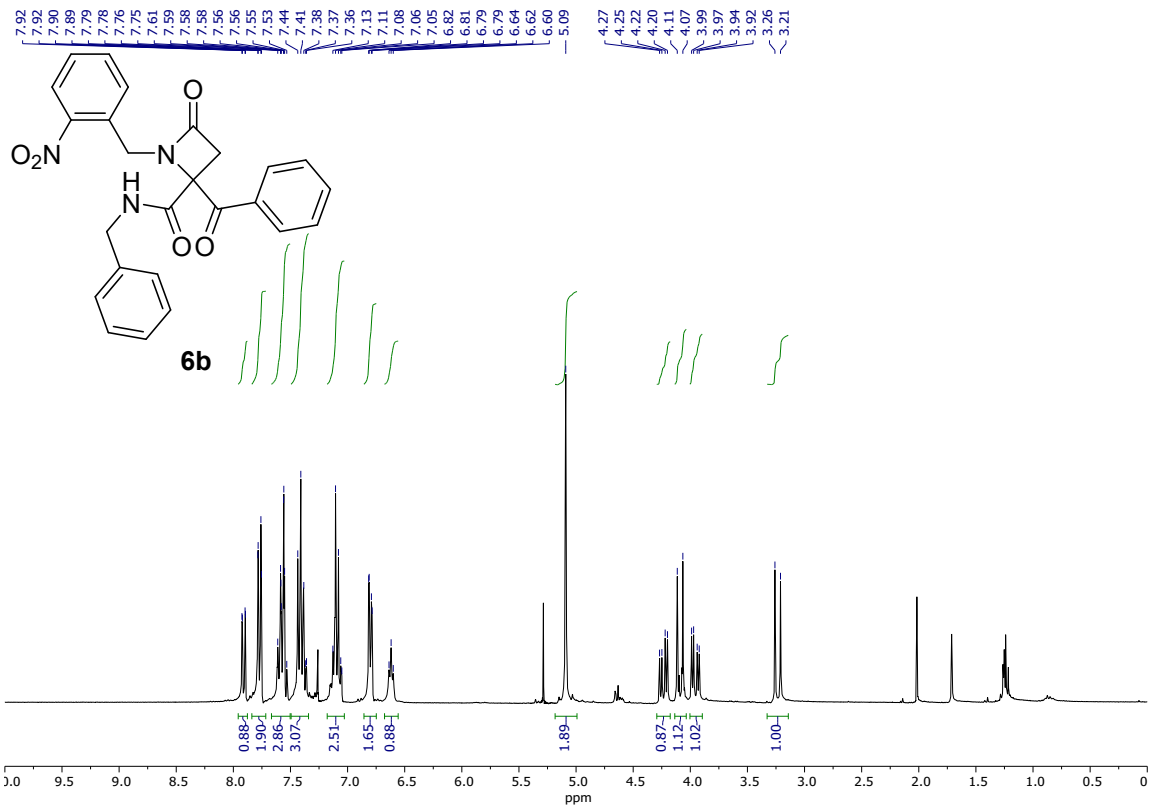


Figure S64. ^{1}H NMR spectrum of **6b** (300 MHz, $CDCl_3$).

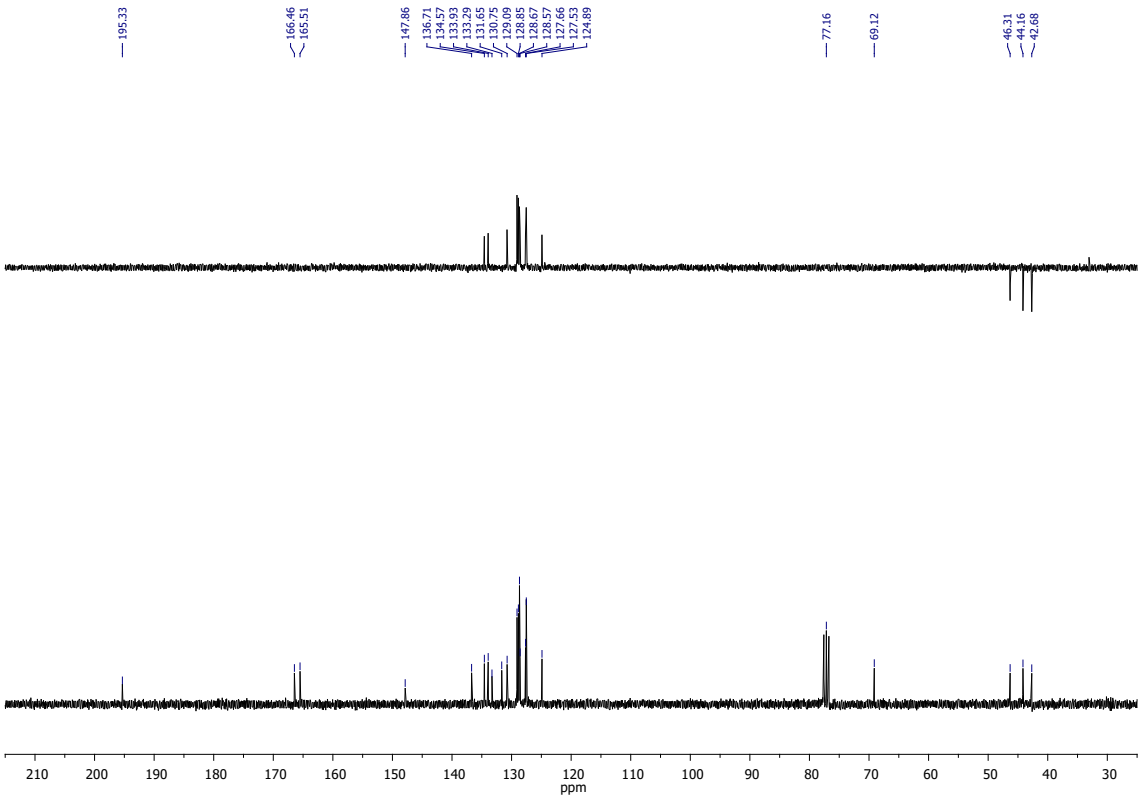


Figure S65. ^{13}C and DEPT-135 NMR spectra of **6b** (75 MHz, $CDCl_3$).

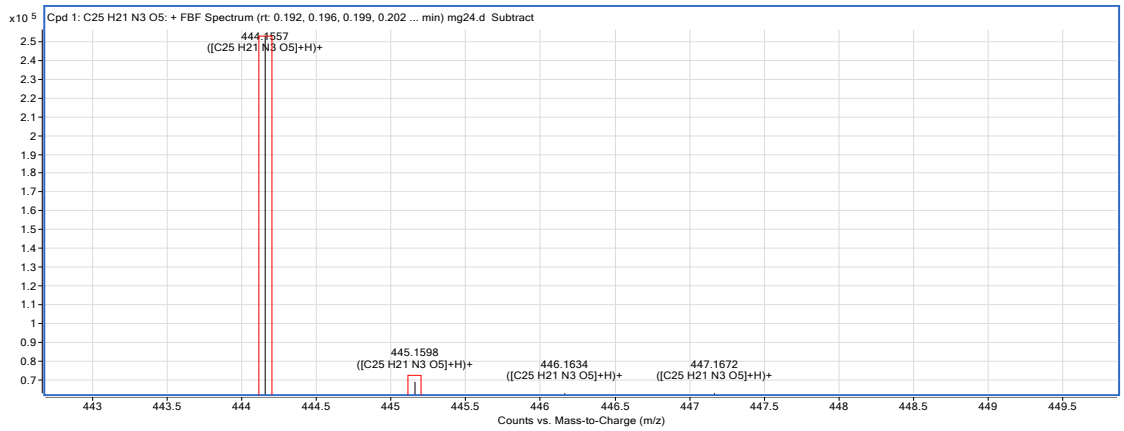


Figure S66. HRMS (+ESI) spectrum of **6b**.

4-Benzoyl-4-(*tert*-butylcarbamoyl)-1-(2-nitrobenzyl)azetidin-2-one (6c)

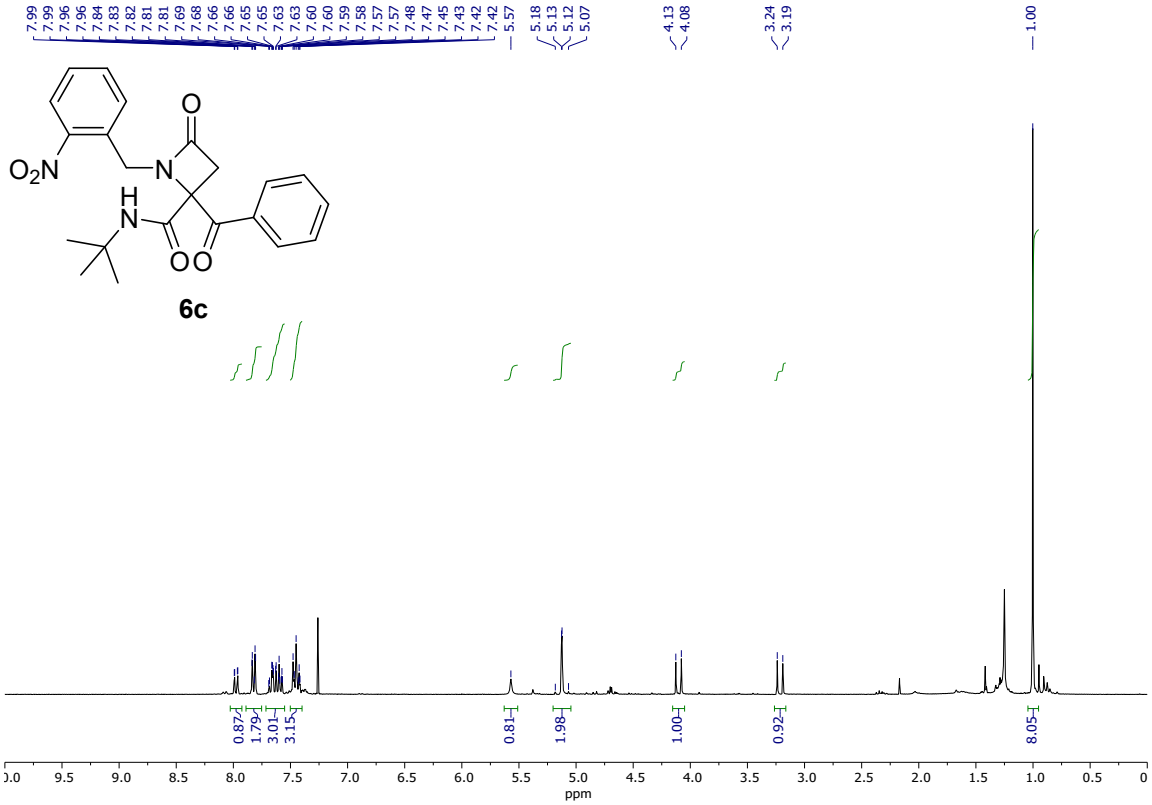


Figure S67. ^{1}H NMR spectrum of **6c** (300 MHz, $CDCl_3$).

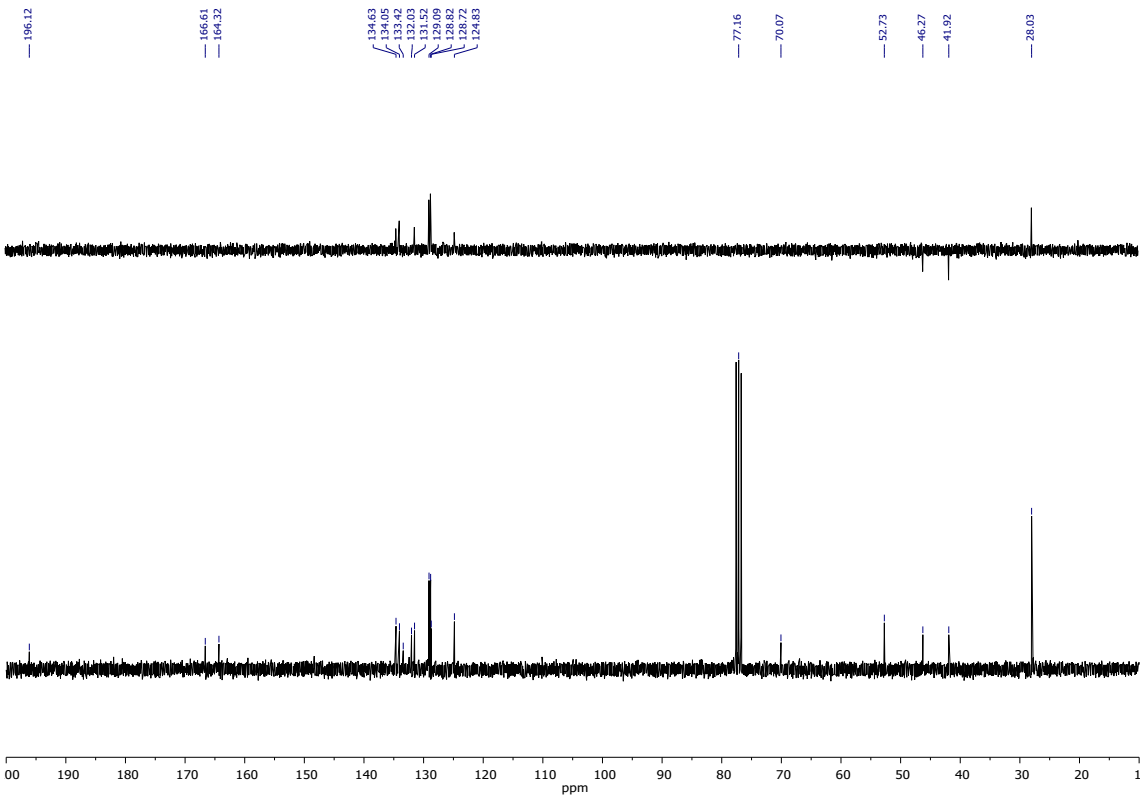


Figure S68. ^{13}C and DEPT-135 NMR spectra of **6c** (75 MHz, $CDCl_3$).

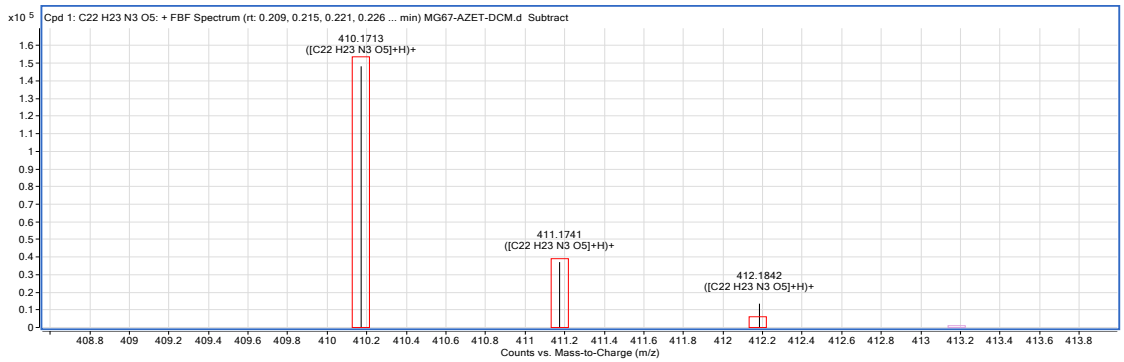


Figure S69. HRMS (+ESI) spectrum of **6c**.

4-Cyclohexylcarbamoyl-4-(4-methylbenzoyl)-1-(2-nitrobenzyl)azetidin-2-one (6d)

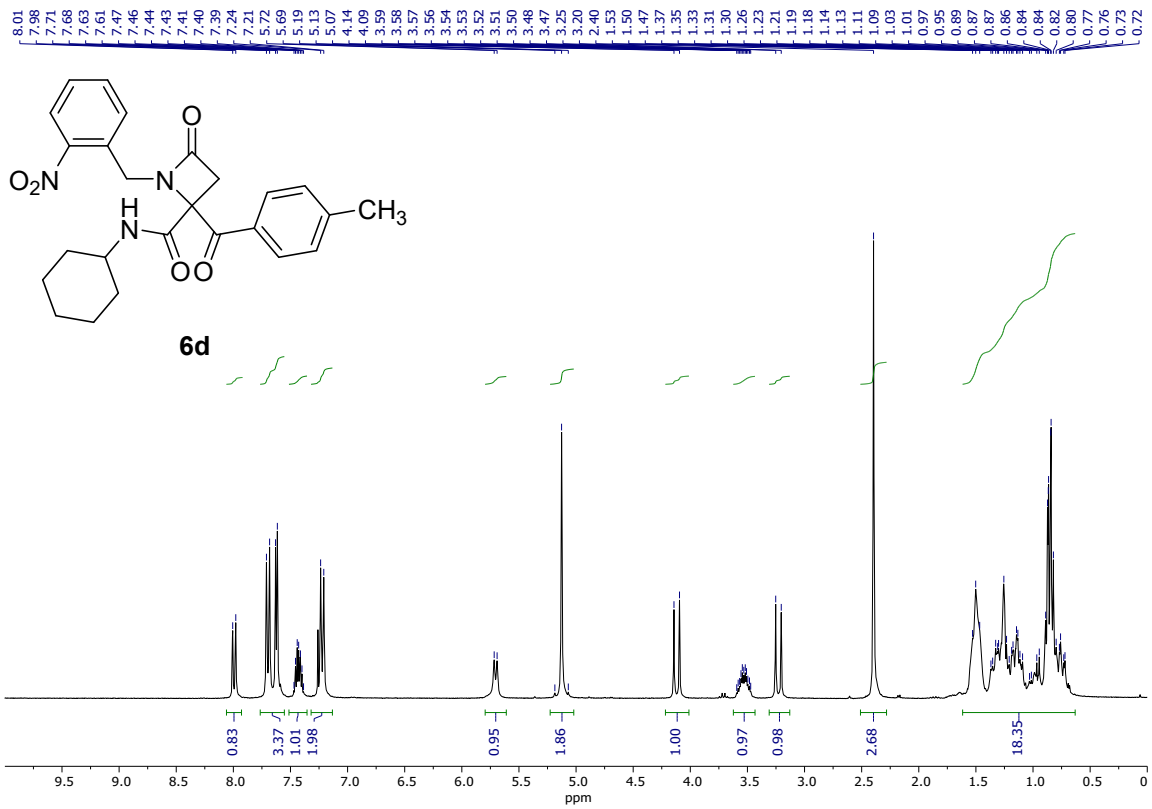


Figure S70. ^{1}H NMR spectrum of **6d** (300 MHz, $CDCl_3$).

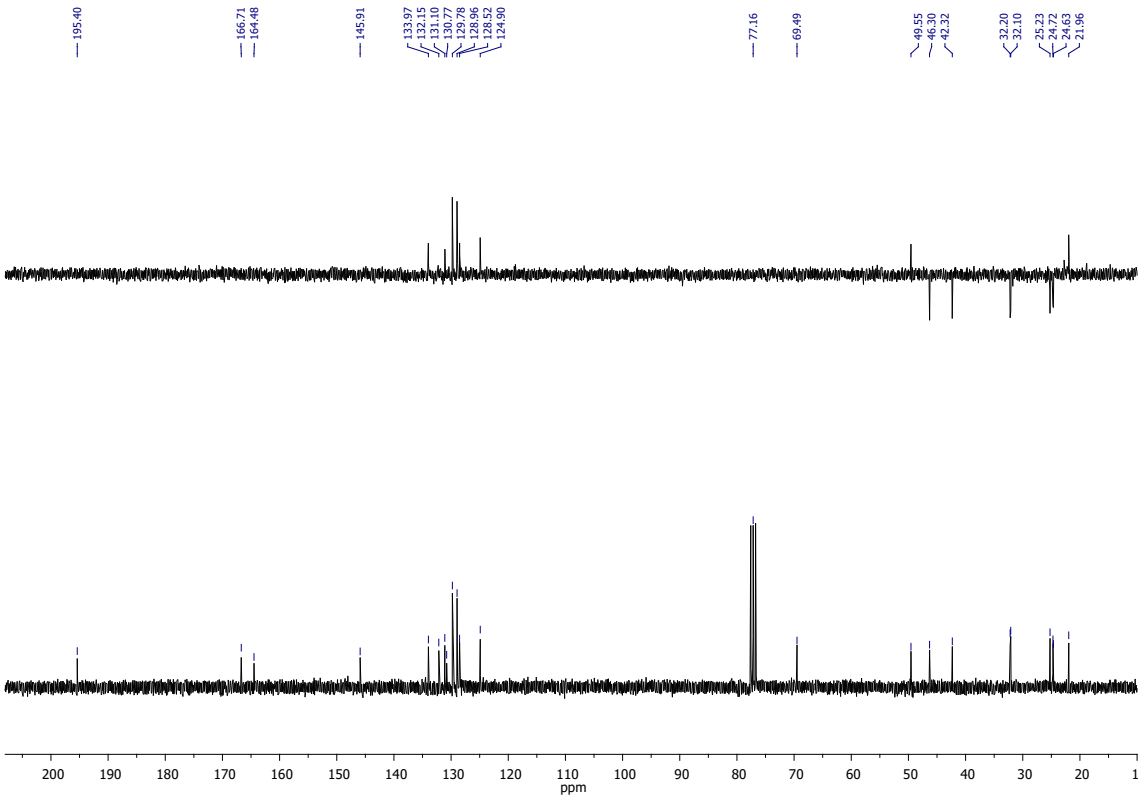


Figure S71. ^{13}C and DEPT-135 NMR spectra of **6d** (75 MHz, $CDCl_3$).

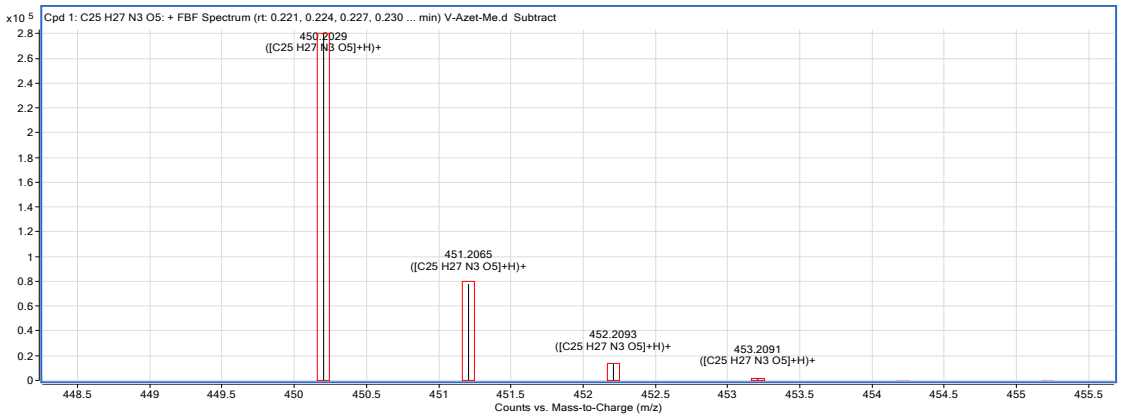


Figure S72. HRMS (+ESI) spectrum of **6d**.

4-(4-Chlorobenzoyl)-4-cyclohexylcarbamoyl-1-(2-nitrobenzyl)azetidin-2-one (6e)

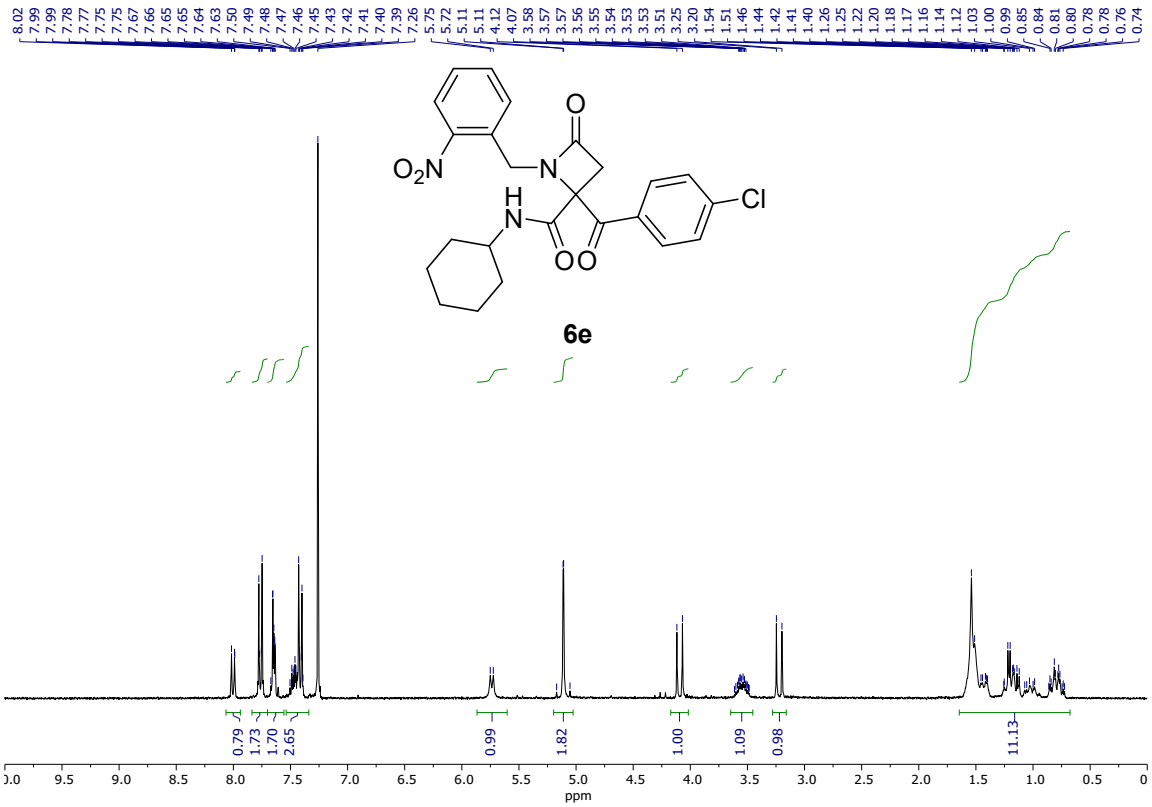


Figure S73. ^{1}H NMR spectrum of **6e** (300 MHz, $CDCl_3$).

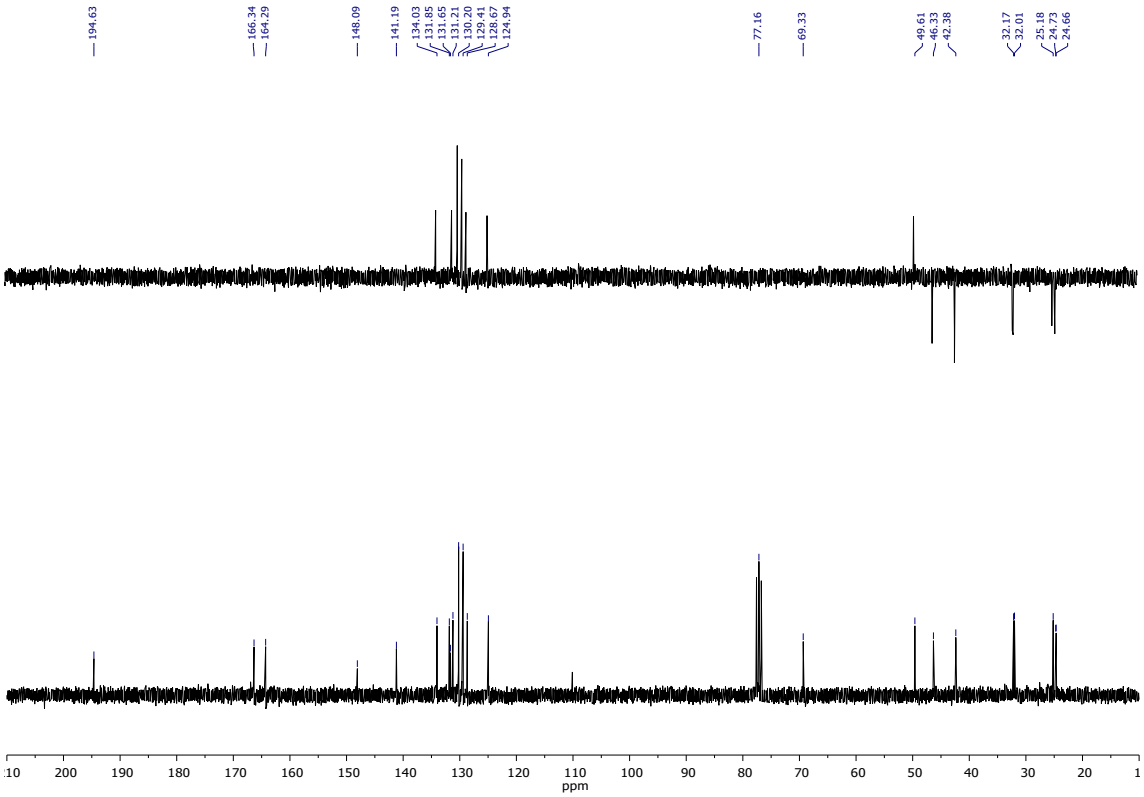


Figure S74. ^{13}C and DEPT-135 NMR spectra of **6e** (75 MHz, $CDCl_3$).

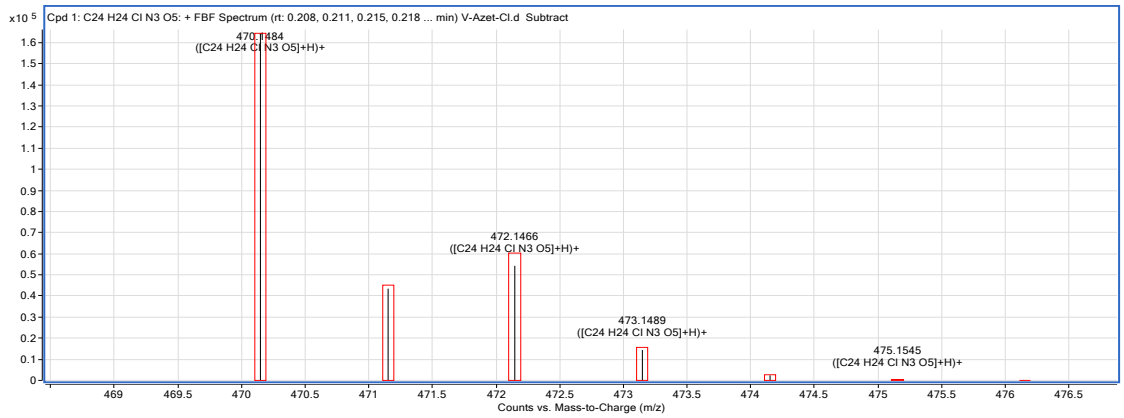


Figure S75. HRMS (+ESI) spectrum of **6e**.

4-Cyclohexylcarbamoyl-4-(4-fluorobenzoyl)-1-(2-nitrobenzyl)azetidin-2-one (6f)

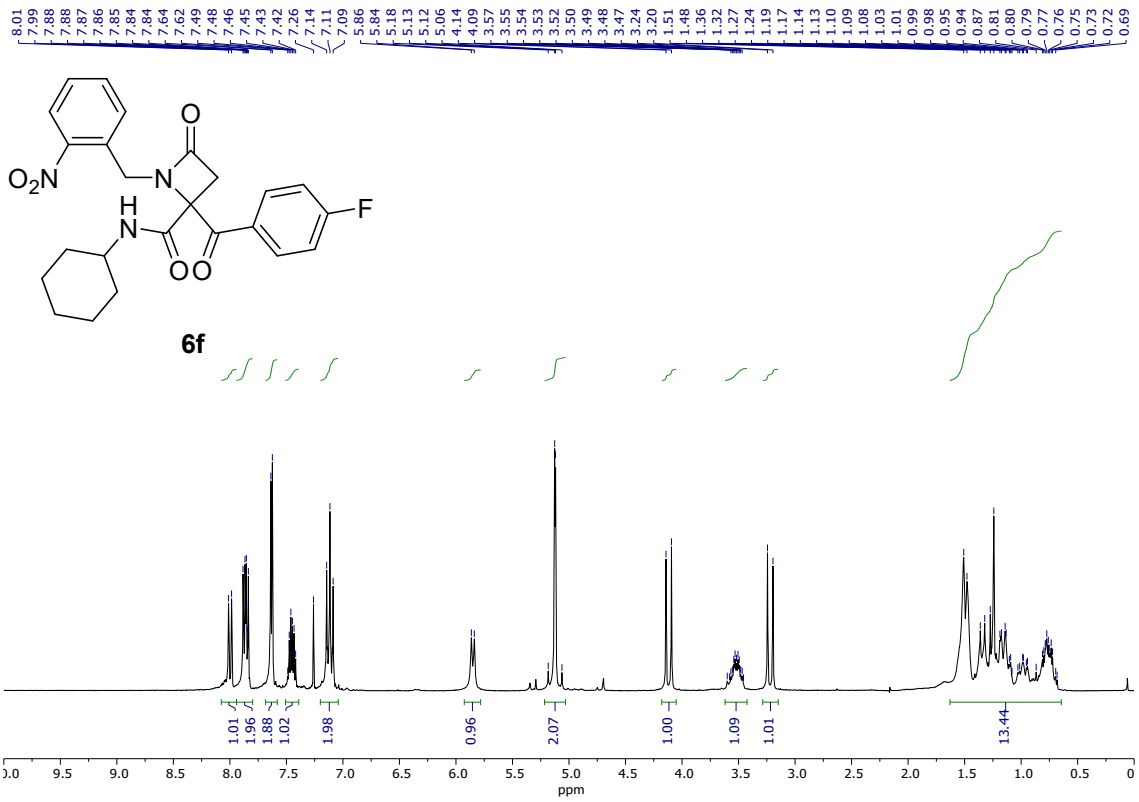


Figure S76. ^{1}H NMR spectrum of **6f** (300 MHz, $CDCl_3$).

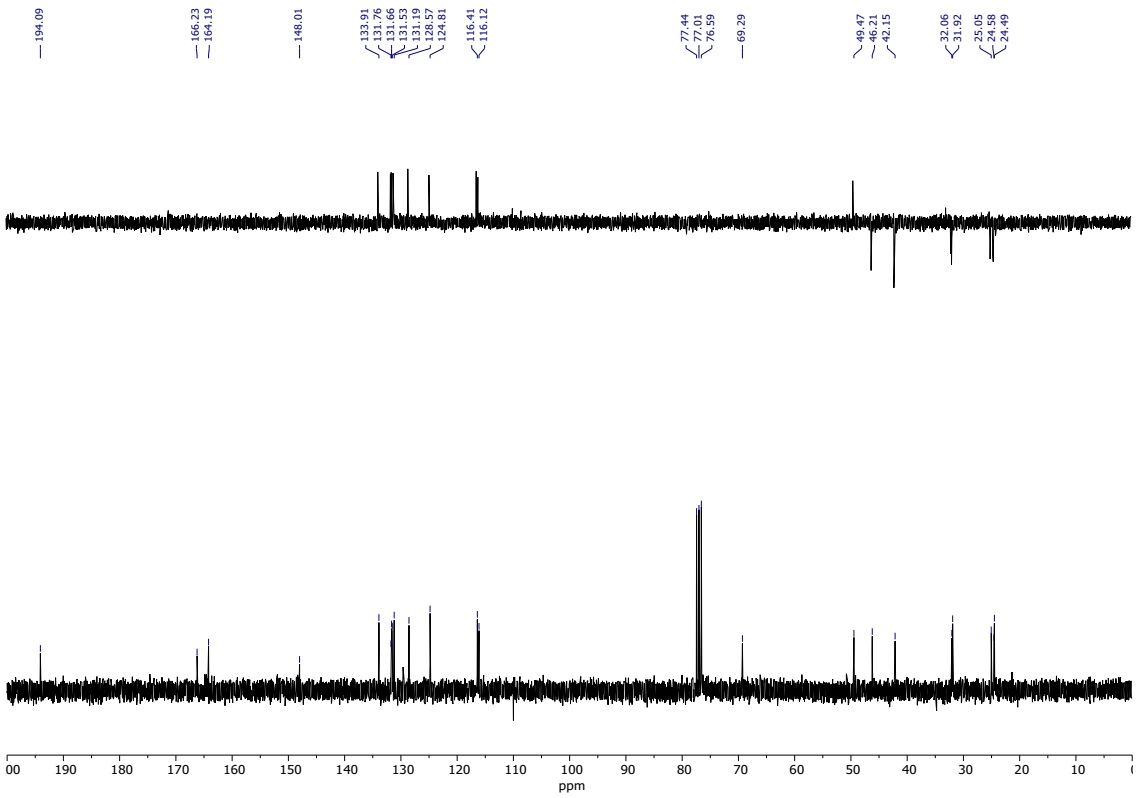


Figure S77. ^{13}C and DEPT-135 NMR spectra of **6f** (75 MHz, $CDCl_3$).

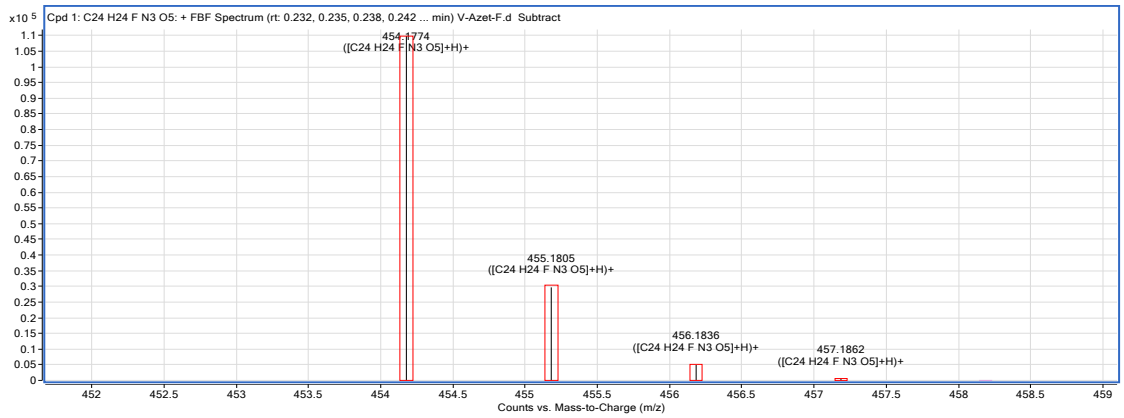


Figure S78. HRMS (+ESI) spectrum of **6f**.

4-Cyclohexylcarbamoyl-4-(4-methoxybenzoyl)-1-(2-nitrobenzyl)azetidin-2-one (6g)

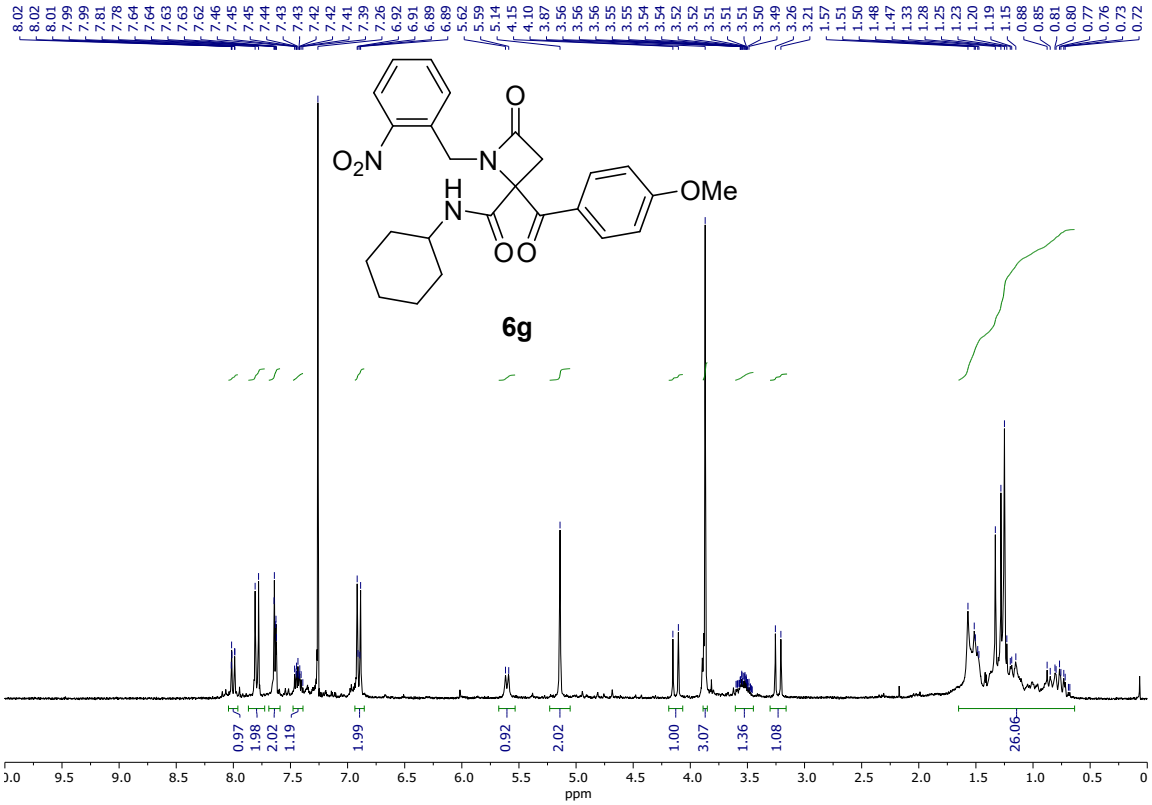


Figure S79. ^{1}H NMR spectrum of **6g** (300 MHz, $CDCl_3$).

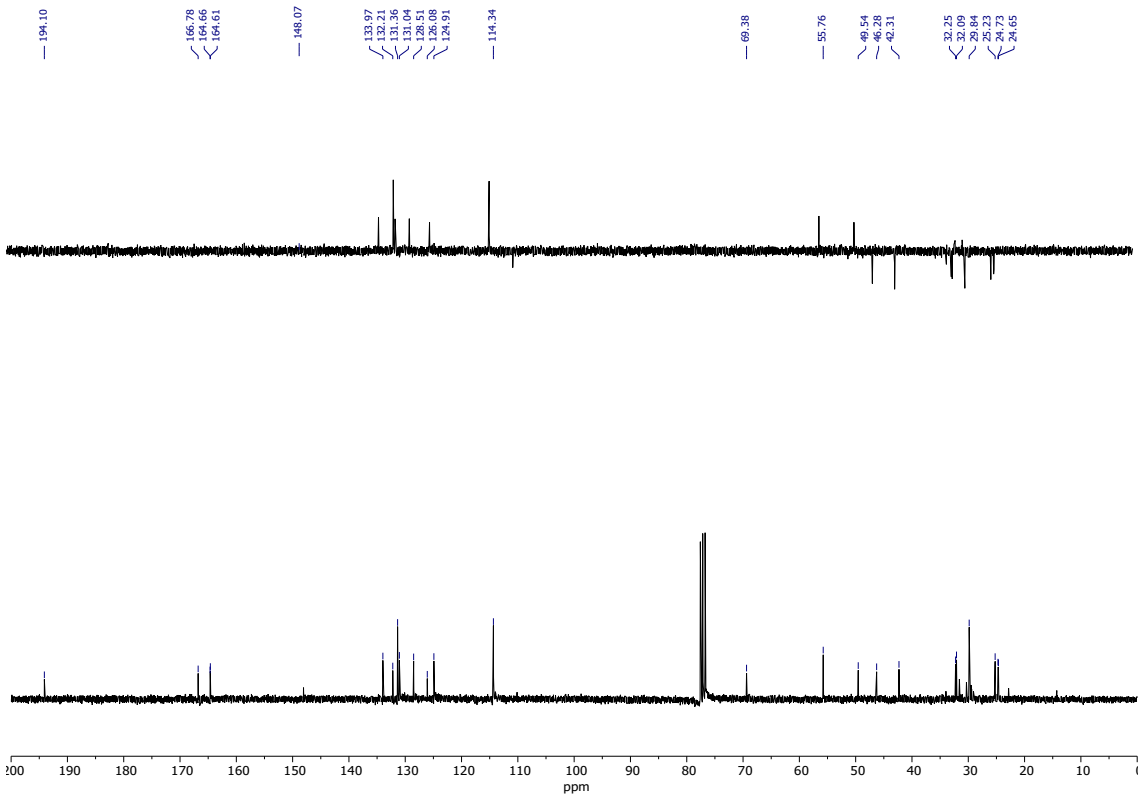


Figure S80. ^{13}C and DEPT-135 NMR spectra of **6g** (75 MHz, $CDCl_3$).

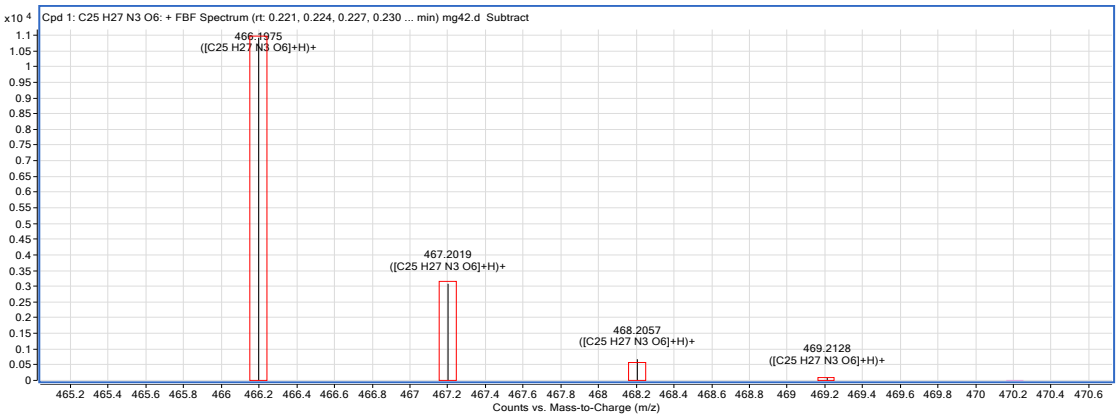


Figure S81. HRMS (+ESI) spectrum of **6g**.

4-Acetyl-4-cyclohexylcarbamoyl-1-(2-nitrobenzyl)azetidin-2-one (6h)

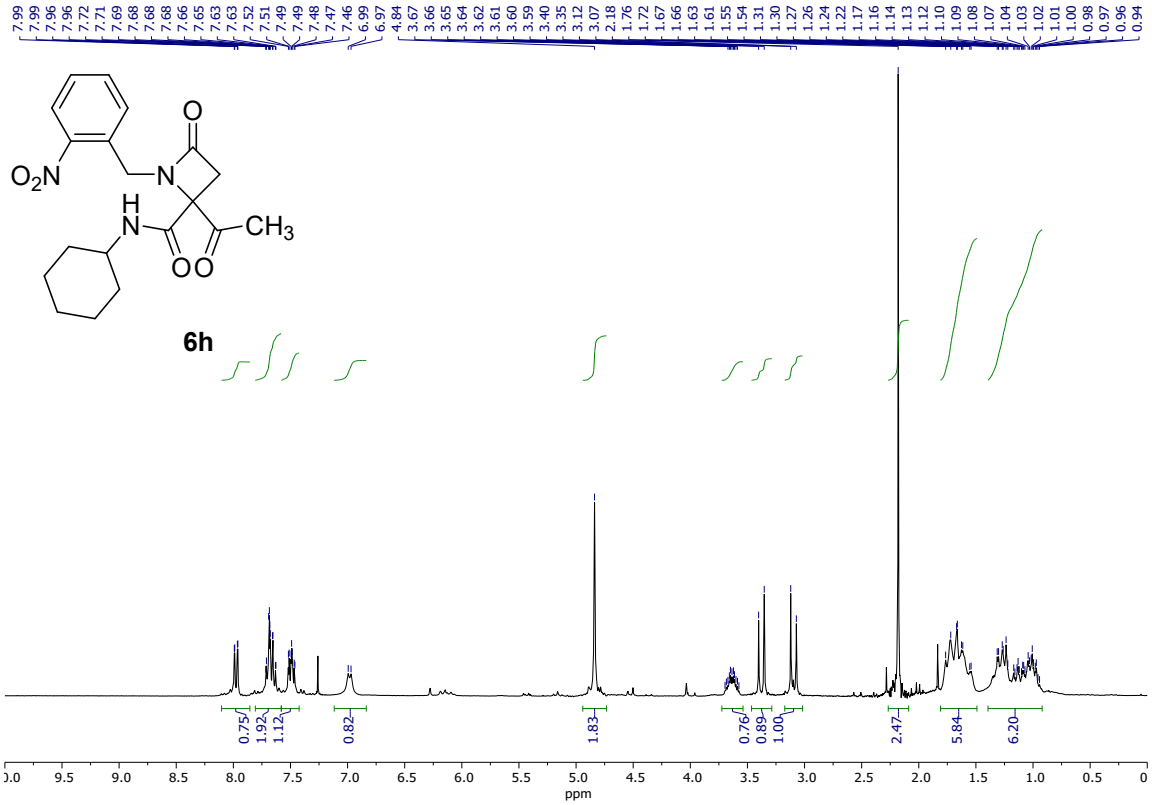


Figure S82. ^{1}H NMR spectrum of **6h** (300 MHz, $CDCl_3$).

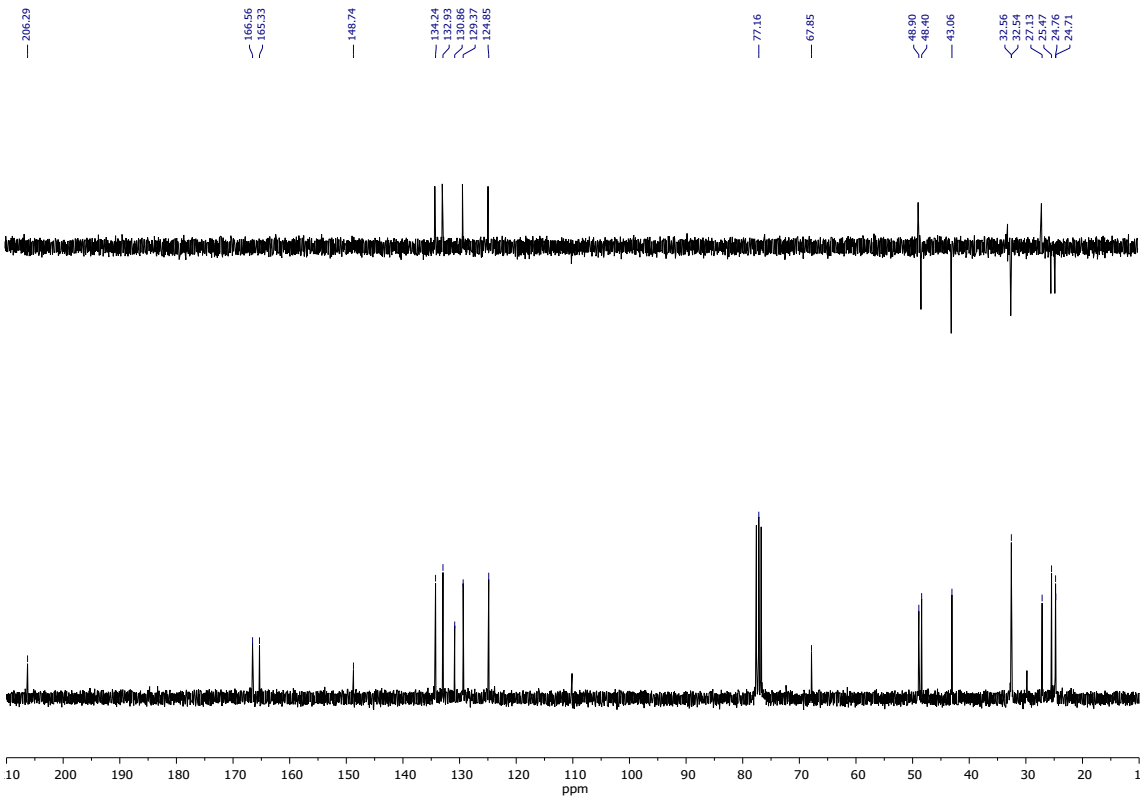


Figure S83. ^{13}C and DEPT-135 NMR spectra of **6h** (75 MHz, $CDCl_3$).

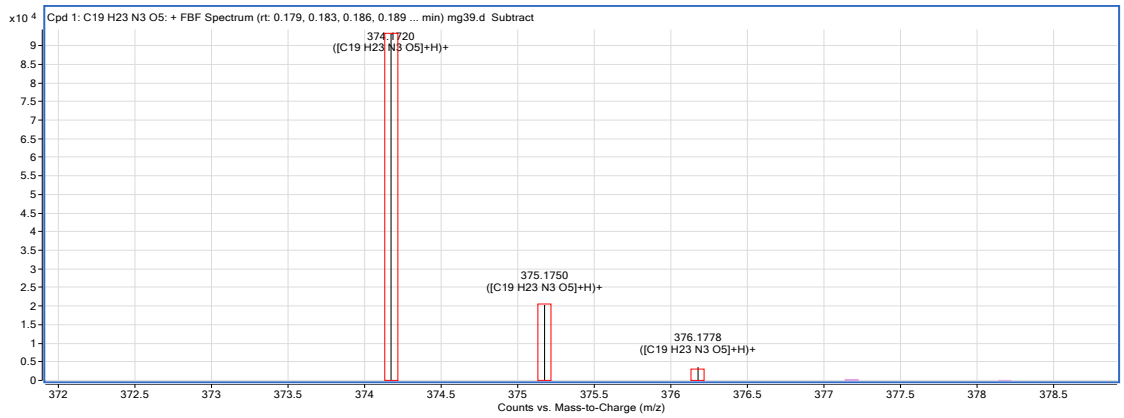


Figure S84. HRMS (+ESI) spectrum of **6h**.

4-Benzoyl-4-cyclohexylcarbamoyl-3-phenyl-1-(2-nitrobenzyl)azetidin-2-one (6i)

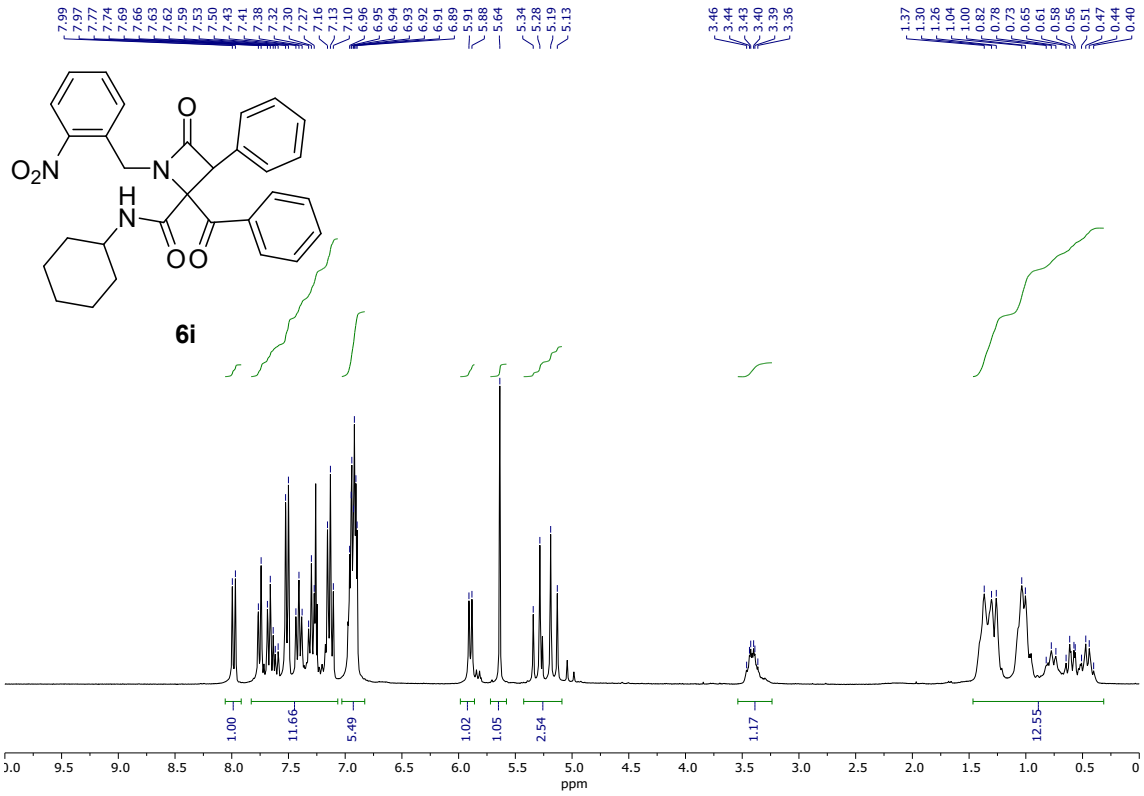


Figure S85. ^{1}H NMR spectrum of **6i** (300 MHz, $CDCl_3$).

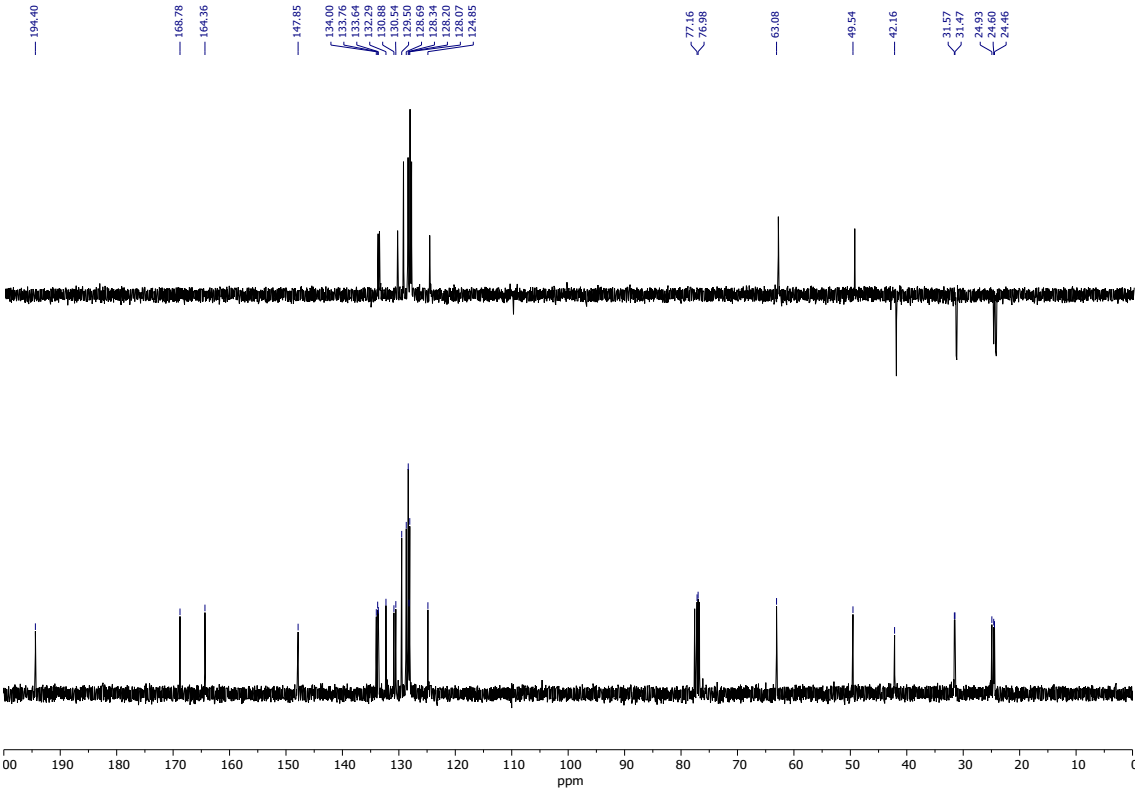


Figure S86. ^{13}C and DEPT-135 NMR spectra of **6i** (75 MHz, $CDCl_3$).

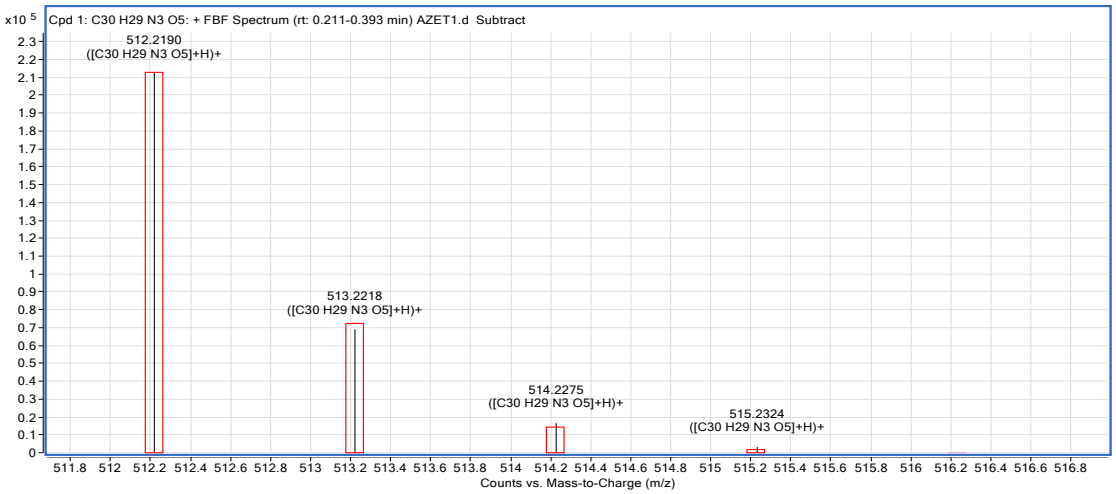


Figure S87. HRMS (+ESI) spectrum of **6i**.

4-Cyclohexylcarbamoyl-4-fluorobenzoyl-3-phenyl-1-(2-nitrobenzyl)azetidin-2-one (6j)

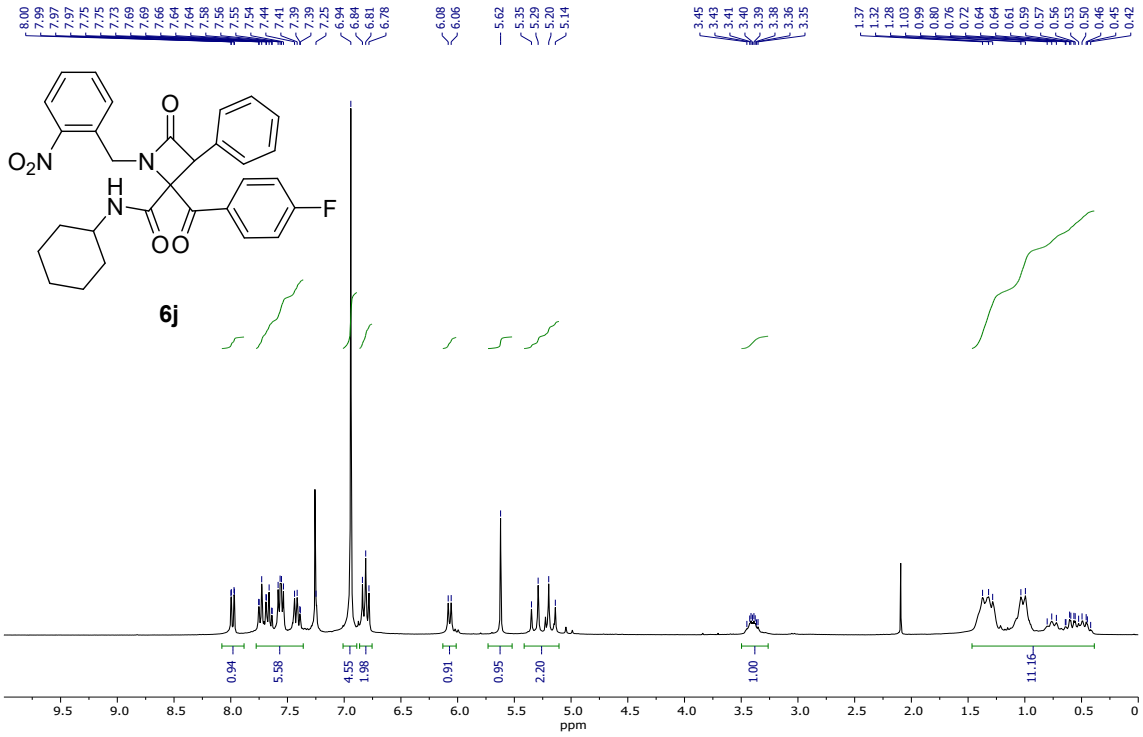


Figure S88. ^{1}H NMR spectrum of **6j** (300 MHz, $CDCl_3$).

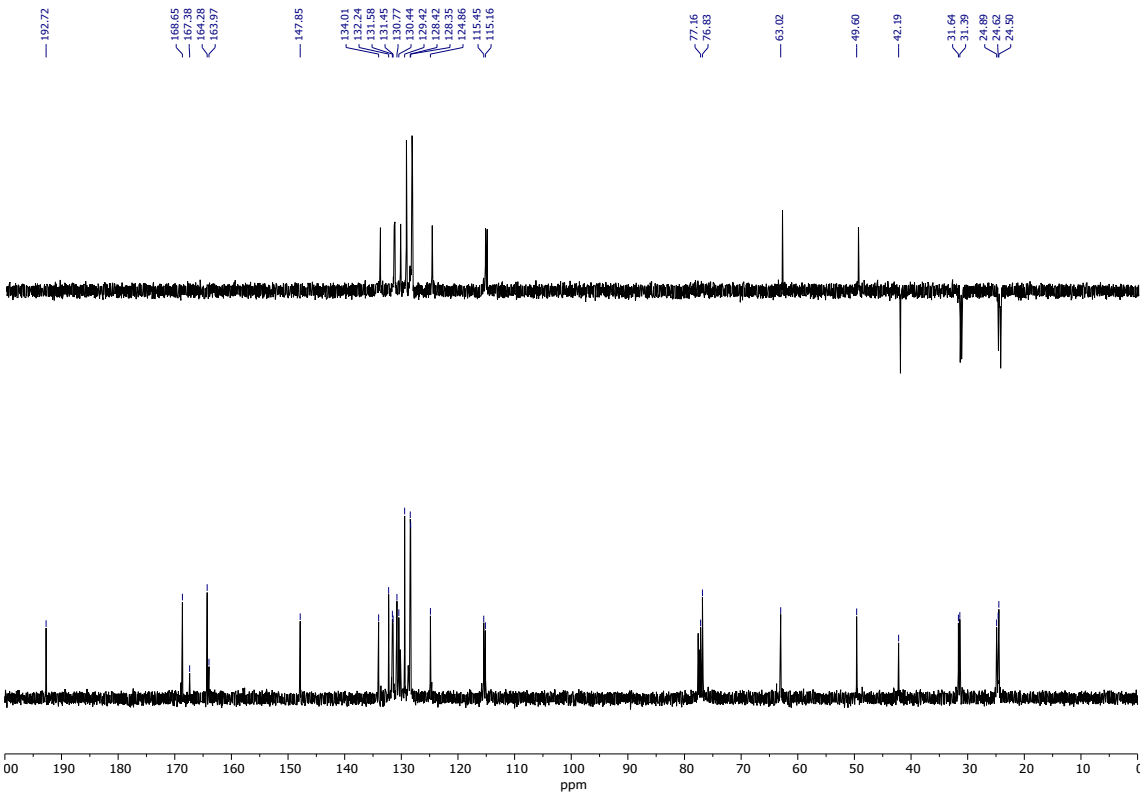


Figure S89. ^{13}C and DEPT-135 NMR spectra of **6j** (75 MHz, $CDCl_3$).

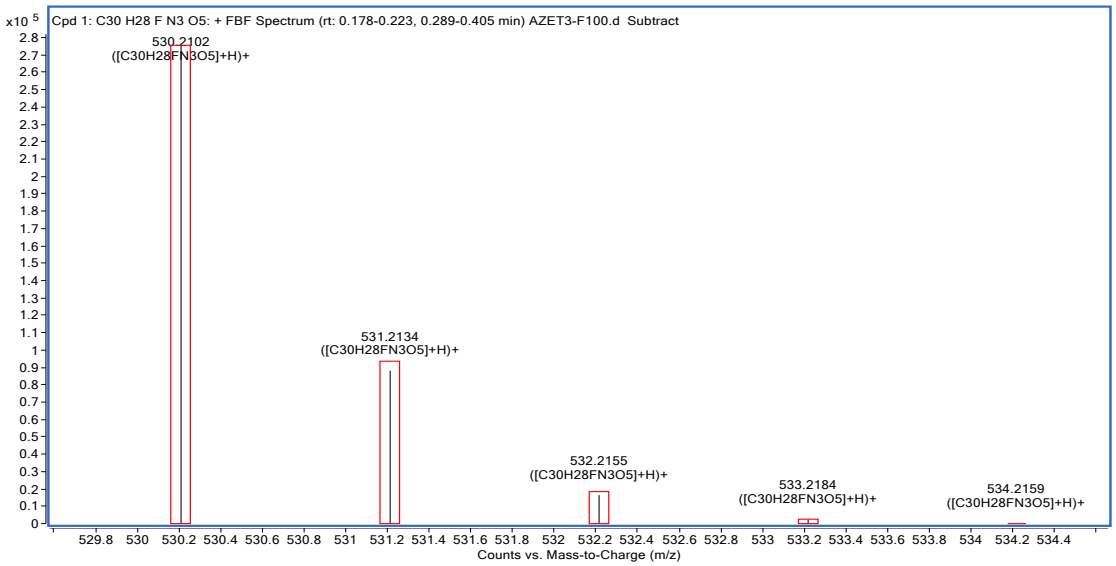


Figure S90. HRMS (+ESI) spectrum of **6j**.

1-Benzyl-4-benzoyl-4-cyclohexylcarbamoylazetidin-2-one (6k)

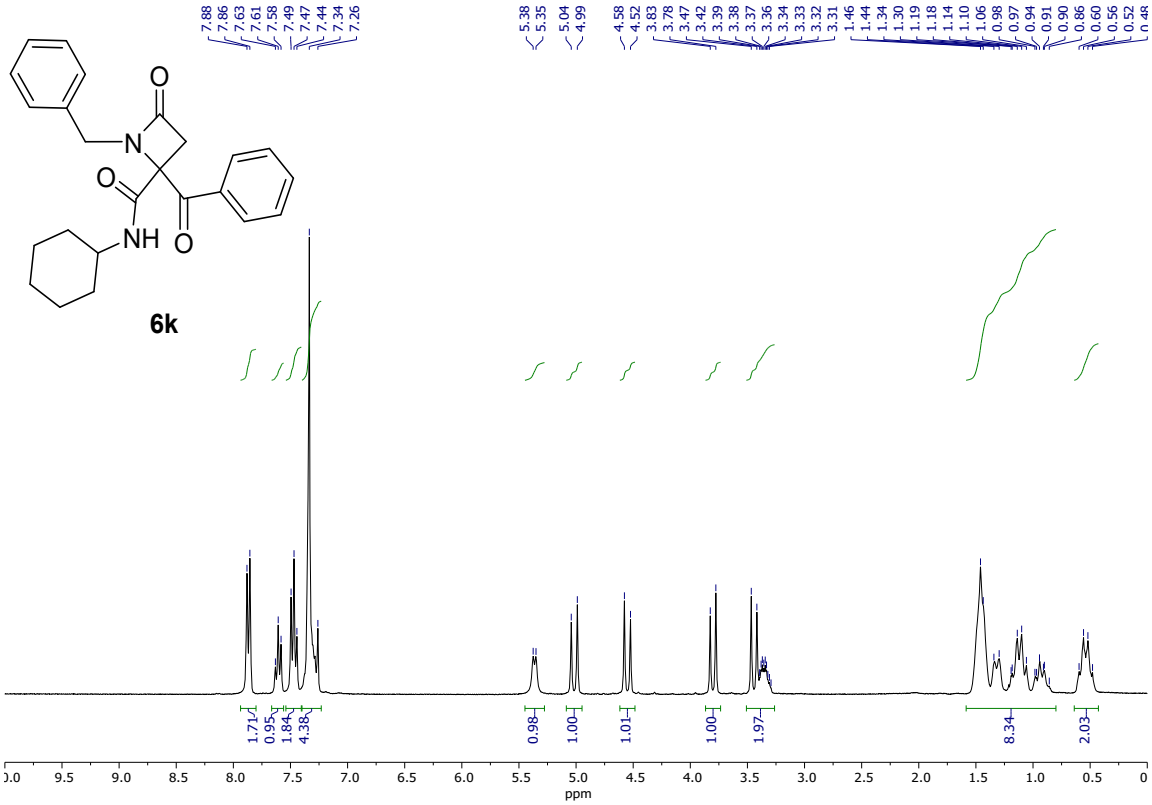


Figure S91. ^{1}H NMR spectrum of **6k** (300 MHz, $CDCl_3$).

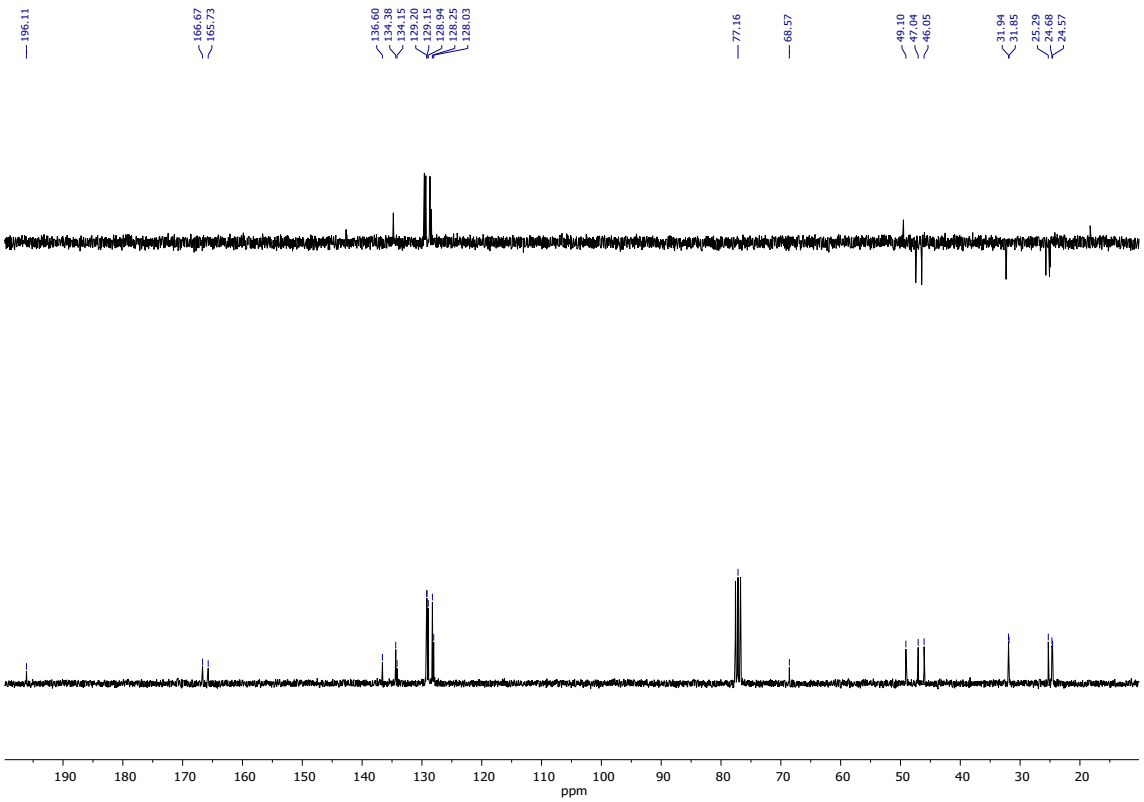


Figure S92. ^{13}C and DEPT-135 NMR spectra of **6k** (75 MHz, $CDCl_3$).

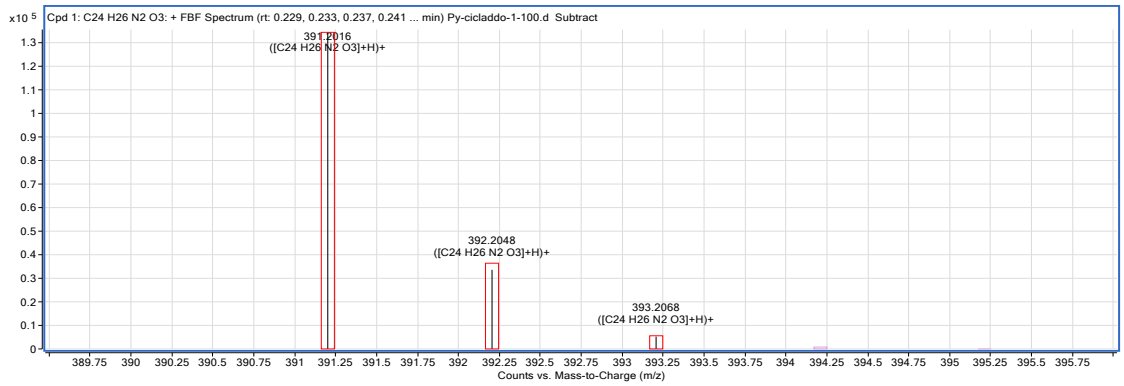


Figure S93. HRMS (+ESI) spectrum of **6k**.

4-Benzoyl-4-cyclohexylcarbamoyl-1-(methoxycarbonylmethyl)azetidin-2-one (6l)

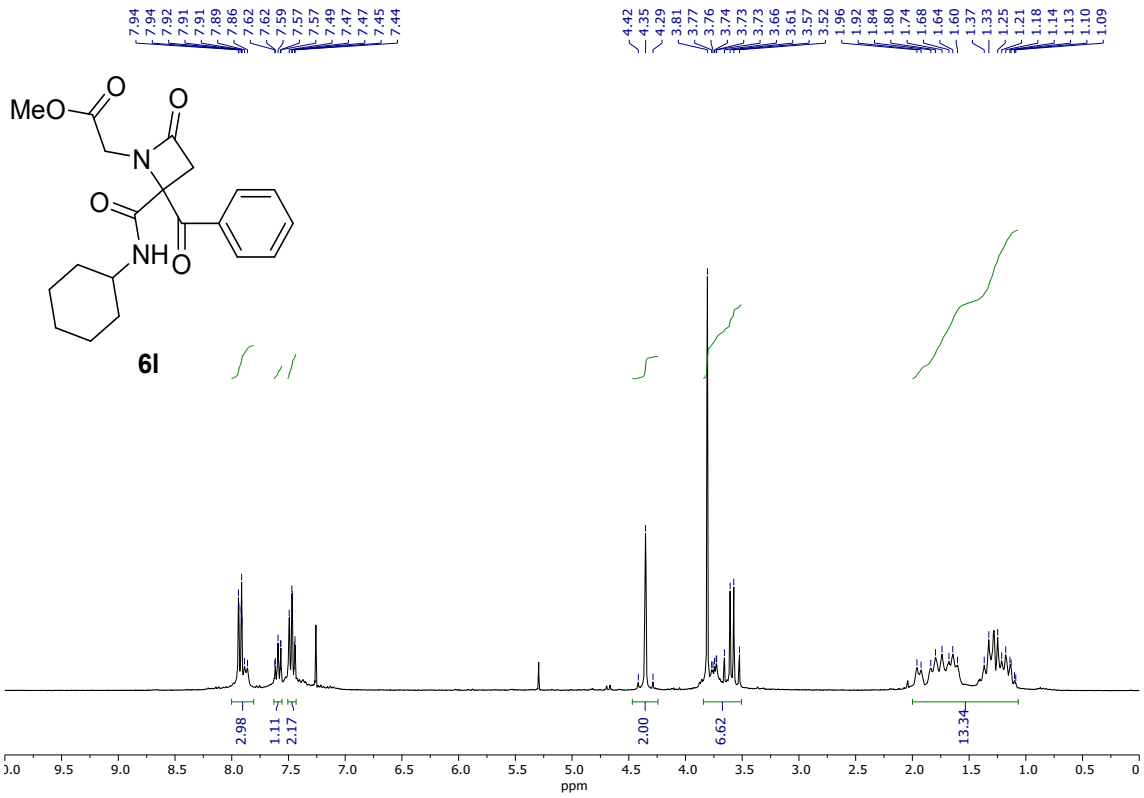


Figure S94. ^{1}H NMR spectrum of **6l** (300 MHz, $CDCl_3$).

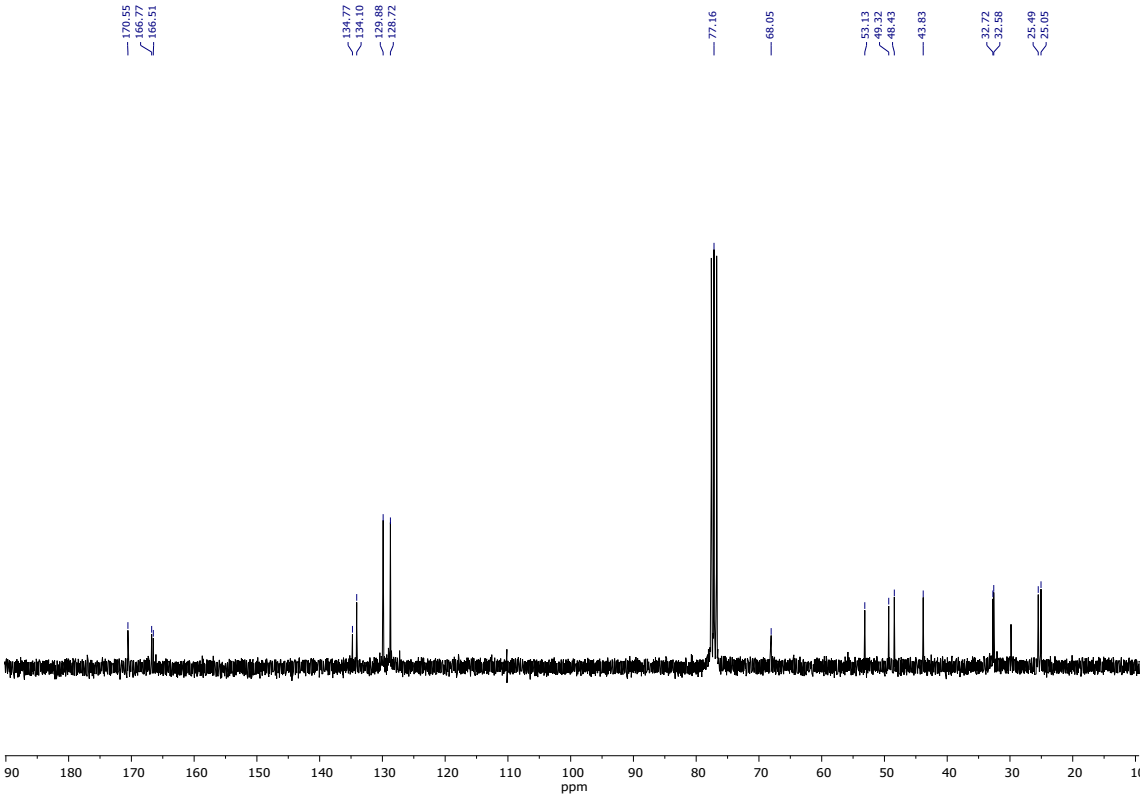


Figure S95. ^{13}C NMR spectrum of **6l** (75 MHz, $CDCl_3$).

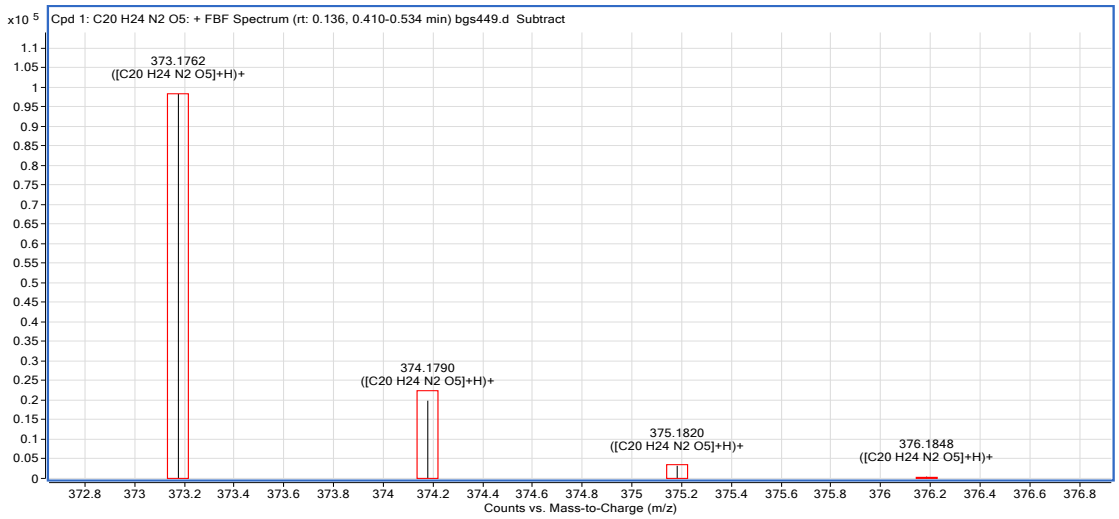


Figure S96. HRMS (+ESI) spectrum of **6l**.

(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-1'-phenylmethyl)-azetidin-2-one (6m)

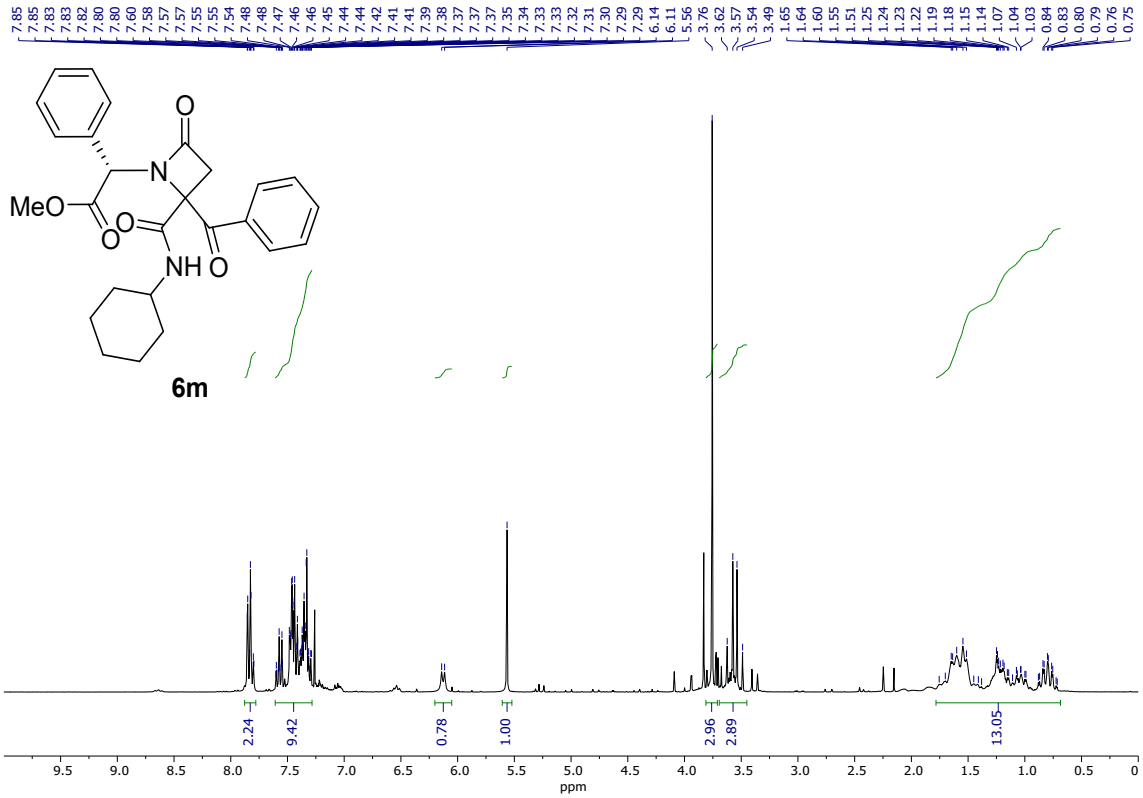


Figure S97. ^{1}H NMR spectrum of **6m** (300 MHz, $CDCl_3$).

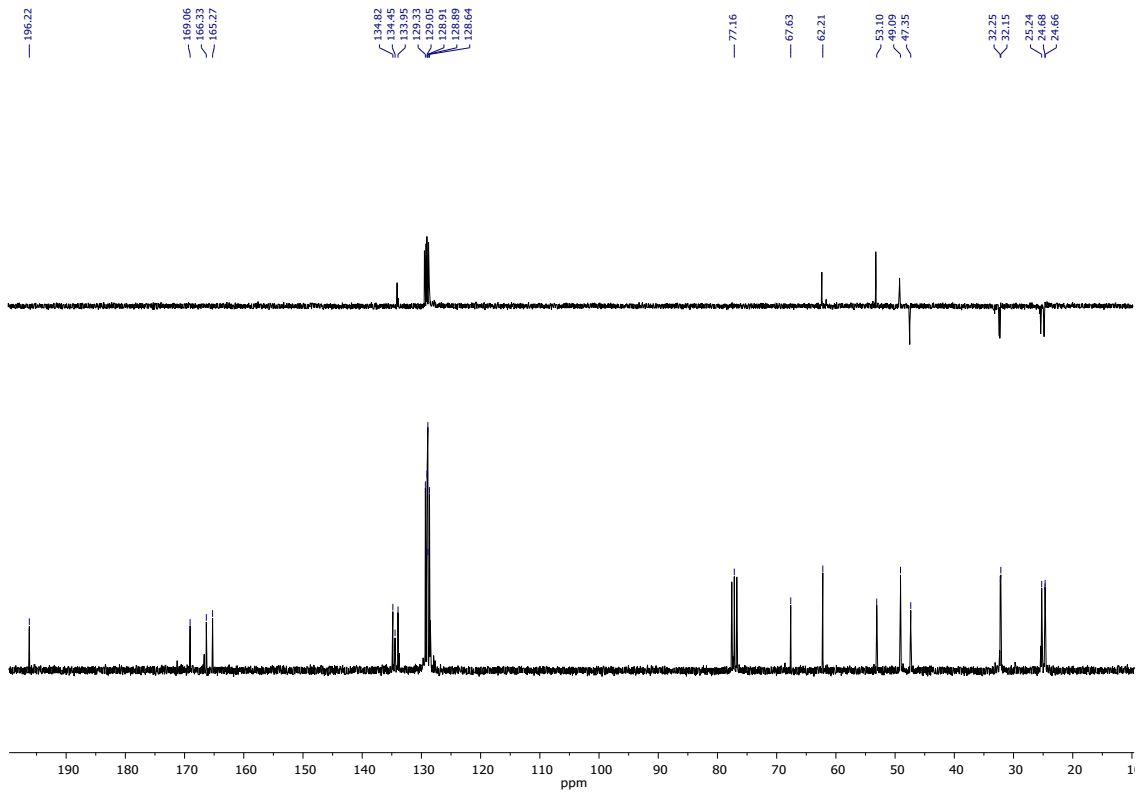


Figure S98. ^{13}C and DEPT-135 NMR spectra of **6m** (75 MHz, $CDCl_3$).

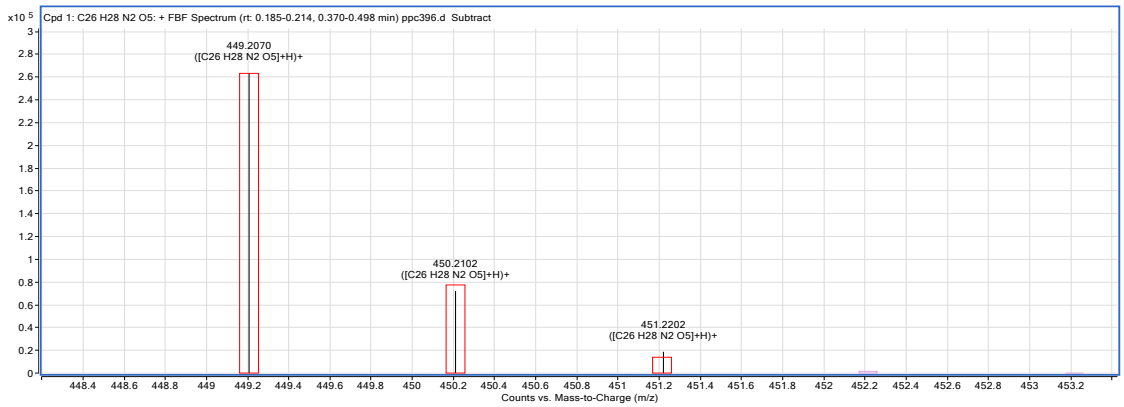


Figure S99. HRMS (+ESI) spectrum of **6m**.

(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonylethyl)-azetidin-2-one (6n)

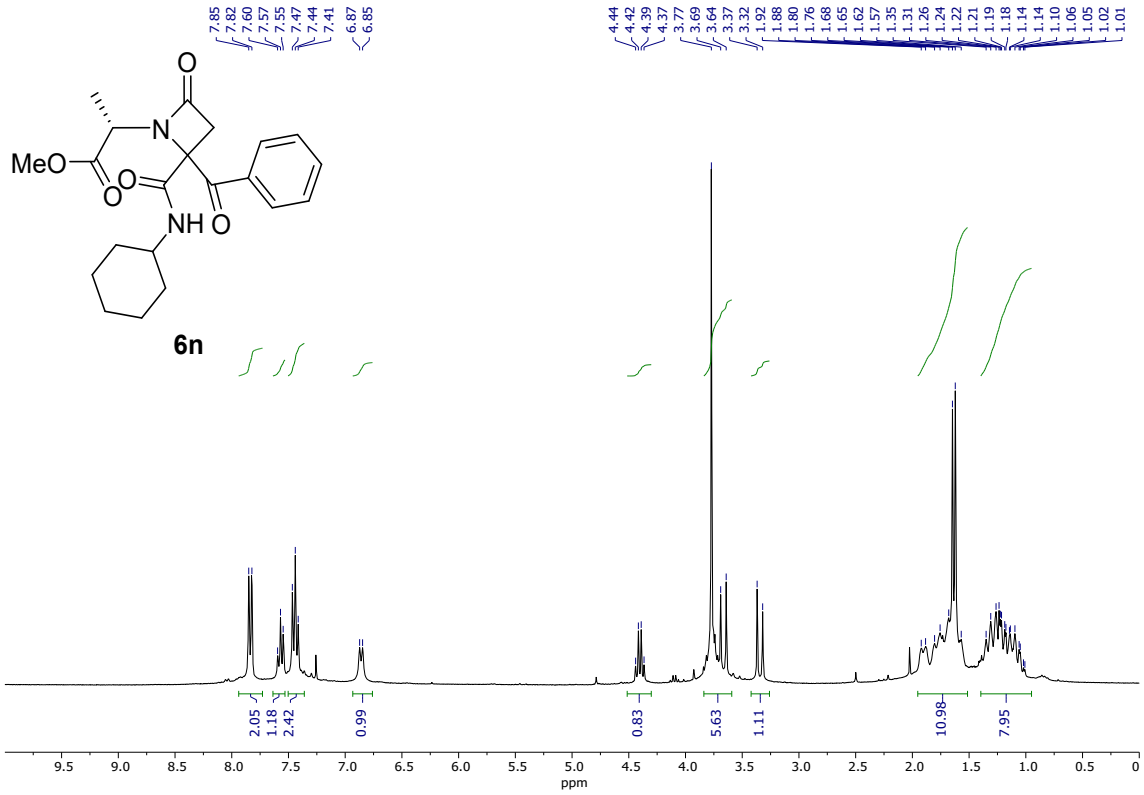


Figure S100. ^{1}H NMR spectrum of **6n** (300 MHz, $CDCl_3$).

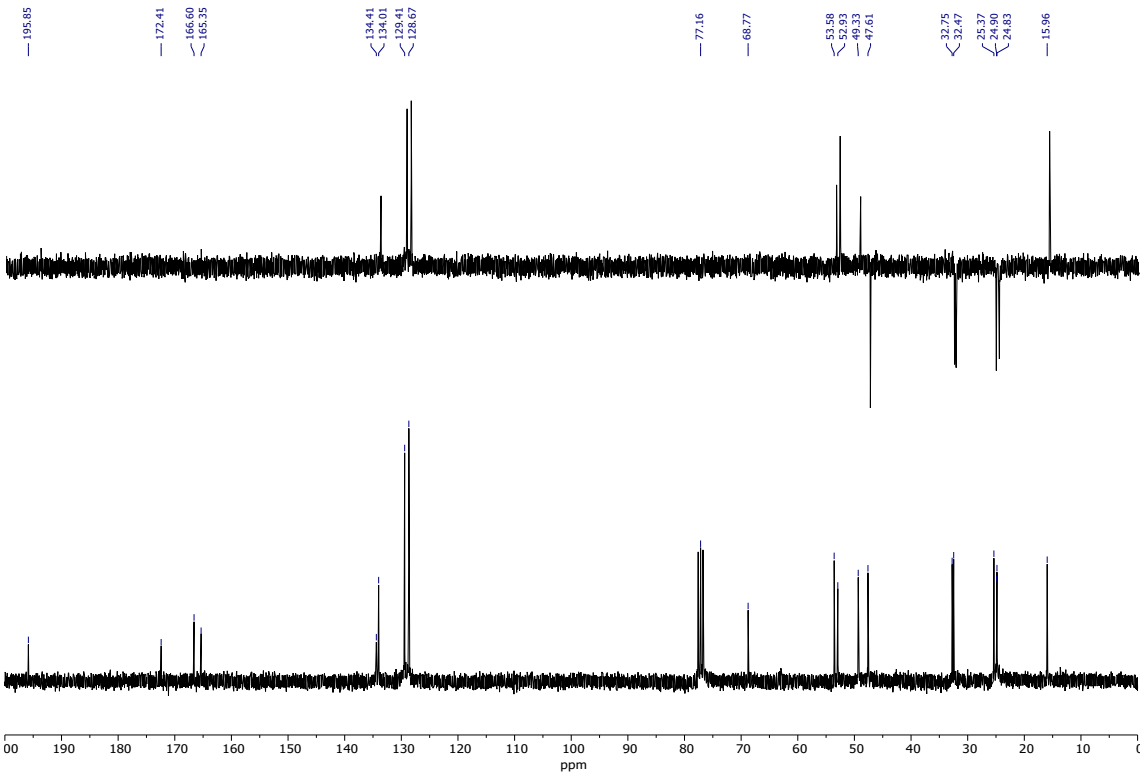


Figure S101. ^{13}C and DEPT-135 NMR spectra of **6n** (75 MHz, $CDCl_3$).

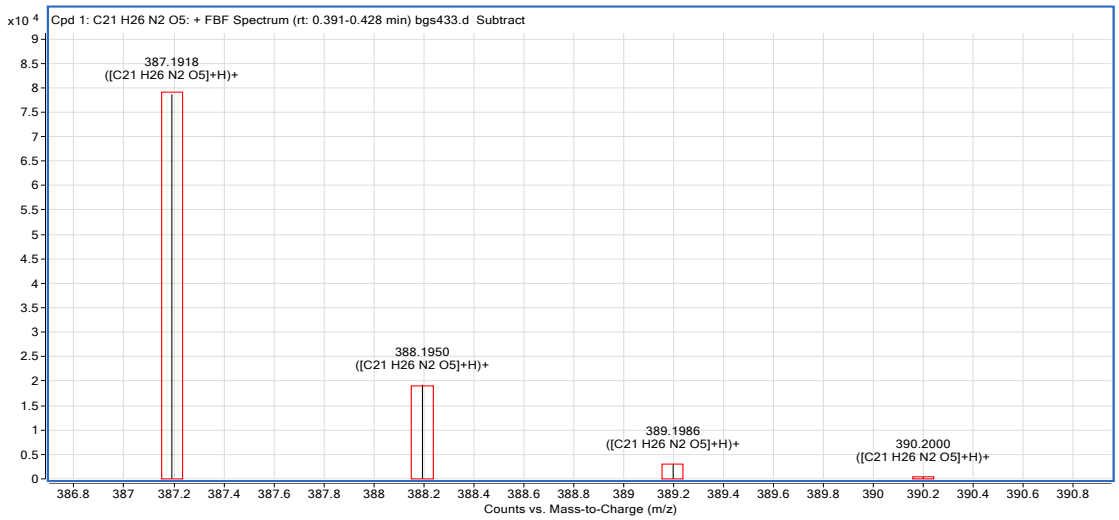


Figure S102. HRMS (+ESI) spectrum of **6n**.

(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-2'-phenylethyl)-azetidin-2-one (6o)

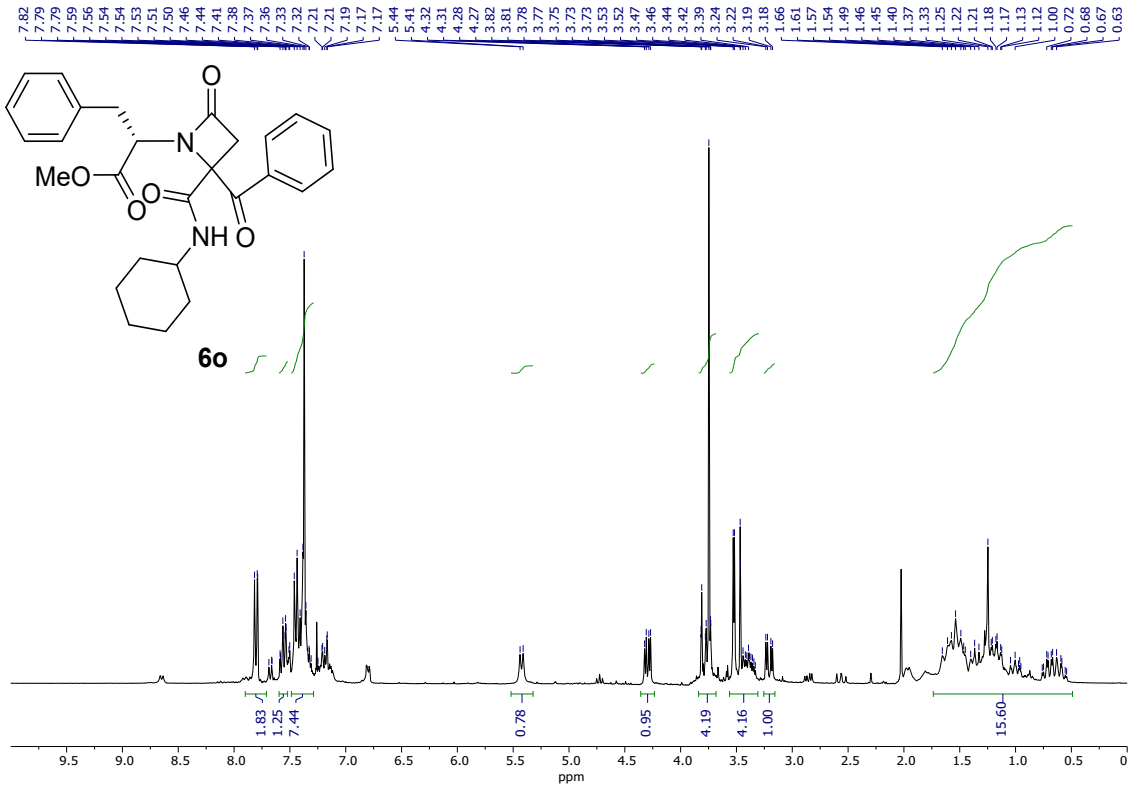


Figure S103. ^{1}H NMR spectrum of **6o** (300 MHz, $CDCl_3$).

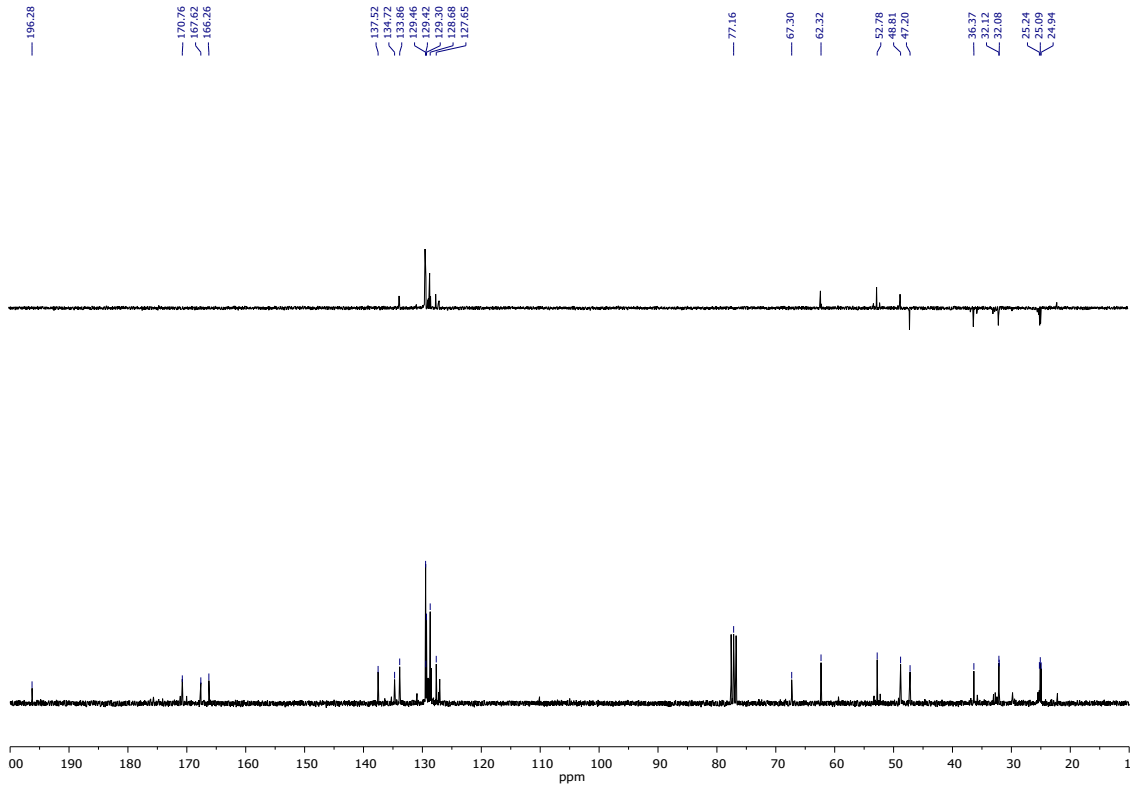


Figure S104. ^{13}C and DEPT-135 NMR spectra of **6o** (75 MHz, $CDCl_3$).

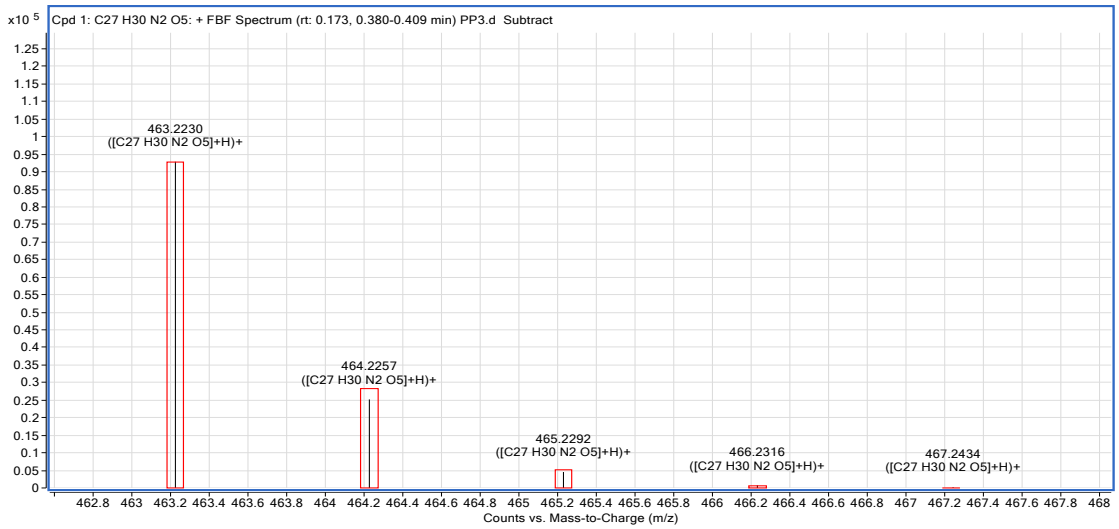


Figure S105. HRMS (+ESI) spectrum of **6o**.

(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-2'-methylpropyl)-azetidin-2-one (6p)

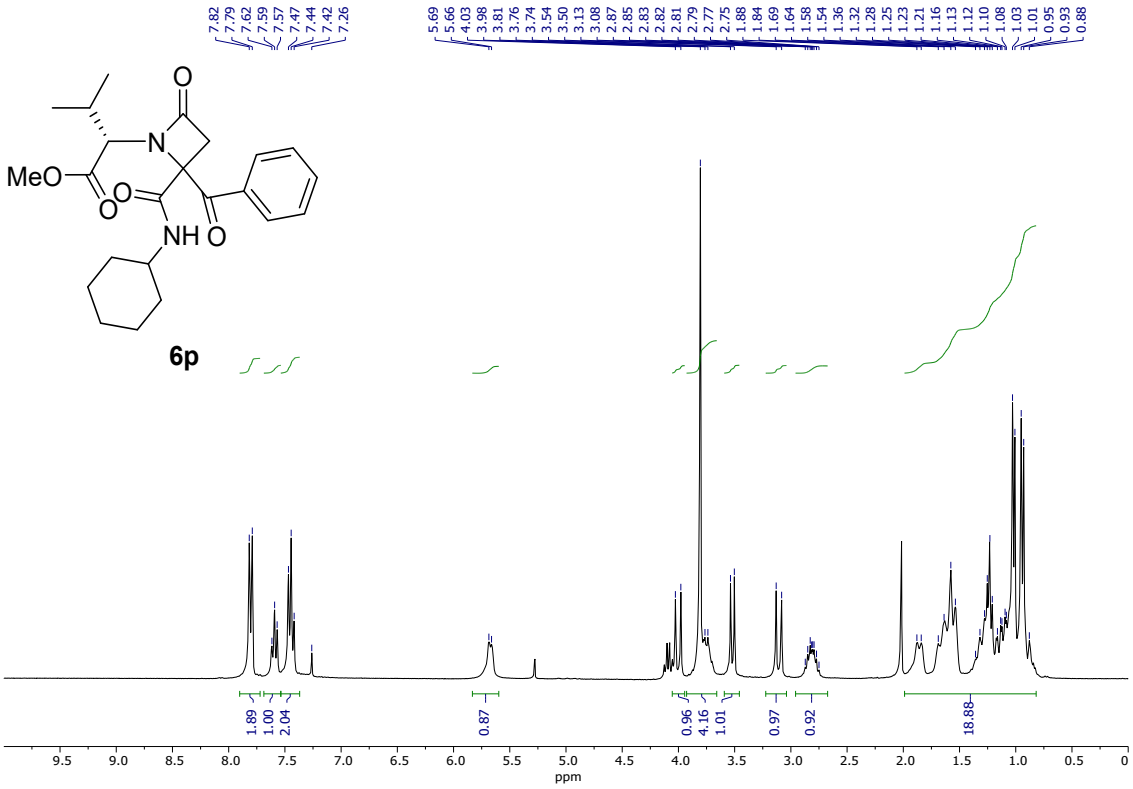


Figure S106. ^{1}H NMR spectrum of **6p** (300 MHz, $CDCl_3$).

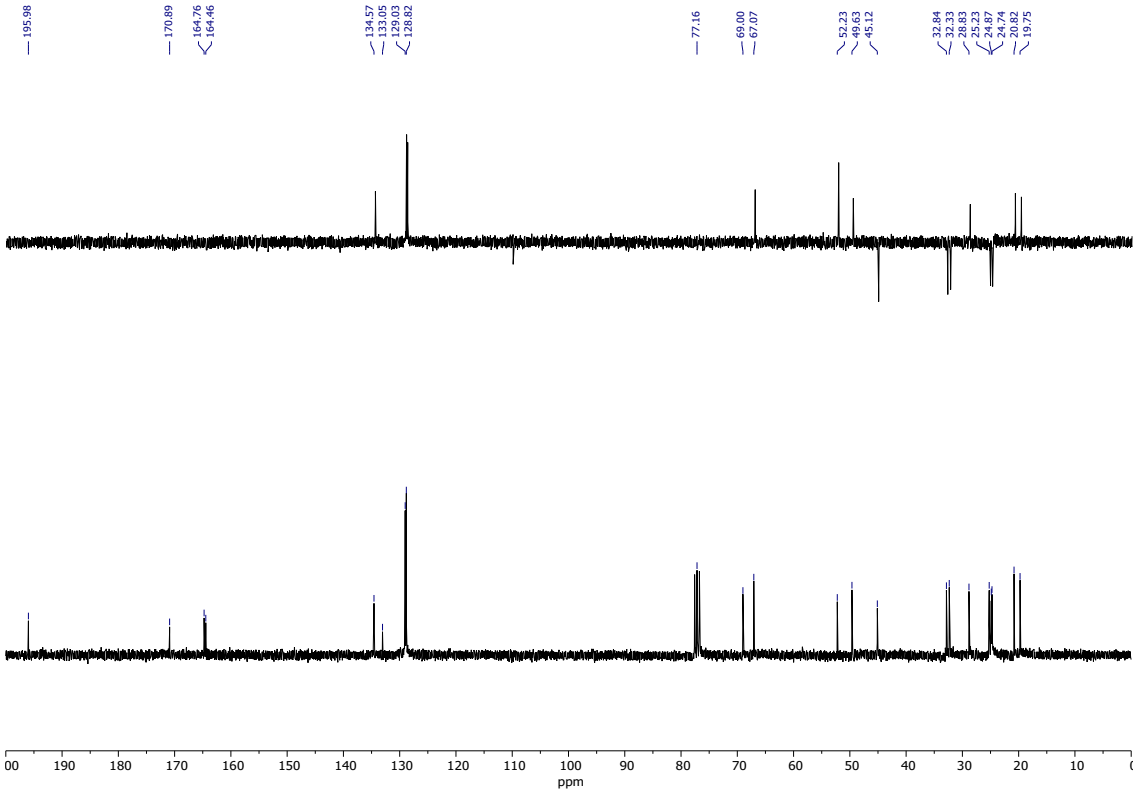


Figure S107. ^{13}C and DEPT-135 NMR spectra of **6p** (75 MHz, $CDCl_3$).

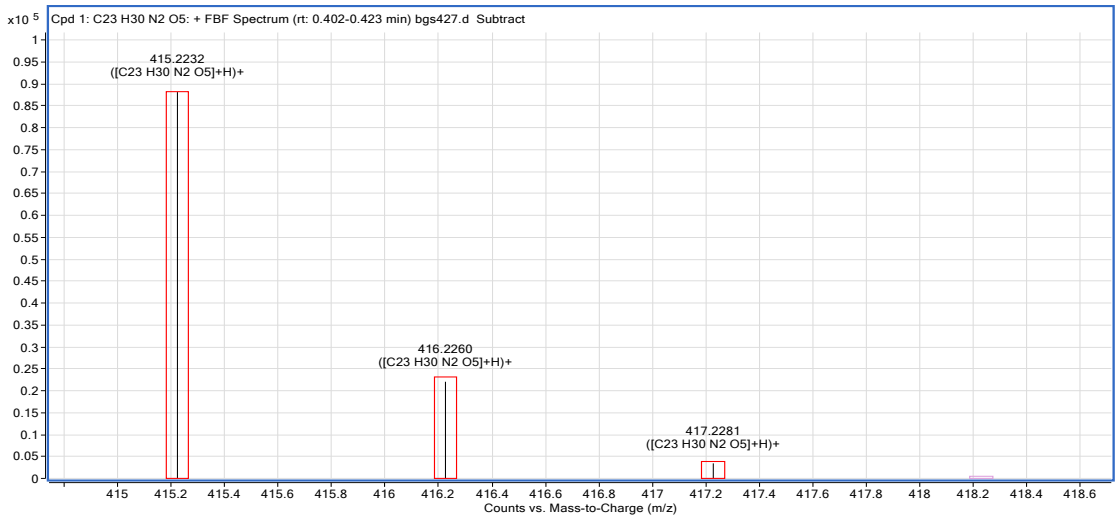


Figure S108. HRMS (+ESI) spectrum of **6p**.

(3*R,4*S**)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(methoxycarbonylmethyl)-3-phenylazetidin-2-one ($6q_{diast1}$)**

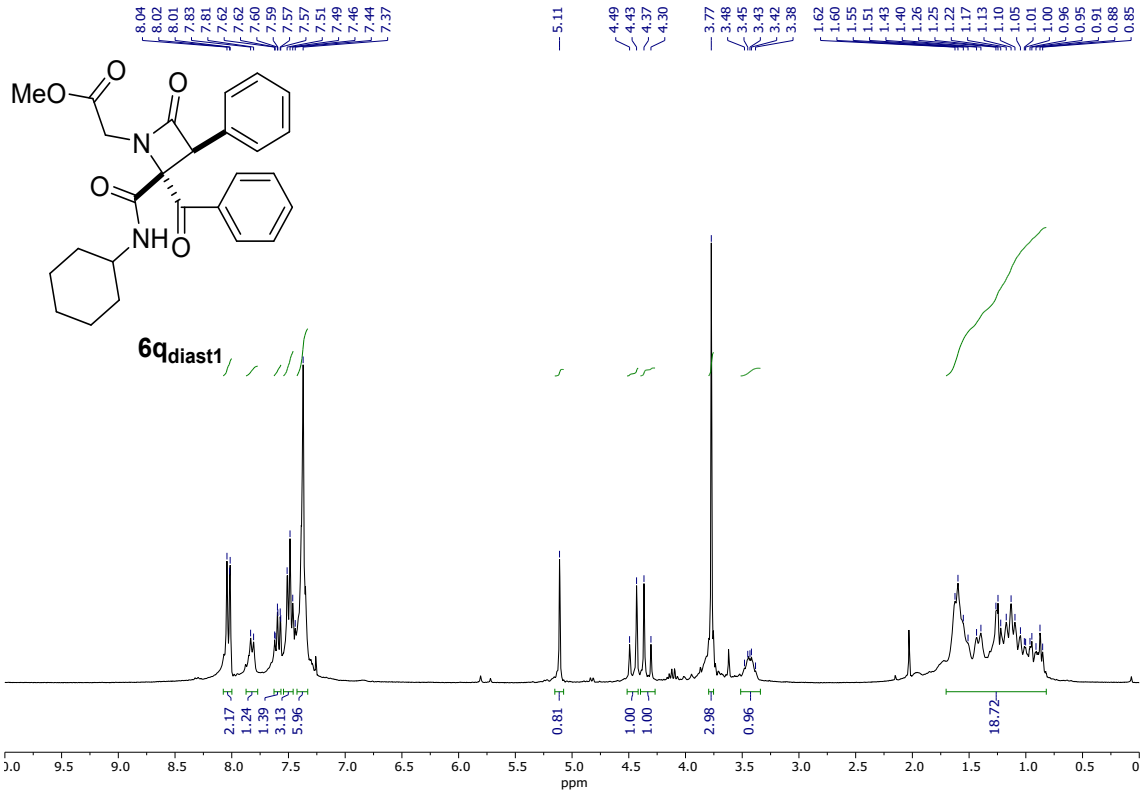


Figure S109. ^{1}H NMR spectrum of **$6q_{diast1}$** (300 MHz, $CDCl_3$).

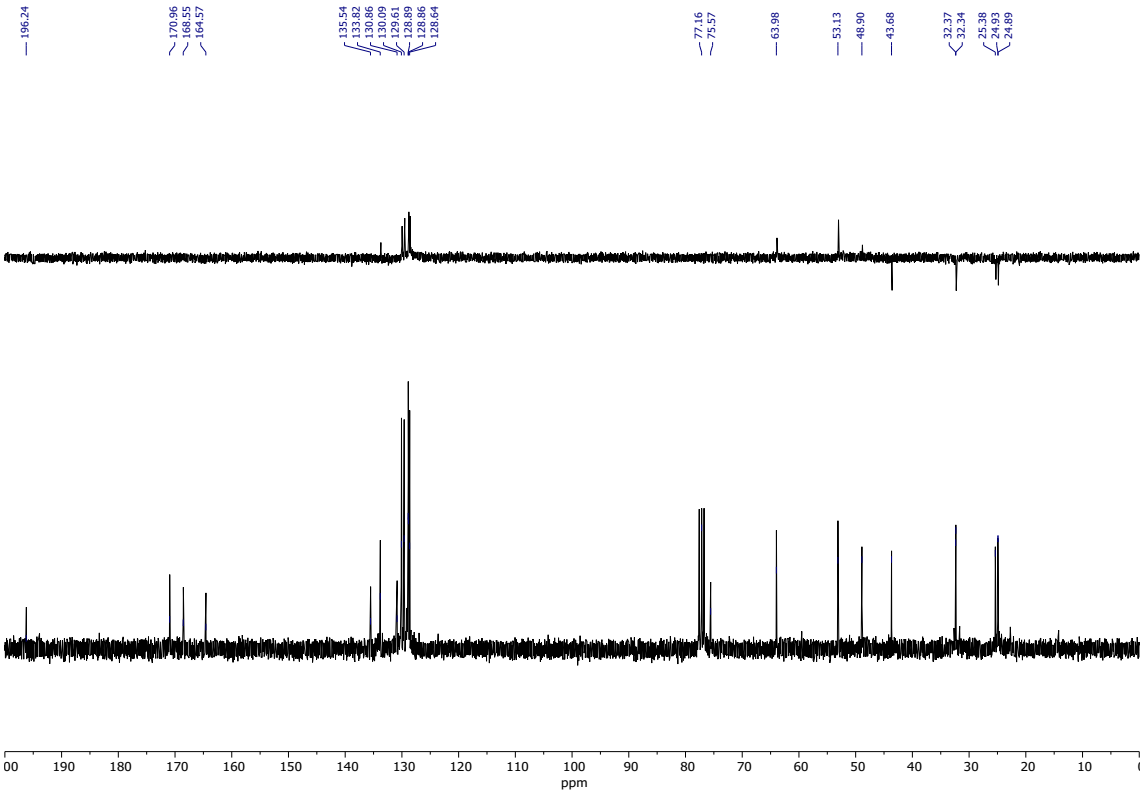


Figure S110. ^{13}C and DEPT-135 NMR spectra of **6q$_{diast1}$** (75 MHz, $CDCl_3$).

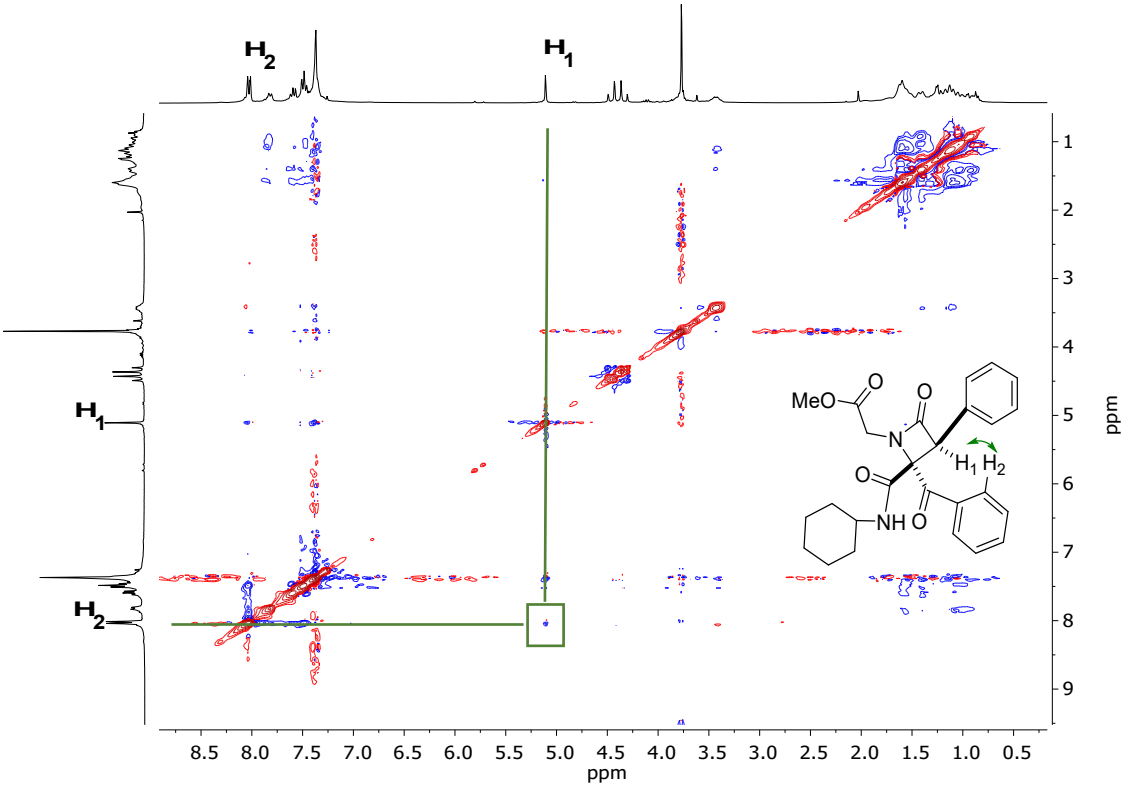


Figure S111. NOESY spectrum of **6q$_{diast1}$** (300 MHz, $CDCl_3$).

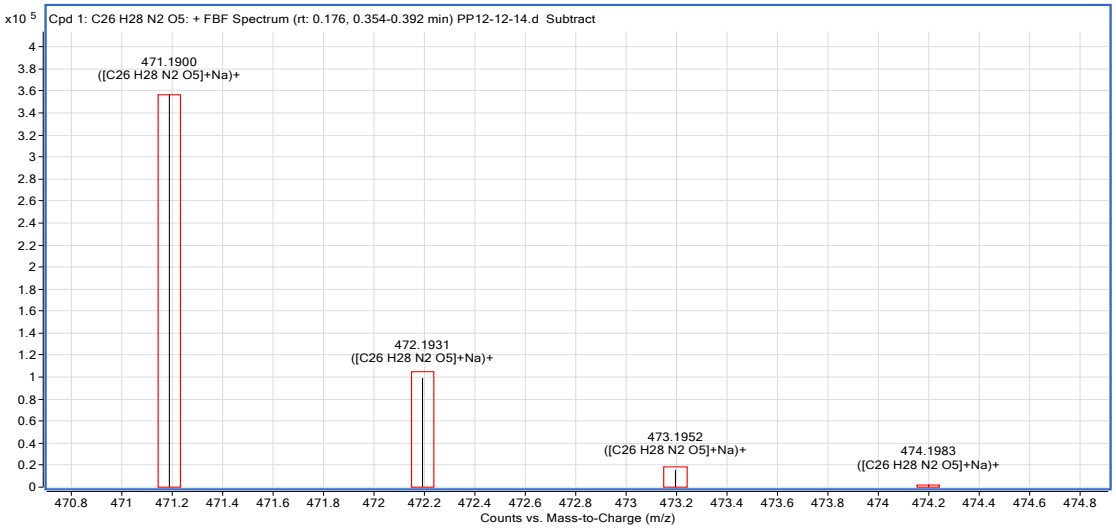


Figure S112. HRMS (+ESI) spectrum of **6q$_{diast1}$**.

(3*R,4*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(methoxycarbonylmethyl)-3-phenylazetidin-2-one ($6q_{diast2}$)**

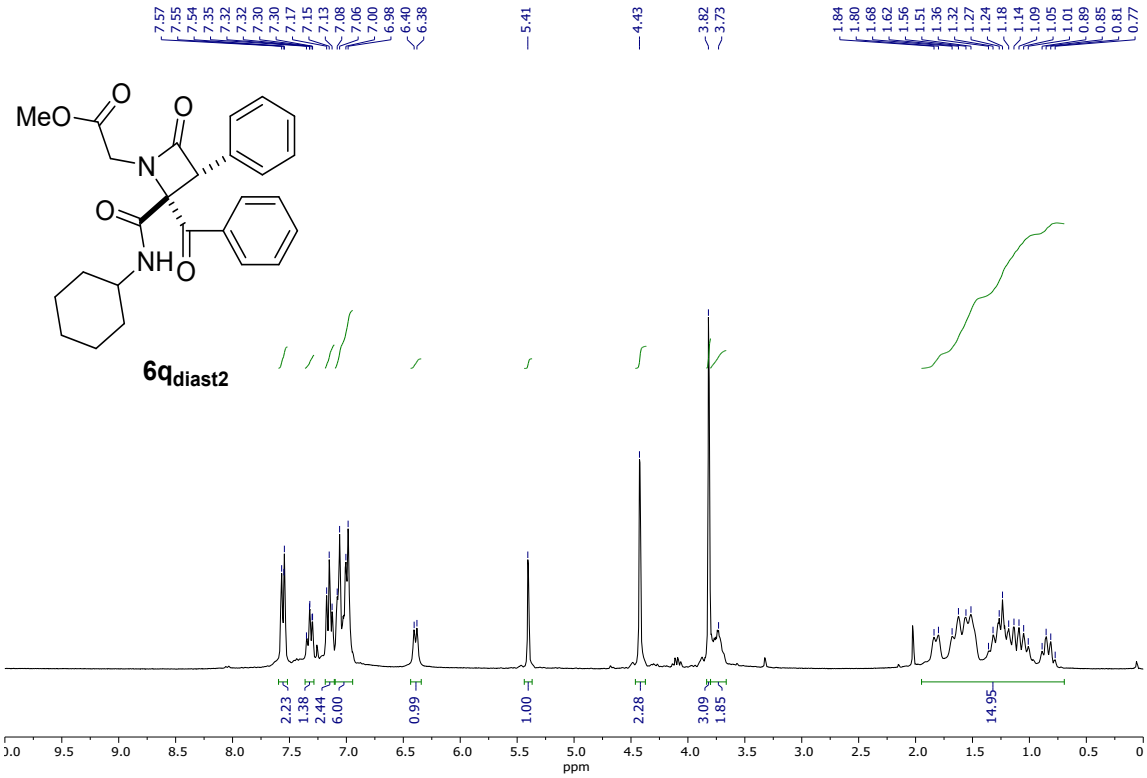


Figure S113. ^{1}H NMR spectrum of **$6q_{diast2}$** (300 MHz, $CDCl_3$).

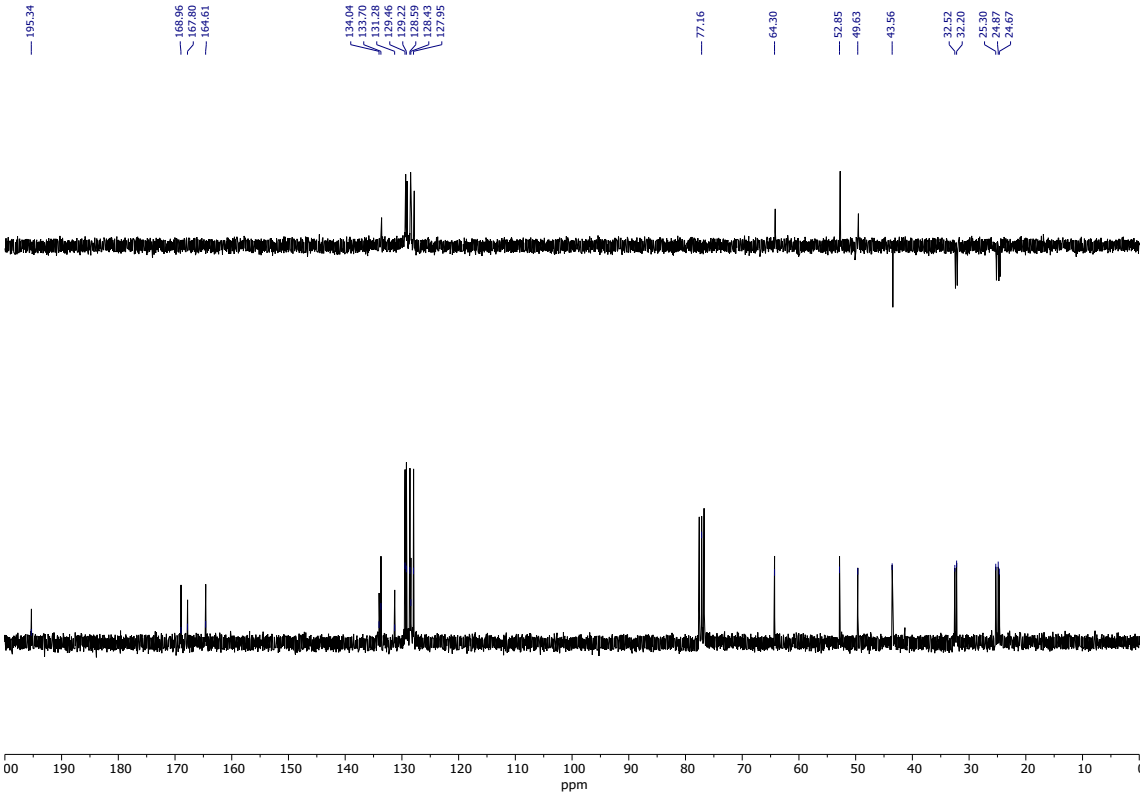


Figure S114. ^{13}C and DEPT-135 NMR spectra of **6q$_{diast2}$** (75 MHz, $CDCl_3$).

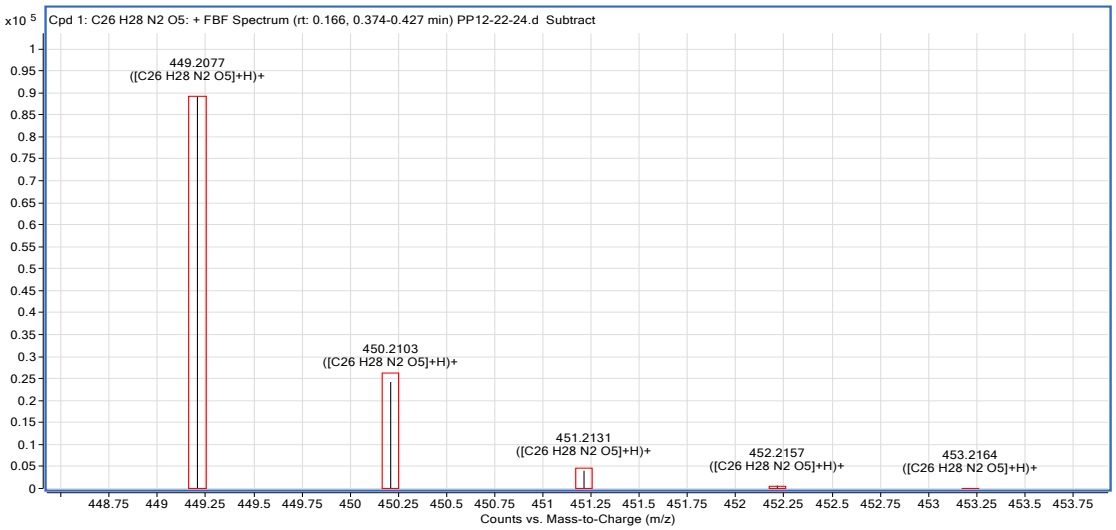


Figure S115. HRMS (+ESI) spectrum of **6q$_{diast2}$**.

(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-1'-phenylmethyl)-3-phenylazetidin-2-one (6r)

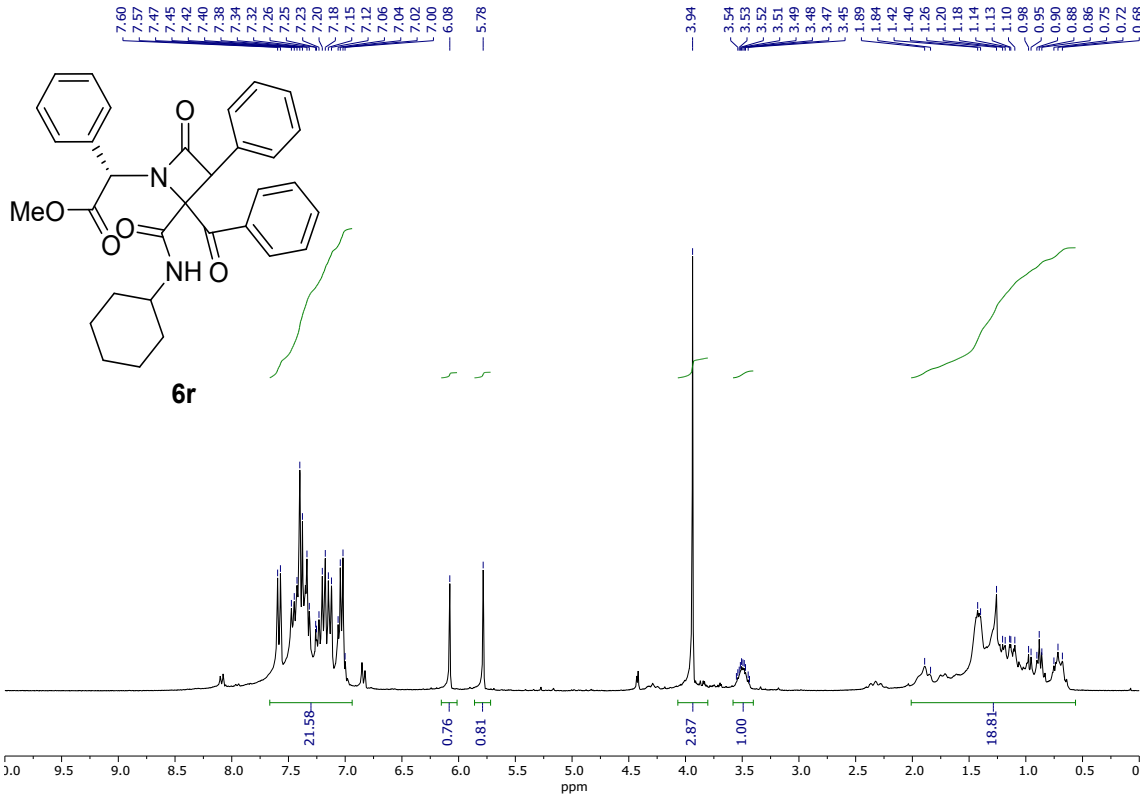


Figure S116. ^{1}H NMR spectrum of **6r** (300 MHz, $CDCl_3$).

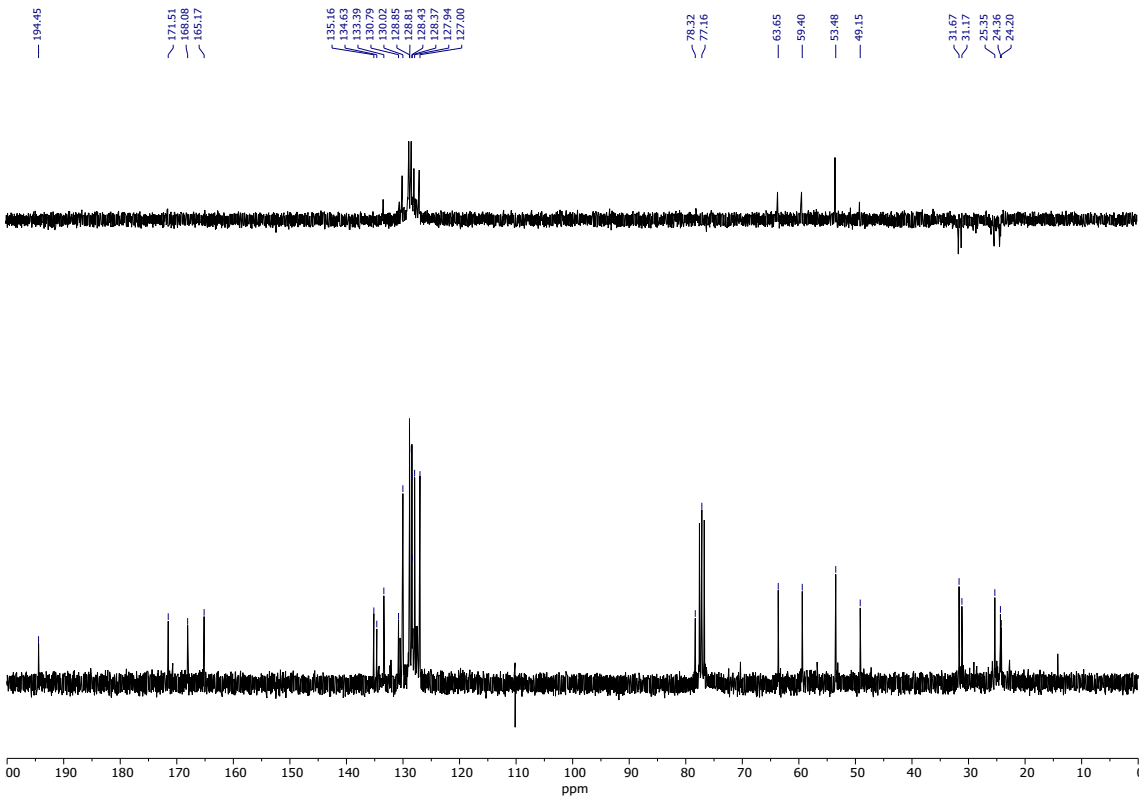


Figure S117. ^{13}C and DEPT-135 NMR spectra of **6r** (75 MHz, $CDCl_3$).

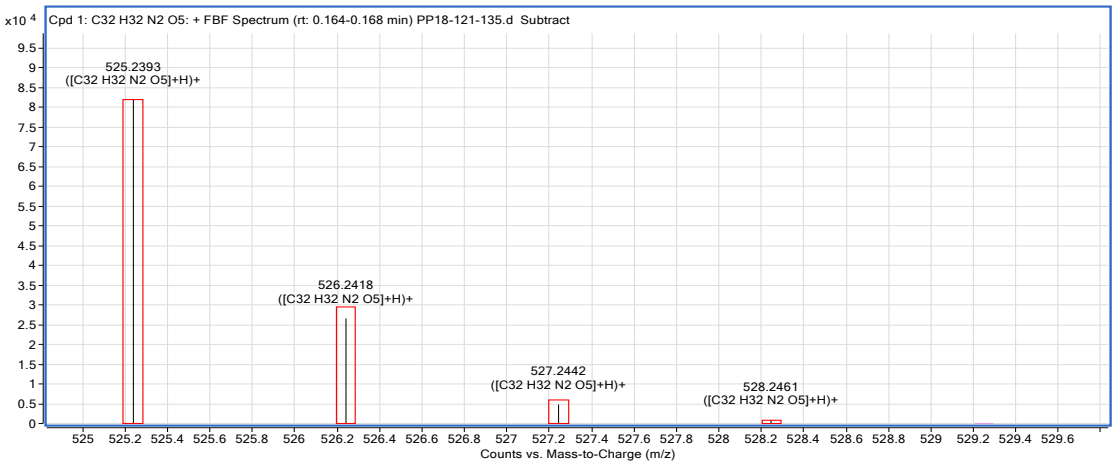


Figure S118. HRMS (+ESI) spectrum of **6r**.

(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonylethyl)-3-in-2-one (6s)

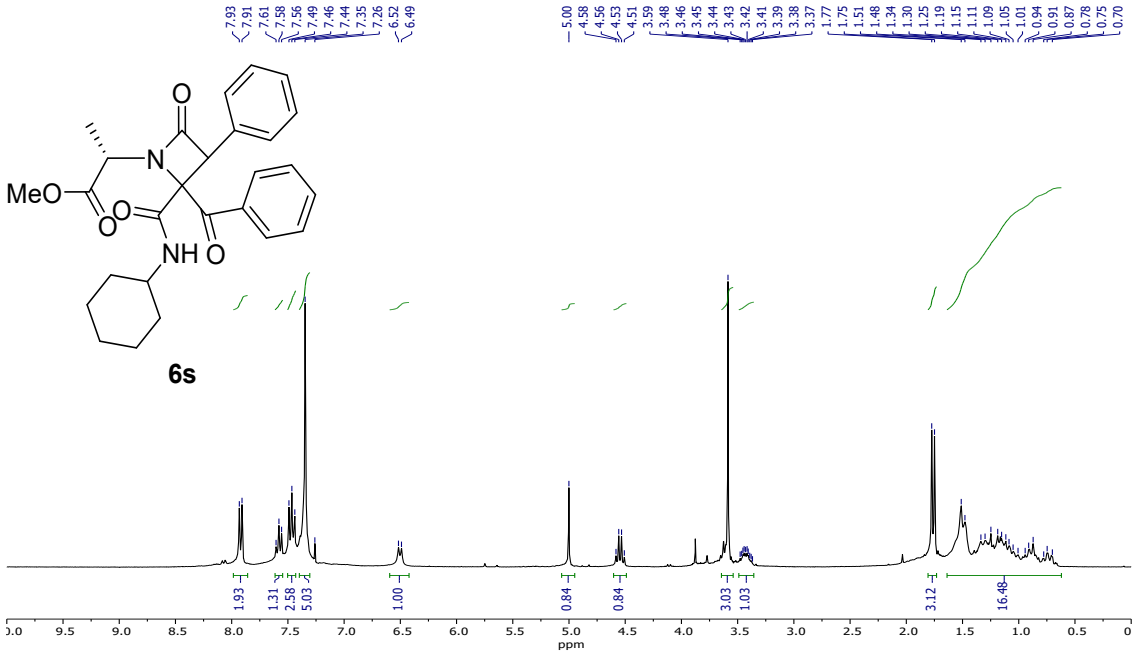


Figure S119. ^{1}H NMR spectrum of **6s** (300 MHz, $CDCl_3$).

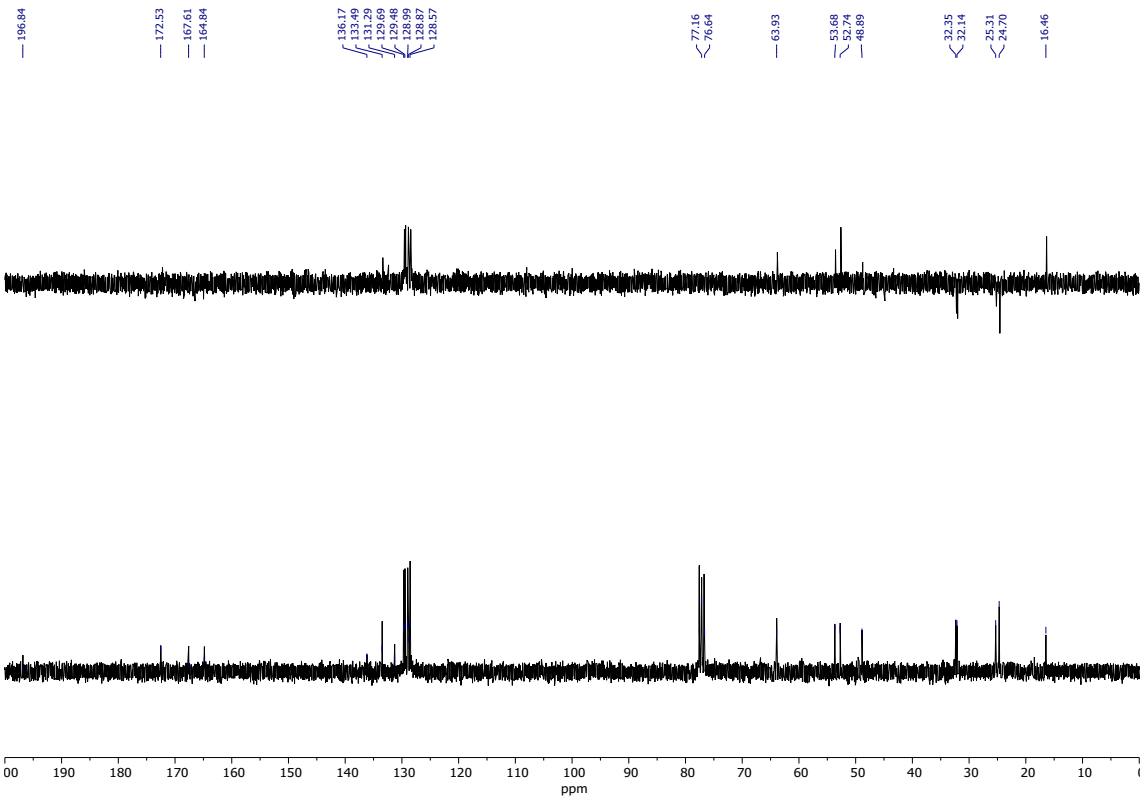


Figure S120. ^{13}C and DEPT-135 NMR spectra of **6s** (75 MHz, $CDCl_3$).

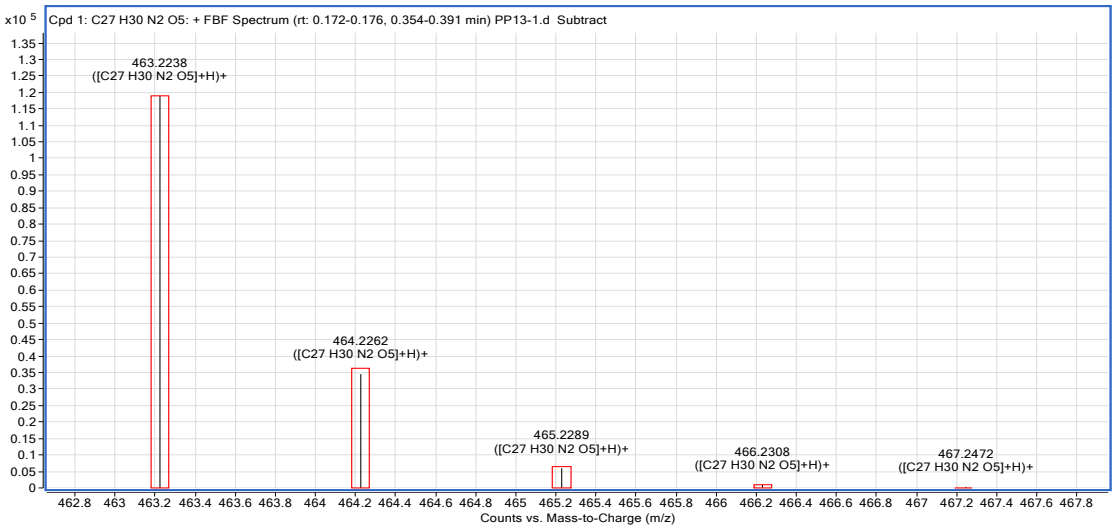


Figure S121. HRMS (+ESI) spectrum of **6s**.

(1'*S*)-4-Benzoyl-4-cyclohexylcarbamoyl-1-(1'-methoxycarbonyl-2'-phenylethyl)-3-phenylazetidin-2-one (6t)

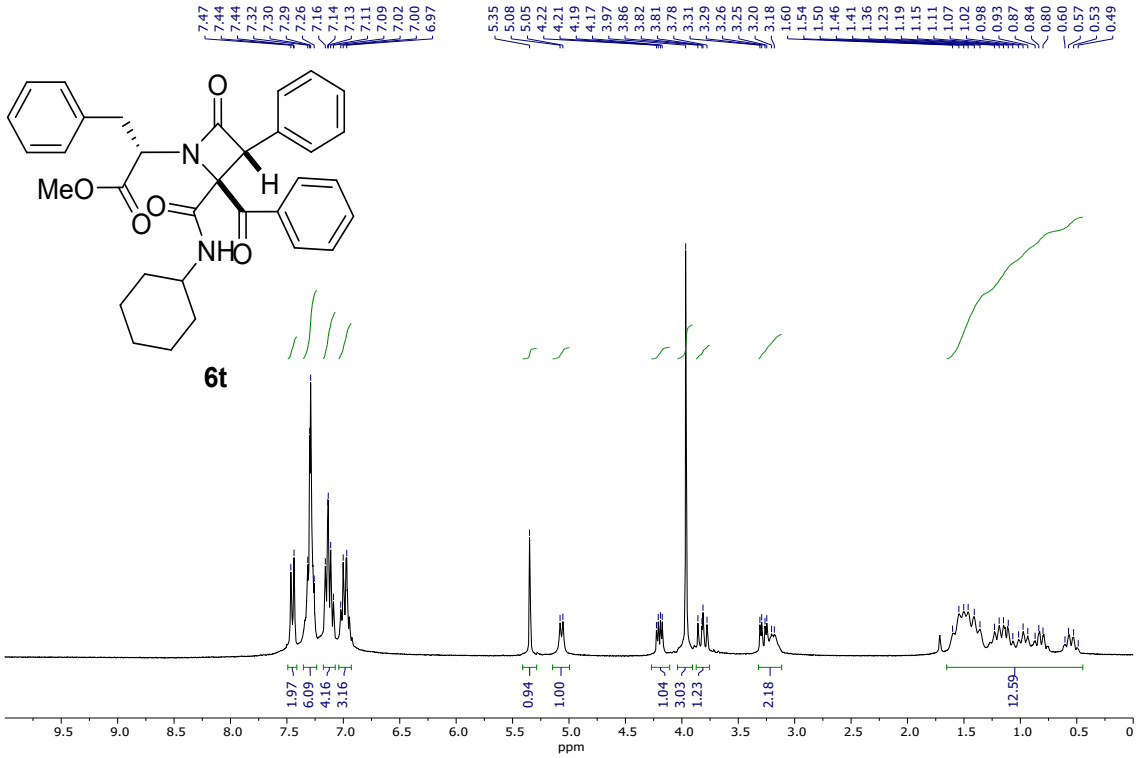


Figure S122. ^{1}H NMR spectrum of **6t** (300 MHz, $CDCl_3$).

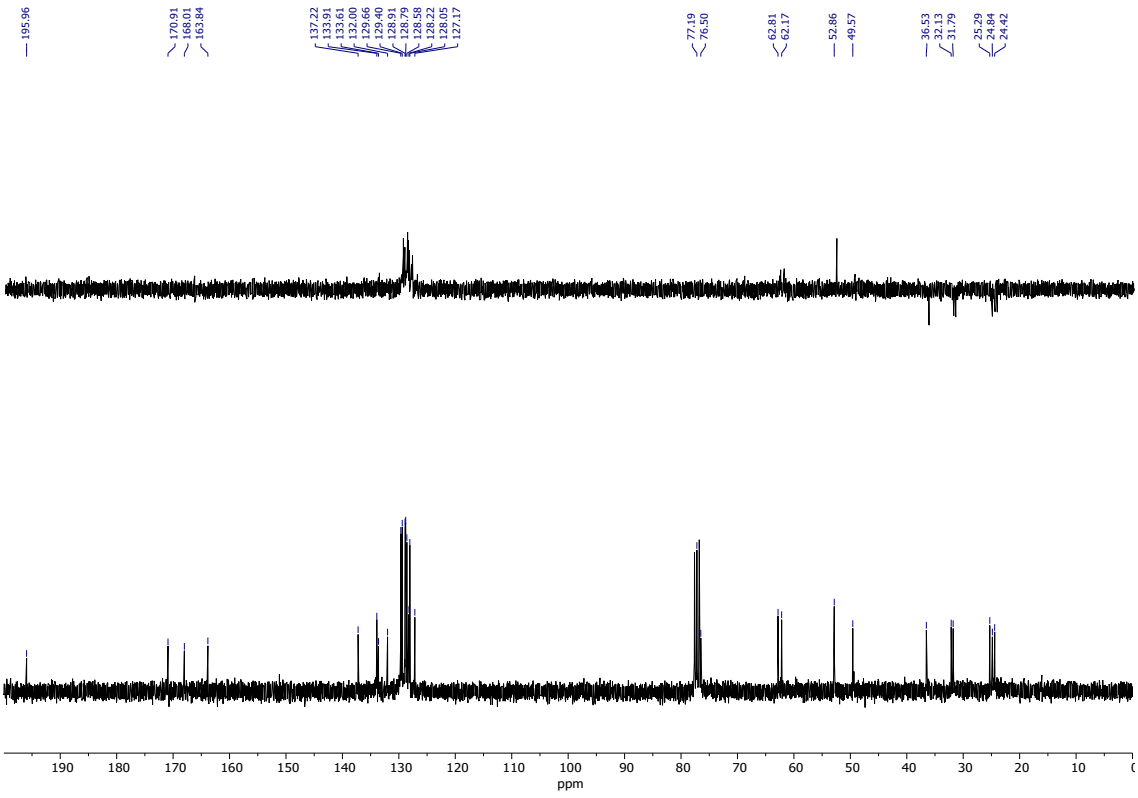


Figure S123. ^{13}C and DEPT-135 NMR spectra of **6t** (75 MHz, $CDCl_3$).

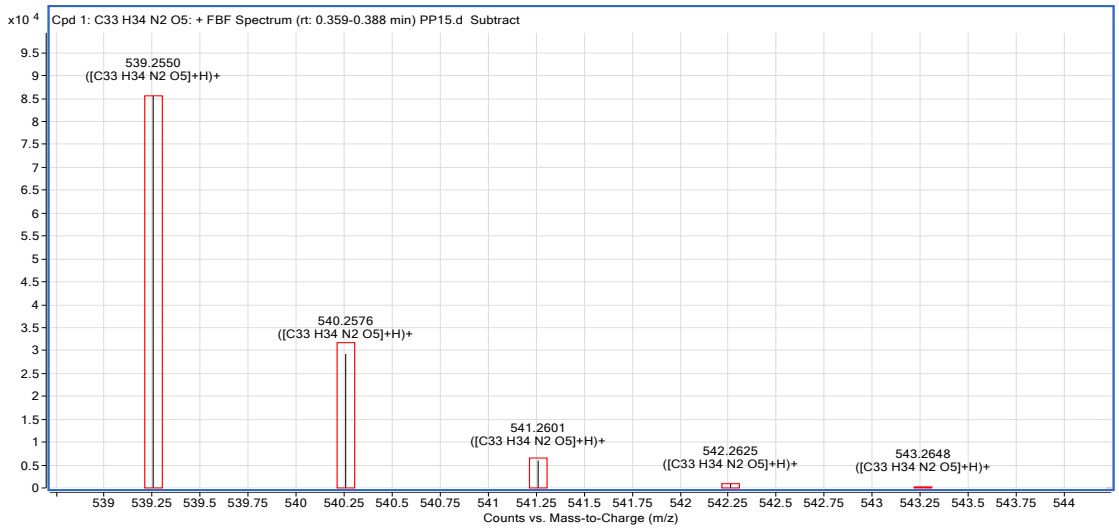


Figure S124. HRMS (+ESI) spectrum of **6t**.

(4*R,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (7a)**

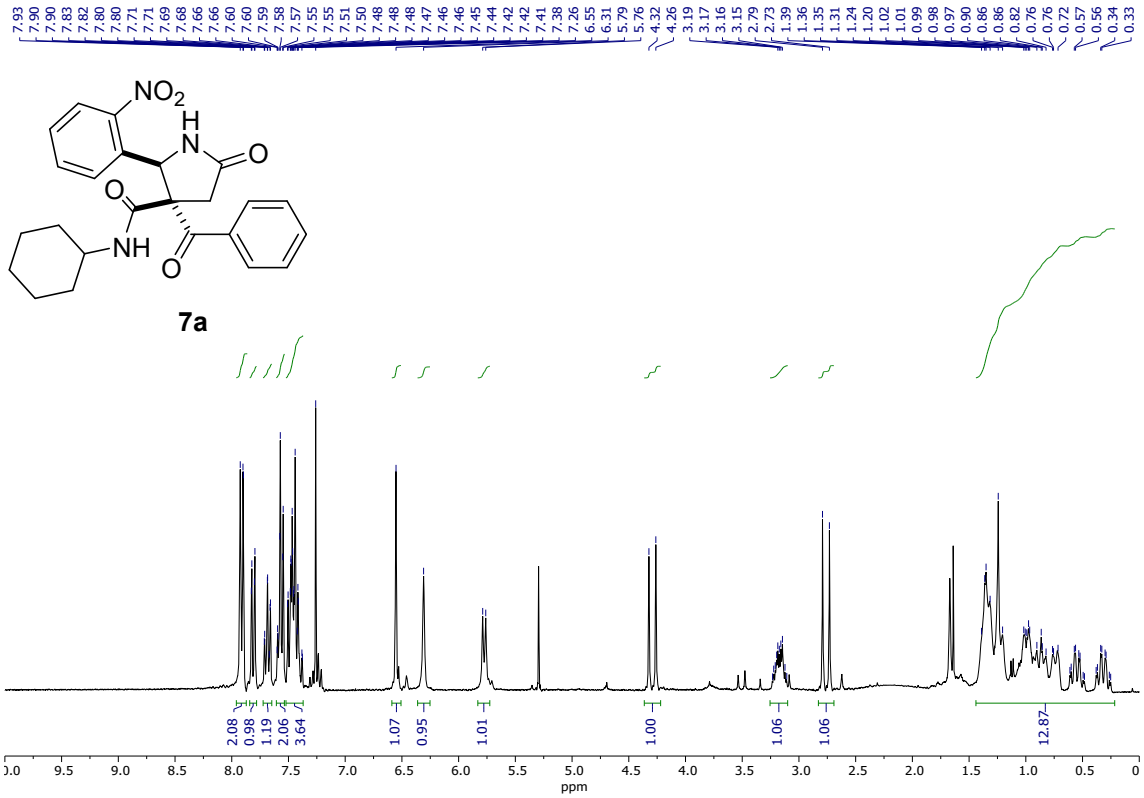


Figure S125. ^{1}H NMR spectrum of **7a** (300 MHz, $CDCl_3$).

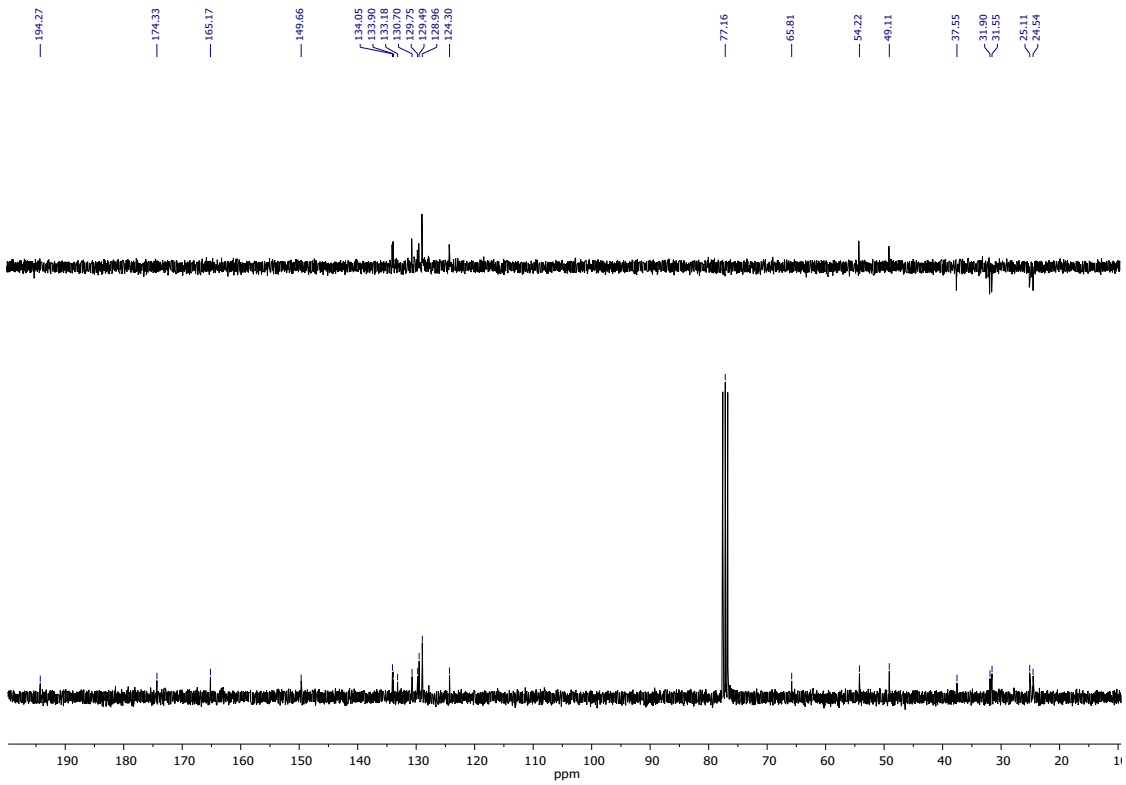


Figure S126. ^{13}C and DEPT-135 NMR spectra of **7a** (75 MHz, $CDCl_3$).

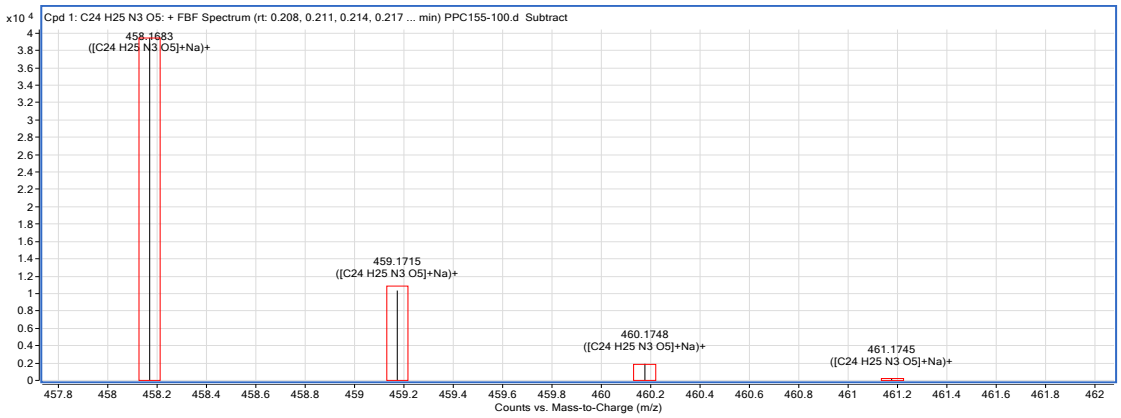


Figure S127. HRMS (+ESI) spectrum of **7a**.

(4*R,5*R**)-4-Benzoyl-4-benzylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (7b)**

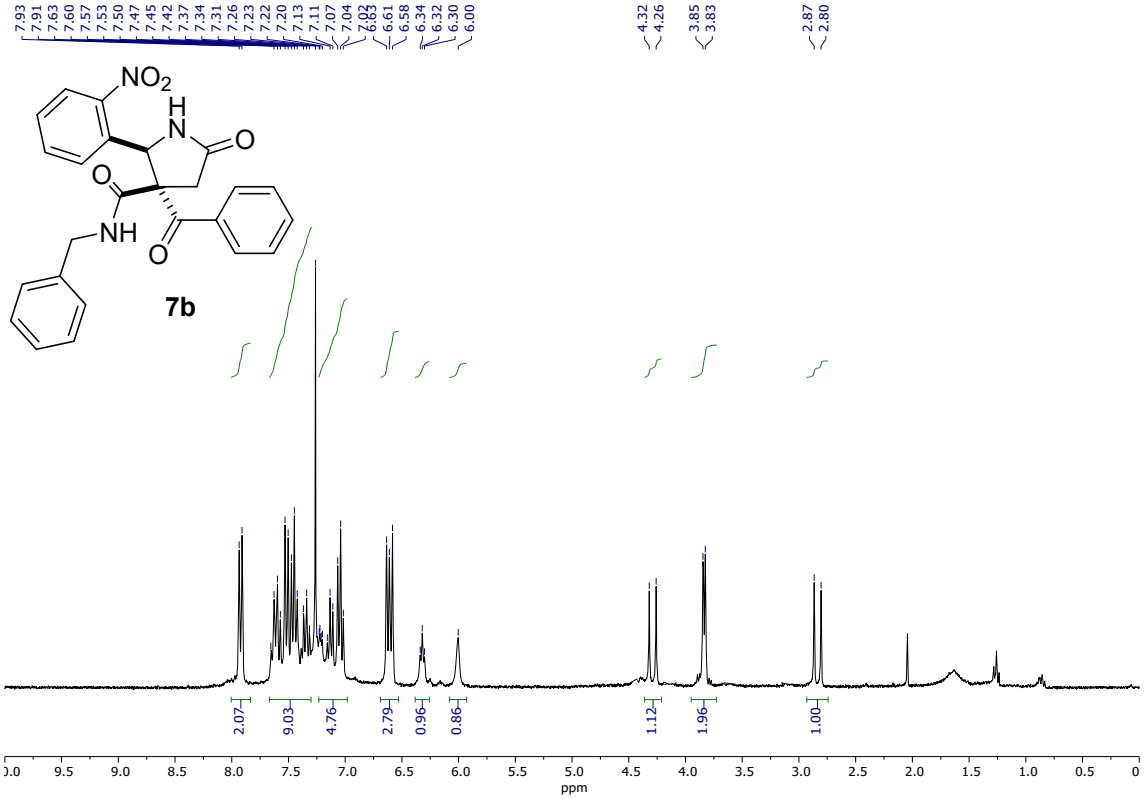


Figure S128. ^{1}H NMR spectrum of **7b** (300 MHz, $CDCl_3$).

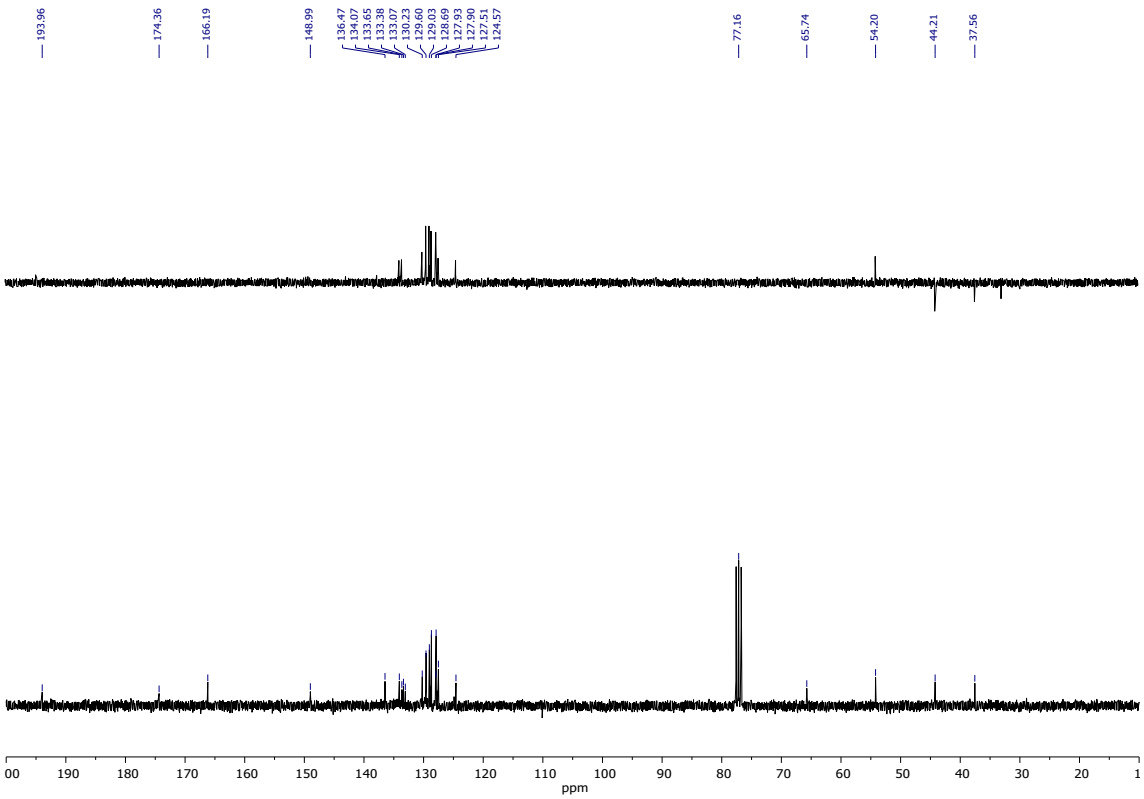


Figure S129. ^{13}C and DEPT-135 NMR spectra of **7b** (75 MHz, $CDCl_3$).

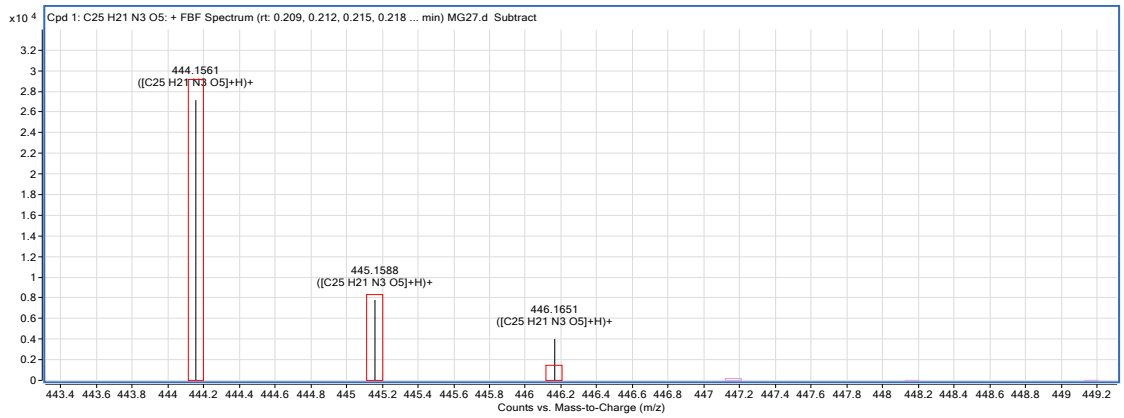


Figure S130. HRMS (+ESI) spectrum of **7b**.

(4*R,5*R**)-4-Benzoyl-4-(*tert*-butylcarbamoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (7c)**

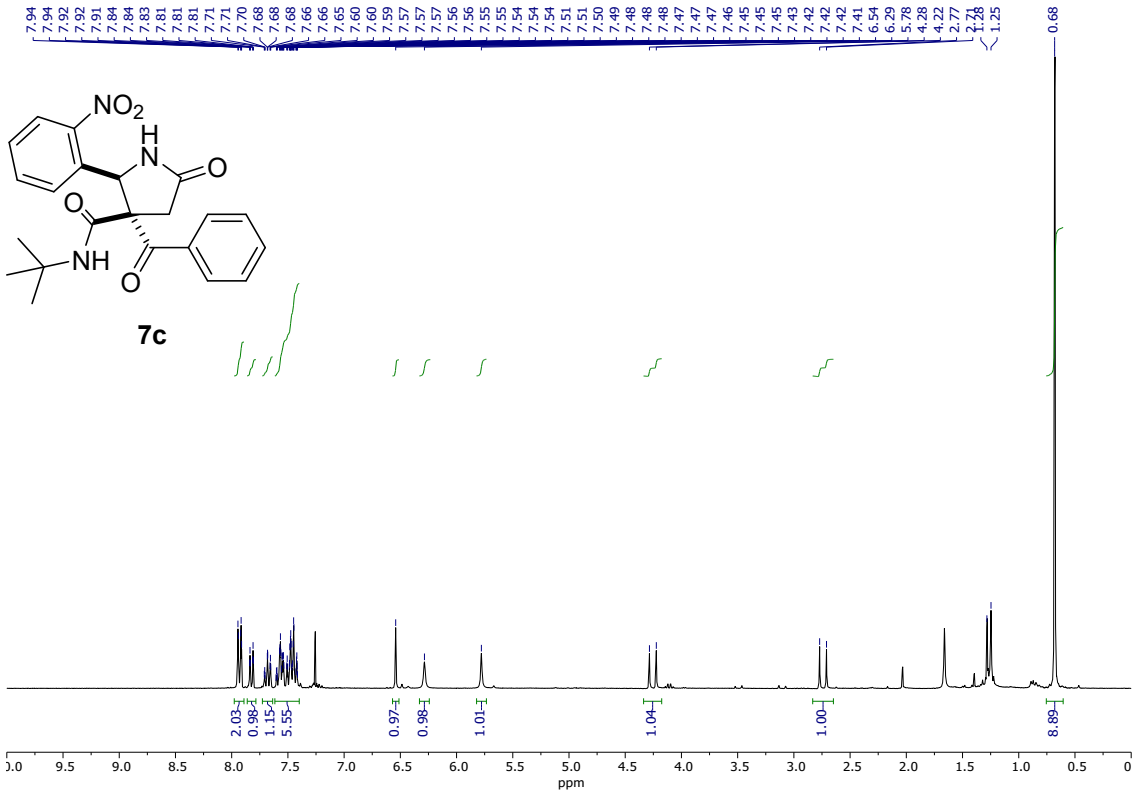


Figure S131. ^{1}H NMR spectrum of **7c** (300 MHz, $CDCl_3$).

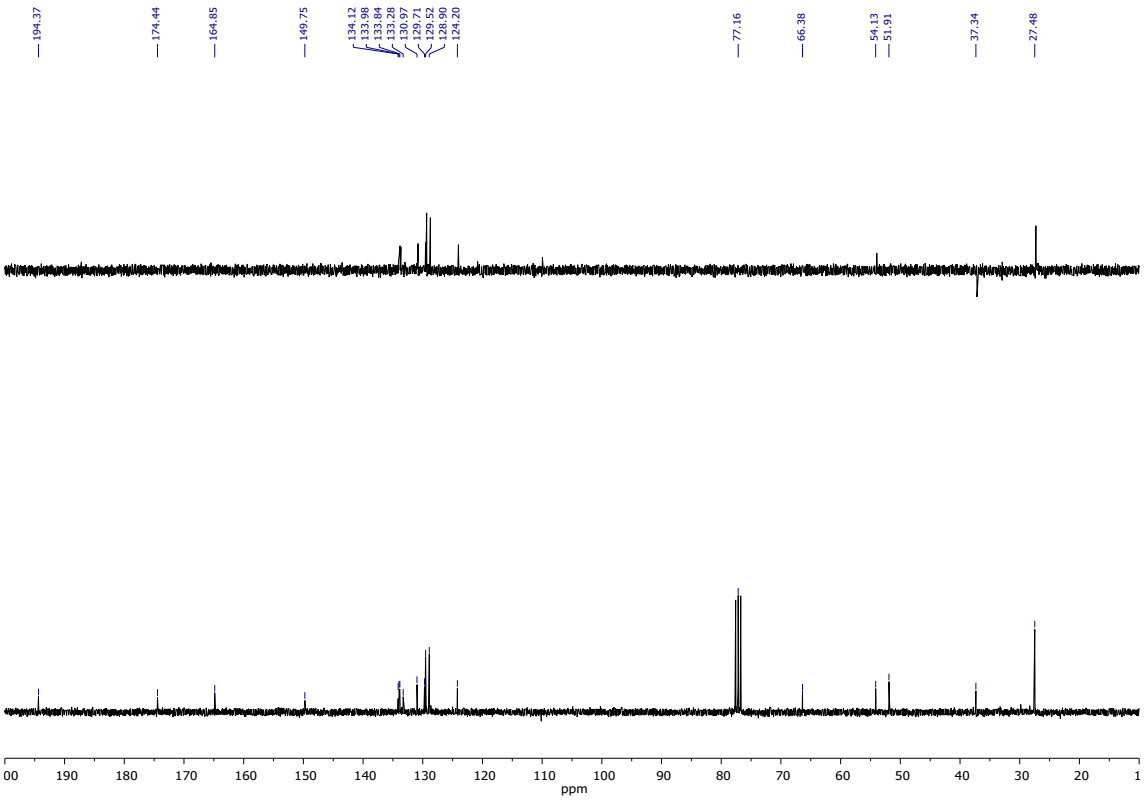


Figure S132. ^{13}C and DEPT-135 NMR spectra of **7c** (75 MHz, $CDCl_3$).

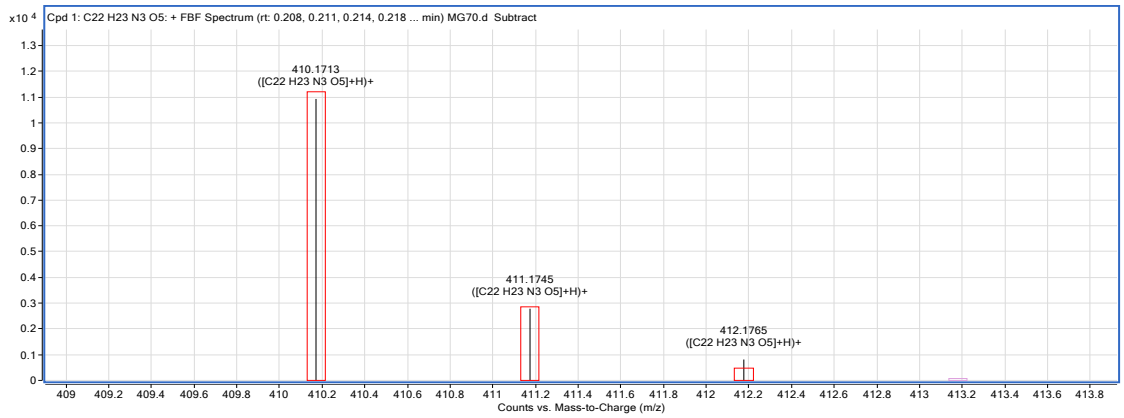


Figure S133. HRMS (+ESI) spectrum of **7c**.

(4*R,5*R**)-4-Cyclohexylcarbamoyl-4-(4-methylbenzoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (7d)**

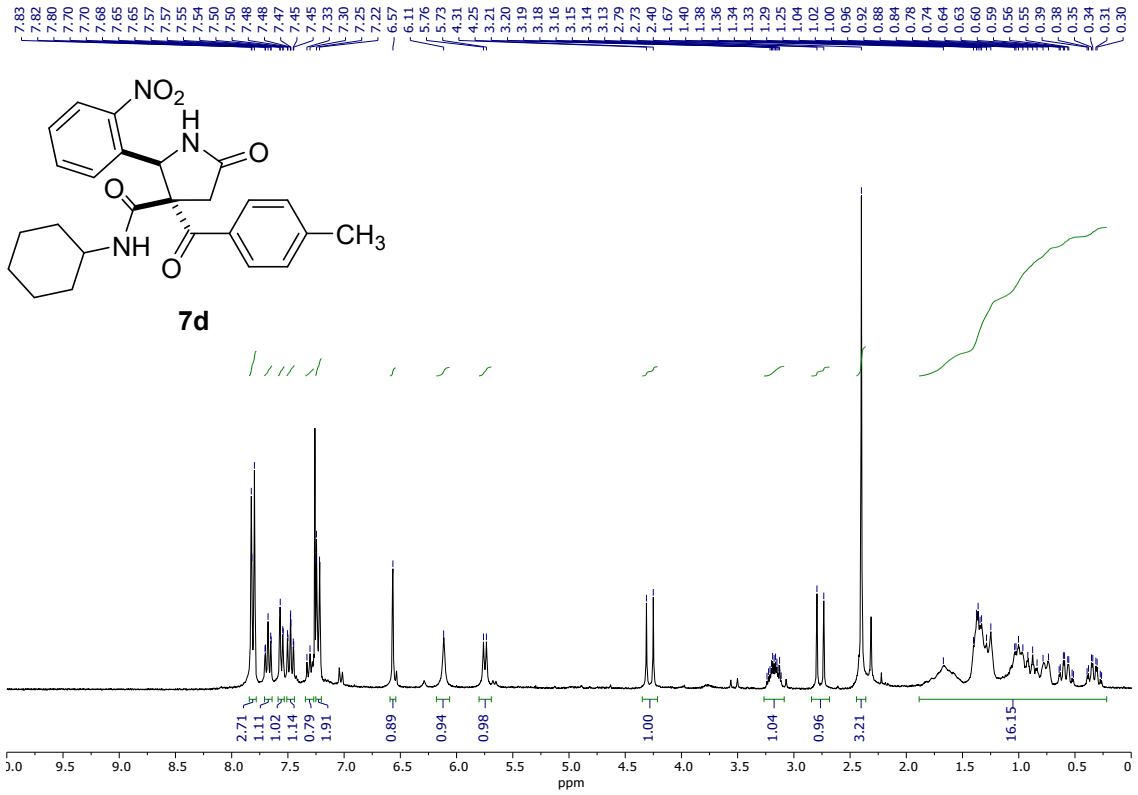


Figure S134. ^{1}H NMR spectrum of **7d** (300 MHz, $CDCl_3$).

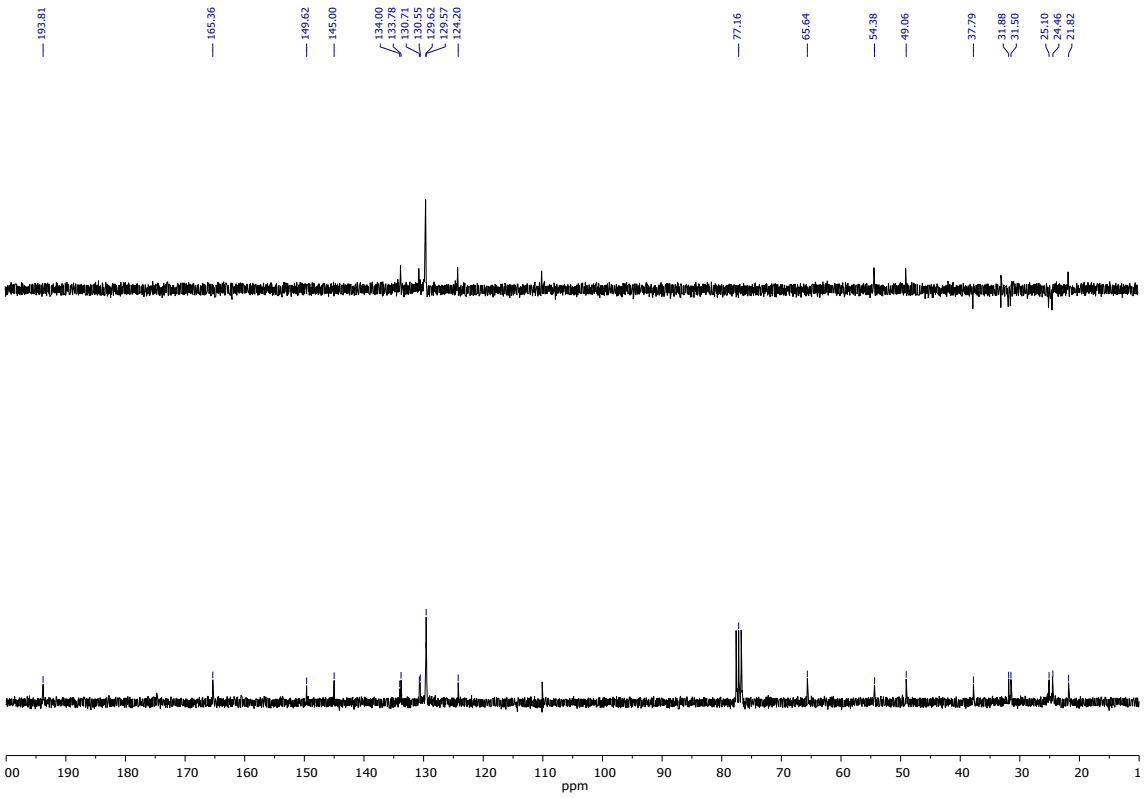


Figure S135. ^{13}C and DEPT-135 NMR spectra of **7d** (75 MHz, $CDCl_3$).

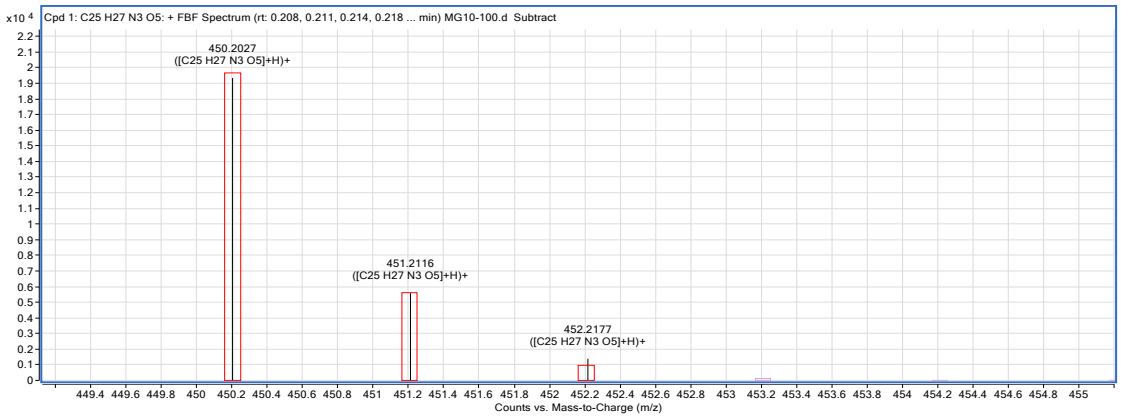


Figure S136. HRMS (+ESI) spectrum of **7d**.

(4*R,5*R**)-4-(4-Chlorobenzoyl)-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (7e)**

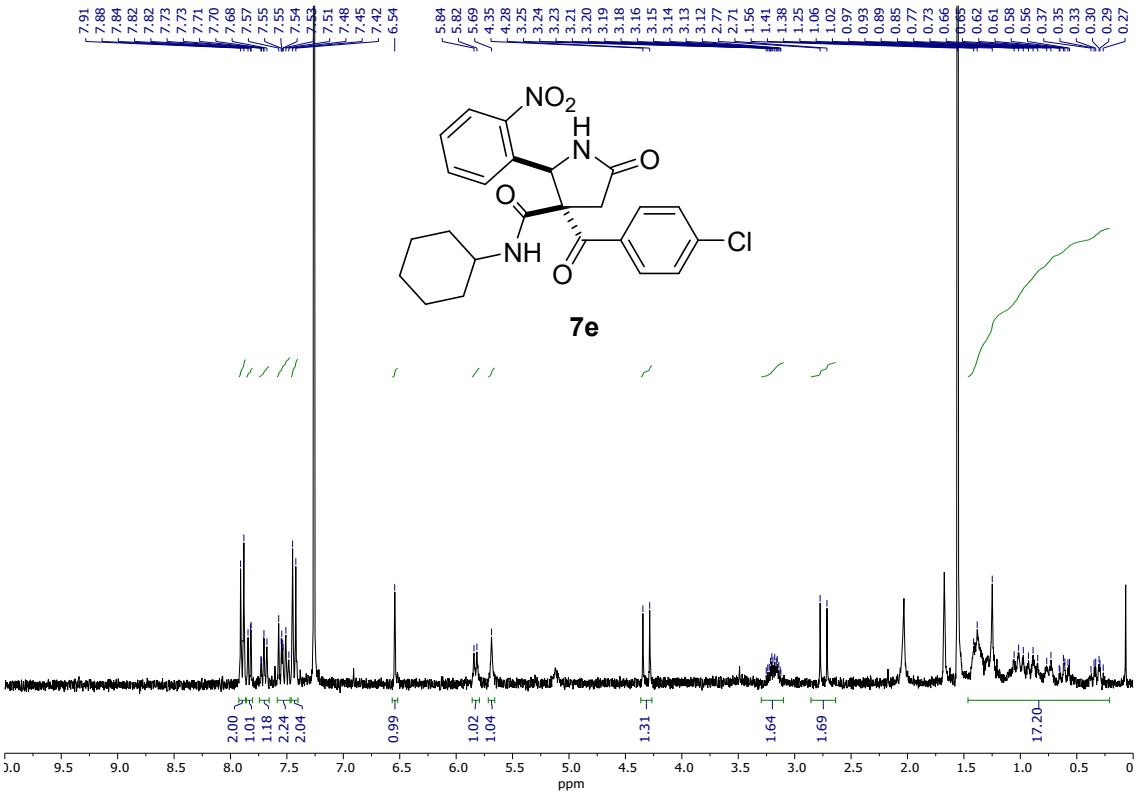


Figure S137. ^{1}H NMR spectrum of **7e** (300 MHz, $CDCl_3$).

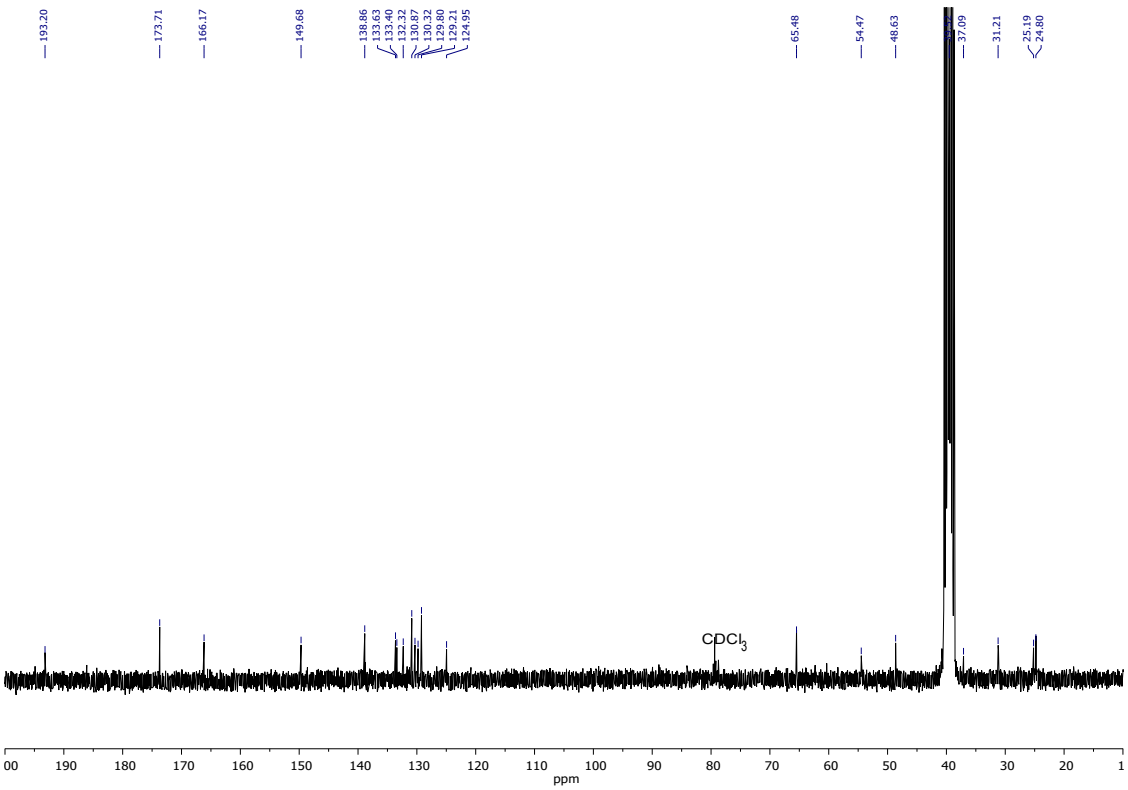


Figure S138. ^{13}C NMR spectrum of **7e** (75 MHz, $CDCl_3$).

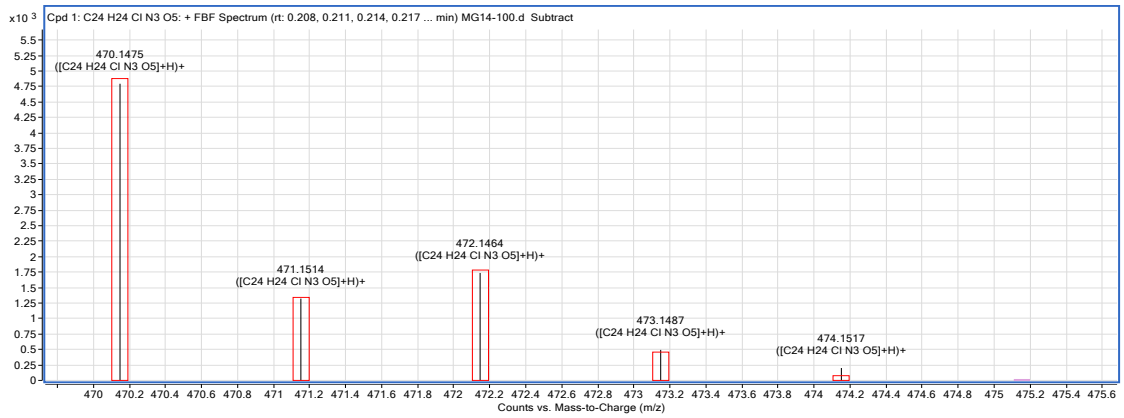


Figure S139. HRMS (+ESI) spectrum of **7e**.

(4*R,5*R**)-4-Cyclohexylcarbamoyl-4-(4-fluorobenzoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (7f)**

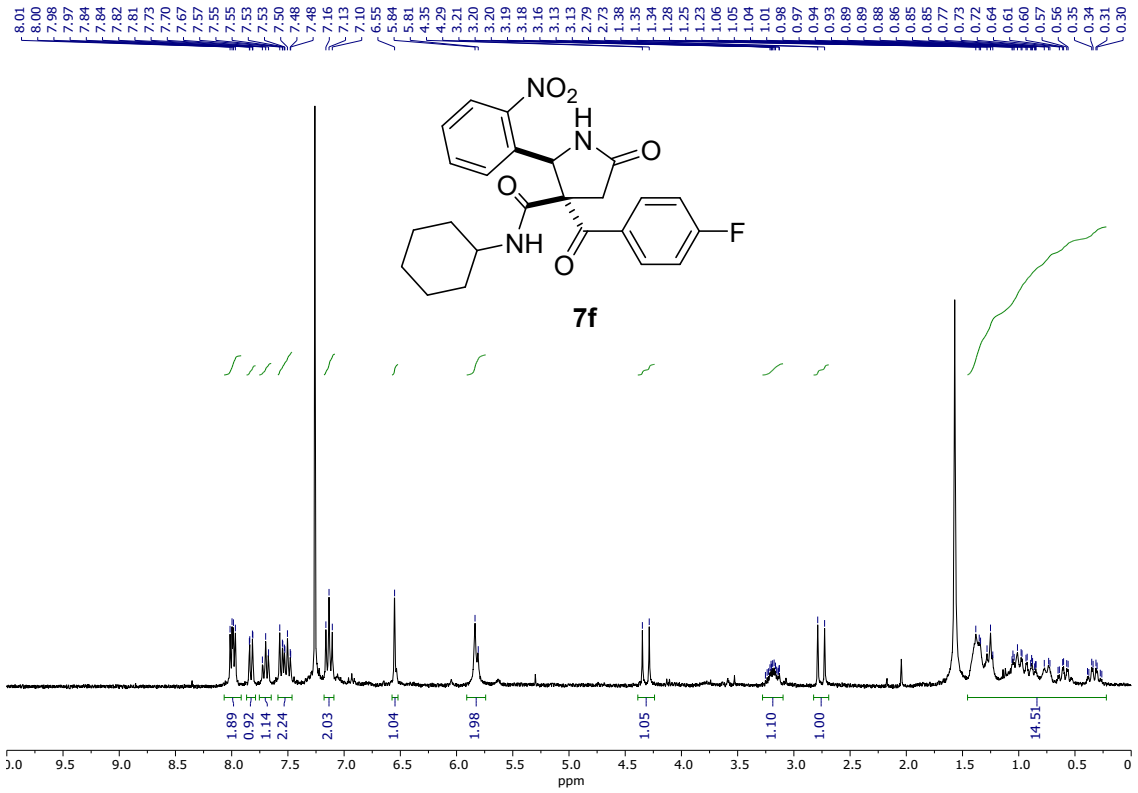


Figure S140. ^{1}H NMR spectrum of **7f** (300 MHz, $CDCl_3$).

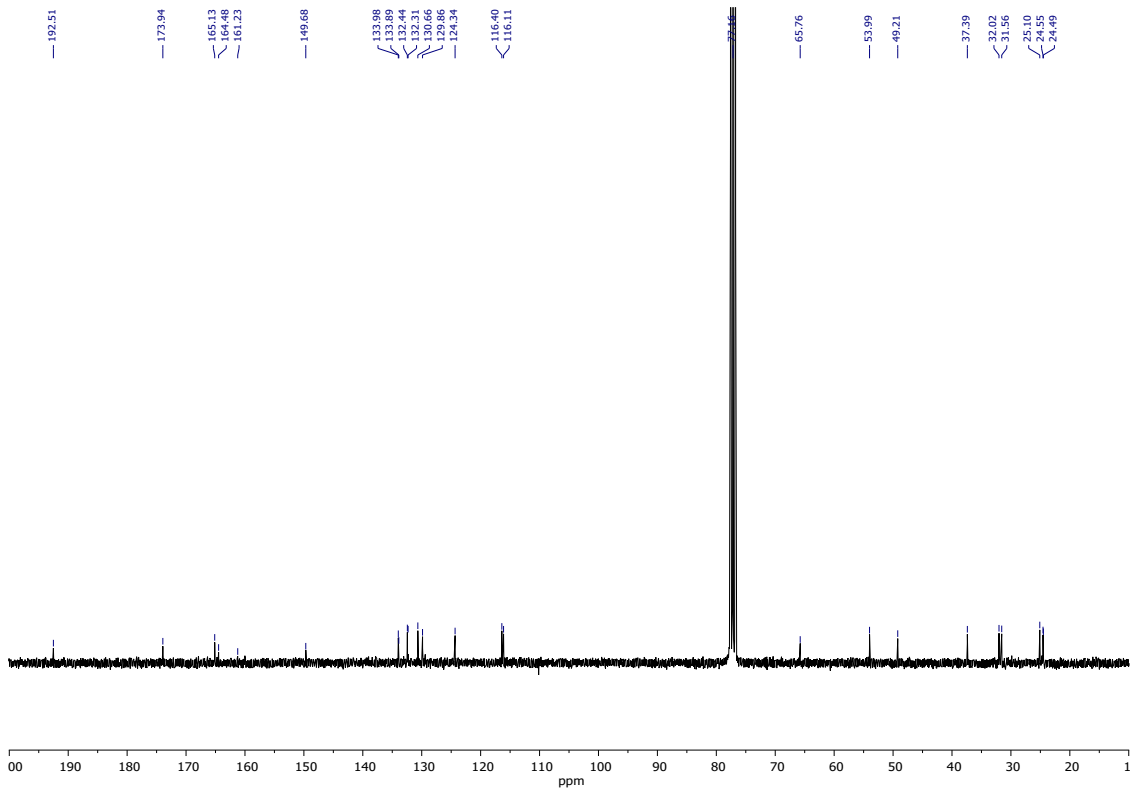


Figure S141. ^{13}C NMR spectrum of **7f** (75 MHz, $CDCl_3$).

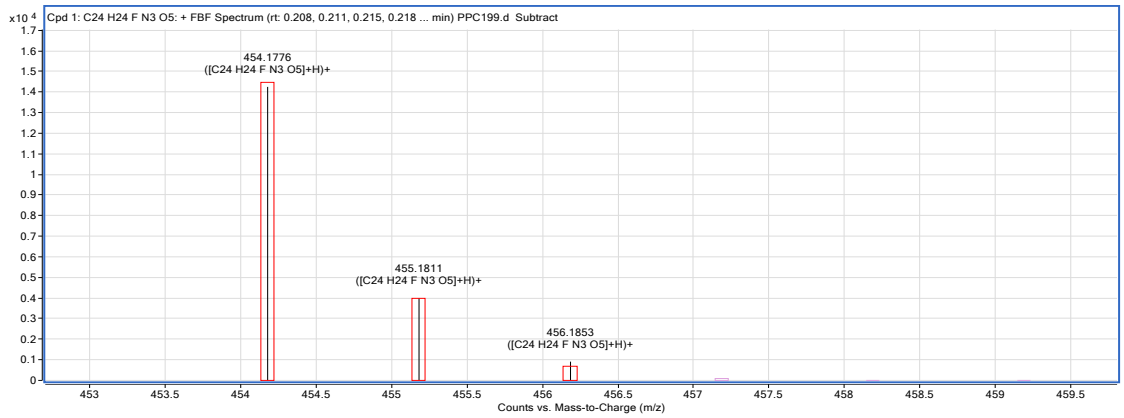


Figure S142. HRMS (+ESI) spectrum of **7f**.

(4*R,5*R**)-4-Cyclohexylcarbamoyl-4-(4-methoxybenzoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (7g)**

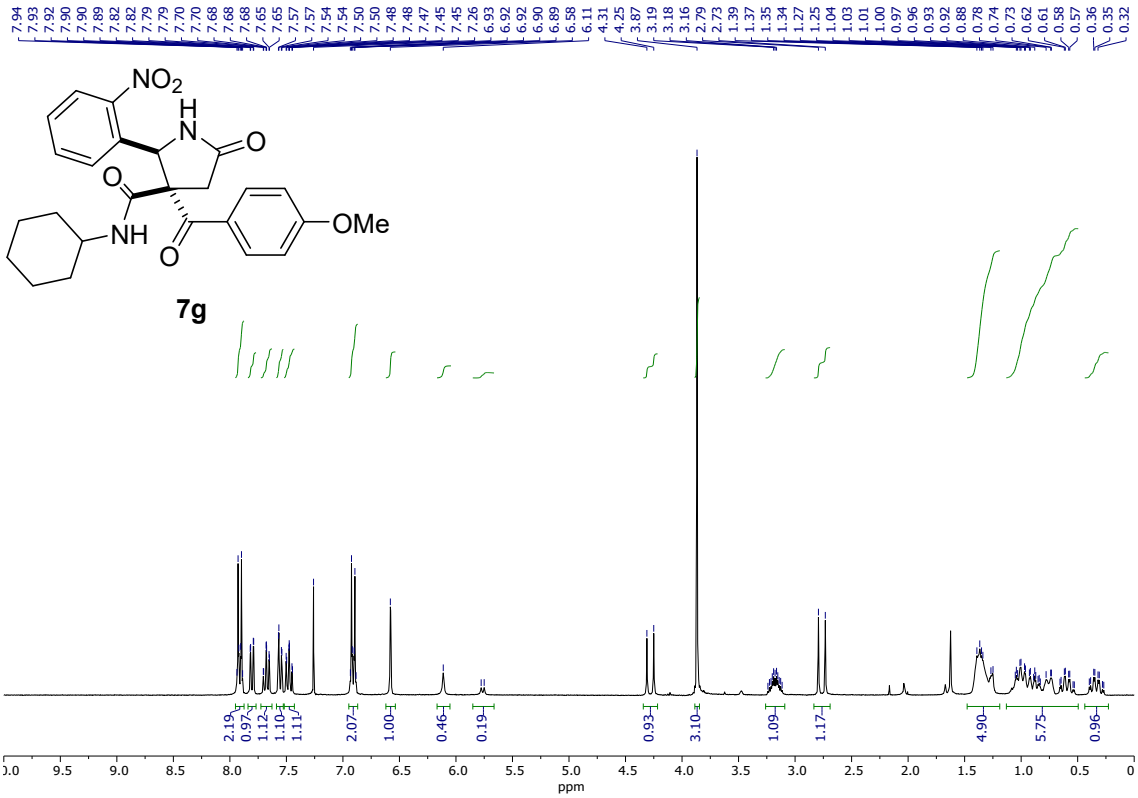


Figure S143. ^{1}H NMR spectrum of **7g** (300 MHz, $CDCl_3$).

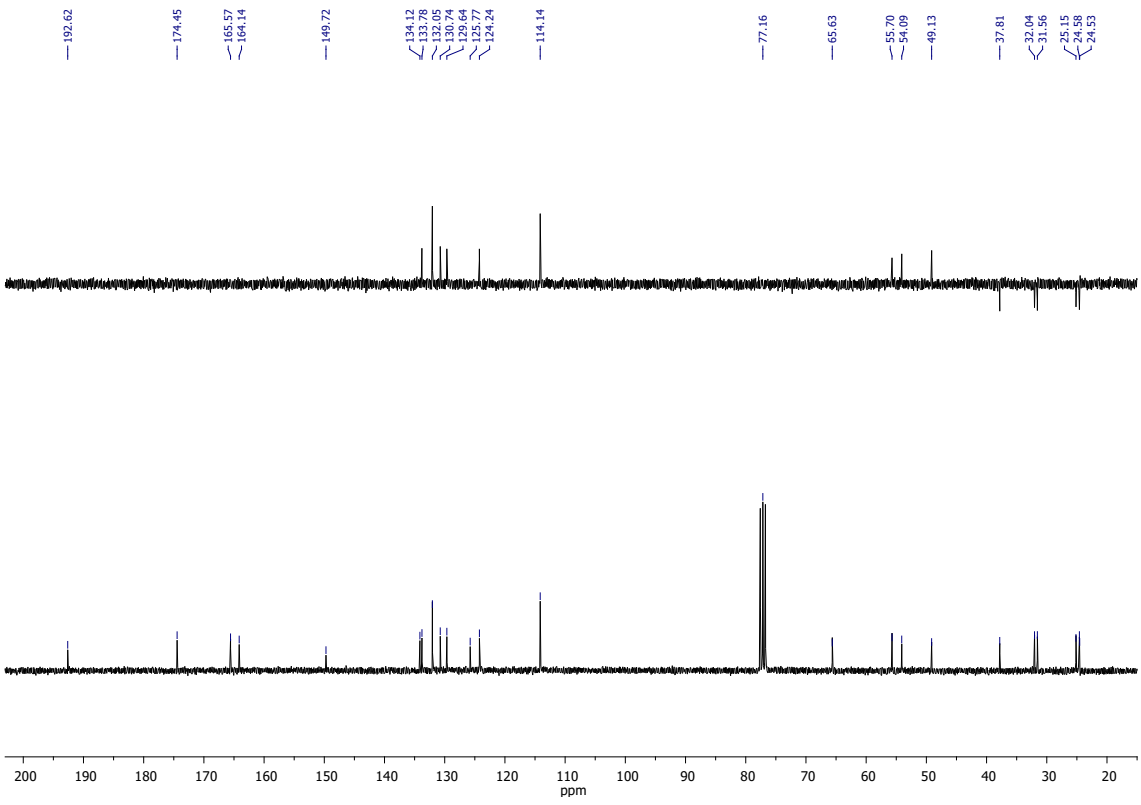


Figure S144. ^{13}C and DEPT-135 NMR spectra of **7g** (75 MHz, $CDCl_3$).

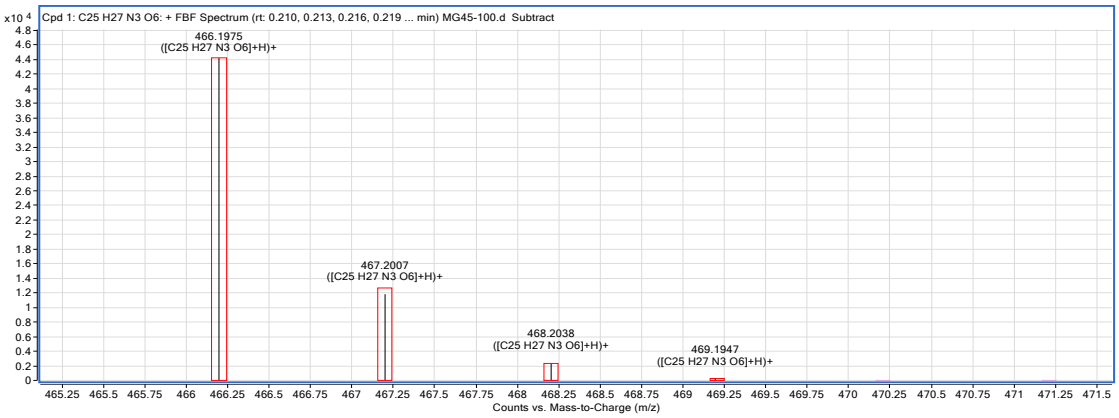


Figure S145. HRMS (+ESI) spectrum of **7g**.

(4*R,5*R**)-4-Acetyl-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (7h)**

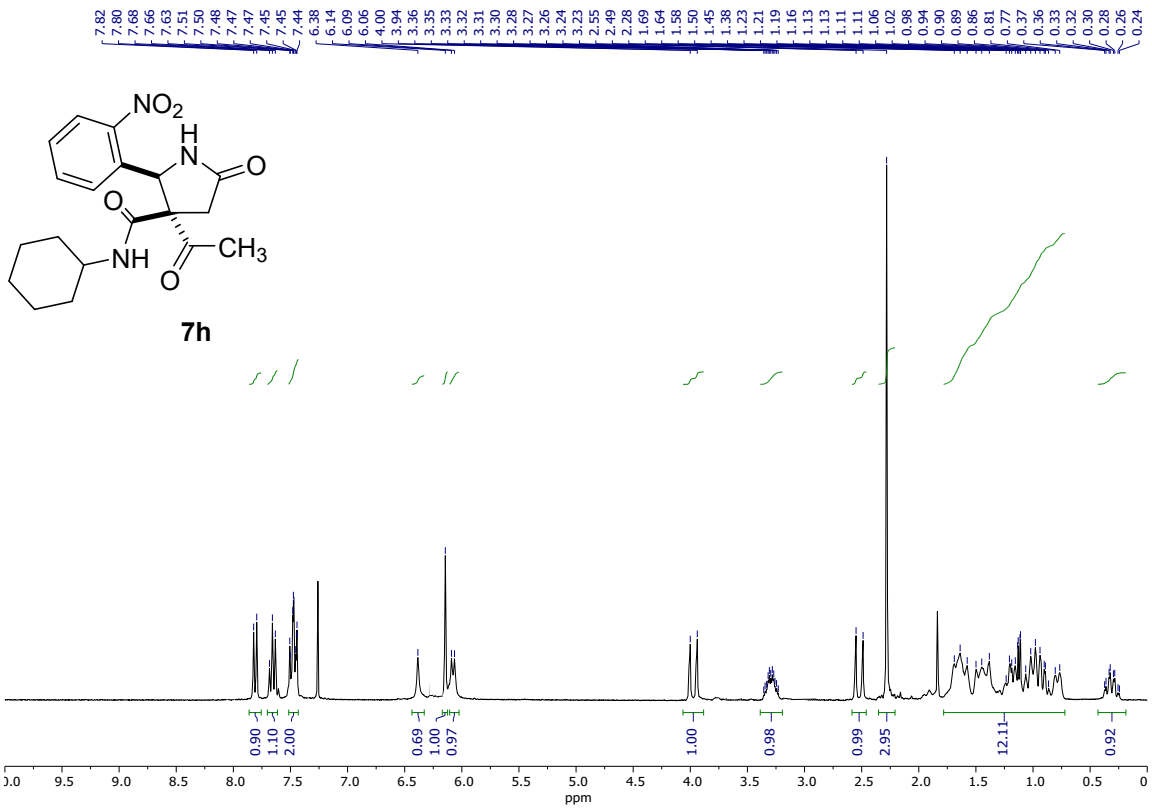


Figure S146. ^{1}H NMR spectrum of **7h** (300 MHz, $CDCl_3$).

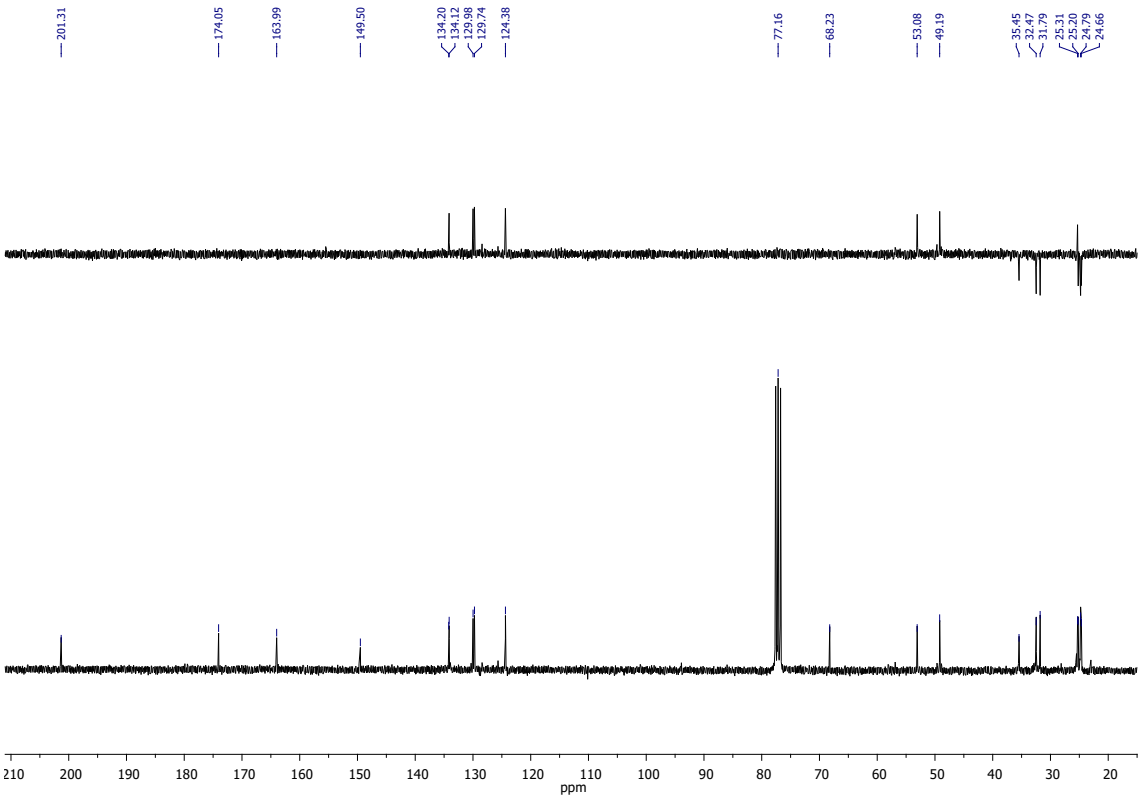


Figure S147. ^{13}C and DEPT-135 NMR spectra of **7h** (75 MHz, $CDCl_3$).

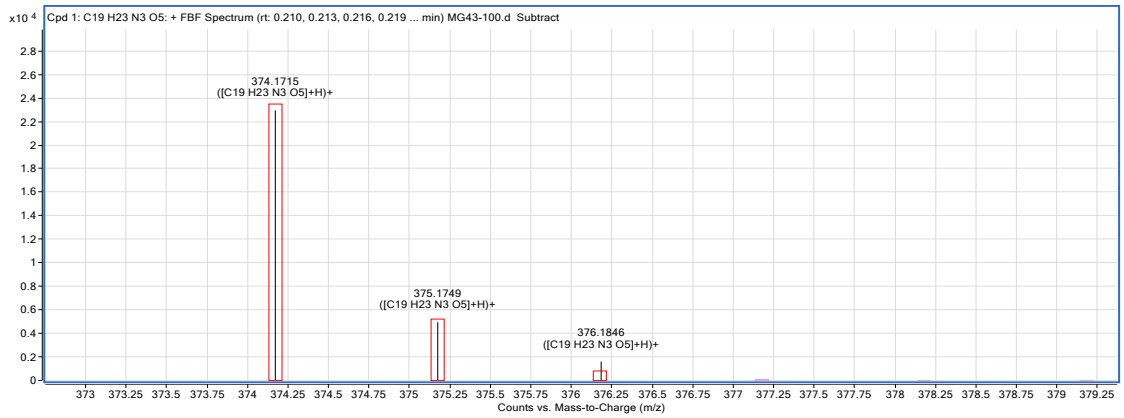


Figure S148. HRMS (+ESI) spectrum of **7h**.

(3*R,4*R**,5*S**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)-3-phenylpyrrolidin-2-one ($7i_{diast1}$)**

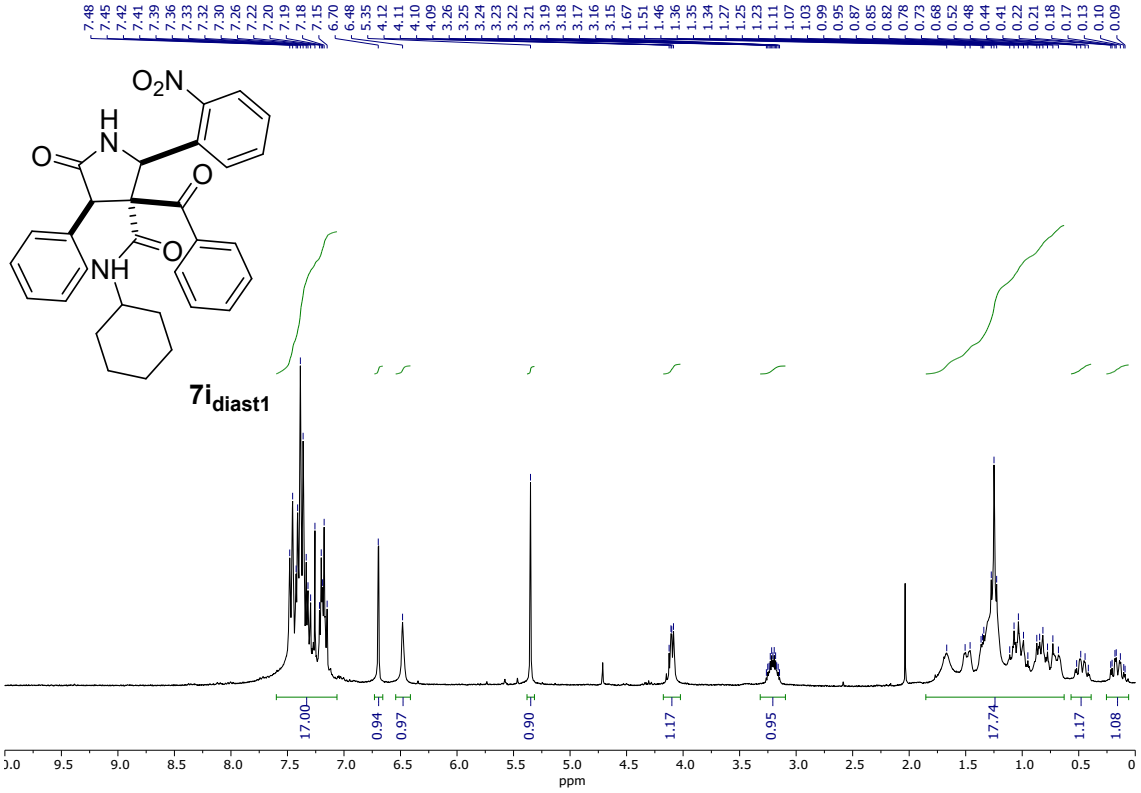


Figure S149. ^{1}H NMR spectrum of **$7i_{diast1}$** (300 MHz, $CDCl_3$).

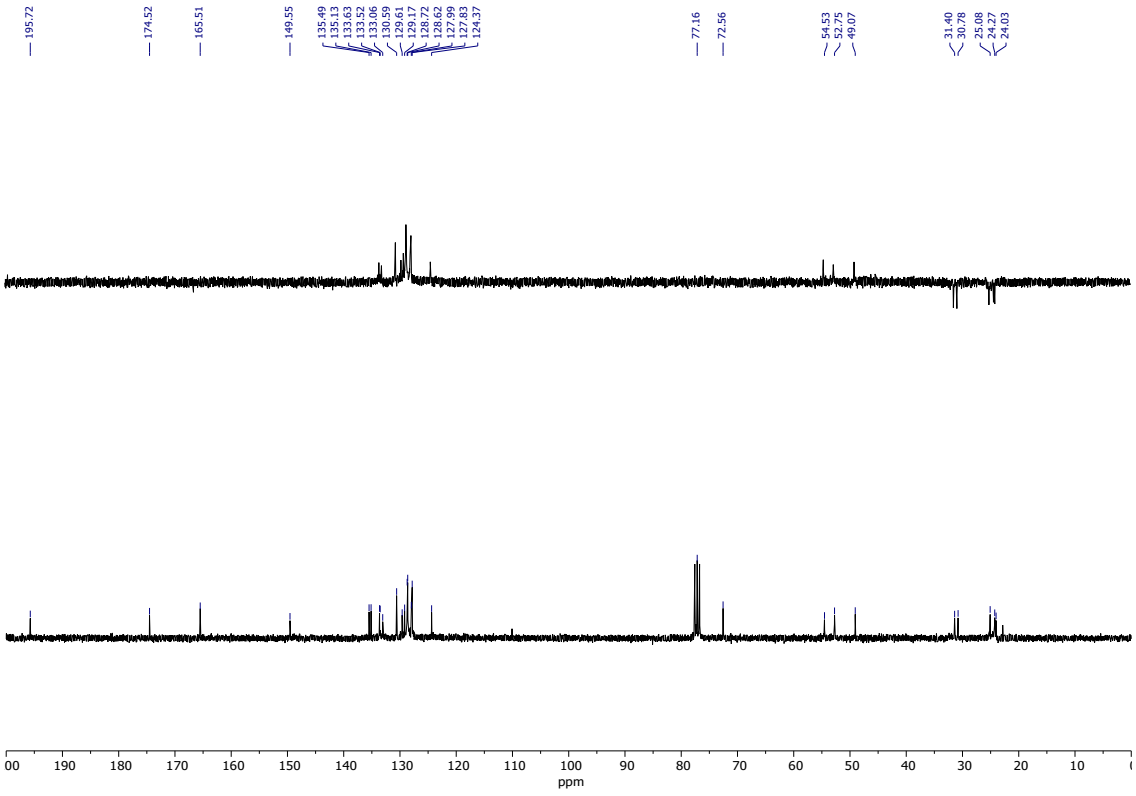


Figure S150. ^{13}C and DEPT-135 NMR spectra of **$7i_{diast1}$** (75 MHz, $CDCl_3$).

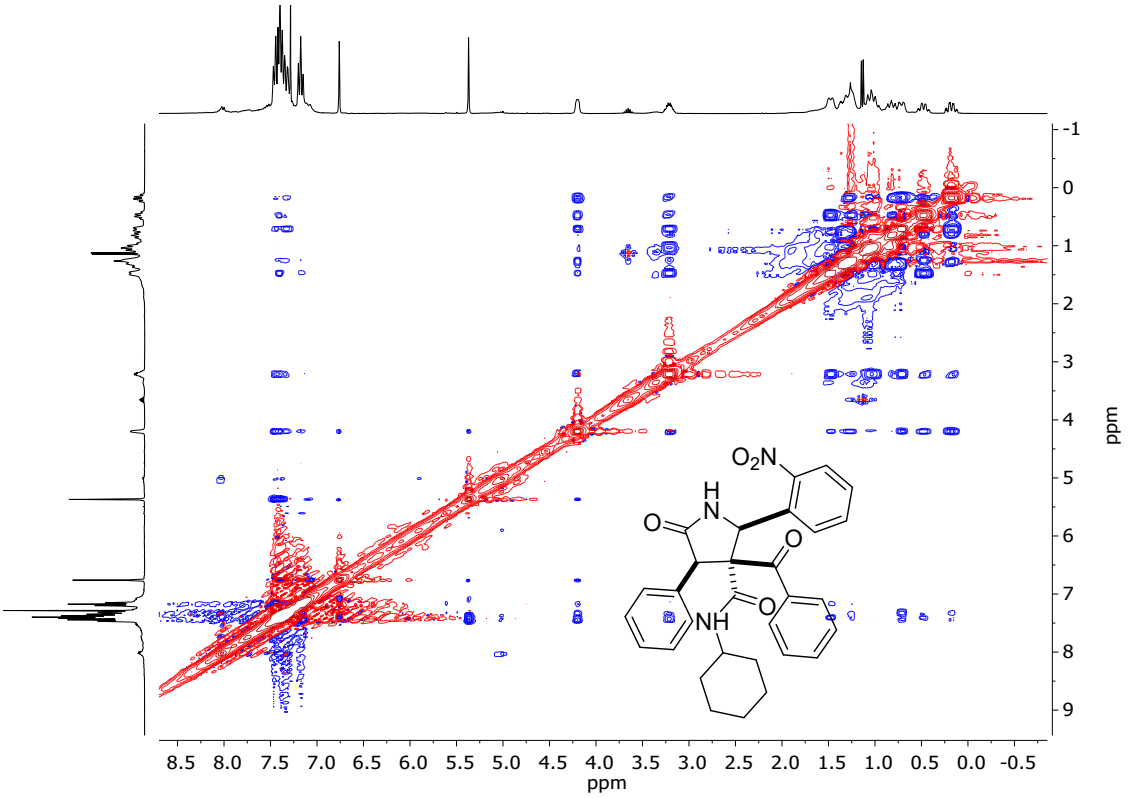


Figure S151. NOESY spectrum of **7i$_{diast1}$** (300 MHz, $CDCl_3$).

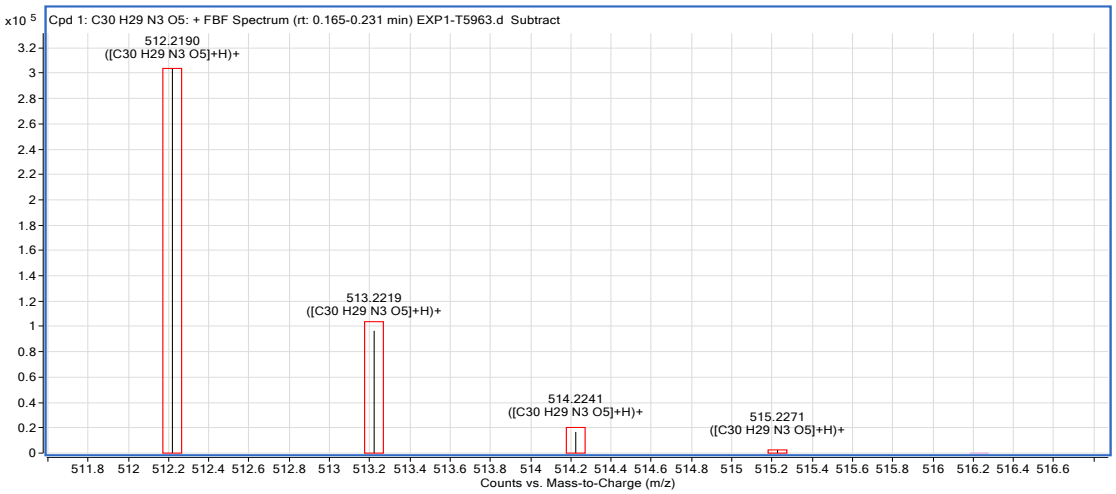


Figure S152. HRMS (+ESI) spectrum of **7i$_{diast1}$**.

(3*R,4*R**,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-(2-nitrophenyl)-3-phenylpyrrolidin-2-one ($7i_{diast2}$)**

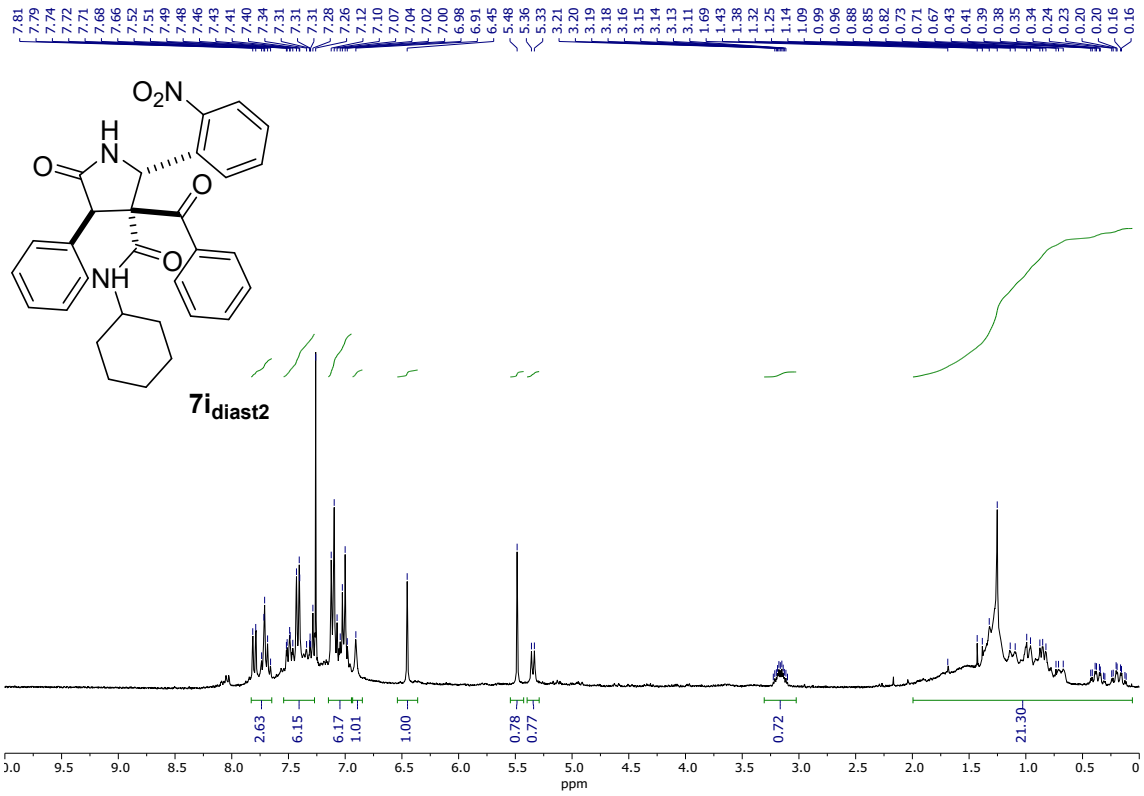


Figure S153. ^{1}H NMR spectrum of **$7i_{diast2}$** (300 MHz, $CDCl_3$).

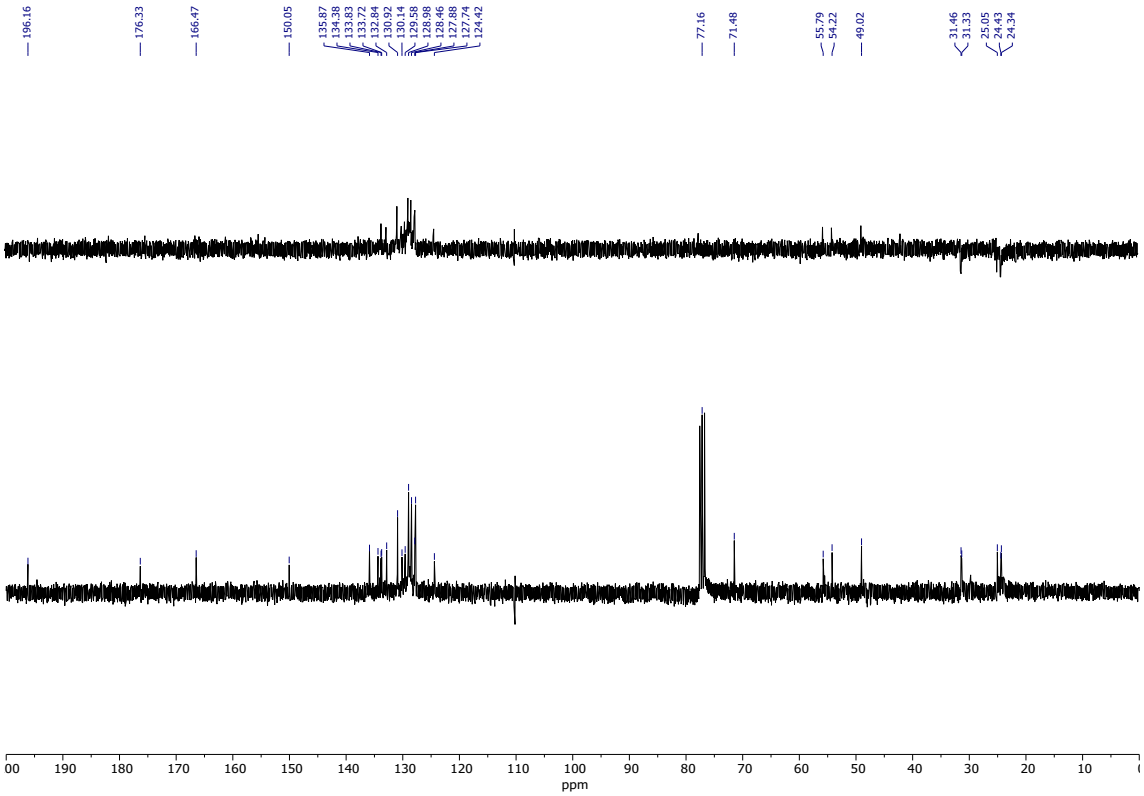


Figure S154. ^{13}C and DEPT-135 NMR spectra of **7i$_{diast2}$** (75 MHz, $CDCl_3$).

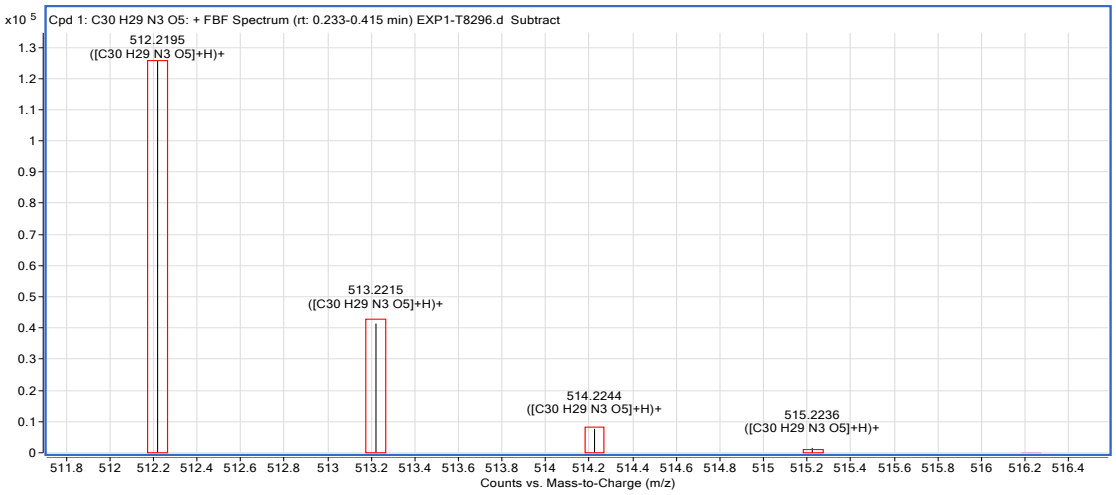


Figure S155. HRMS (+ESI) spectrum of **7i$_{diast2}$**.

(3*R,4*R**,5*S**)-4-cyclohexylcarbamoyl-4-(4-fluorobenzoyl)-5-(2-nitrophenyl)-3-phenylpyrrolidin-2-one ($7j_{diast1}$)**

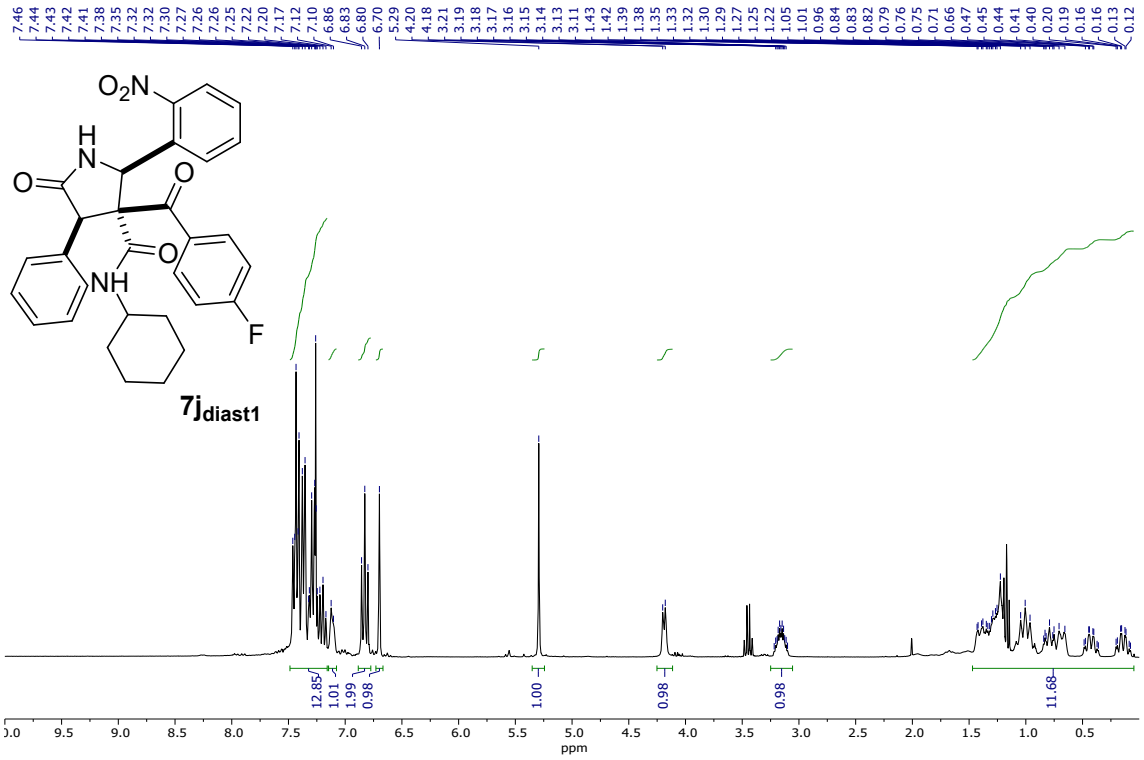


Figure S156. ^{1}H NMR spectrum of $\mathbf{7j_{diast1}}$ (300 MHz, $CDCl_3$).

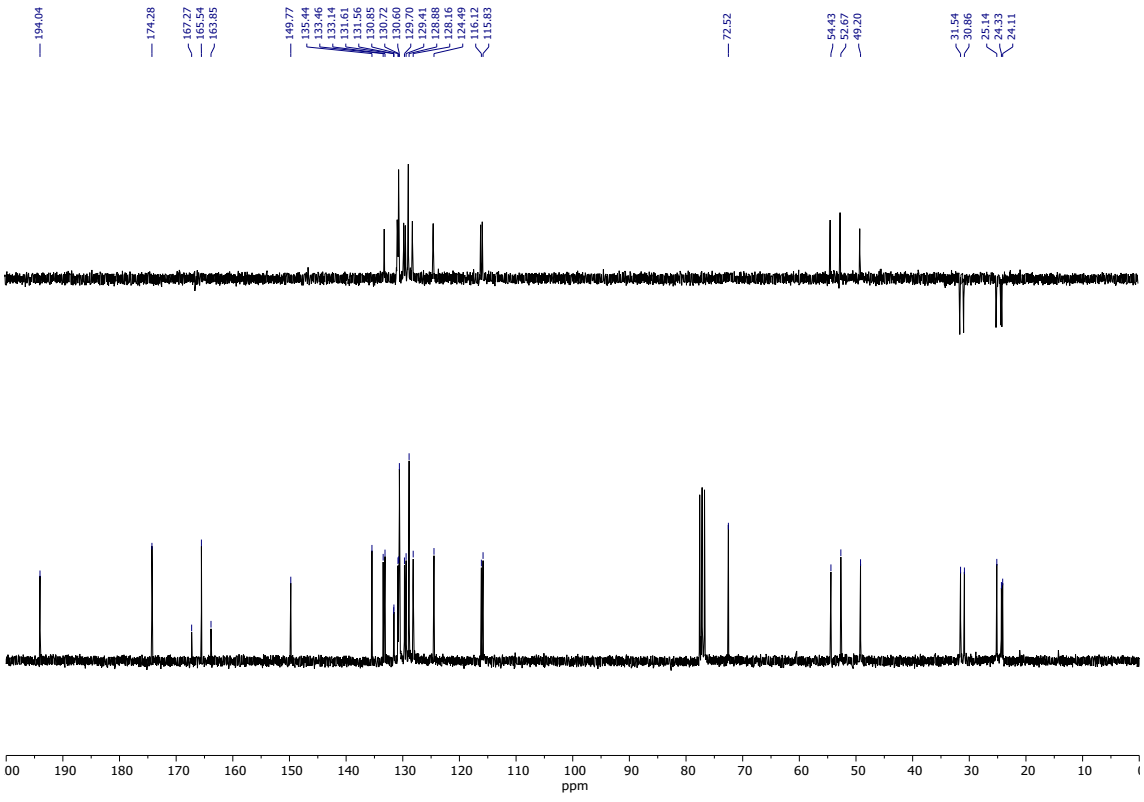


Figure S157. ^{13}C and DEPT-135 NMR spectra of **7j$_{diast1}$** (75 MHz, $CDCl_3$).

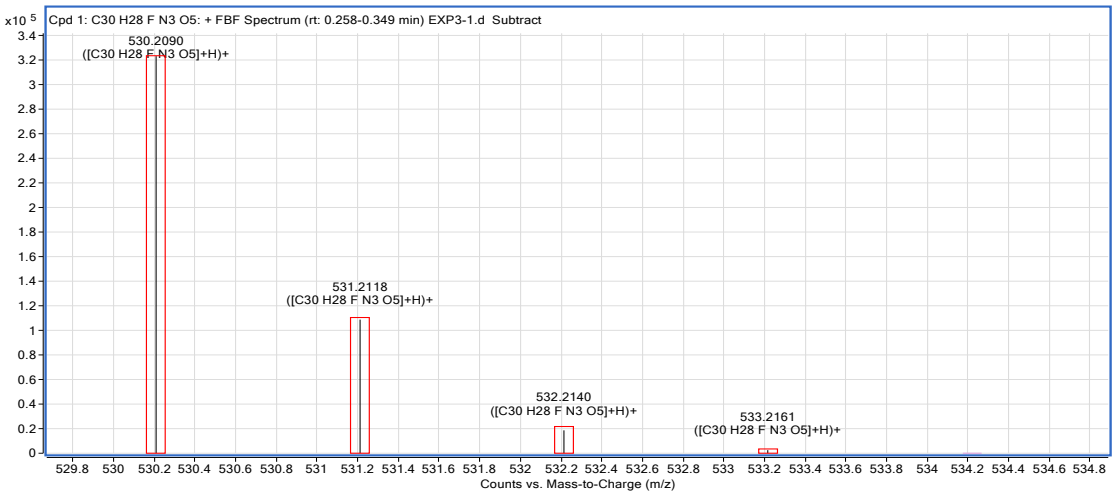


Figure S158. HRMS (+ESI) spectrum of **7j$_{diast1}$**.

(3*R,4*R**,5*R**)-4-Cyclohexylcarbamoyl-4-(4-fluorobenzoyl)-5-(2-nitrophenyl)-3-phenylpyrrolidin-2-one ($7j_{diast2}$)**

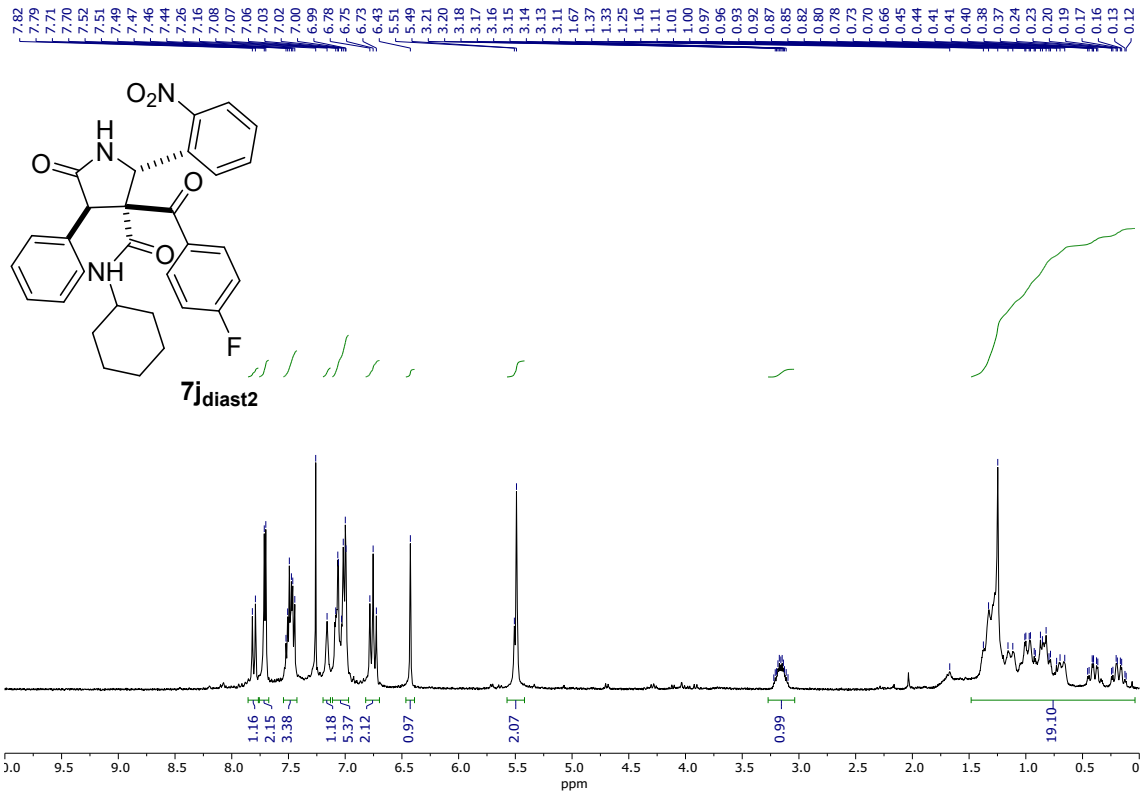


Figure S159. ^{1}H NMR spectrum of $\mathbf{7j_{diast2}}$ (300 MHz, $CDCl_3$).

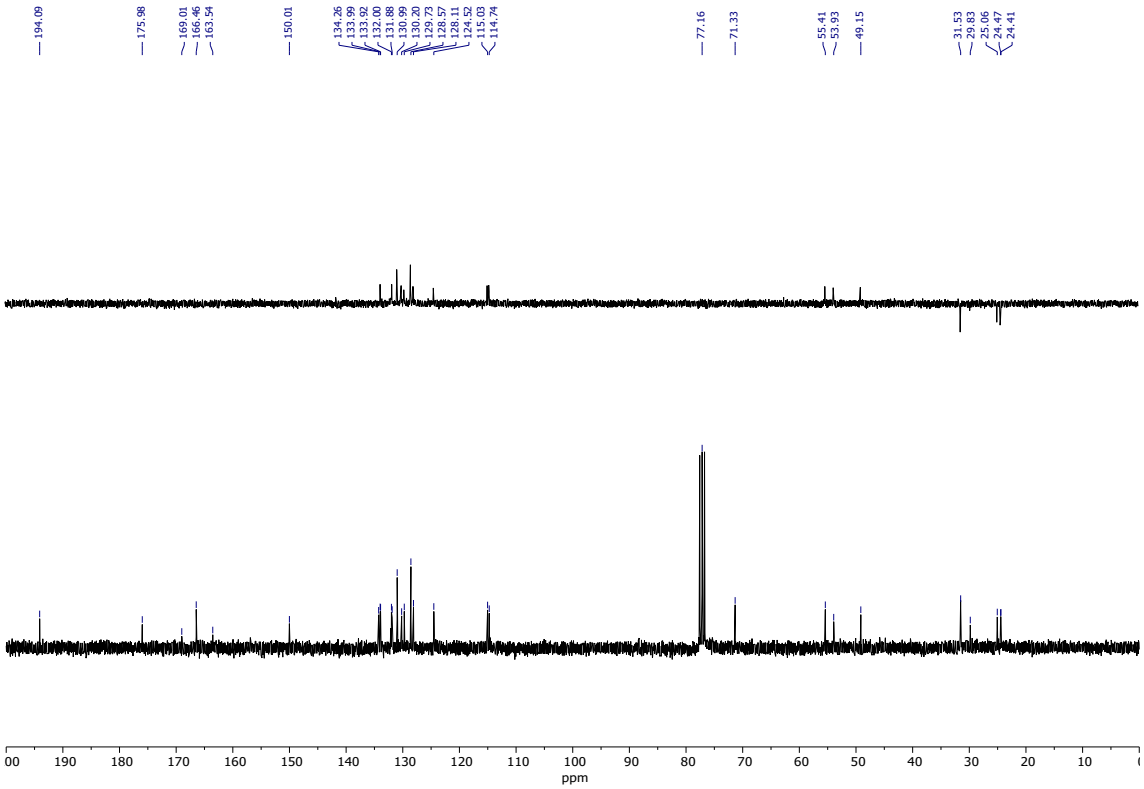


Figure S160. ^{13}C and DEPT-135 NMR spectra of **7j$_{diast2}$** (75 MHz, $CDCl_3$).

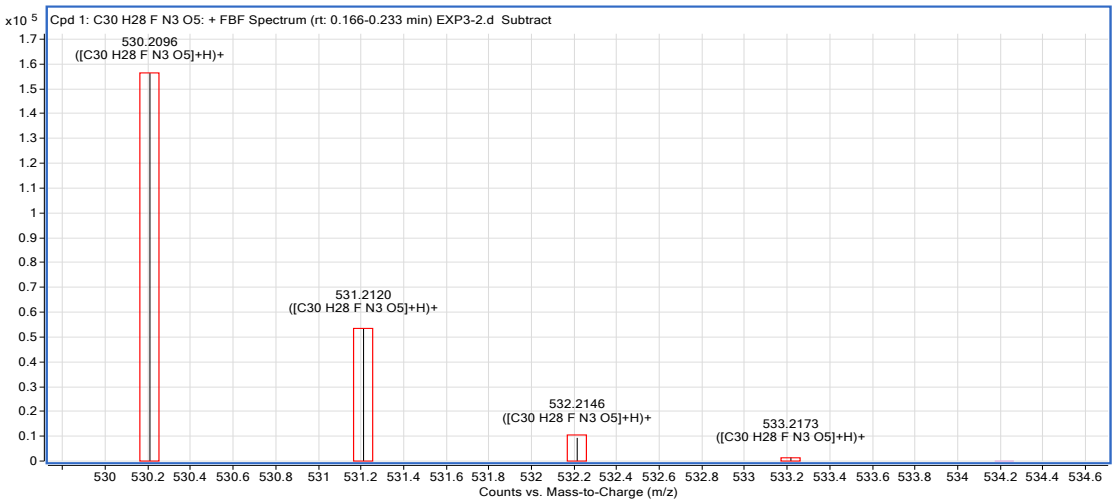


Figure S161. HRMS (+ESI) spectrum of **7j$_{diast2}$**.

(4*R,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-(methoxycarbonyl)pyrrolidin-2-one (7l)**

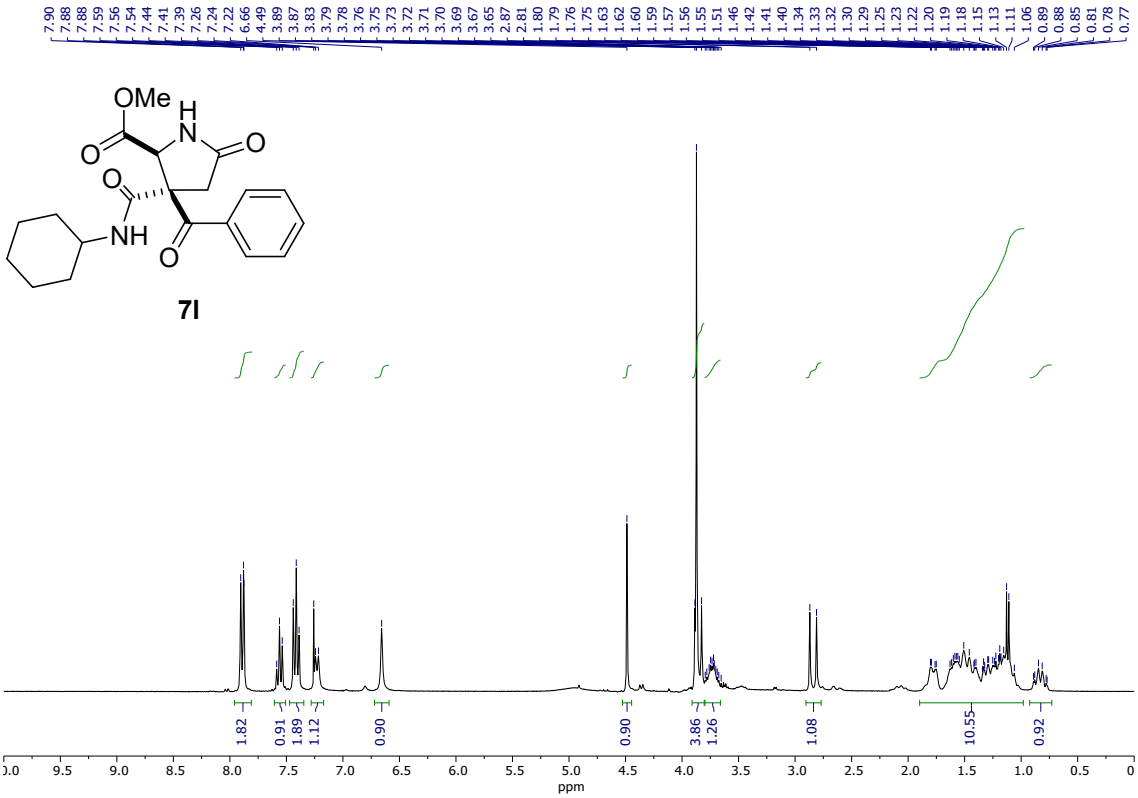


Figure S162. ^{1}H NMR spectrum of **7l** (300 MHz, $CDCl_3$).

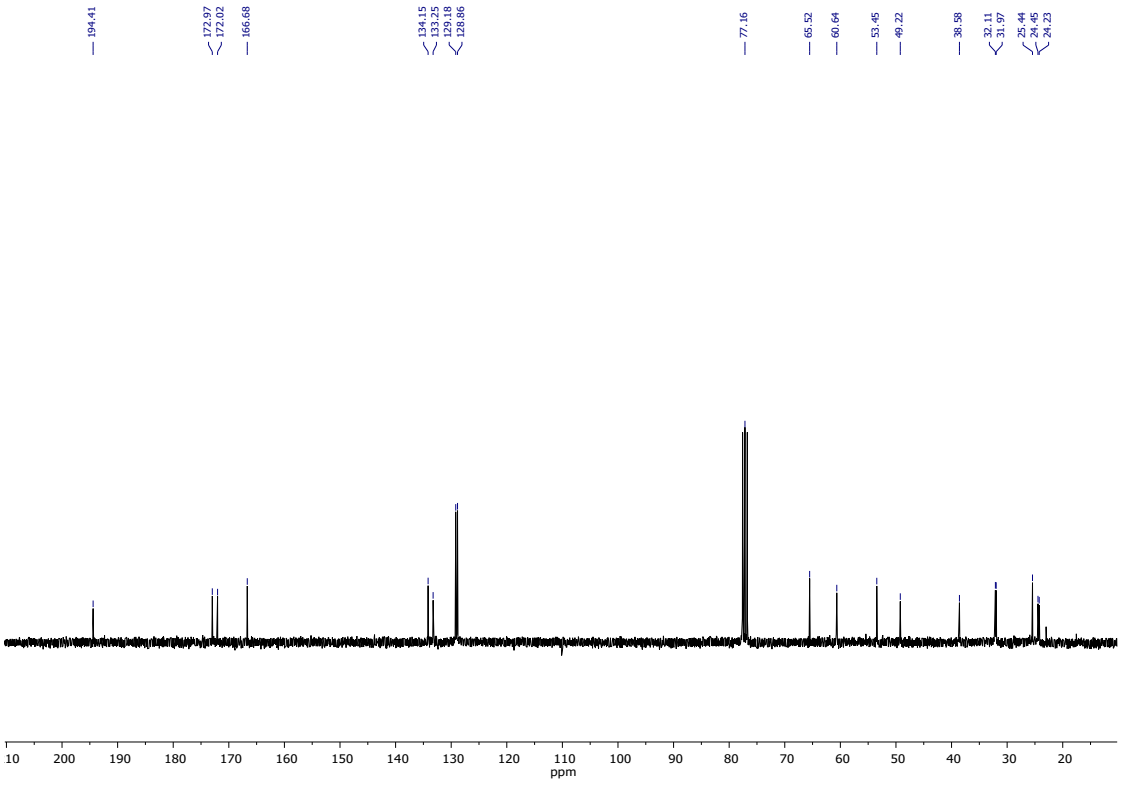


Figure S163. ^{13}C NMR spectrum of **7l** (75 MHz, $CDCl_3$).

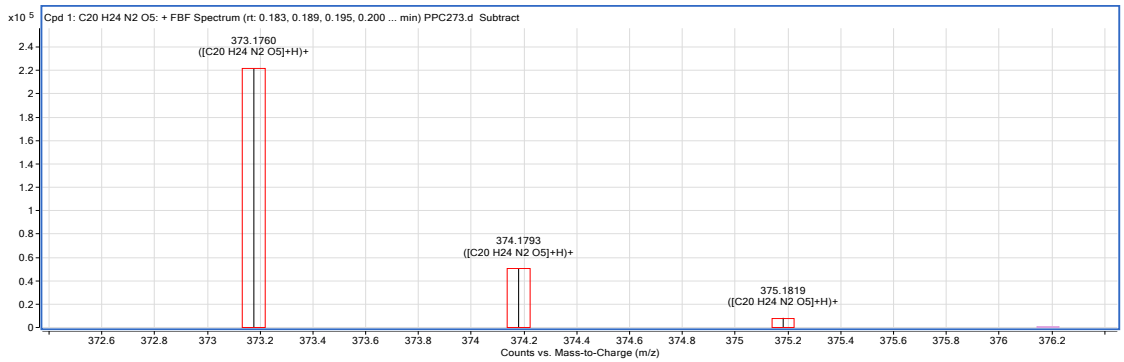


Figure S164. HRMS (+ESI) spectrum of **7l**.

(3a*R,6a*S**)-5-Cyclohexyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9l)**

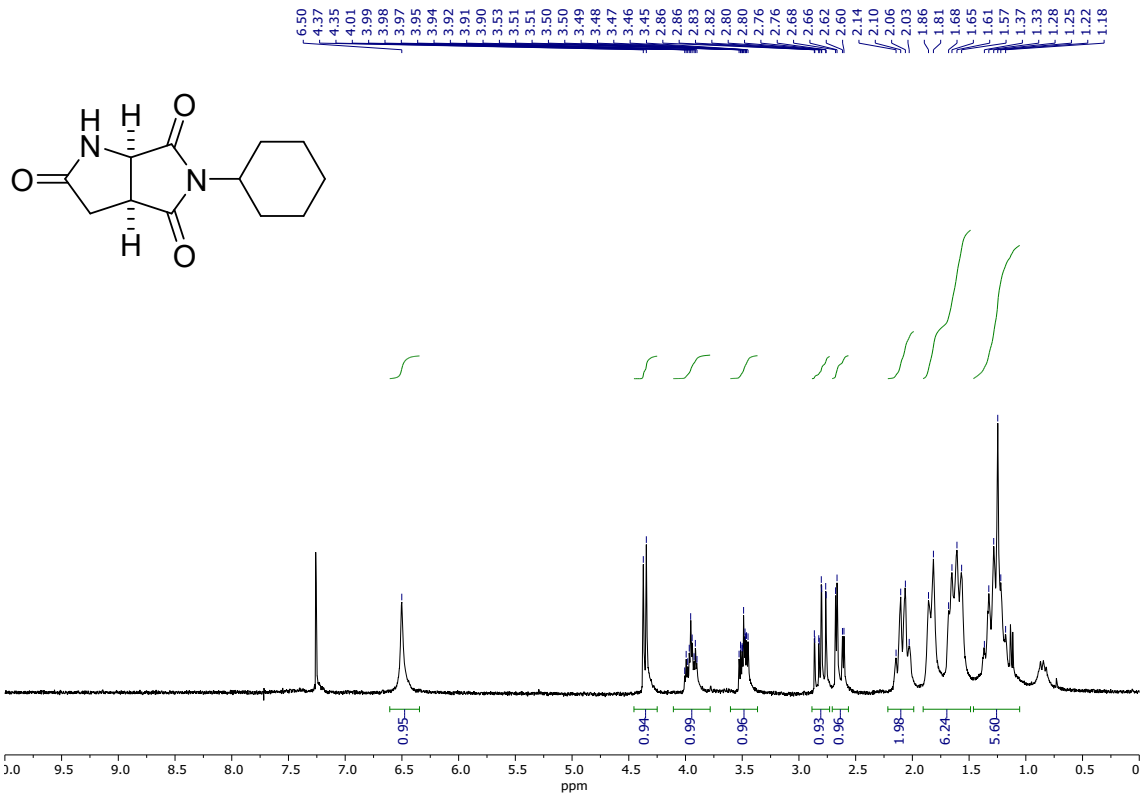


Figure S165. ^{1}H NMR spectrum of **9l** (300 MHz, $CDCl_3$).

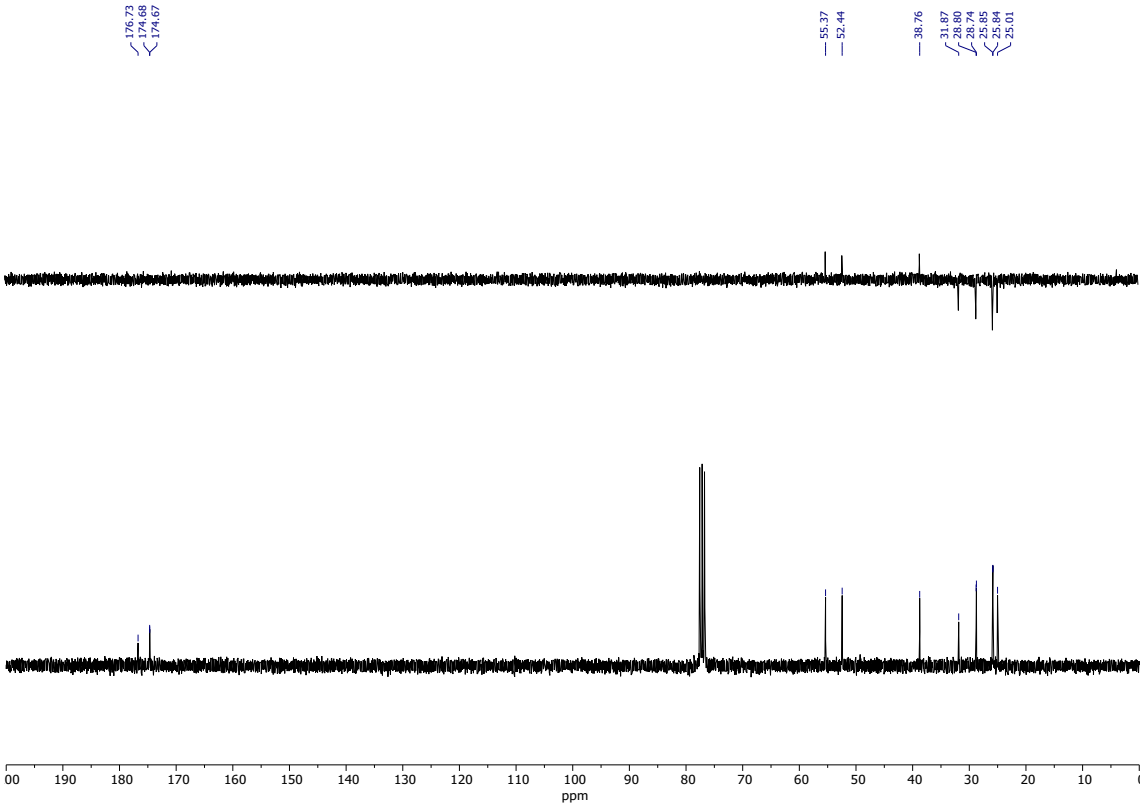


Figure S166. ^{13}C and DEPT-135 NMR spectra of **9l** (75 MHz, $CDCl_3$).

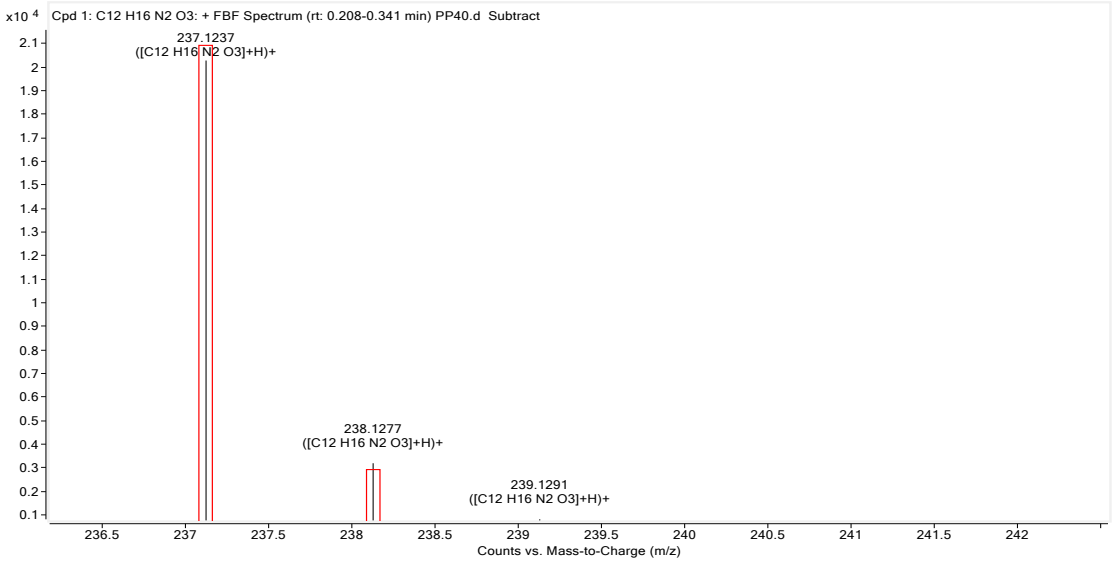


Figure S167. HRMS (+ESI) spectrum of **9l**.

(3a*R,6a*S**)-3a-Benzoyl-5-cyclohexyl-6a-phenyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8m)**

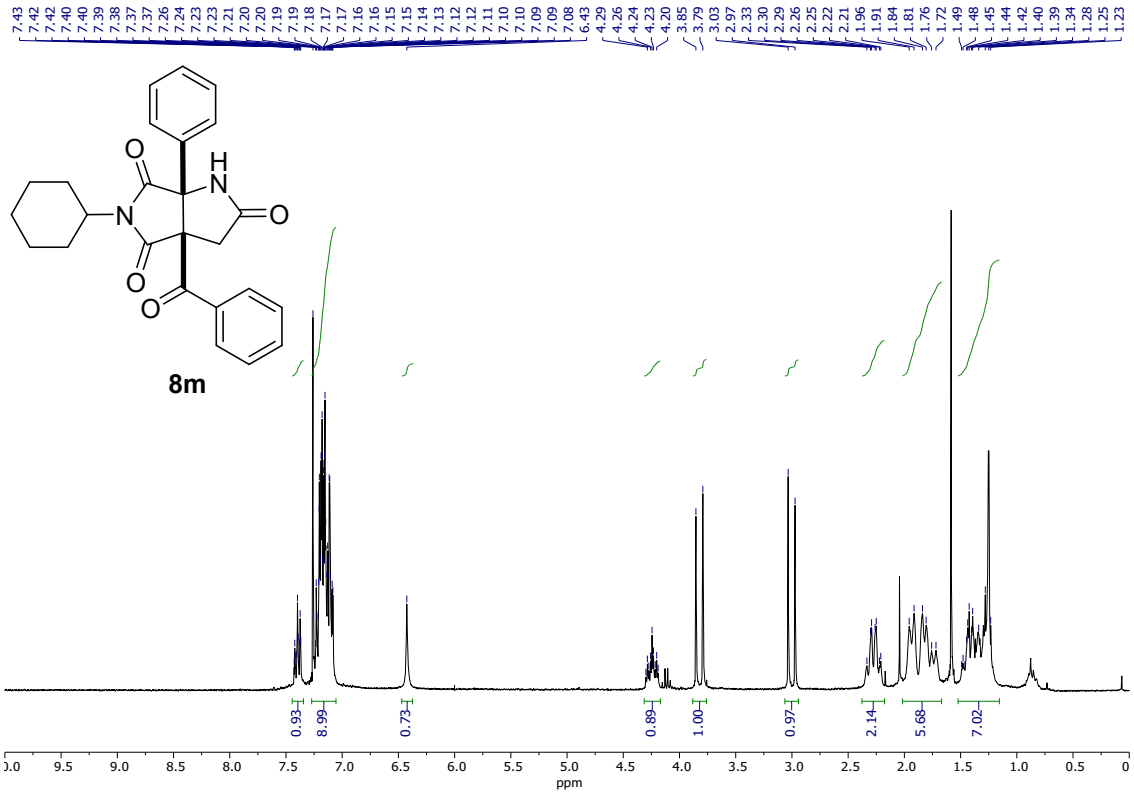


Figure S168. ^{1}H NMR spectrum of **8m** (300 MHz, $CDCl_3$).

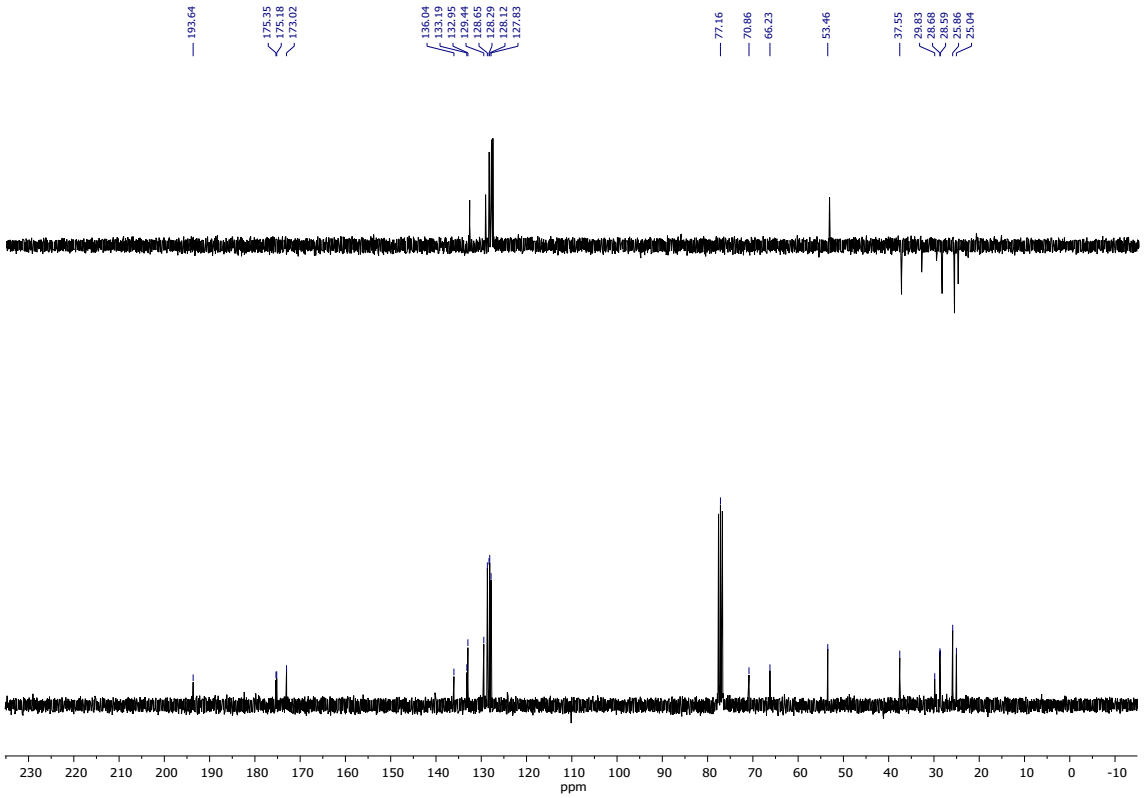


Figure S169. ^{13}C and DEPT-135 NMR spectra of **8m** (75 MHz, $CDCl_3$).

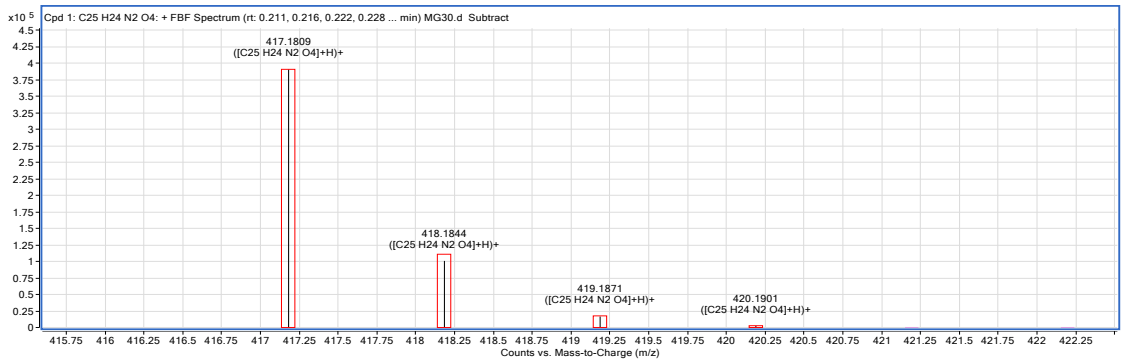


Figure S170. HRMS (+ESI) spectrum of **8m**.

(3a*R,6a*S**)-5-Cyclohexyl-6a-phenyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9m)**

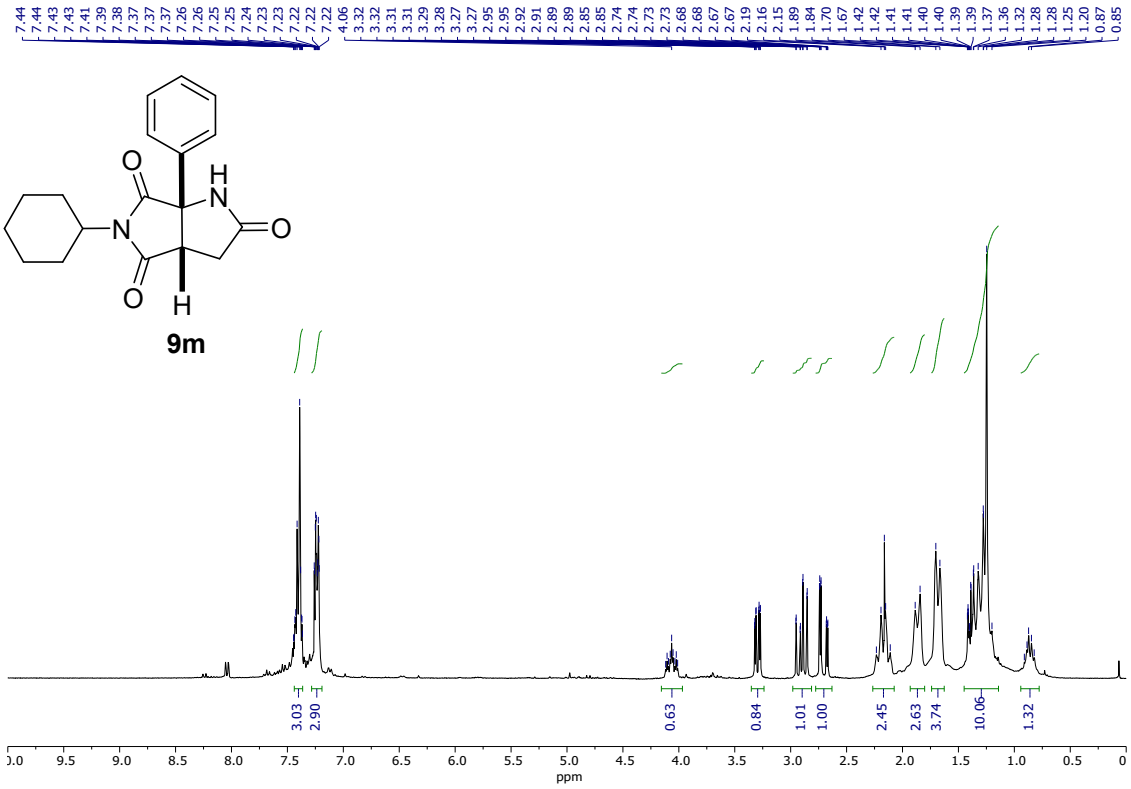


Figure S171. ^{1}H NMR spectrum of **9m** (300 MHz, $CDCl_3$).

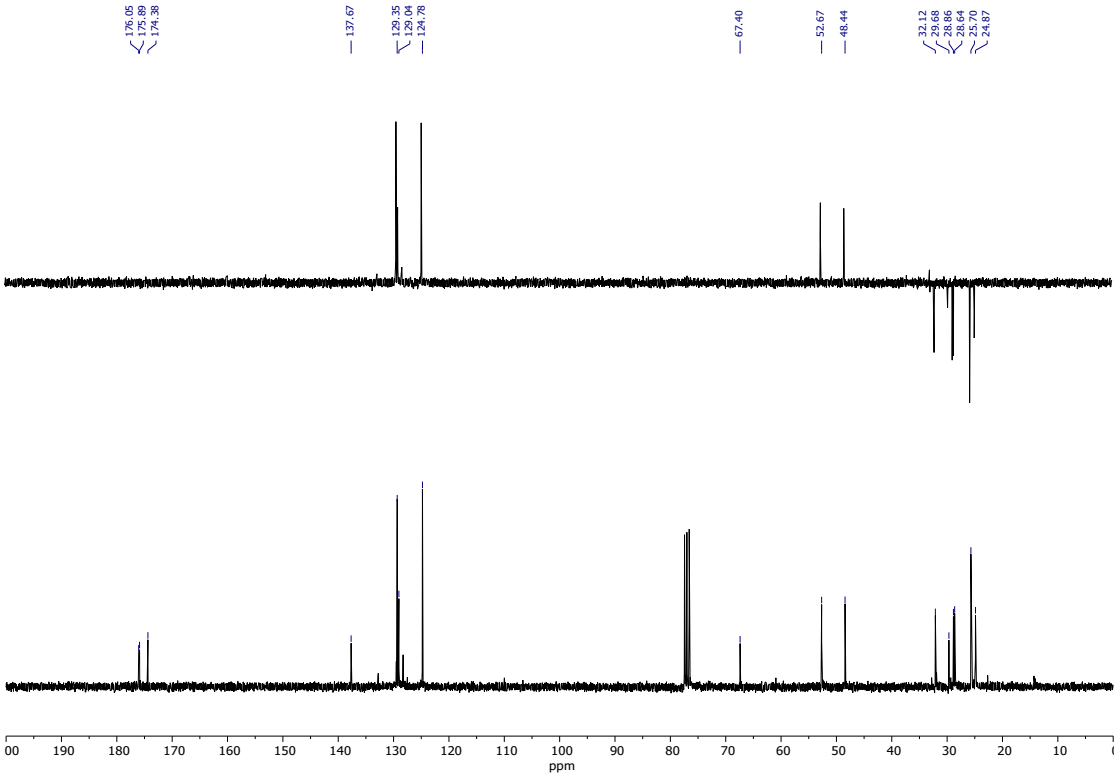


Figure S172. ^{13}C and DEPT-135 NMR spectra of **9m** (75 MHz, $CDCl_3$).

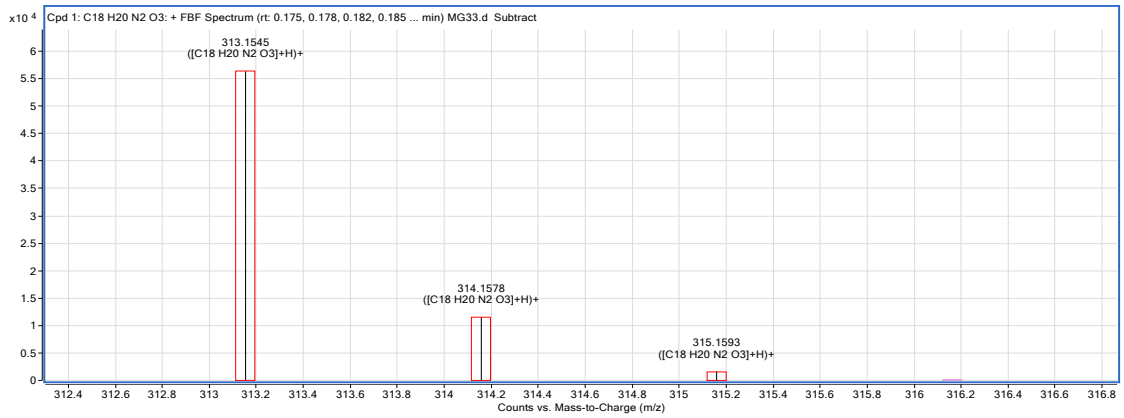


Figure S173. HRMS (+ESI) spectrum of **9m**.

(4*R,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-5-methylpyrrolidin-2-one (7n)**

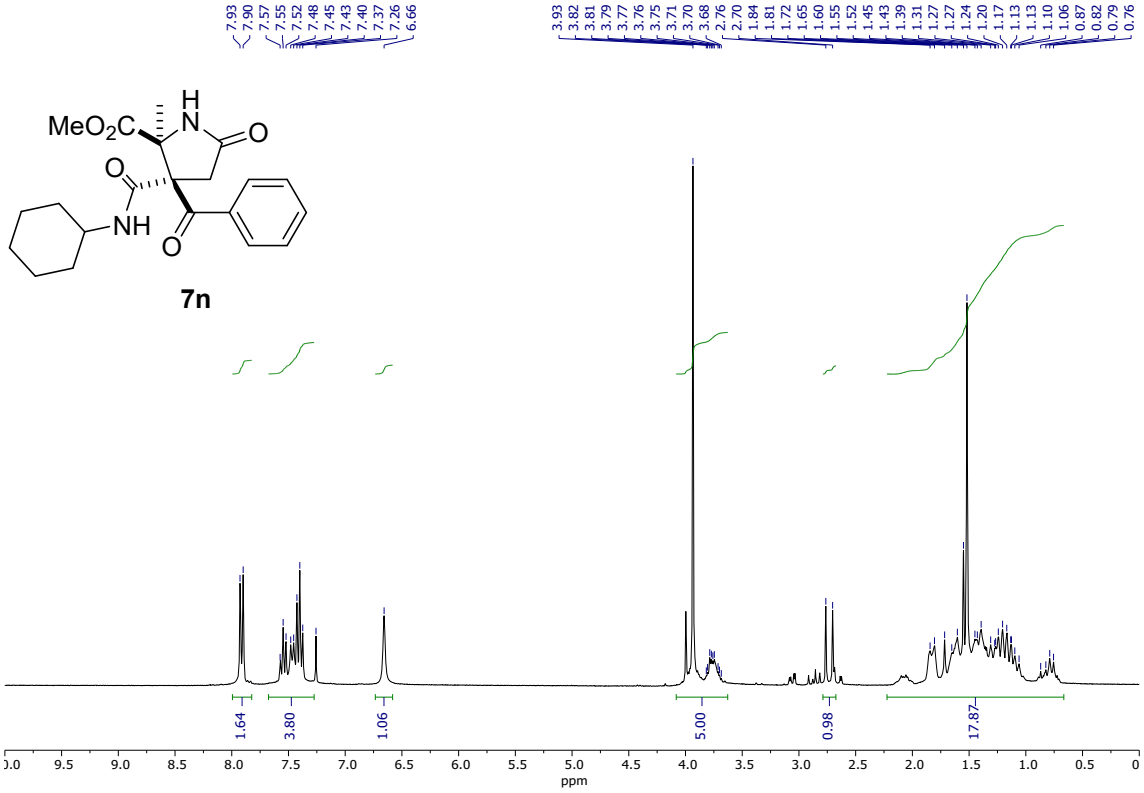


Figure S174. ^{1}H NMR spectrum of **7n** (300 MHz, $CDCl_3$).

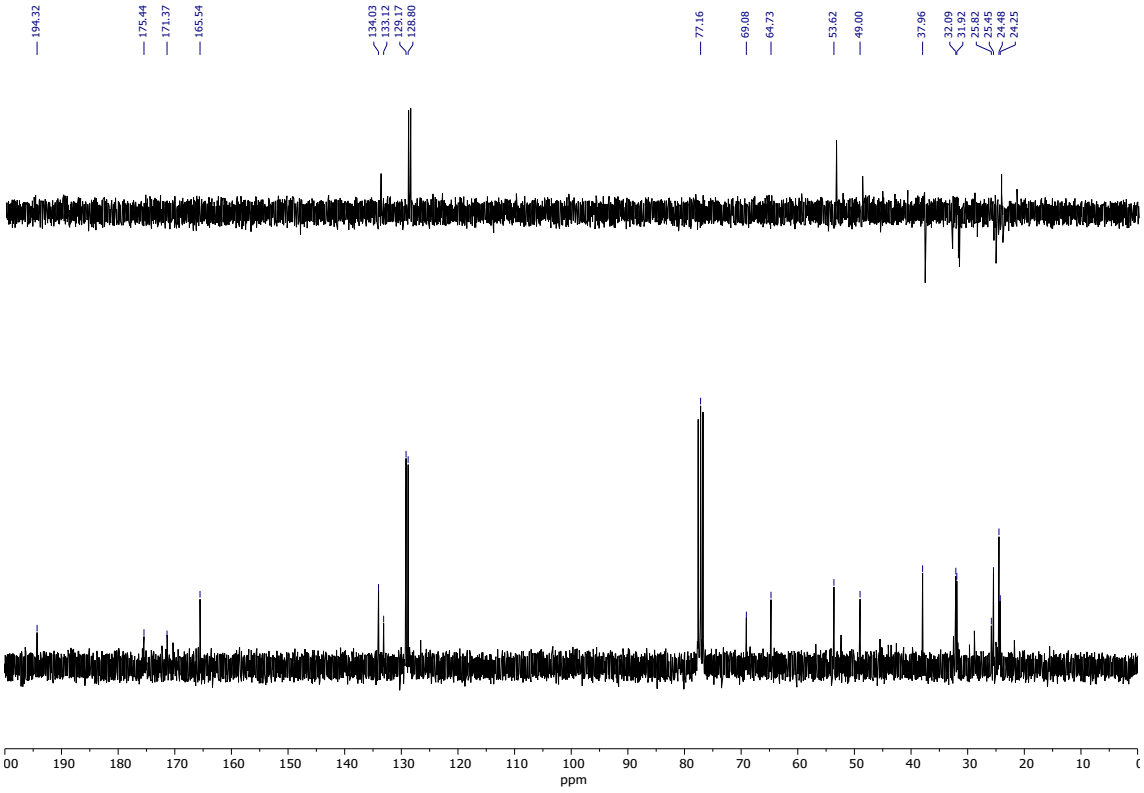


Figure S175. ^{13}C and DEPT-135 NMR spectra of **7n** (75 MHz, $CDCl_3$).

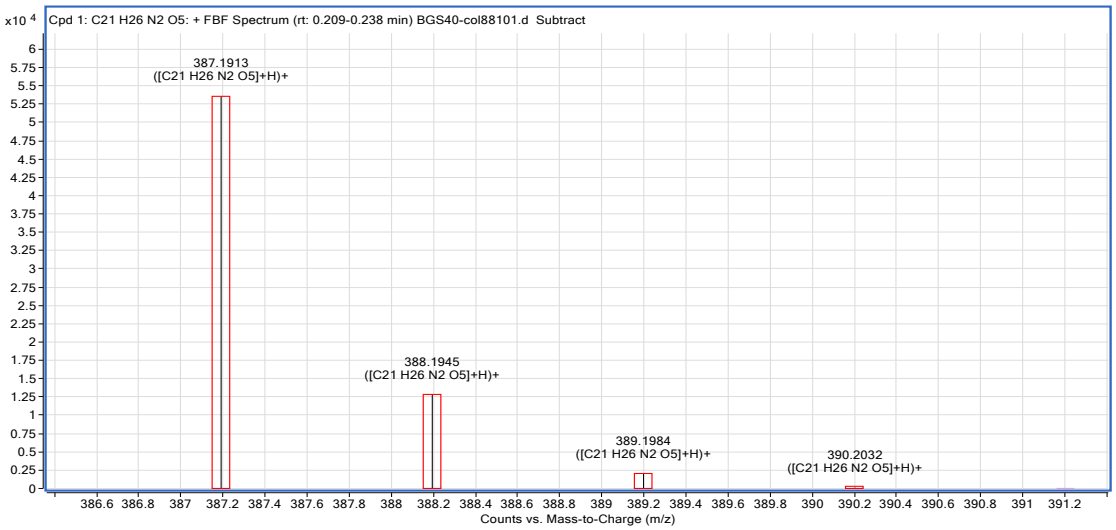


Figure S176. HRMS (+ESI) spectrum of **7n**.

(3a*R,6a*S**)-3a-Benzoyl-5-cyclohexyl-6a-methyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8n)**

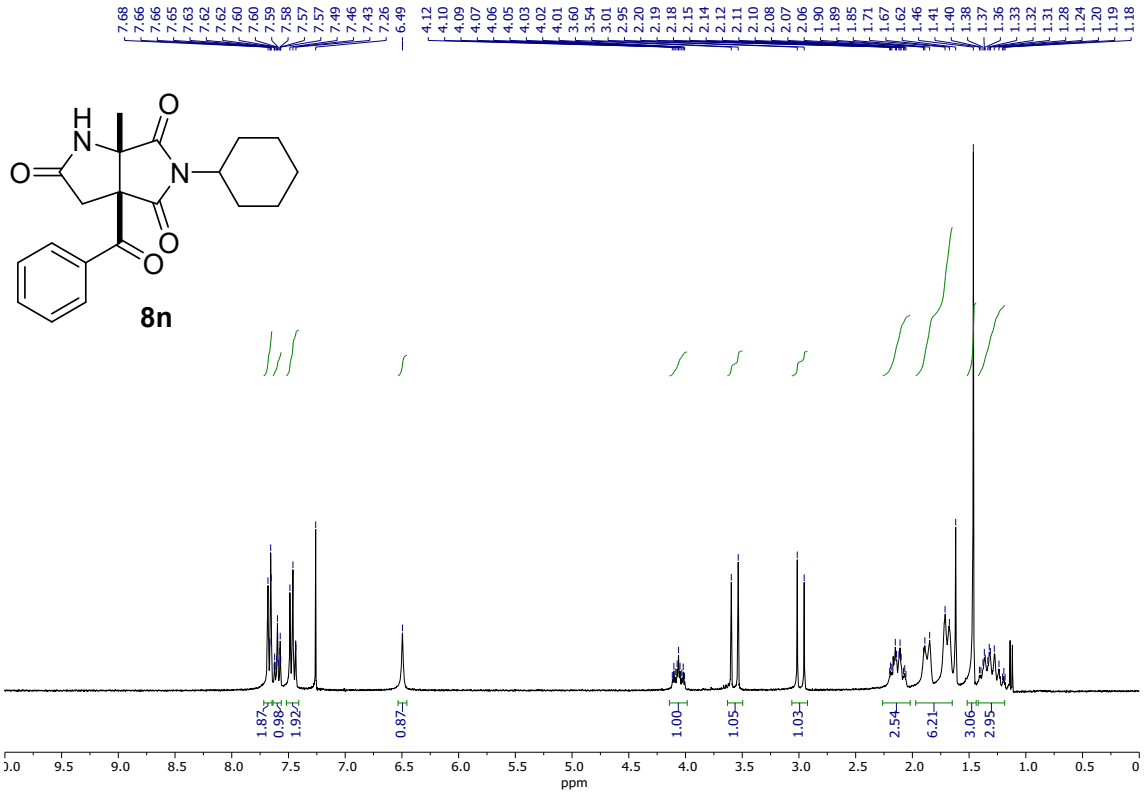


Figure S177. ^{1}H NMR spectrum of **8n** (300 MHz, $CDCl_3$).

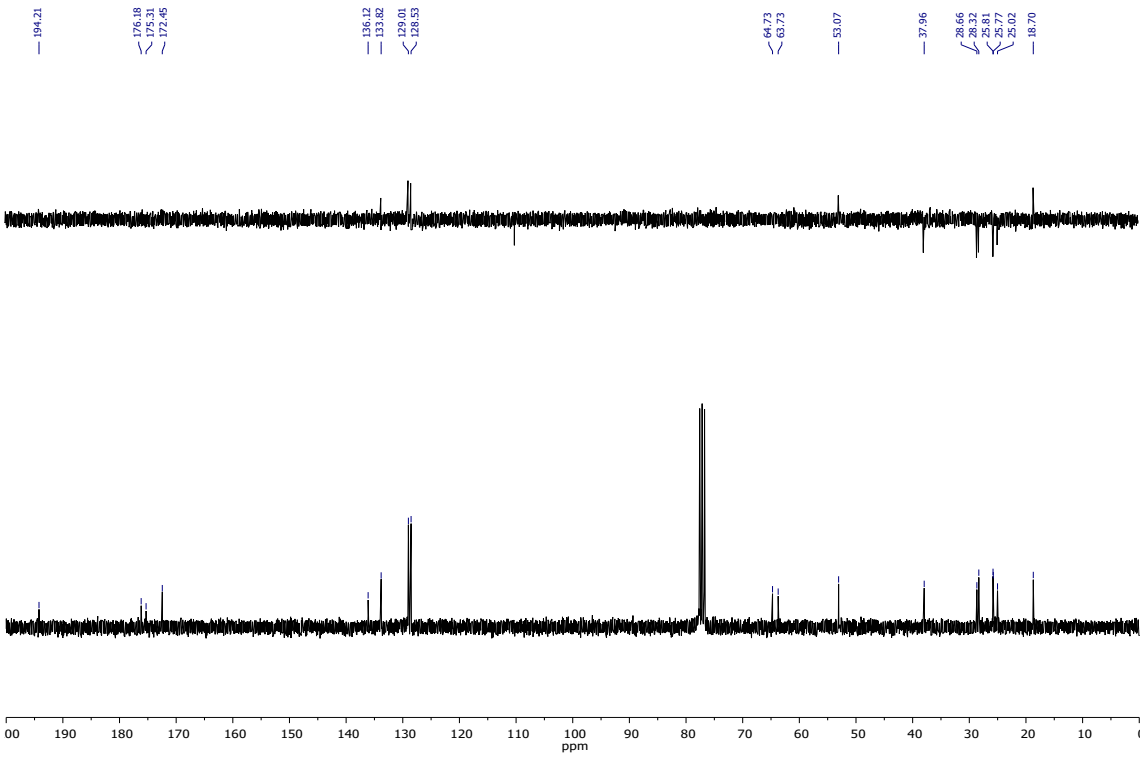


Figure S178. ^{13}C and DEPT-135 NMR spectra of **8n** (75 MHz, $CDCl_3$).

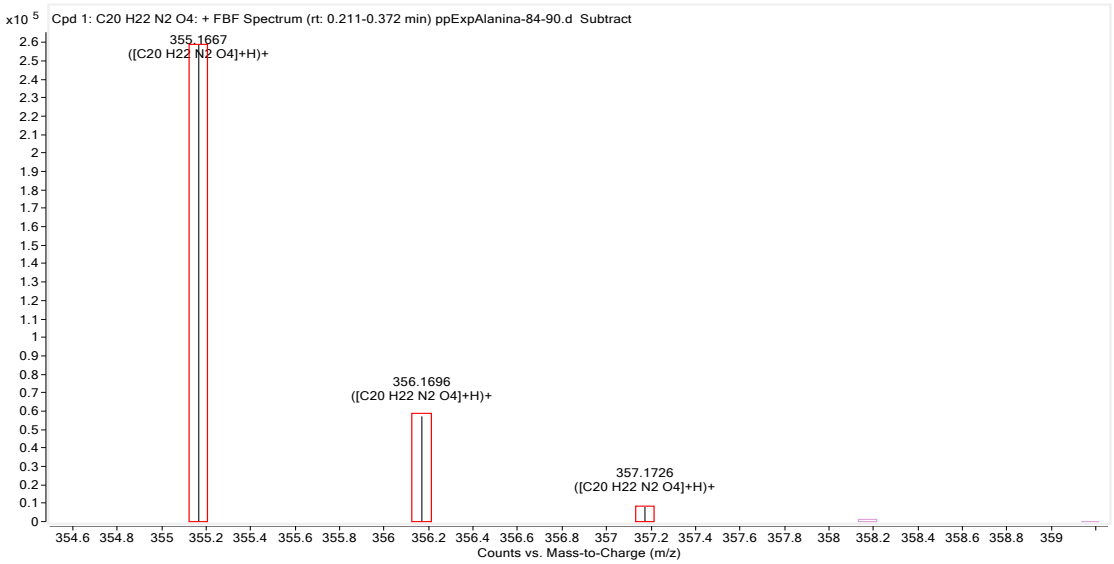


Figure S179. HRMS (+ESI) spectrum of **8n**.

(3a*R,6a*S**)-5-Cyclohexyl-6a-methyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9n)**

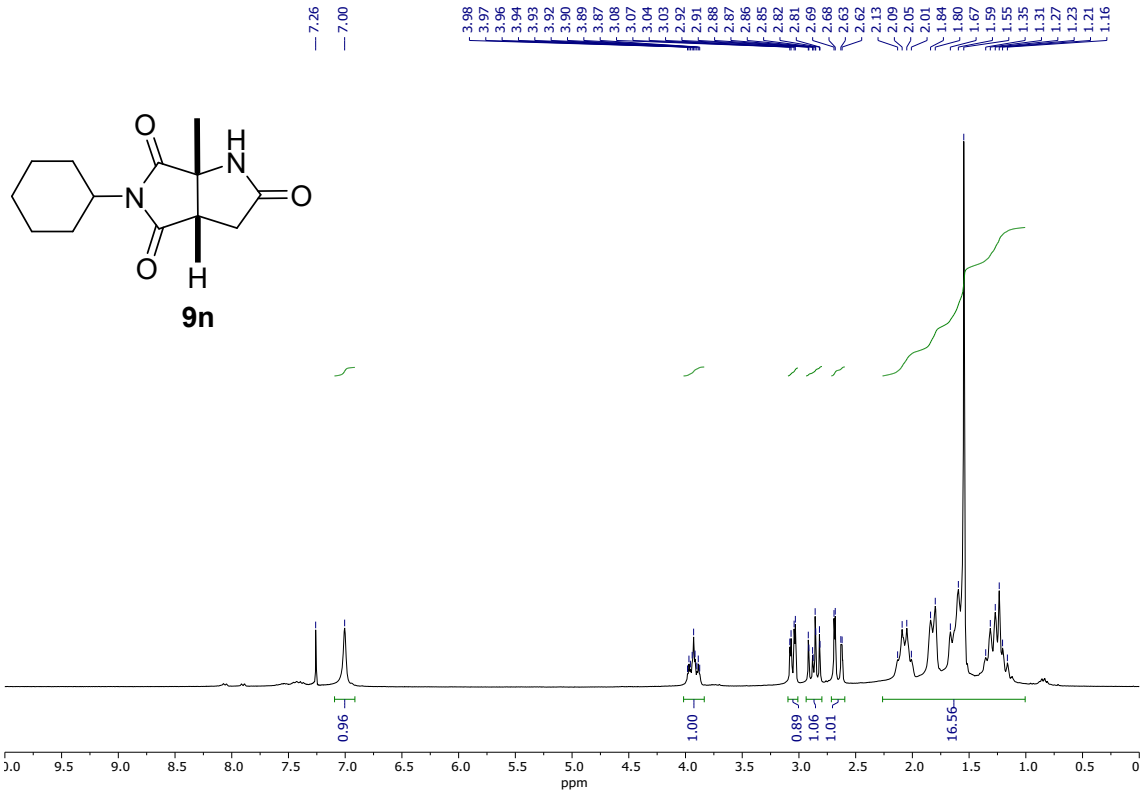


Figure S180. ^{1}H NMR spectrum of **9n** (300 MHz, $CDCl_3$).

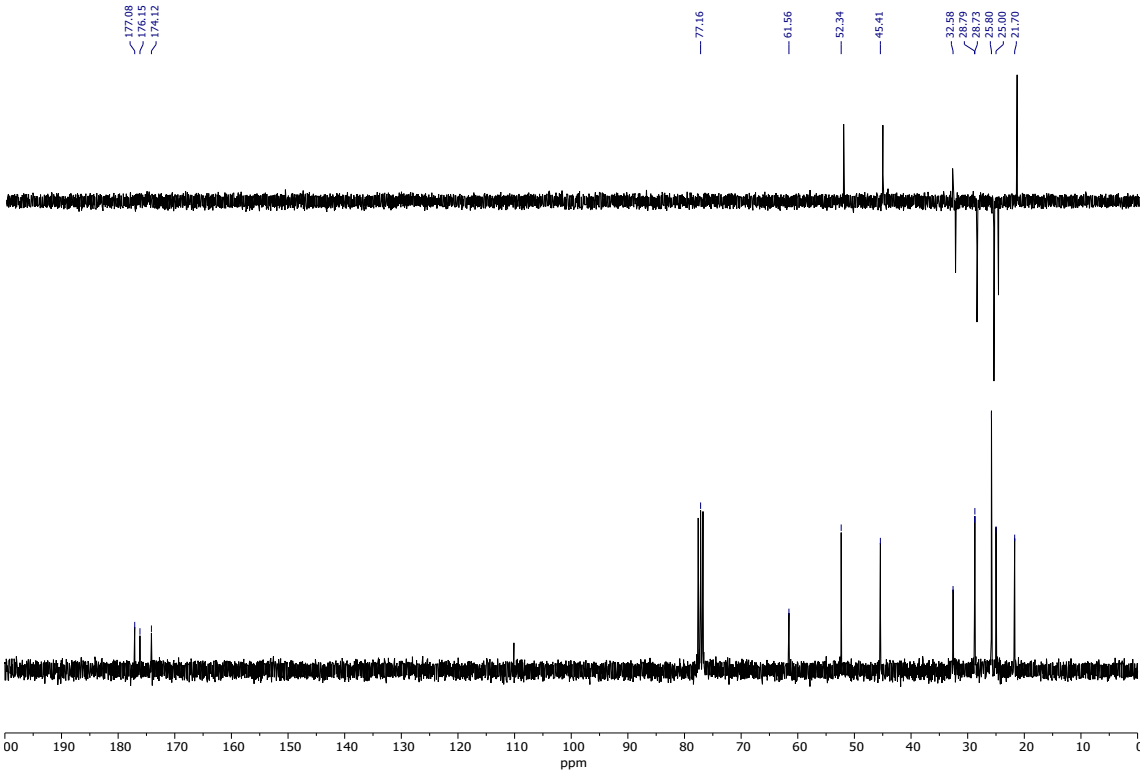


Figure S181. ^{13}C and DEPT-135 NMR spectra of **9n** (75 MHz, $CDCl_3$).

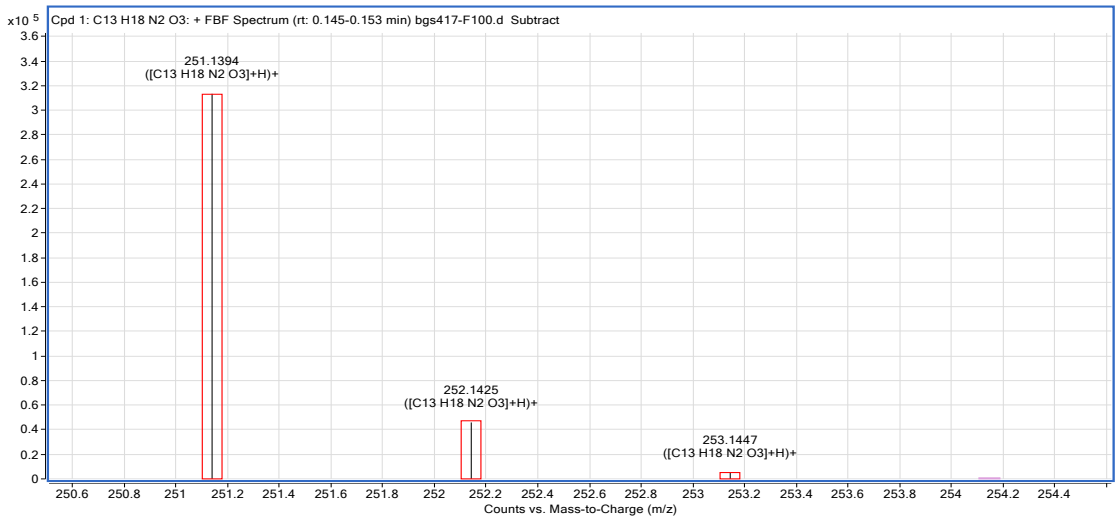


Figure S182. HRMS (+ESI) spectrum of **9n**.

(4*R,5*R**)-4-Benzoyl-5-benzyl-4-cyclohexylcarbamoyl-5-(methoxycarbonyl)pyrrolidin-2-one (7o)**

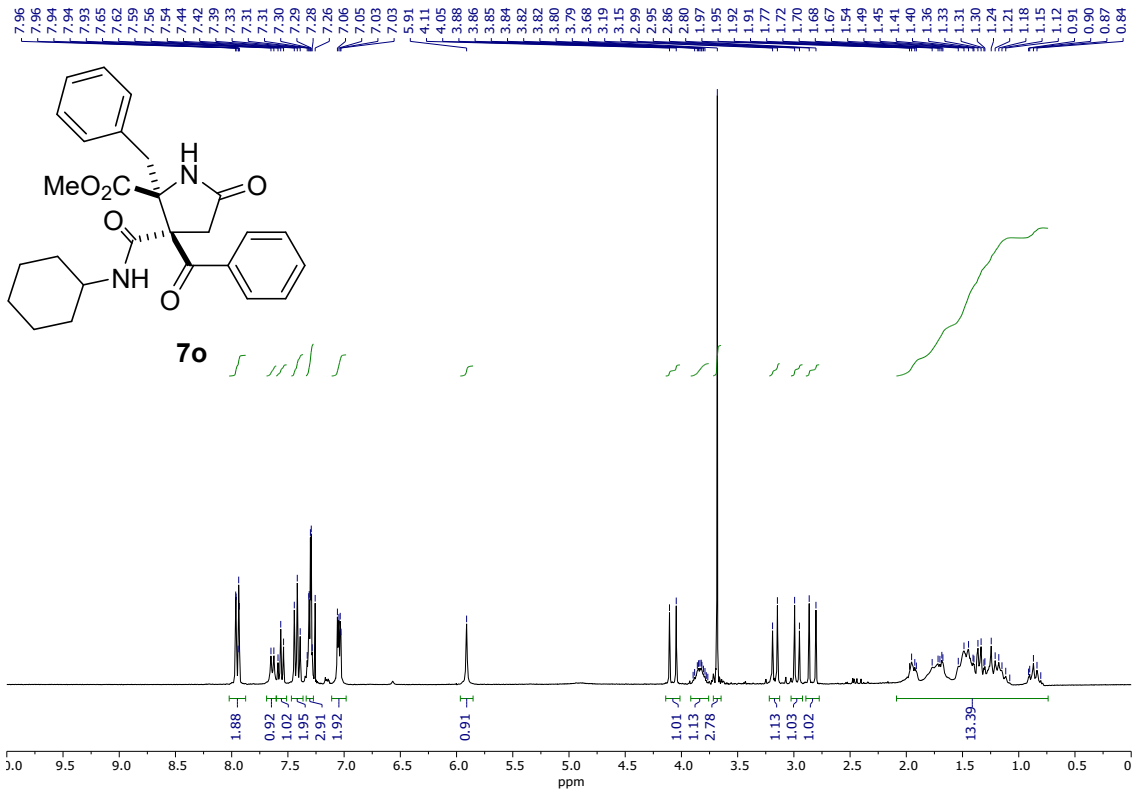


Figure S183. ^{1}H NMR spectrum of **7o** (300 MHz, $CDCl_3$).

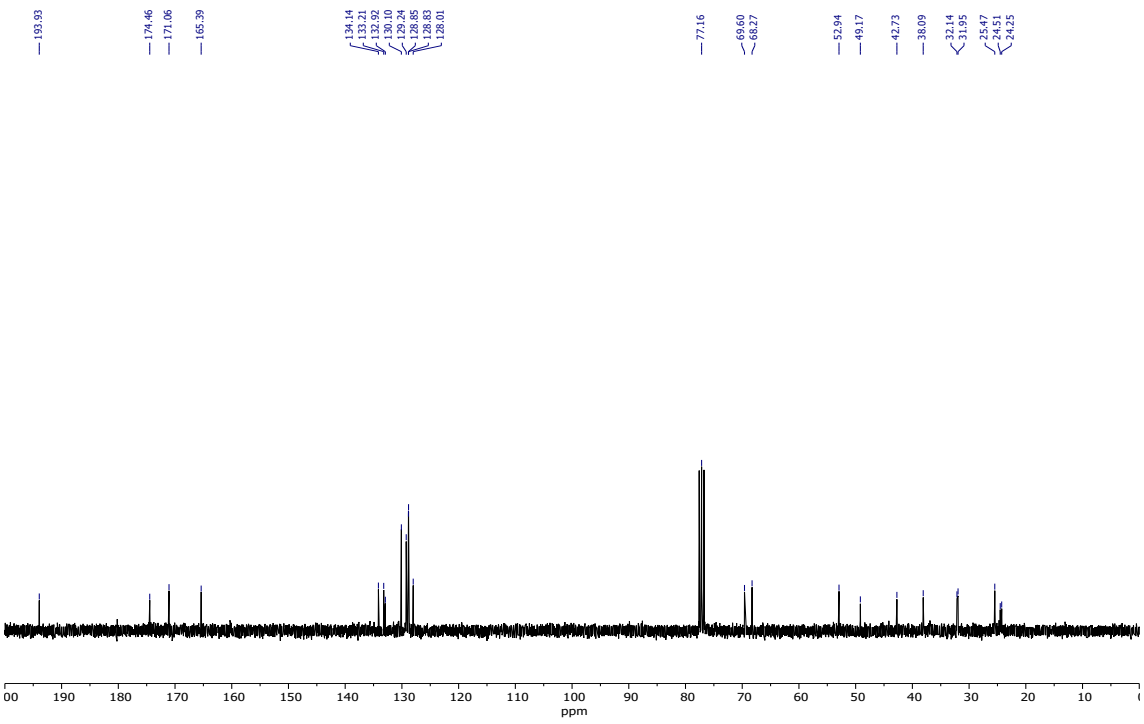


Figure S184. ^{13}C NMR spectrum of **7o** (75 MHz, $CDCl_3$).

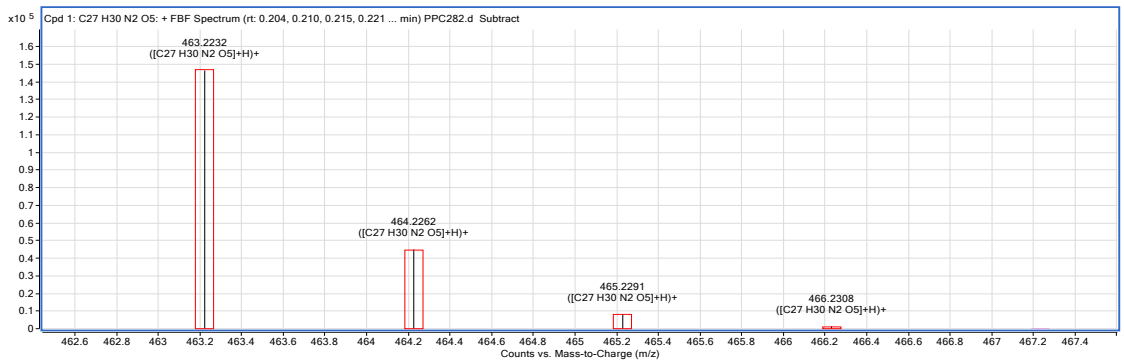


Figure S185. HRMS (+ESI) spectrum of **7o**.

(3a*R,6a*S**)-3a-Benzoyl-6a-benzyl-5-cyclohexyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8o)**

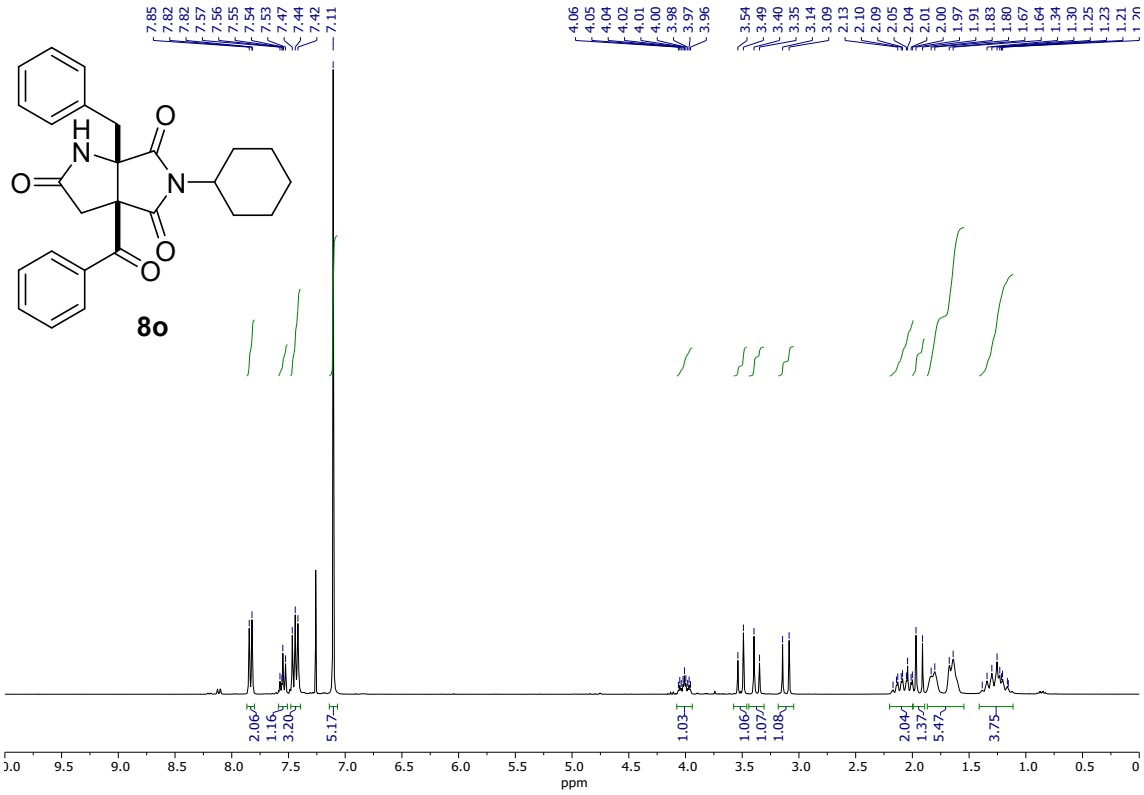


Figure S186. ^{1}H NMR spectrum of **8o** (300 MHz, $CDCl_3$).

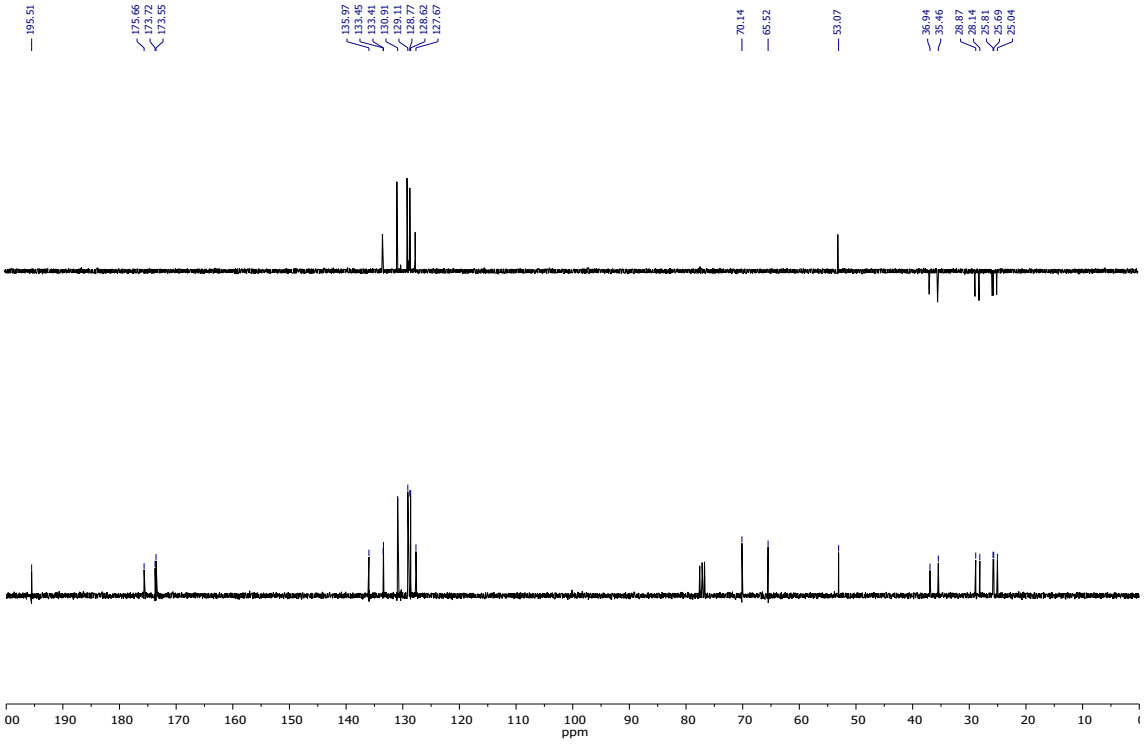


Figure S187. ^{13}C and DEPT-135 NMR spectra of **8o** (75 MHz, $CDCl_3$).

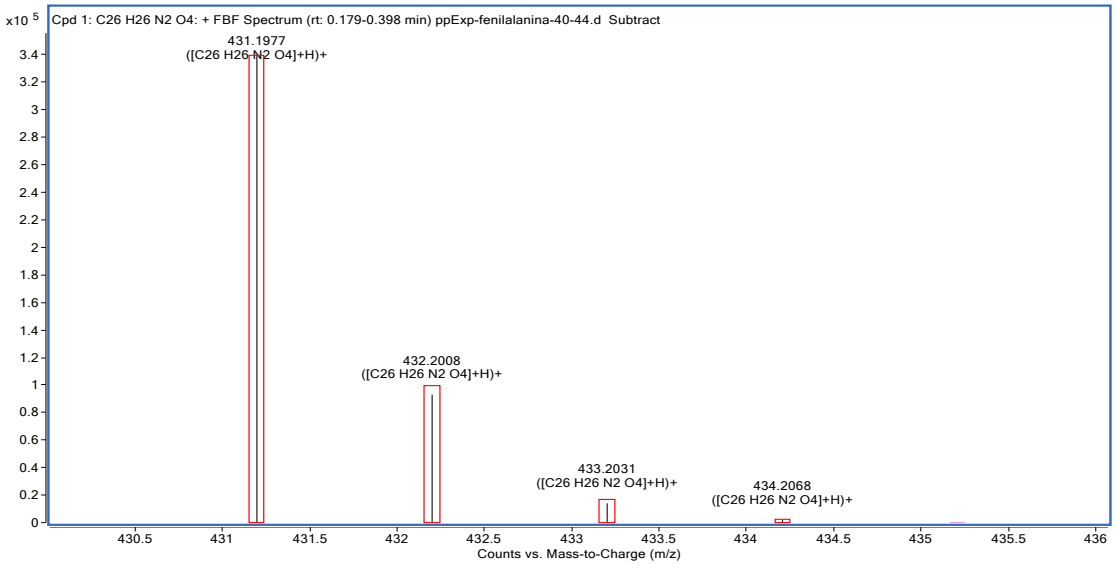


Figure S188. HRMS (+ESI) spectrum of **8o**.

(3a*R,6a*S**)-6a-Benzyl-5-cyclohexyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9o)**

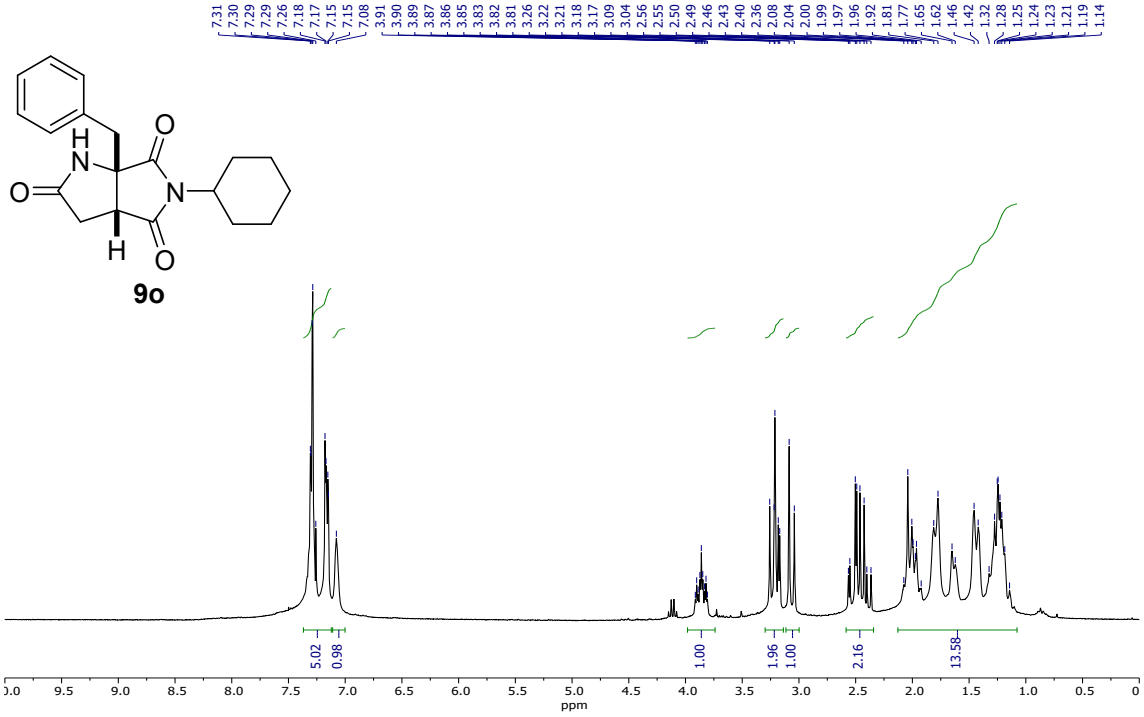


Figure S189. ^{1}H NMR spectrum of **9o** (300 MHz, $CDCl_3$).

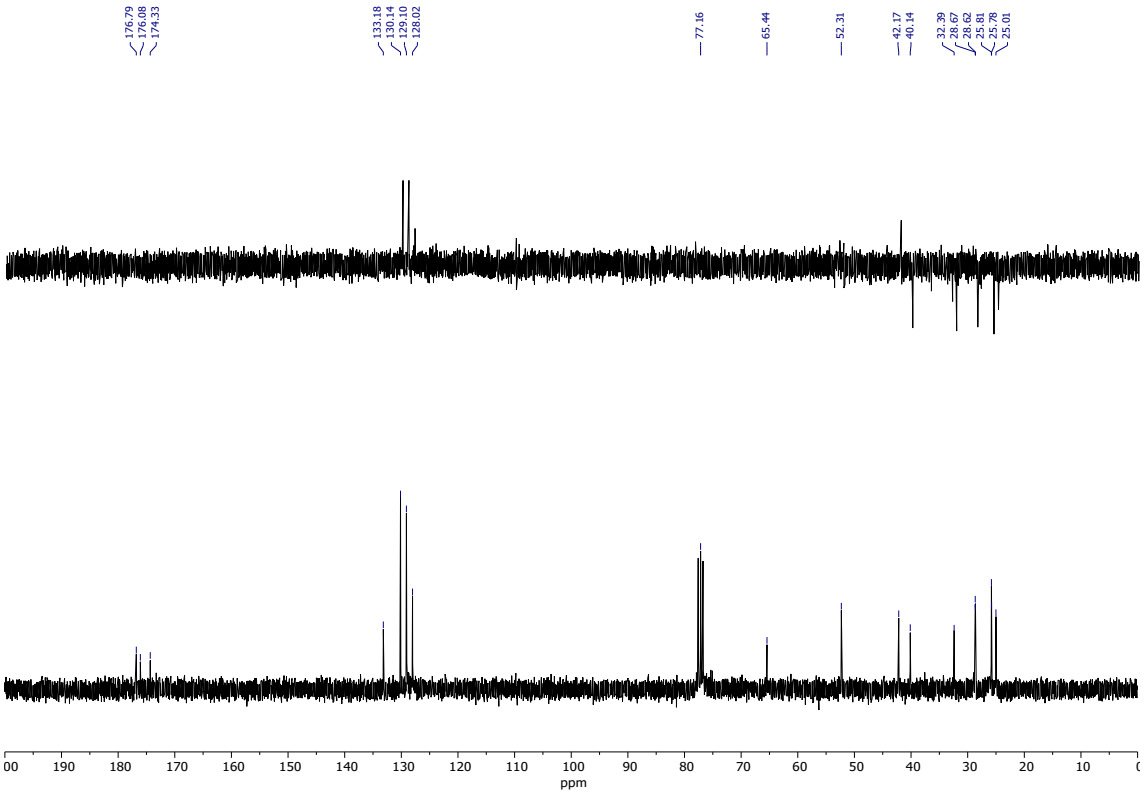


Figure S190. ^{13}C and DEPT-135 NMR spectra of **9o** (75 MHz, $CDCl_3$).

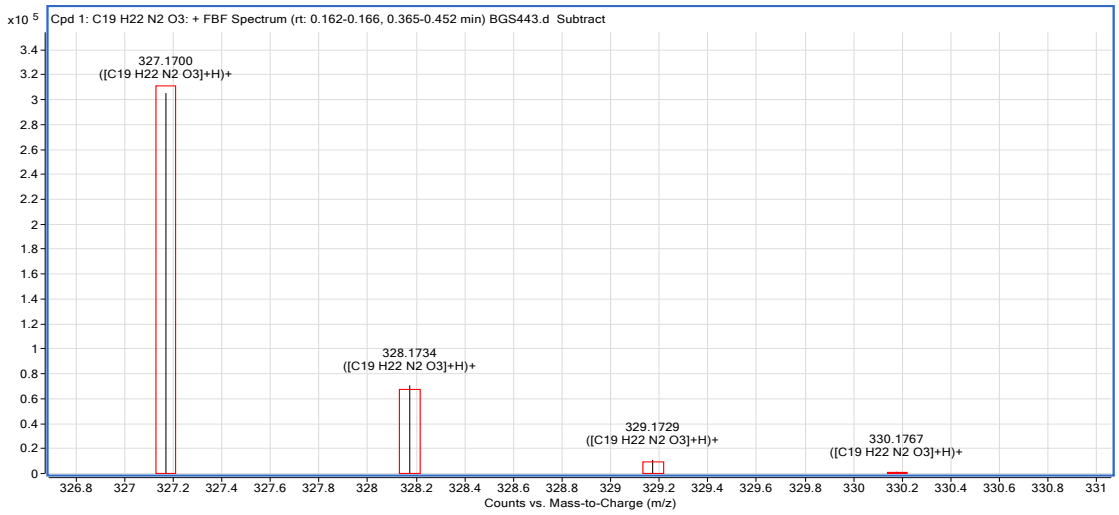


Figure S191. HRMS (+ESI) spectrum of **9o**.

(3a*R,6a*S**)-3a-Benzoyl-6a-isopropyl-5-cyclohexyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8p)**

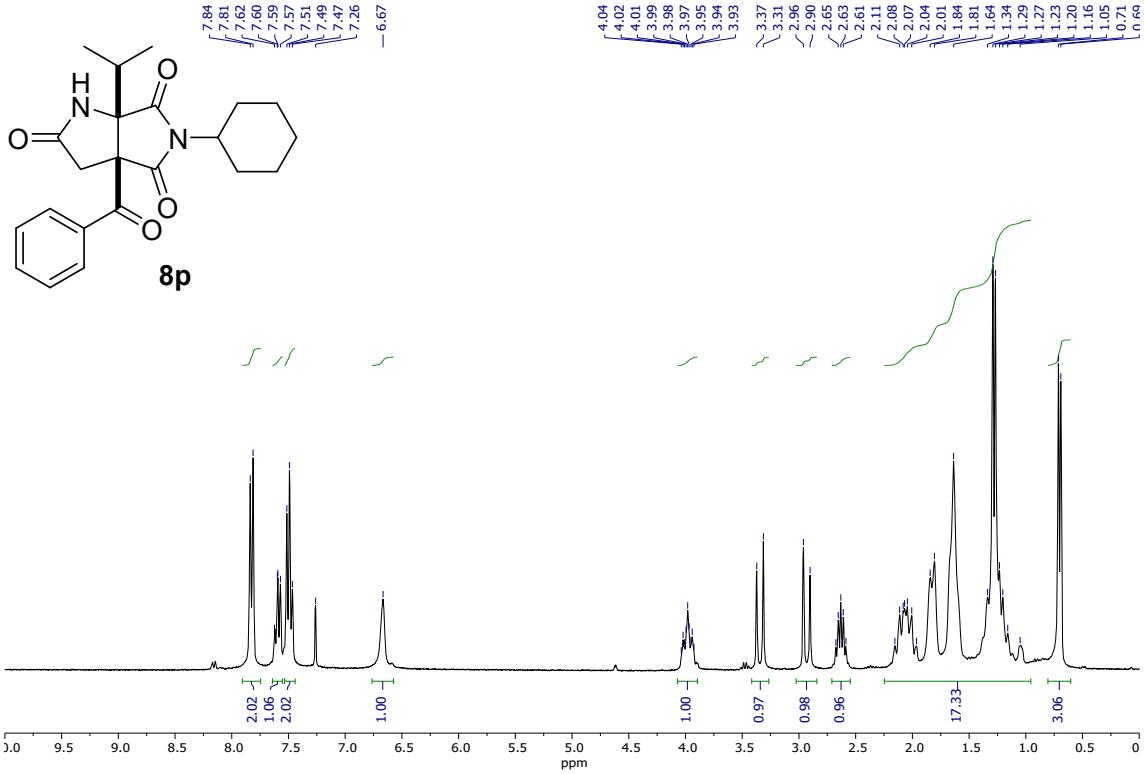


Figure S192. ^{1}H NMR spectrum of **8p** (300 MHz, $CDCl_3$).

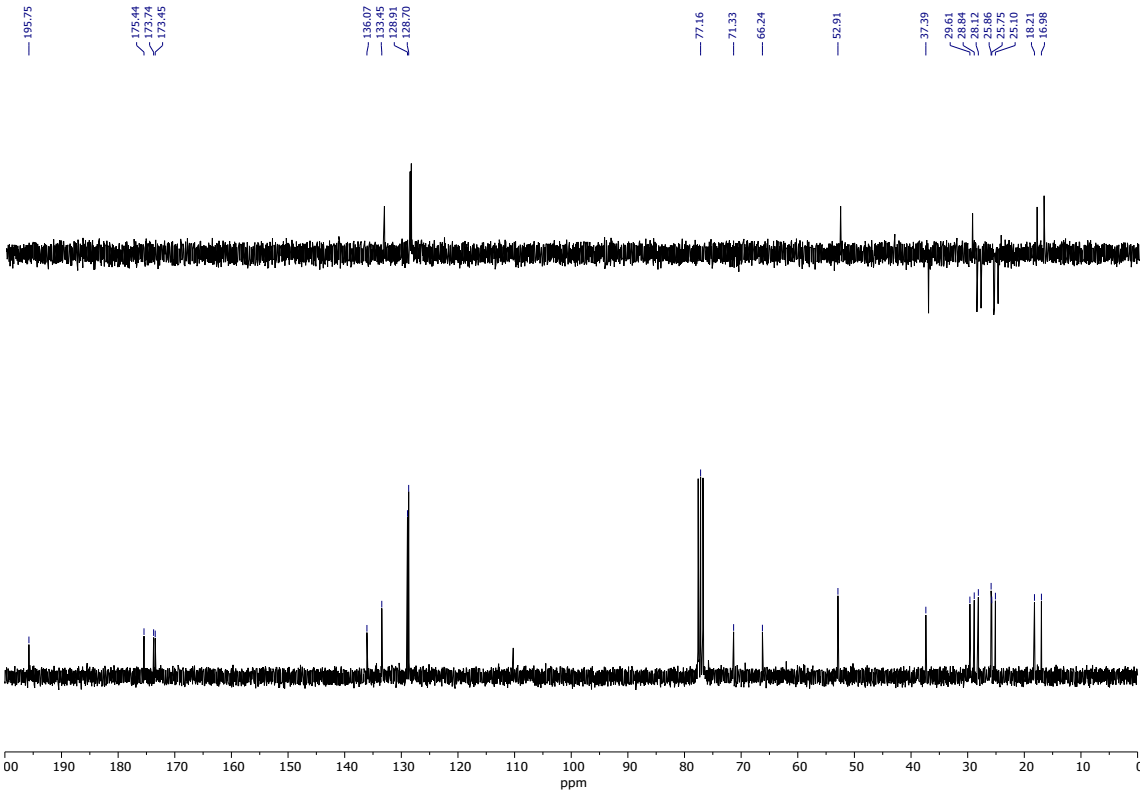


Figure S193. ^{13}C and DEPT-135 NMR spectra of **8p** (75 MHz, $CDCl_3$).

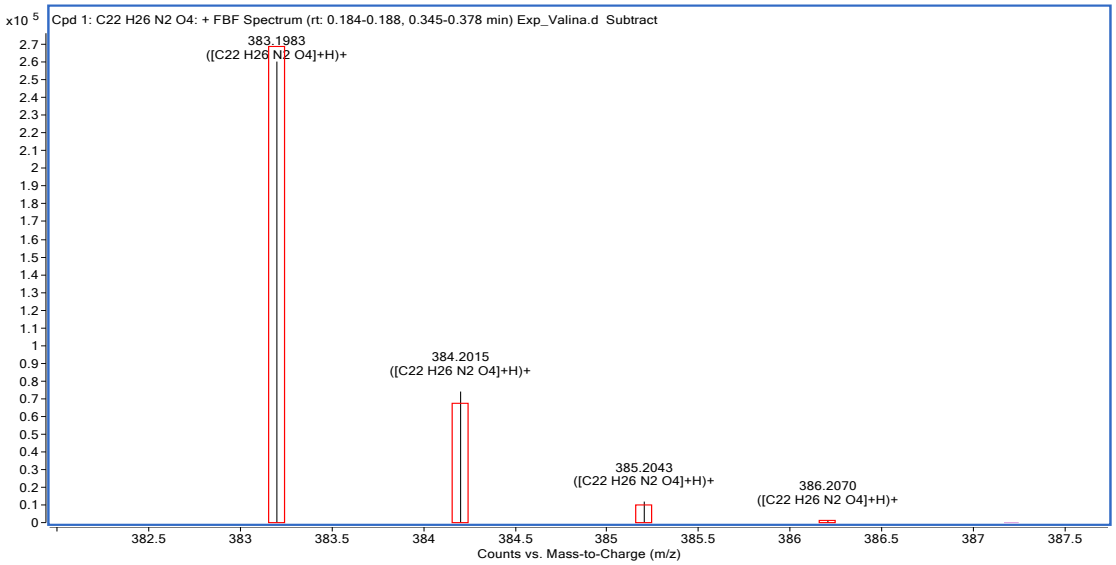


Figure S194. HRMS (+ESI) spectrum of **8p**.

(3a*R,6a*S**)-5-Cyclohexyl-6a-isopropyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (9p)**

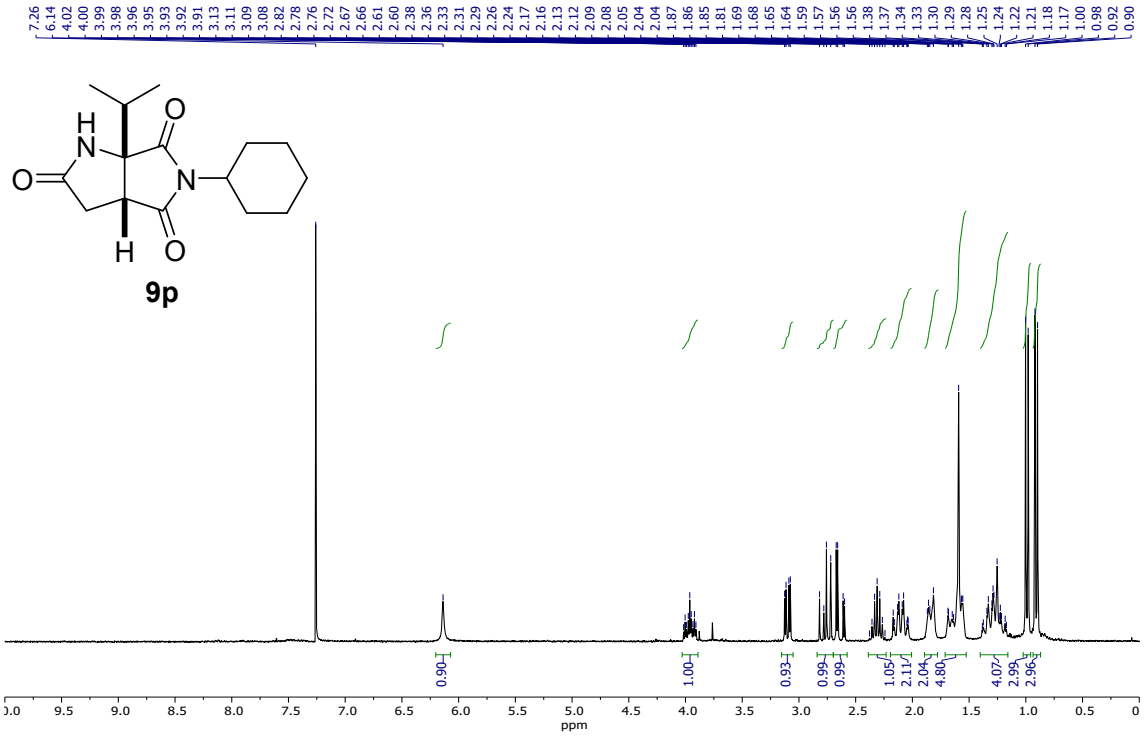


Figure S195. ^{1}H NMR spectrum of **9p** (300 MHz, $CDCl_3$).

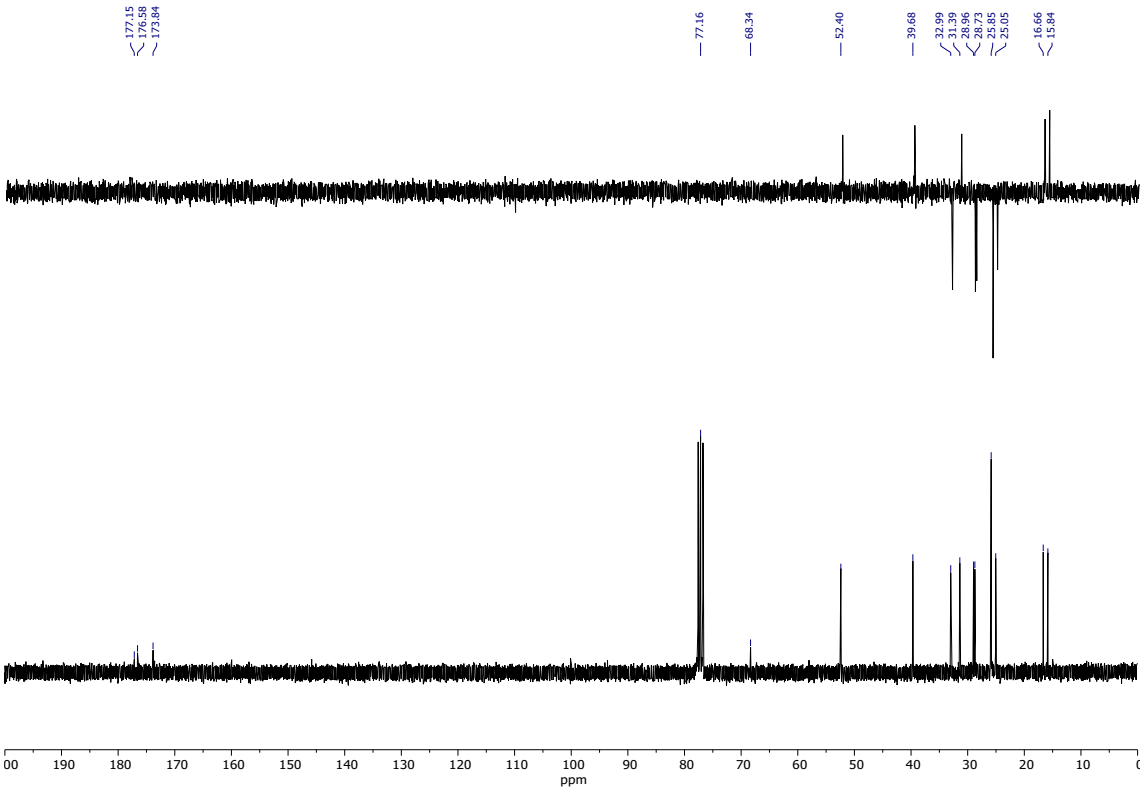


Figure S196. ^{13}C and DEPT-135 NMR spectra of **9p** (75 MHz, $CDCl_3$).

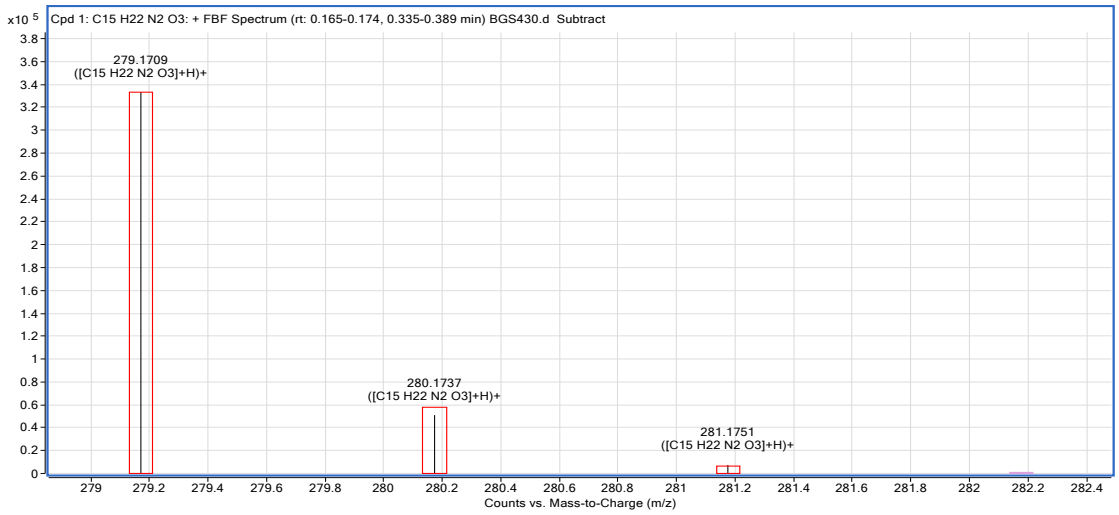


Figure S197. HRMS (+ESI) spectrum of **9p**.

(3*R,4*R**,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-3-phenylpyrrolidin-2-one ($7q_{diast1}$)**

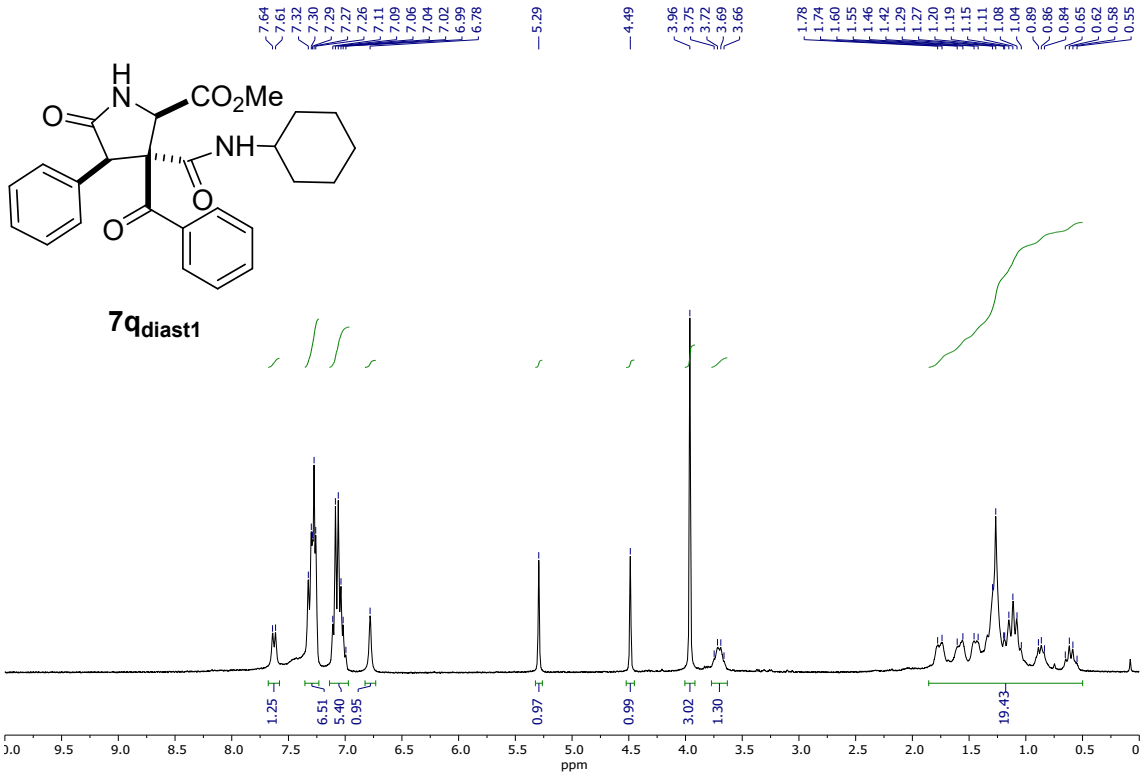


Figure S198. ^{1}H NMR spectrum of $7q_{diast1}$ (300 MHz, $CDCl_3$).

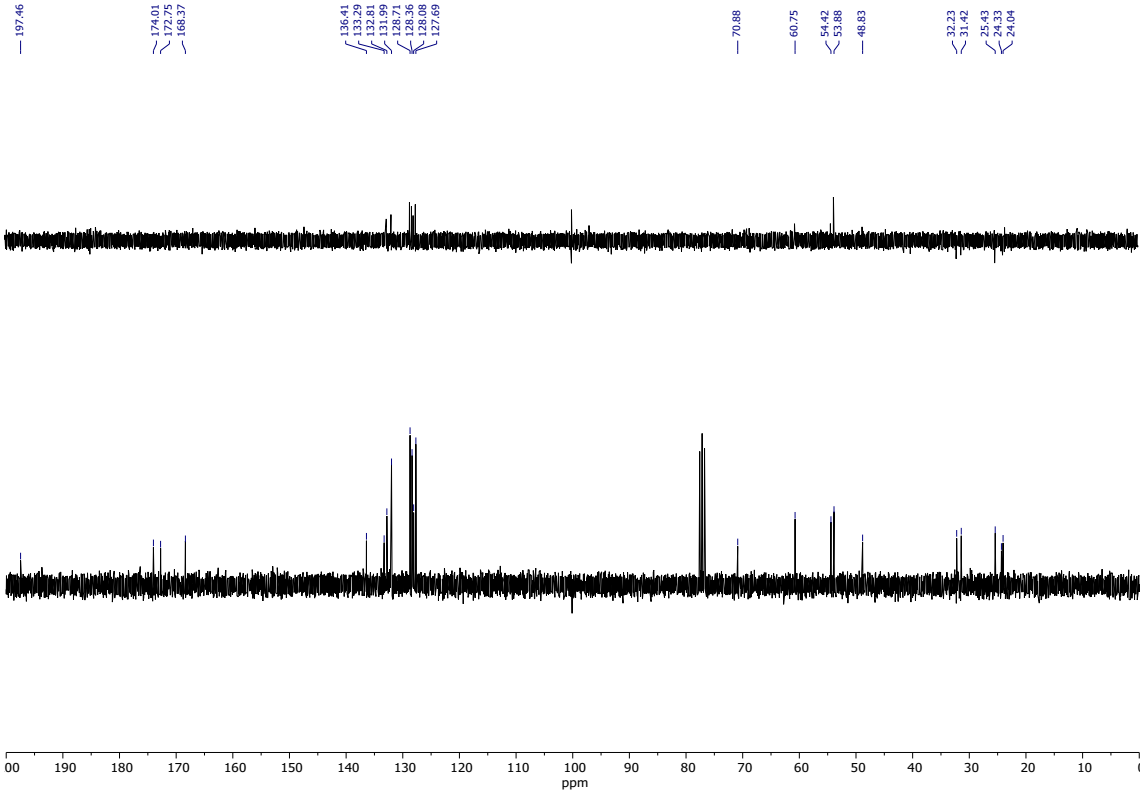


Figure S199. ^{13}C and DEPT-135 NMR spectra of **7q$_{diast1}$** (75 MHz, $CDCl_3$).

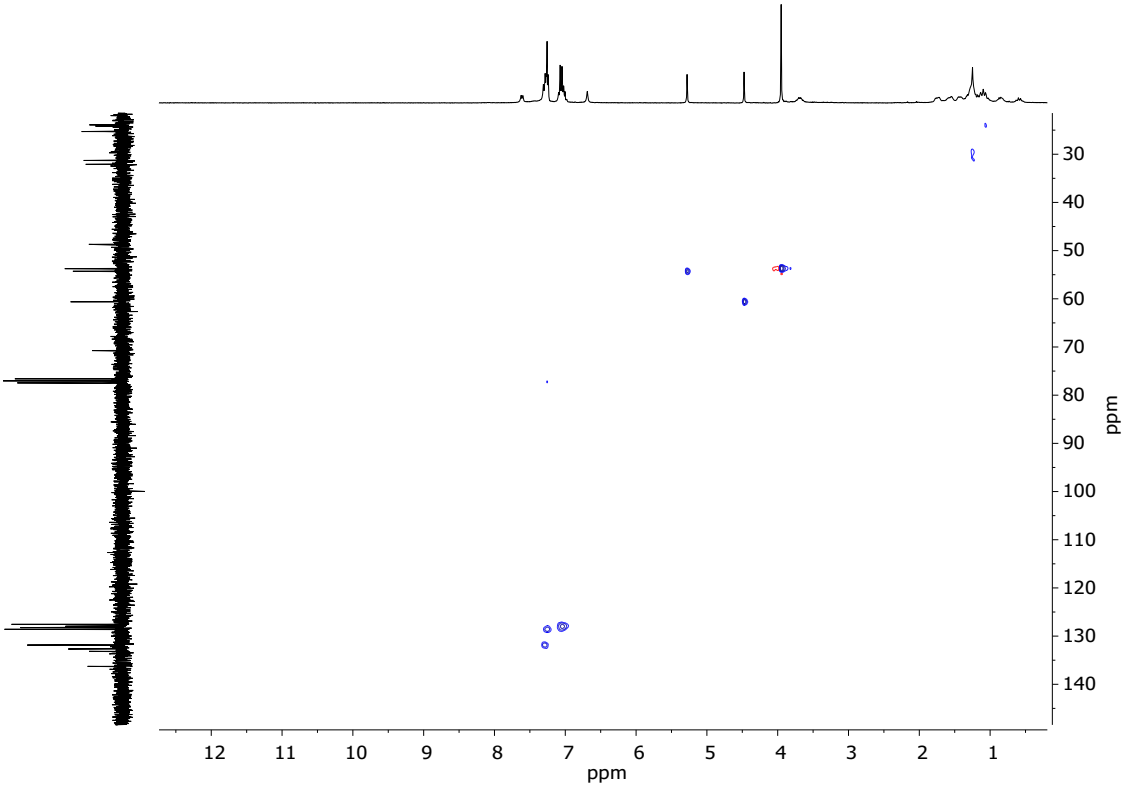


Figure S200. HMQC spectrum of **7q$_{diast1}$** (300 MHz, $CDCl_3$).

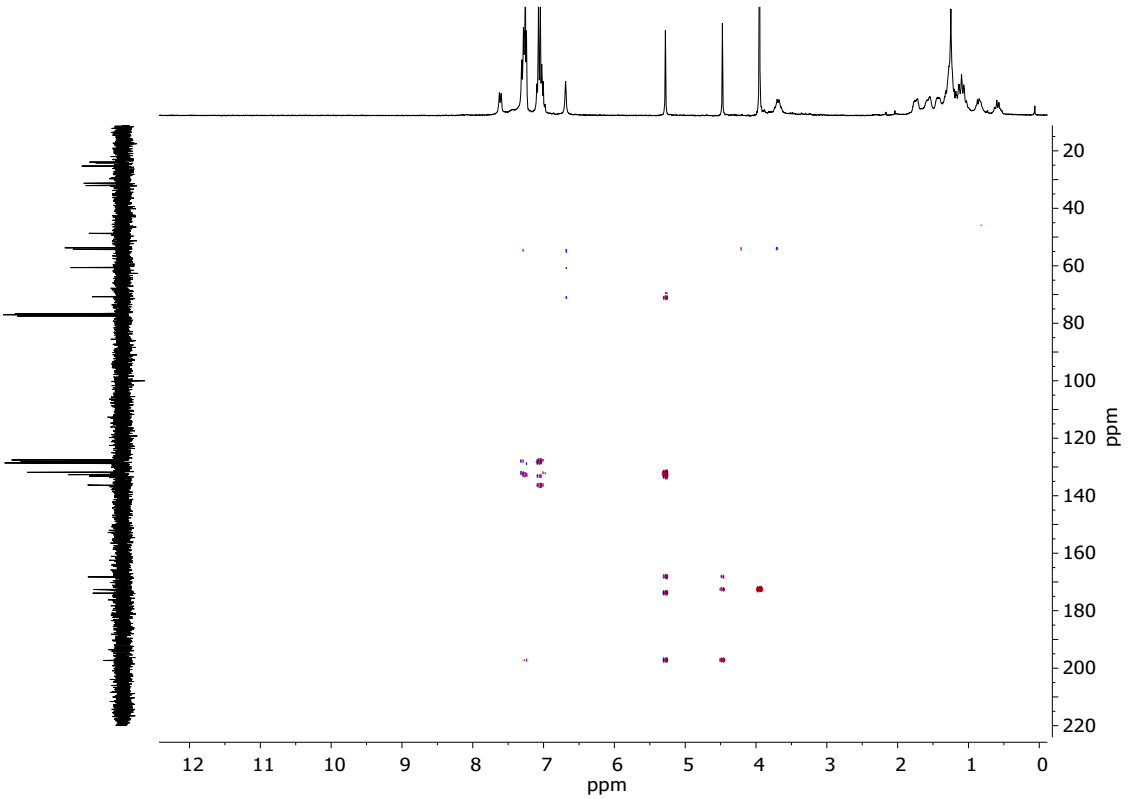


Figure S201. HMBC spectrum of **7q$_{diast1}$** (300 MHz, $CDCl_3$).

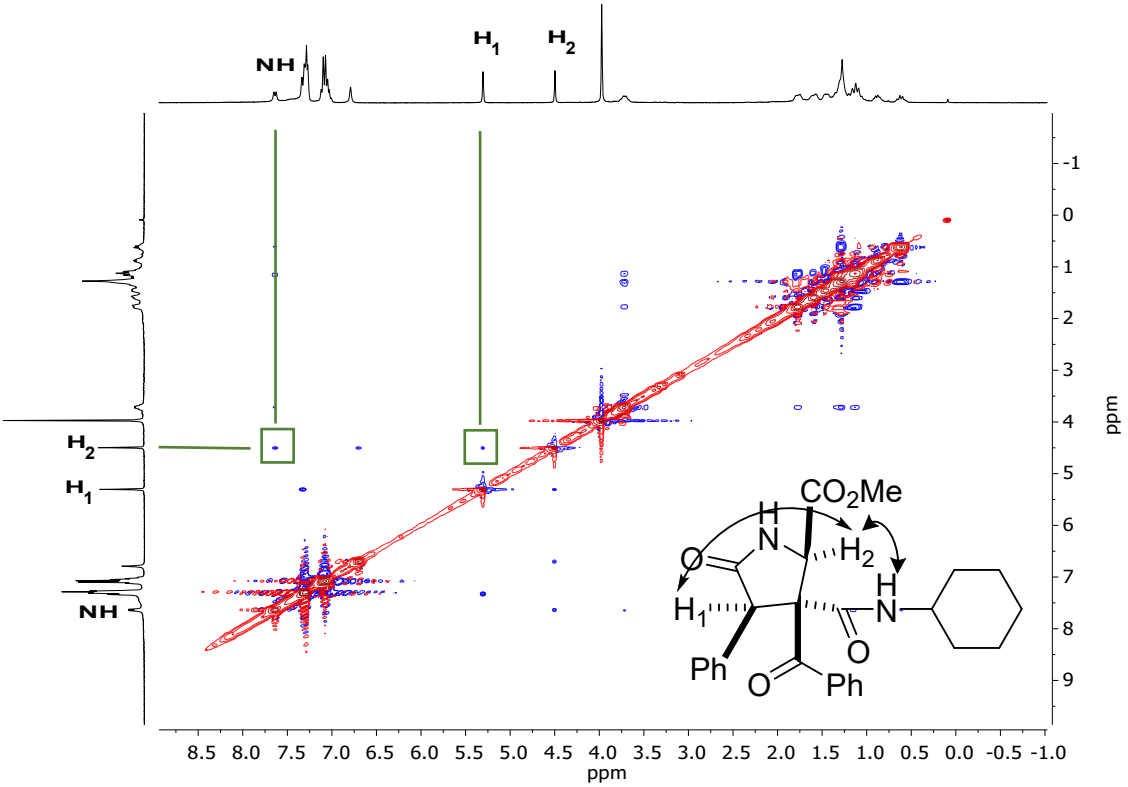


Figure S202. NOESY spectrum of **7q$_{diast1}$** (300 MHz, $CDCl_3$).

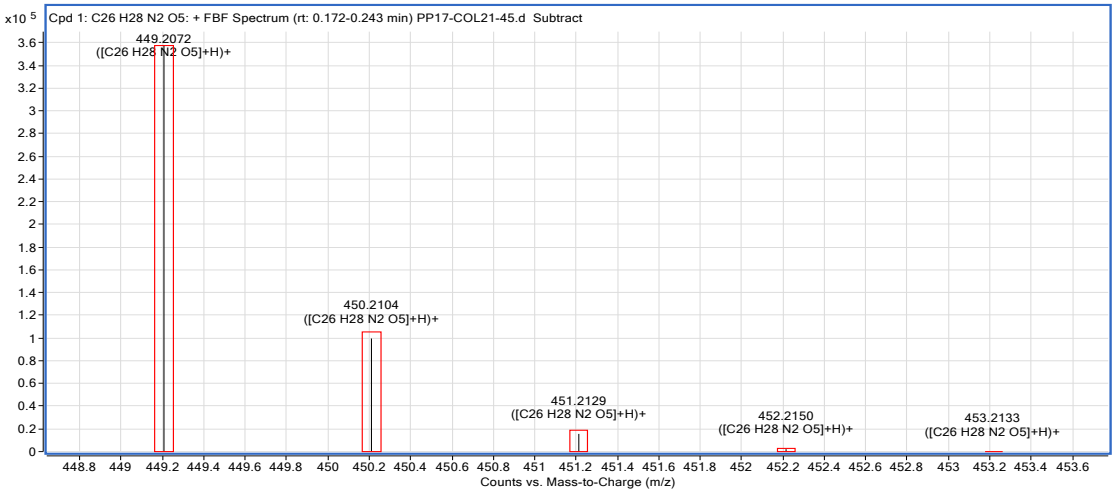


Figure S203. HRMS (+ESI) spectrum of **7q$_{diast1}$**.

(3*R,4*S**,5*S**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-3-phenylpyrrolidin-2-one ($7q_{diast2}$)**

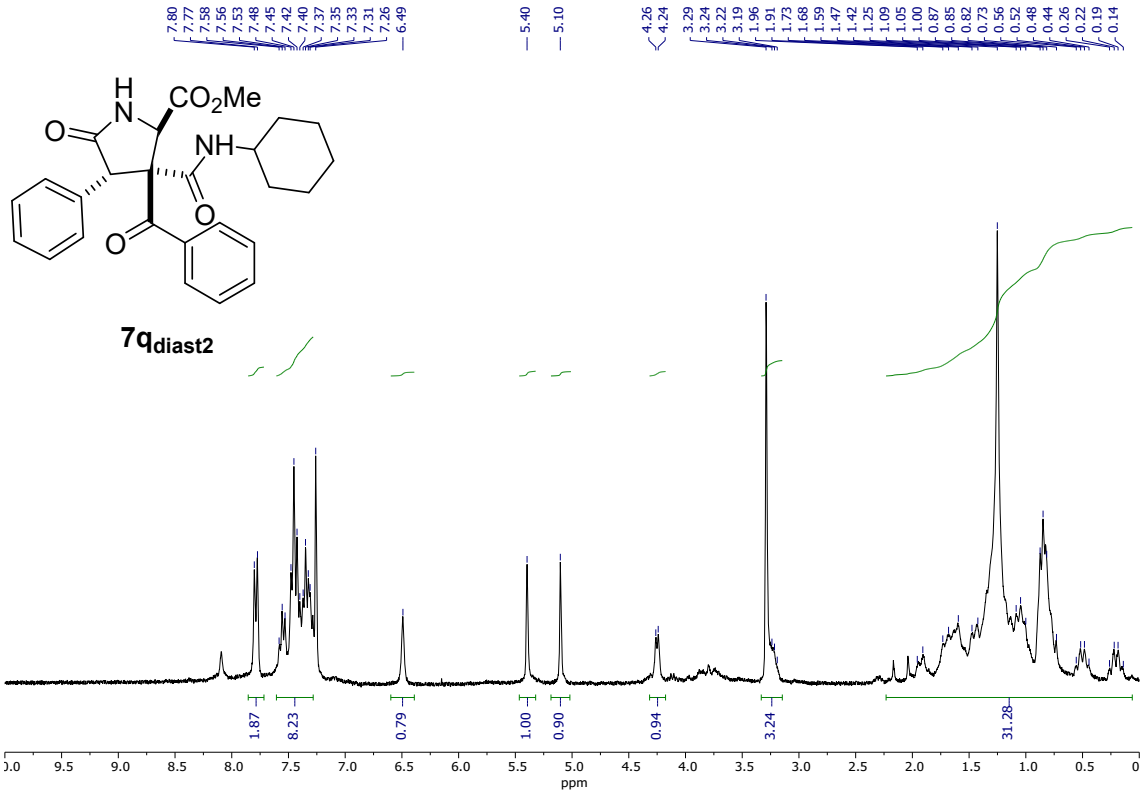


Figure S204. ^{1}H NMR spectrum of $7q_{diast2}$ (300 MHz, $CDCl_3$).

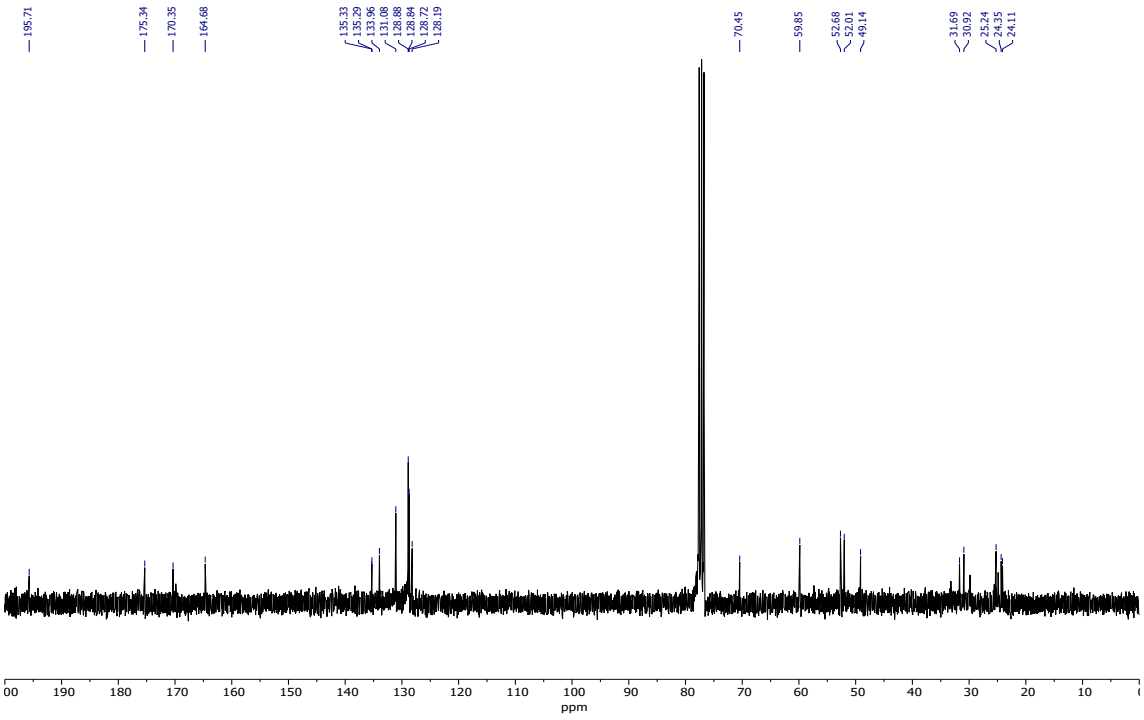


Figure S205. ^{13}C NMR spectrum of $7q_{diast2}$ (75 MHz, $CDCl_3$).

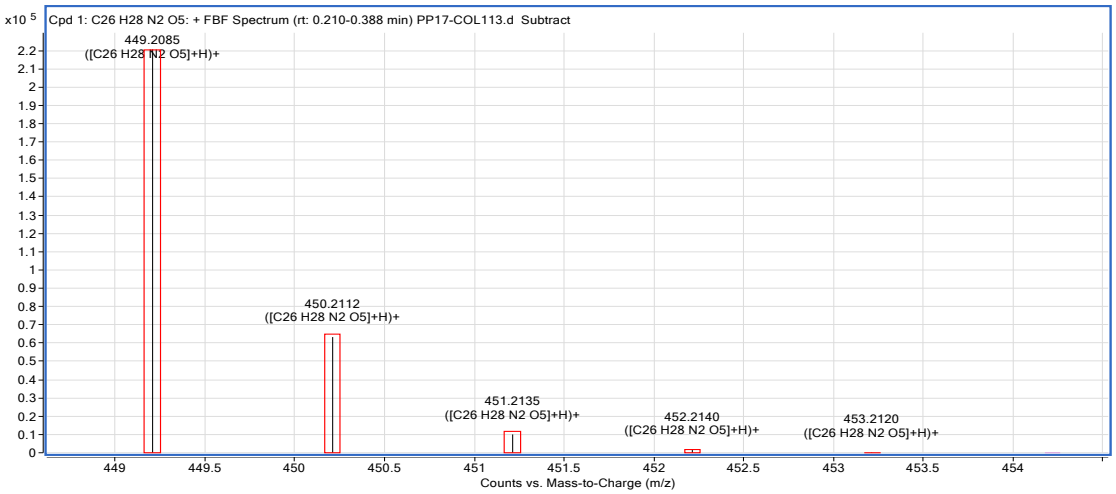


Figure S206. HRMS (+ESI) spectrum of **7q$_{diast2}$**.

(3a*R,6a*S**)-3a-Benzoyl-5-cyclohexyl-3,6a-diphenyltetrahydropyrrolo[3,4-*b*]pyrrole-2,4,6(5*H*)-trione (8r)**

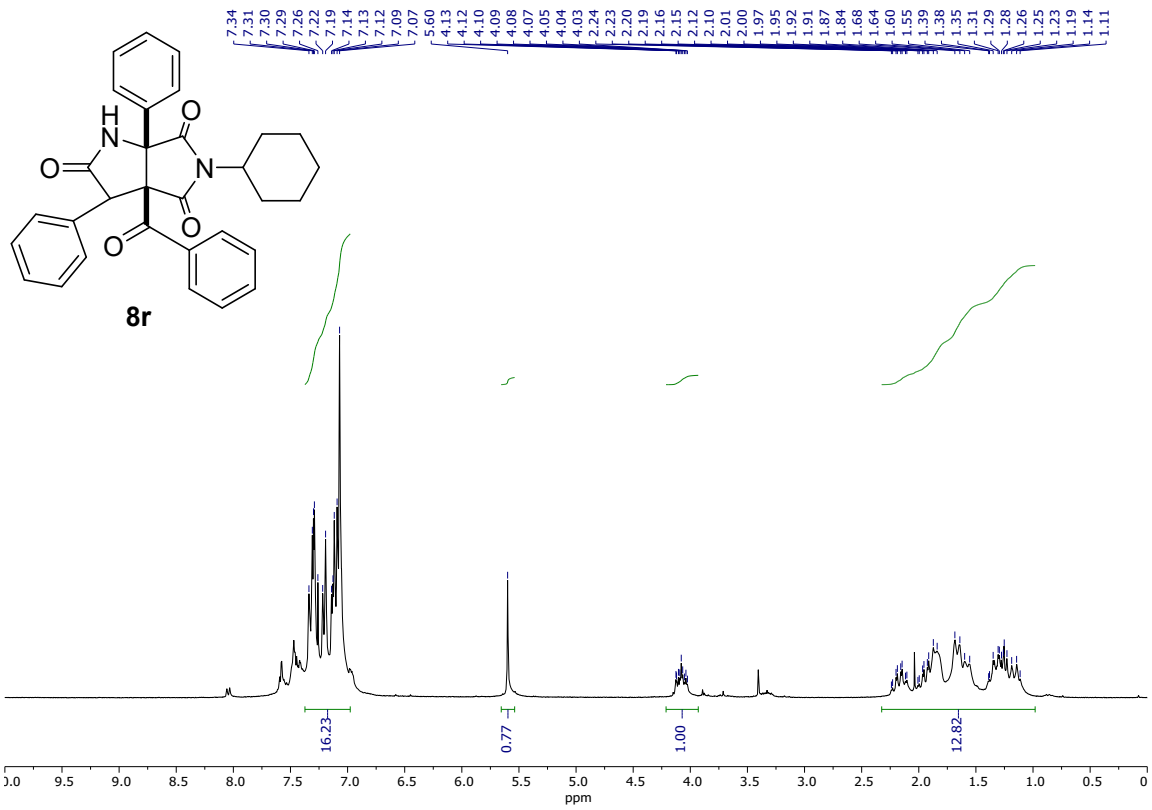


Figure S207. ^{1}H NMR spectrum of **8r** (300 MHz, $CDCl_3$).

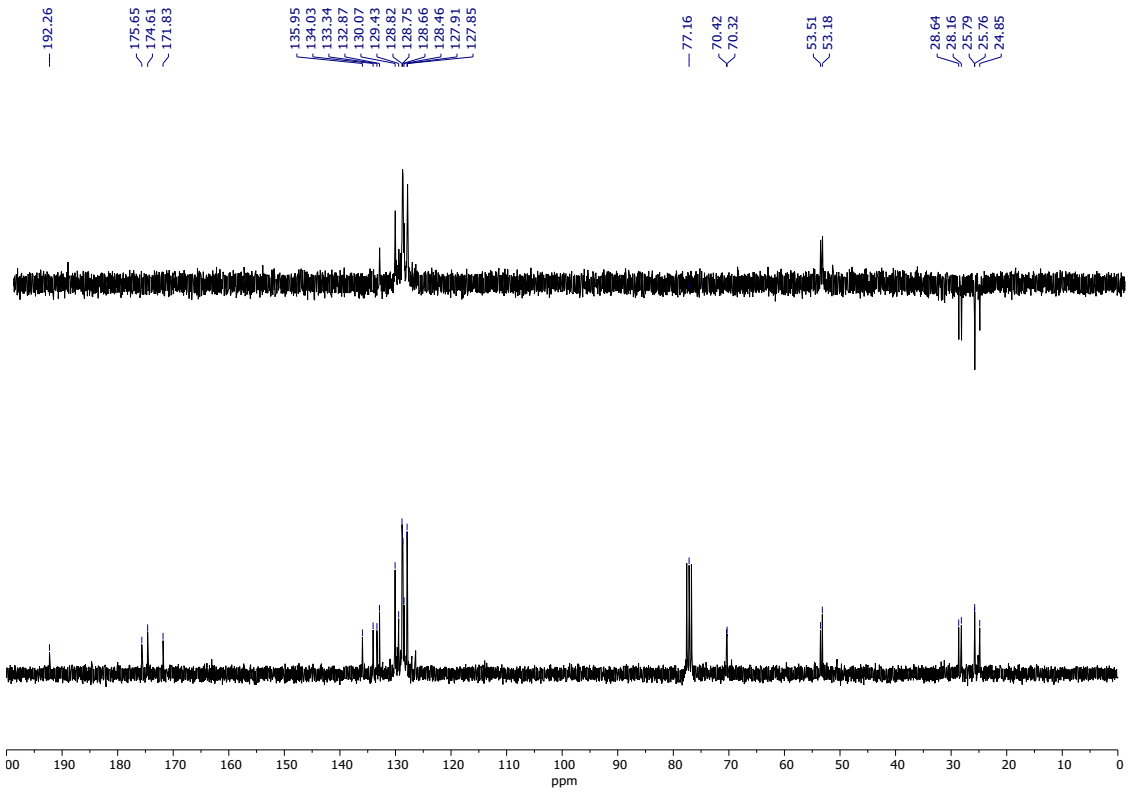


Figure S208. ^{13}C and DEPT-135 NMR spectra of **8r** (75 MHz, $CDCl_3$).

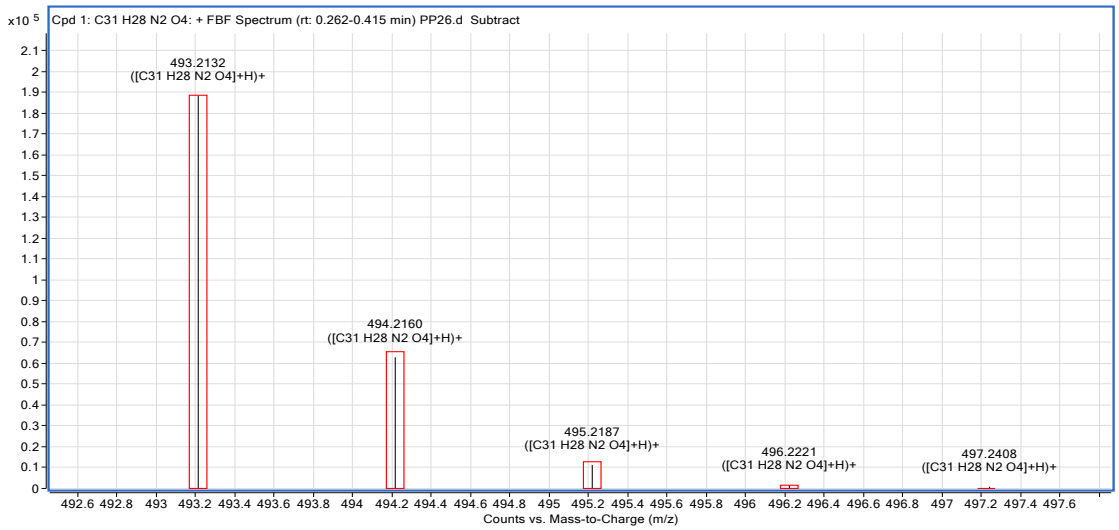


Figure S209. HRMS (+ESI) spectrum of **8r**.

(3*R,4*R**,5*R**)-4-Benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-5-methyl-3-phenylpyrrolidin-2-one (7s)**

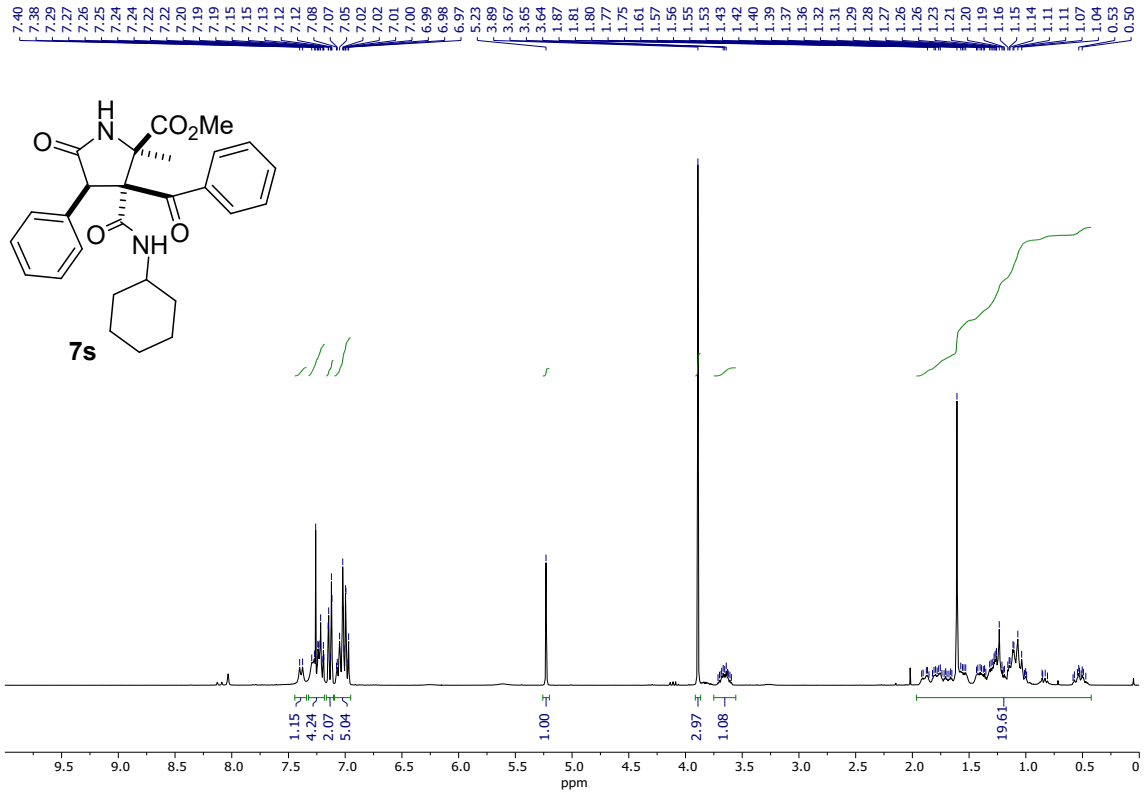


Figure S210. ^{1}H NMR spectrum of **7s** (300 MHz, $CDCl_3$).

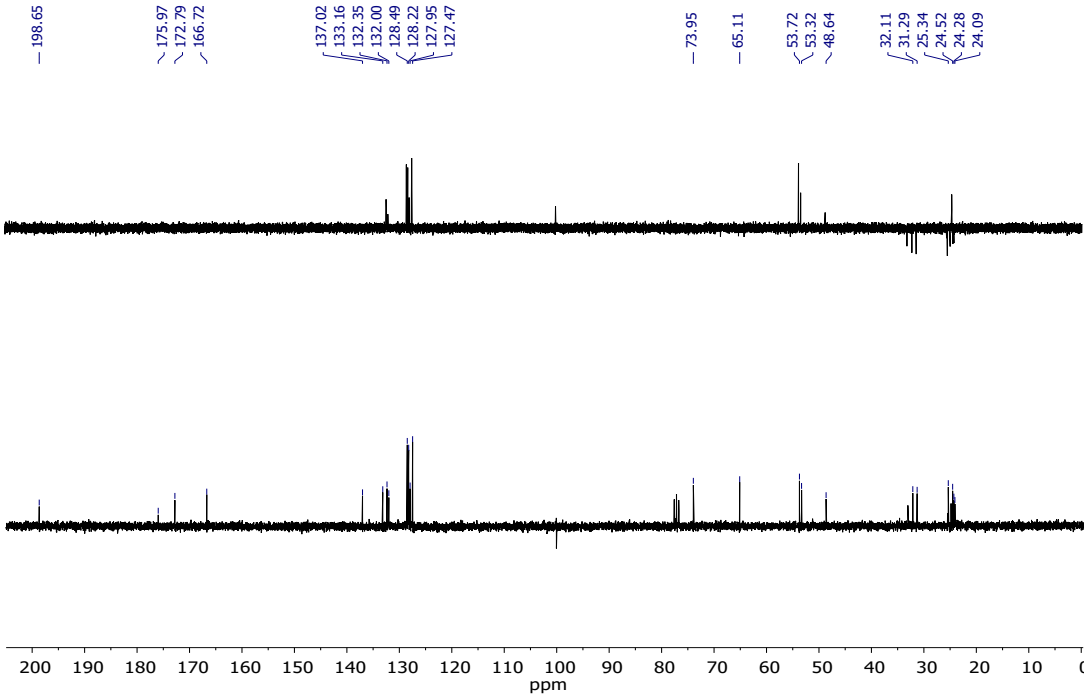


Figure S211. ^{13}C and DEPT-135 NMR spectra of **7s** (75 MHz, $CDCl_3$).

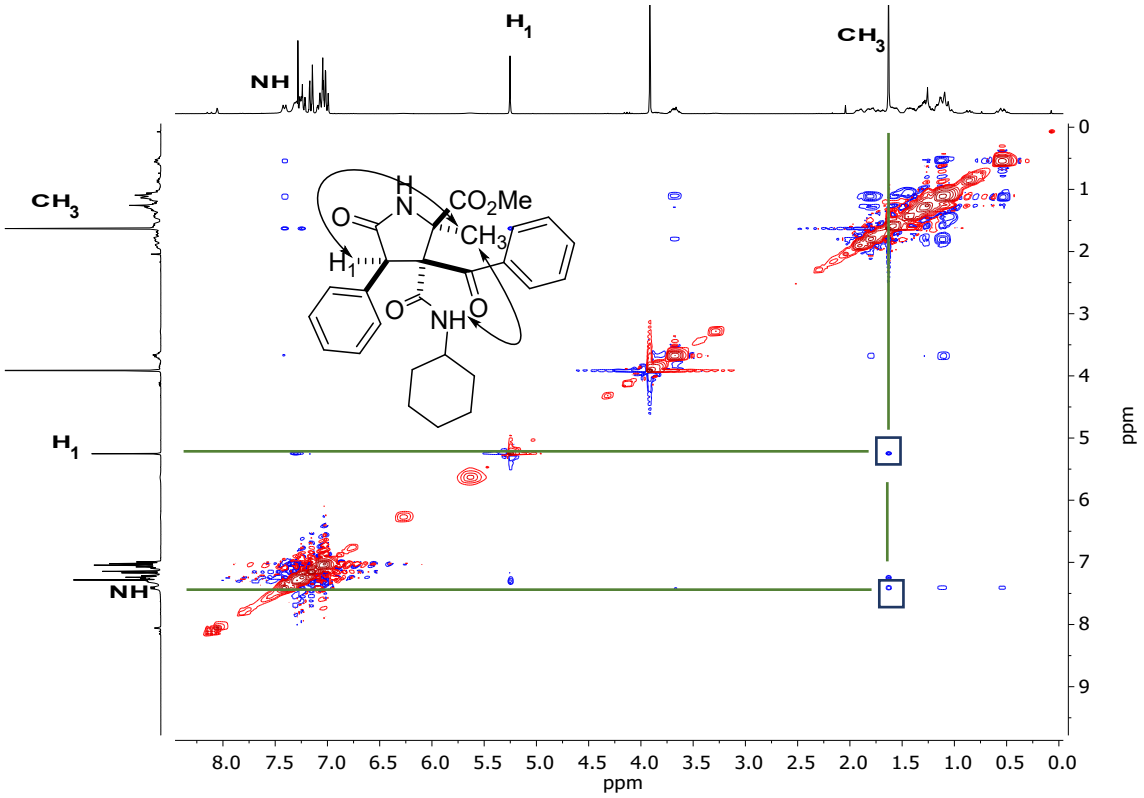


Figure S212. NOESY spectrum of **7s** (300 MHz, $CDCl_3$).

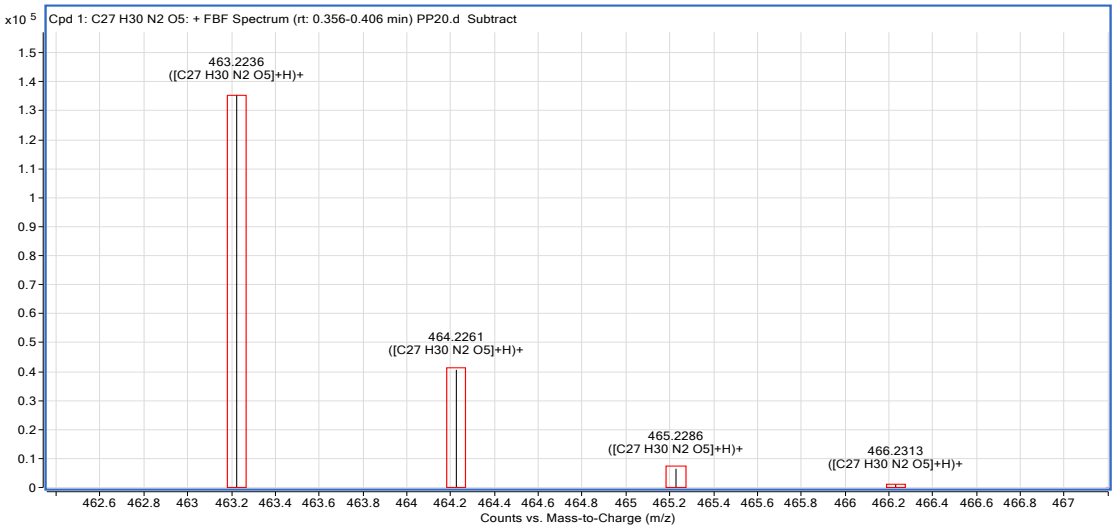


Figure S213. HRMS (+ESI) spectrum of **7s**.

(3*R,4*R**,5*R**)-5-Benzyl-4-benzoyl-4-cyclohexylcarbamoyl-5-methoxycarbonyl-3-phenylpyrrolidin-2-one (7t)**

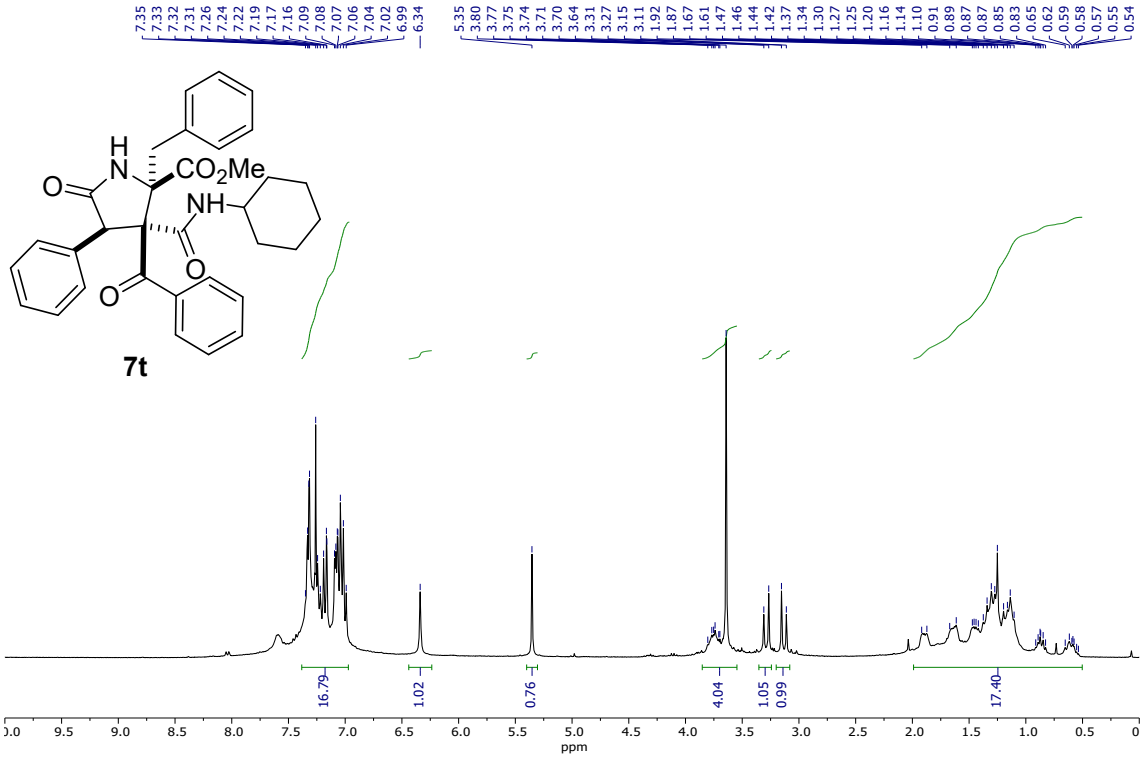


Figure S214. ^{1}H NMR spectrum of **7t** (300 MHz, $CDCl_3$).

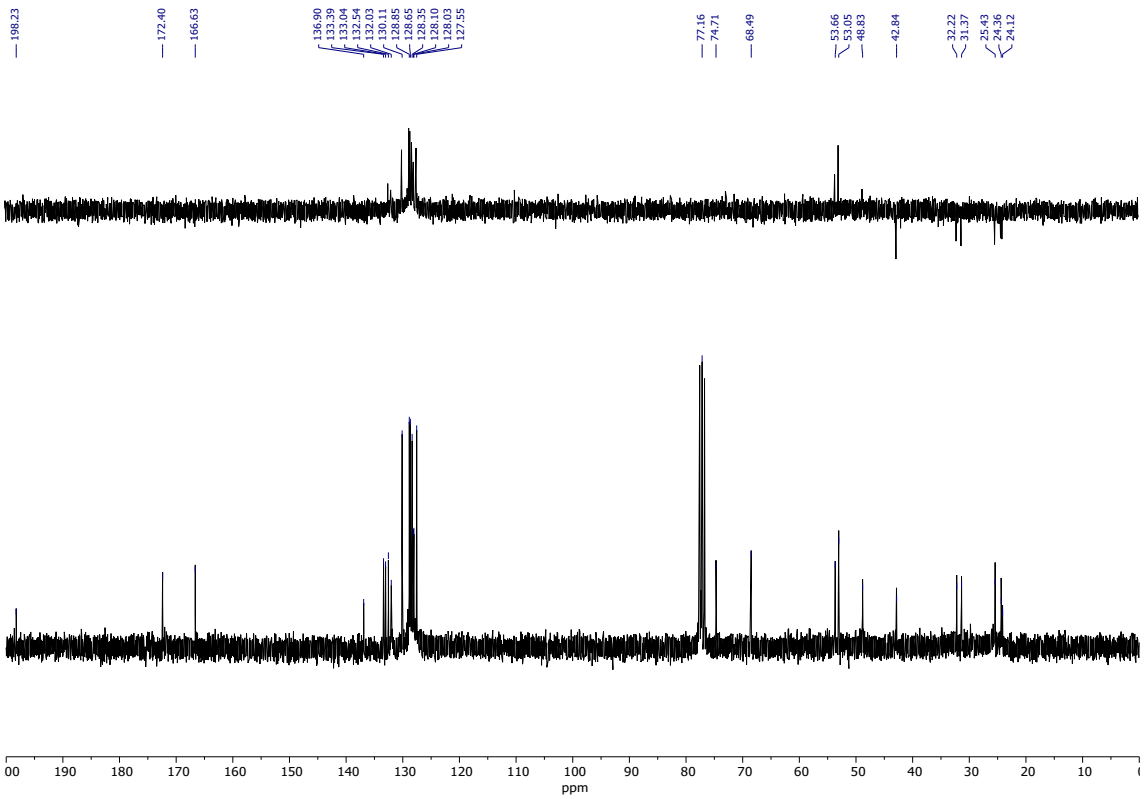


Figure S215. ^{13}C and DEPT-135 NMR spectra of **7t** (75 MHz, $CDCl_3$).

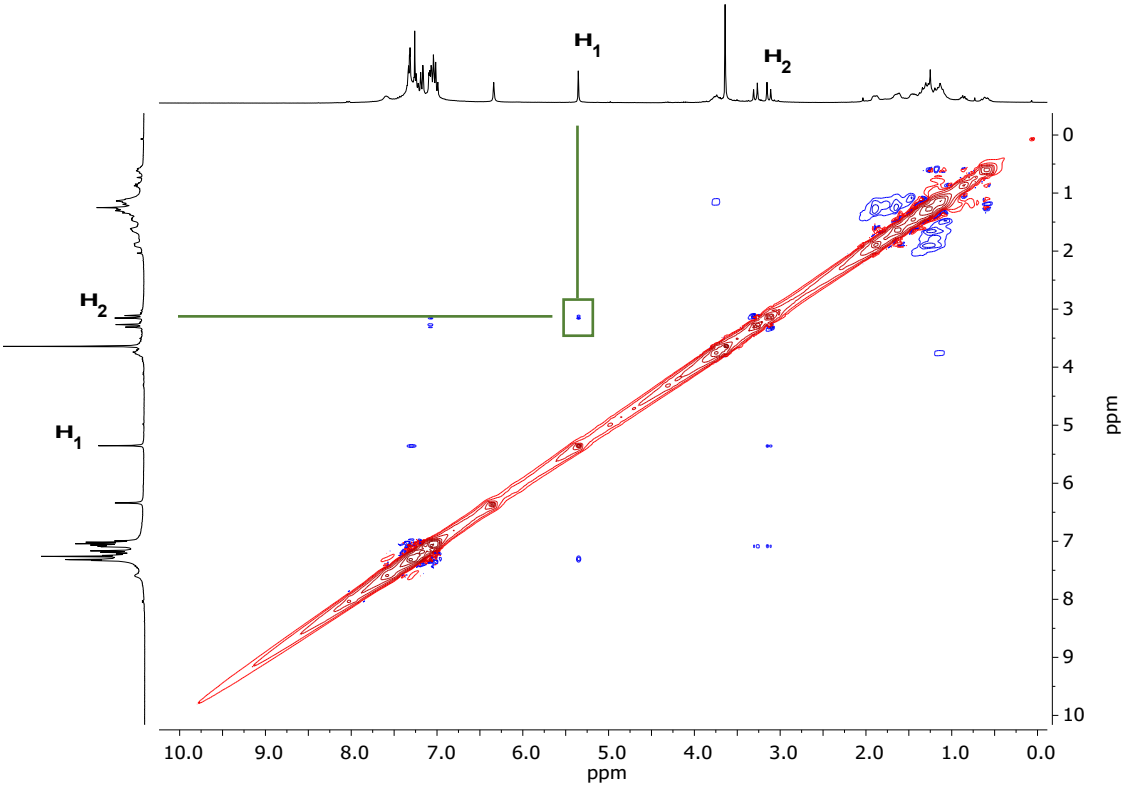


Figure S216. NOESY spectrum of **7t** (300 MHz, $CDCl_3$).

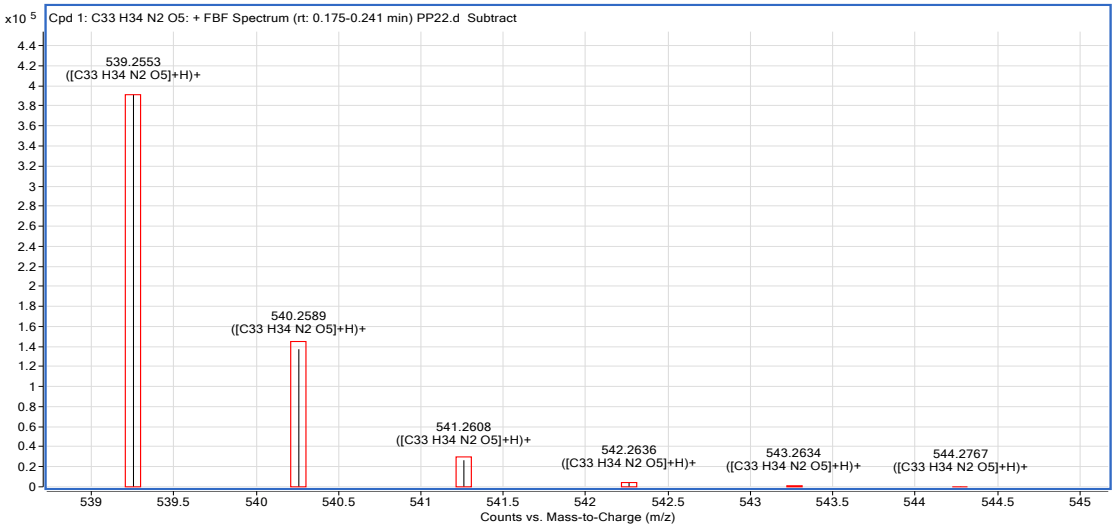


Figure S217. HRMS (+ESI) spectrum of **7t**.

(4*R,5*S**)-4-Cyclohexylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (10a)**

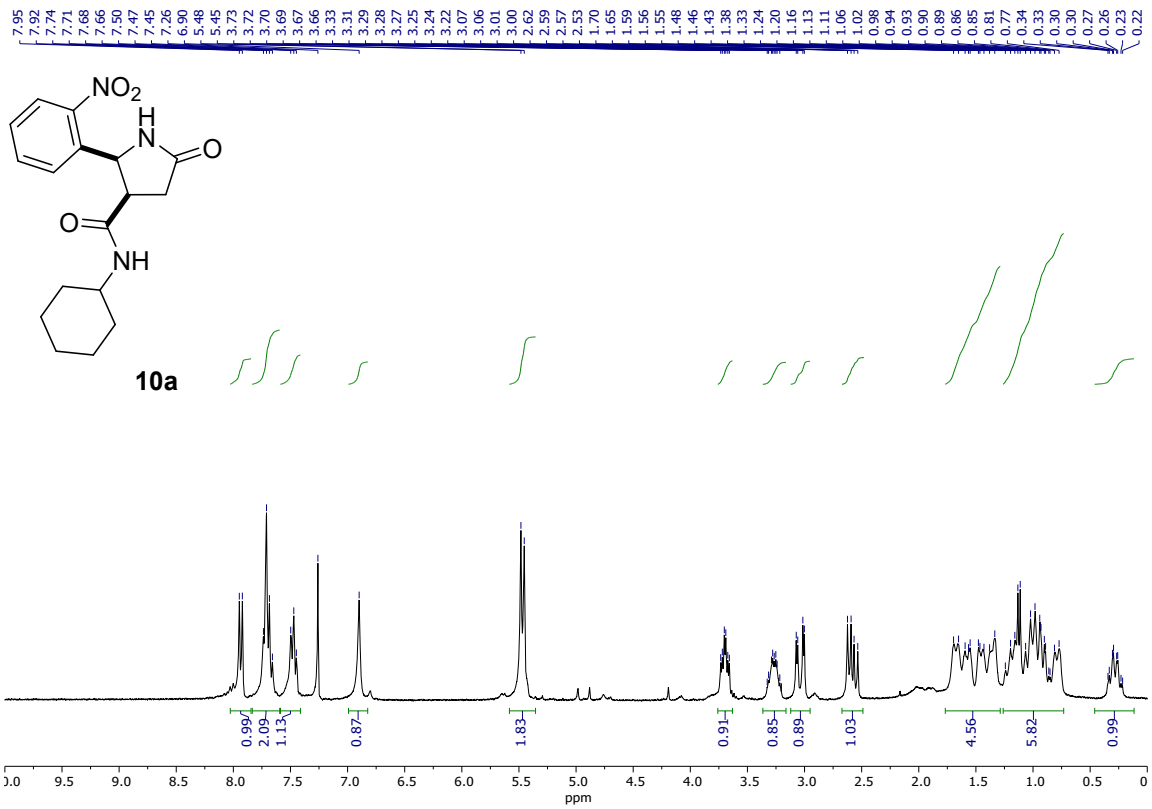


Figure S218. ^{1}H NMR spectrum of **10a** (300 MHz, $CDCl_3$).

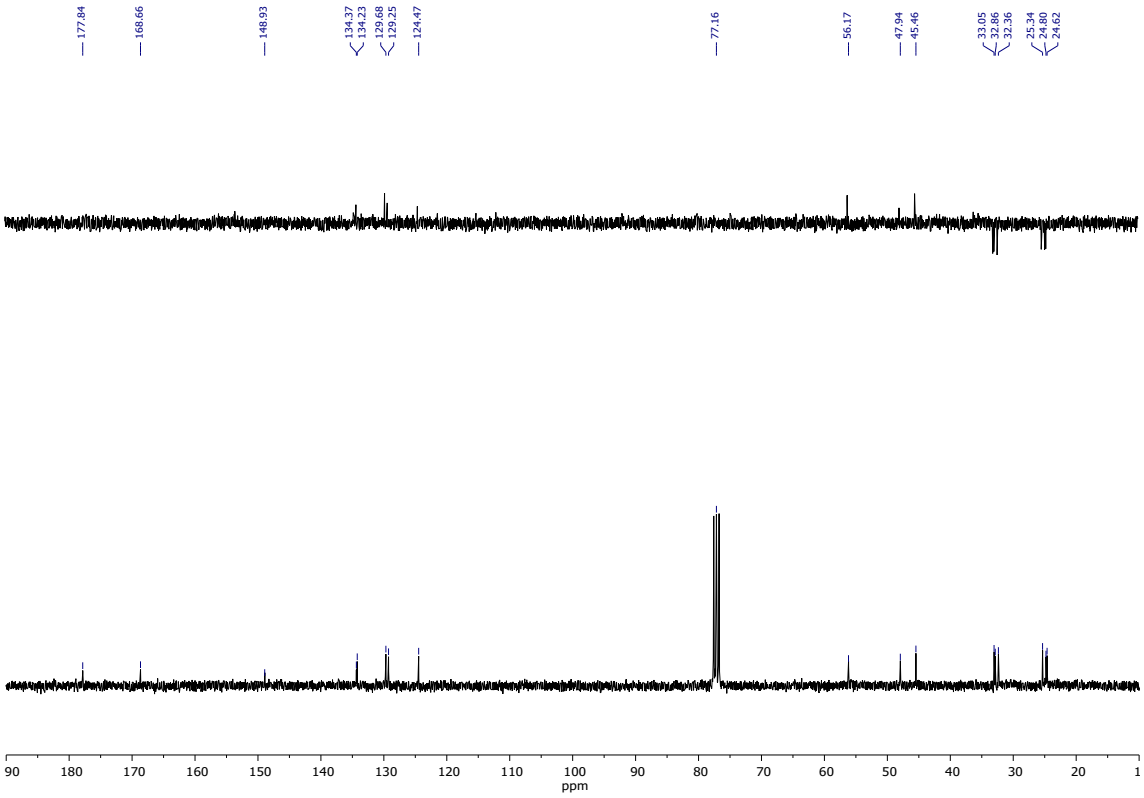


Figure S219. ^{13}C and DEPT-135 NMR spectra of **10a** (75 MHz, $CDCl_3$).

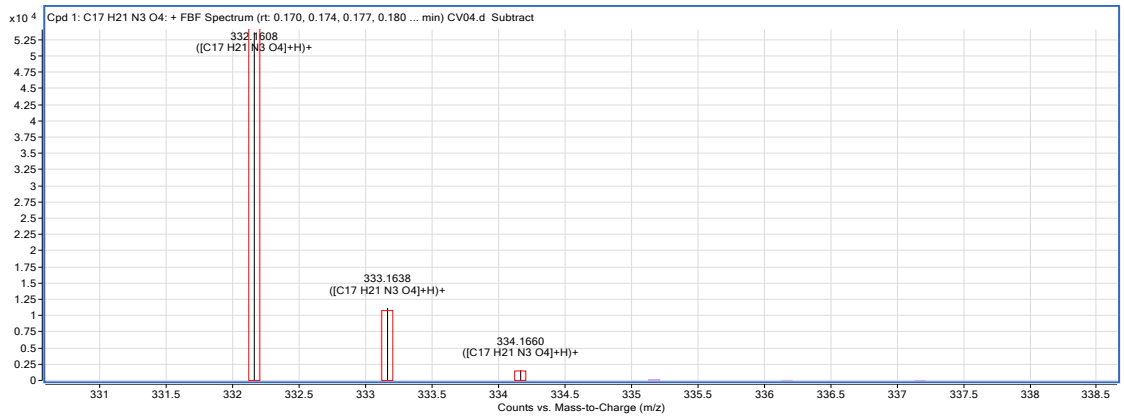


Figure S220. HRMS (+ESI) spectrum of **10a**.

(4*R,5*S**)-4-Benzylcarbamoyl-5-(2-nitrophenyl)pyrrolidin-2-one (10b)**

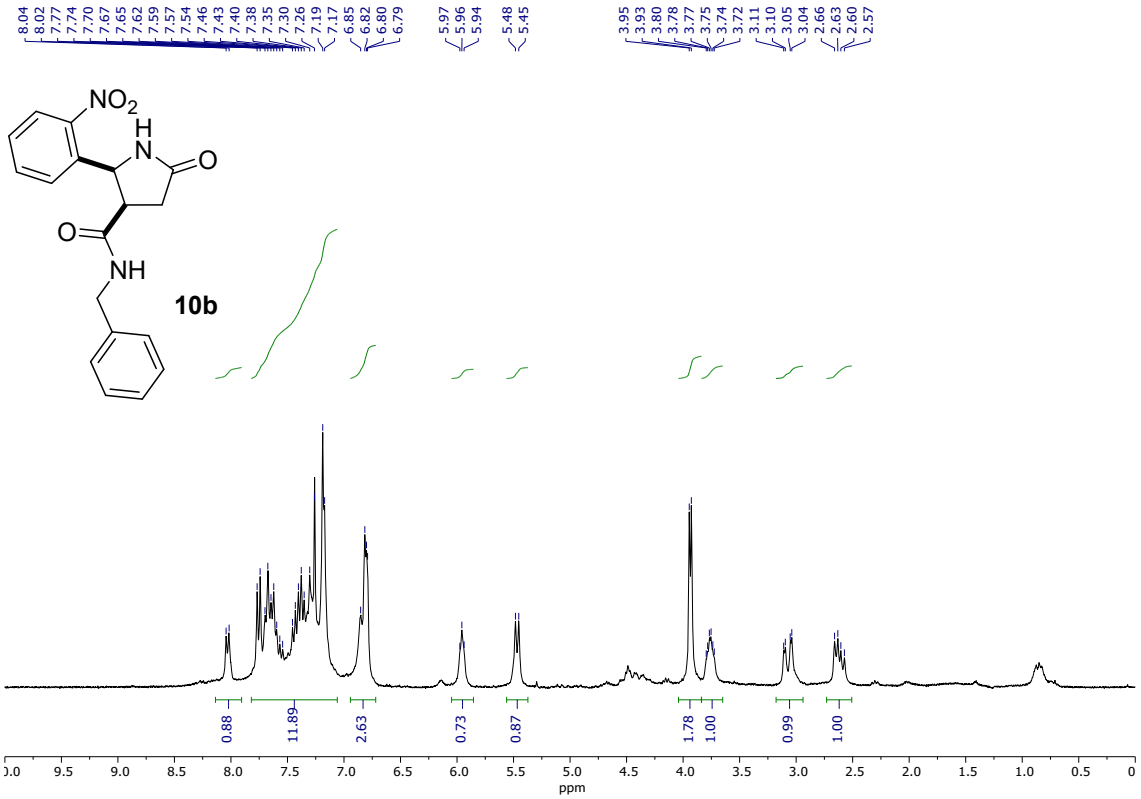


Figure S221. ^{1}H NMR spectrum of **10b** (300 MHz, $CDCl_3$).

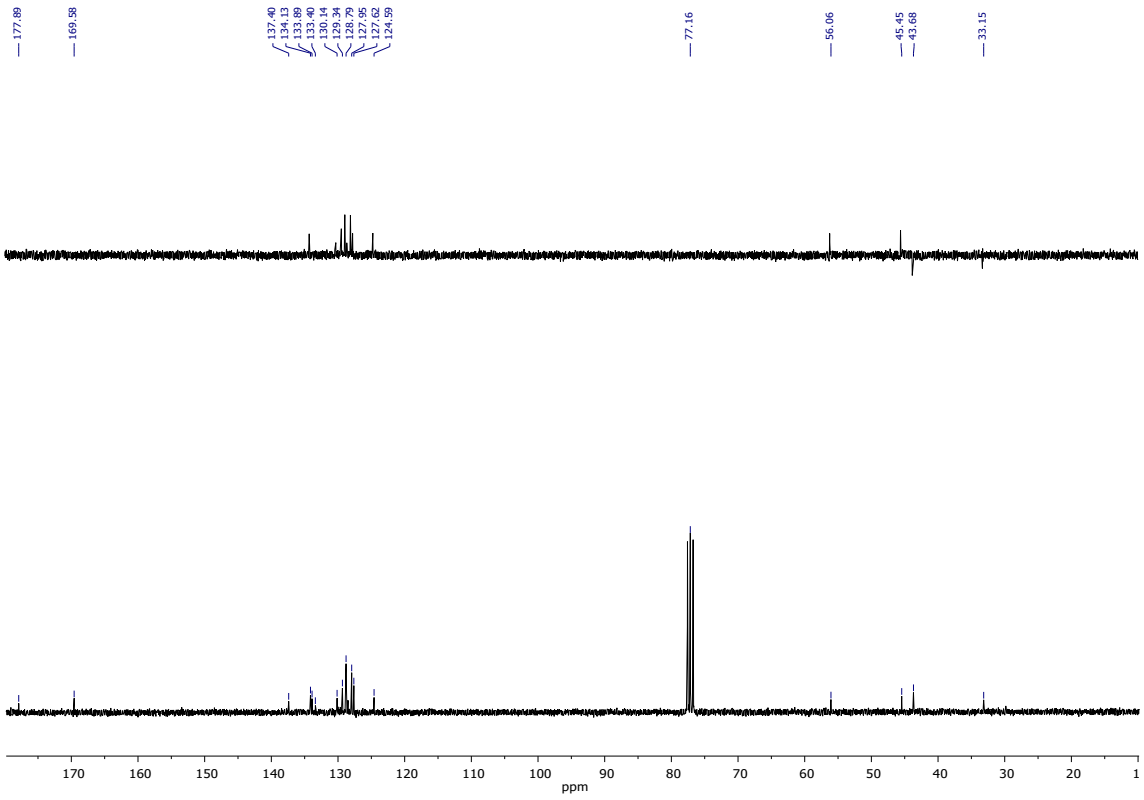


Figure S222. ^{13}C and DEPT-135 NMR spectra of **10b** (75 MHz, $CDCl_3$).

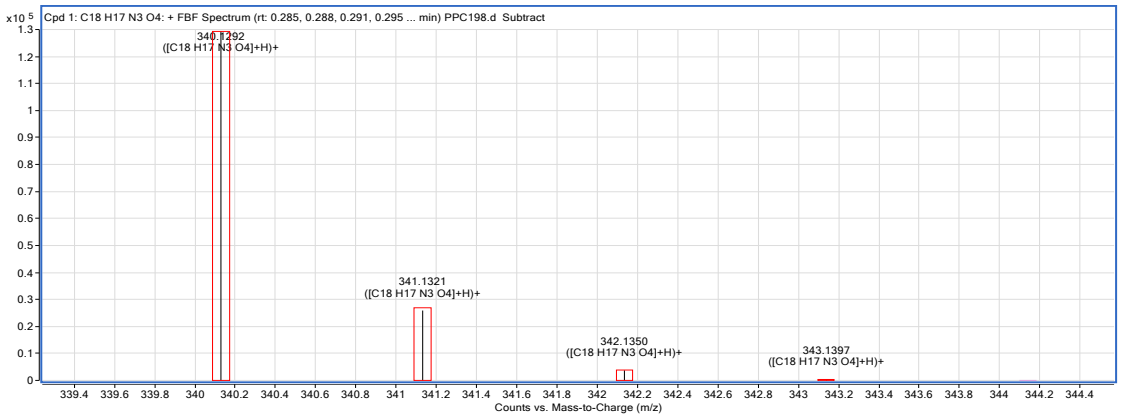


Figure S223. HRMS (+ESI) spectrum of **10b**.

(4*R,5*S**)-4-(*tert*-Butylcarbamoyl)-5-(2-nitrophenyl)pyrrolidin-2-one (10c)**

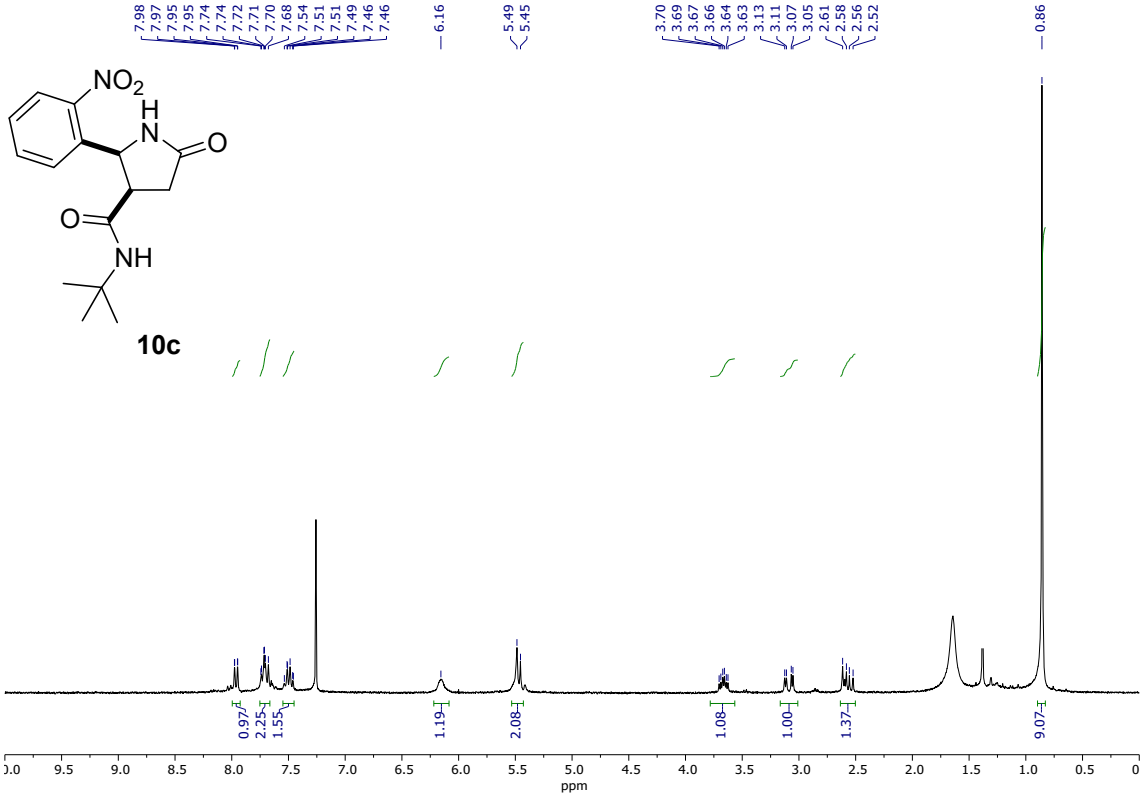


Figure S224. ^{1}H NMR spectrum of **10c** (300 MHz, $CDCl_3$).

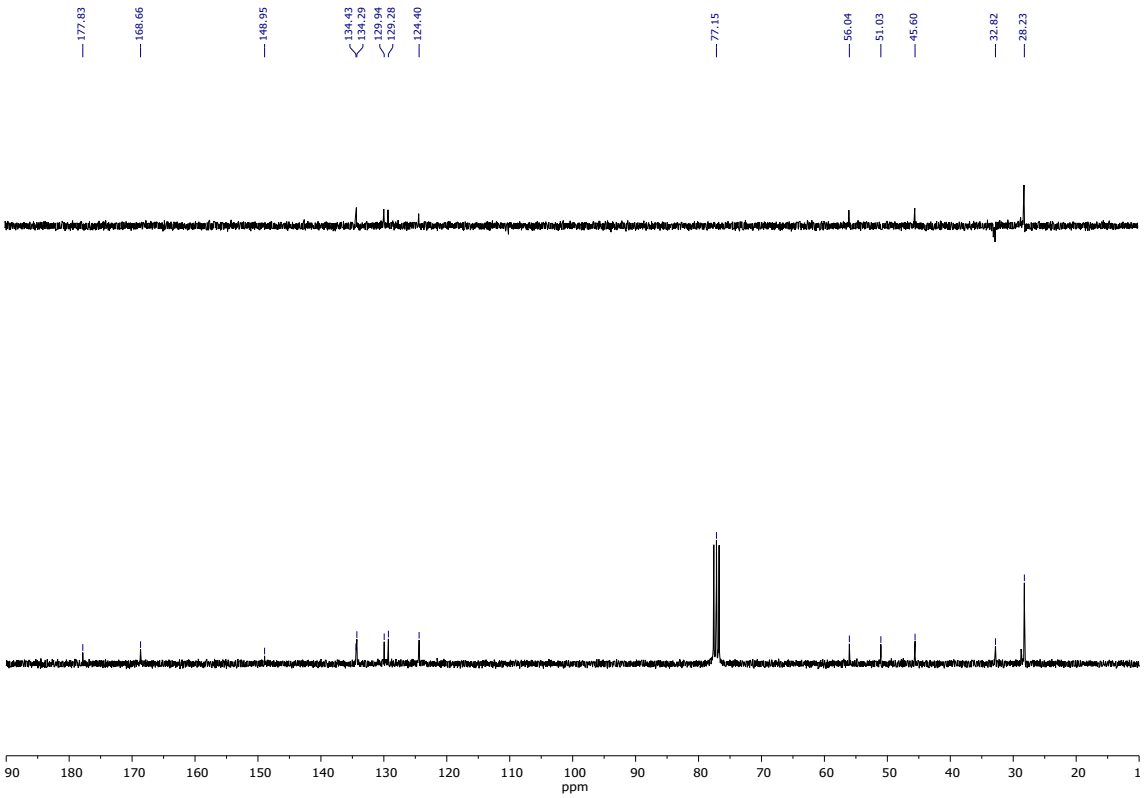


Figure S225. ^{13}C and DEPT-135 NMR spectra of **10c** (75 MHz, $CDCl_3$).

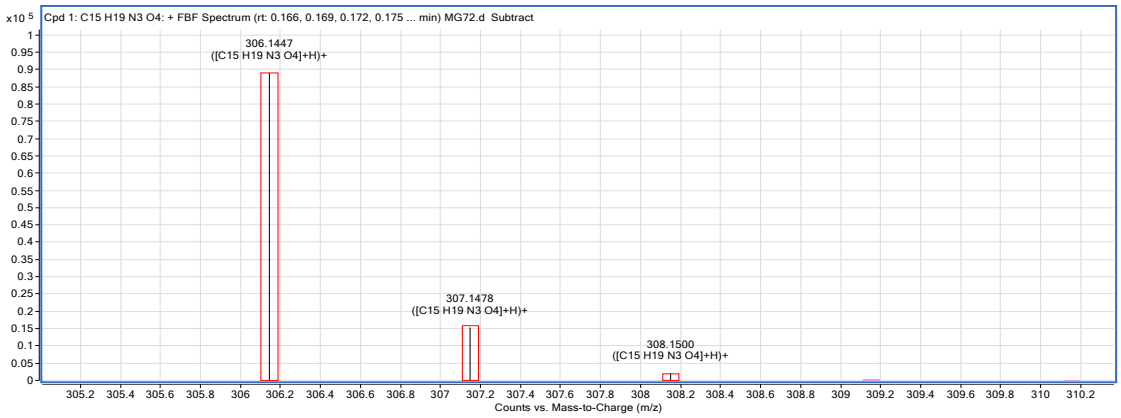


Figure S226. HRMS (+ESI) spectrum of **10c**.

1-Benzyl-4-cyclohexylcarbamoyl-2-azetidinone (11)

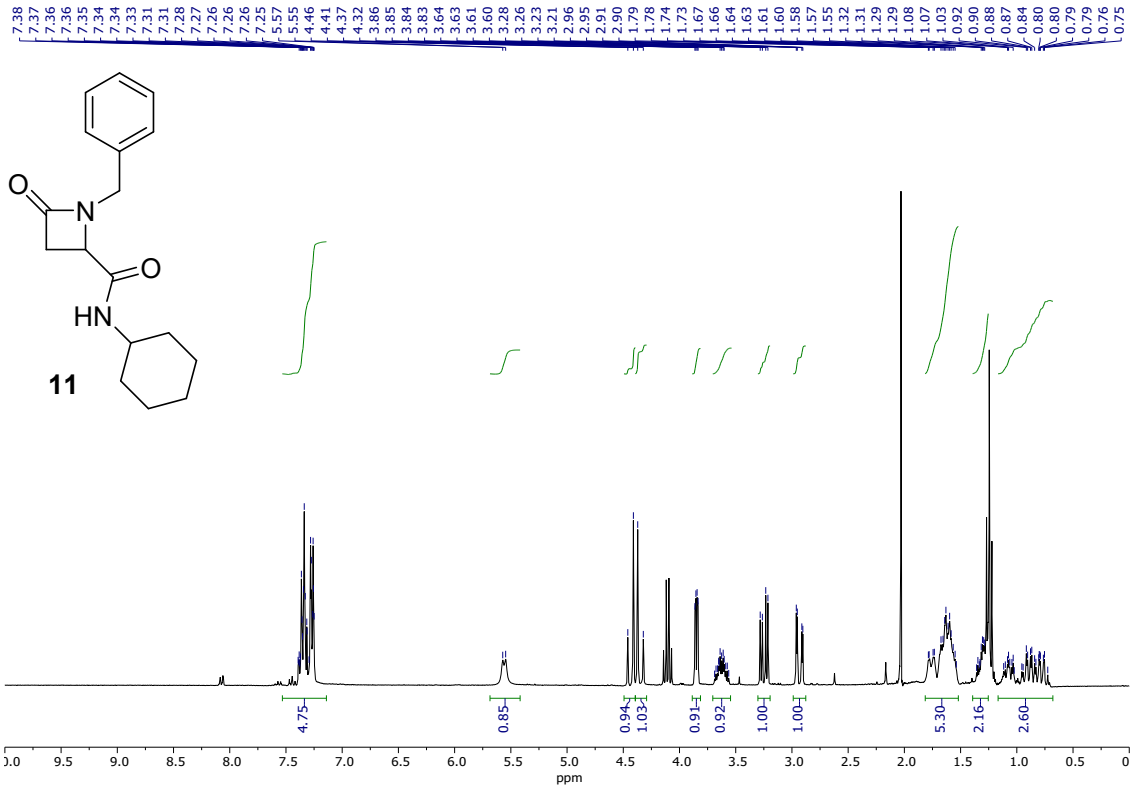


Figure S227. ^{1}H NMR spectrum of **11** (300 MHz, $CDCl_3$).

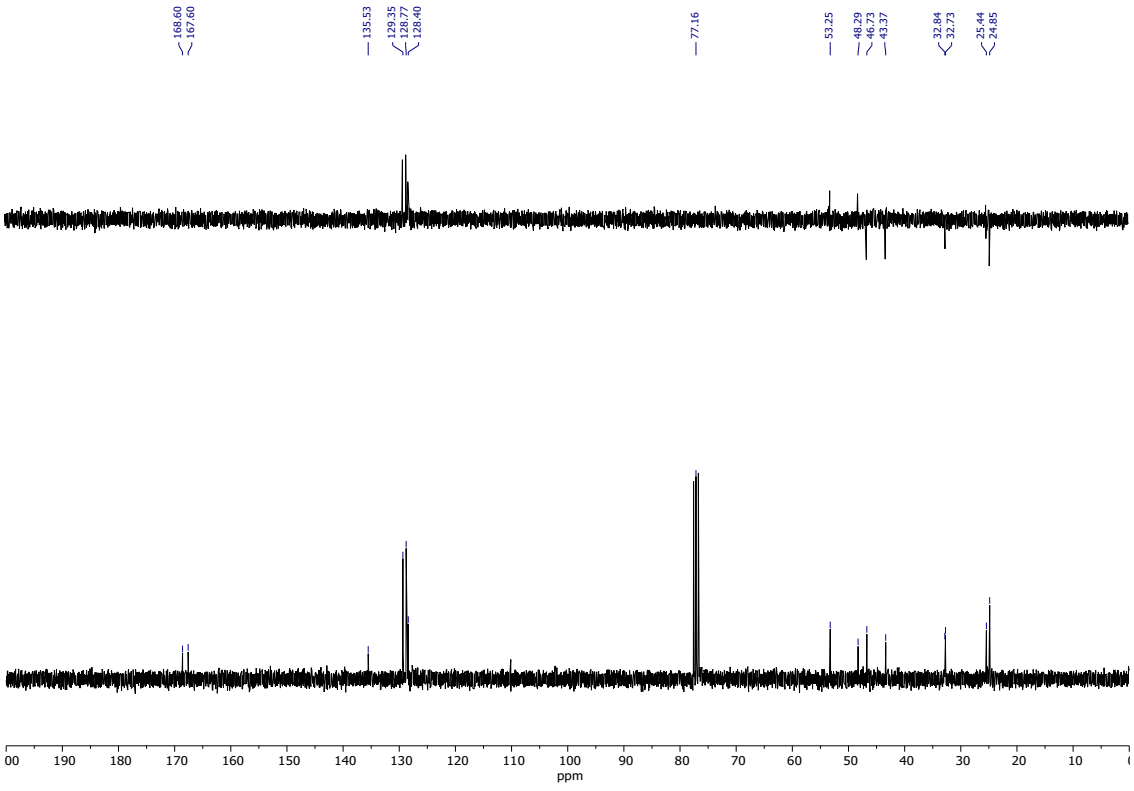


Figure S228. ^{13}C and DEPT-135 NMR spectra of **11** (75 MHz, $CDCl_3$).

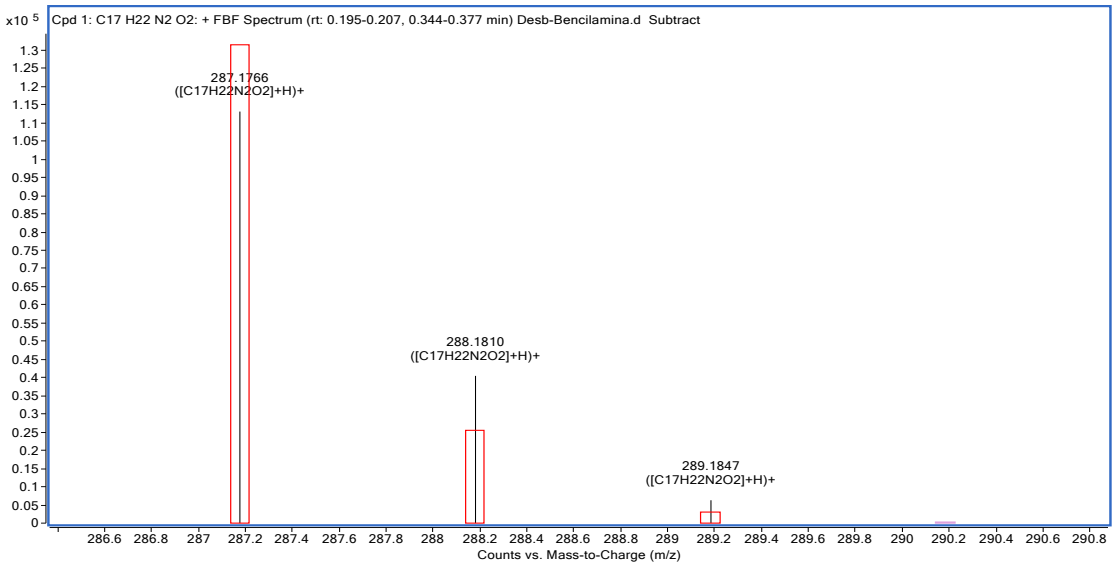


Figure S229. HRMS (+ESI) spectrum of **11**.

4-Benzoyl-4-cyclohexylcarbamoyl-5-phenylpyrrolidin-2-one (7k)

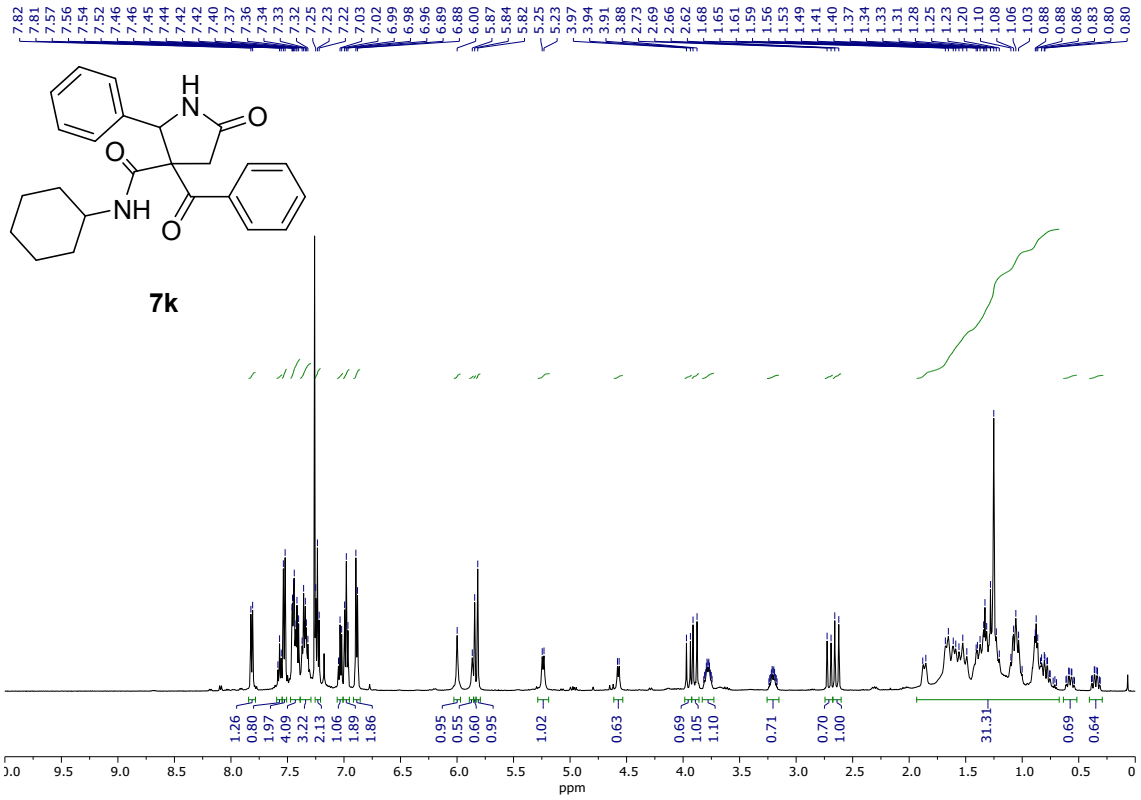


Figure S230. ^{1}H NMR spectrum of **7k** (500 MHz, $CDCl_3$).

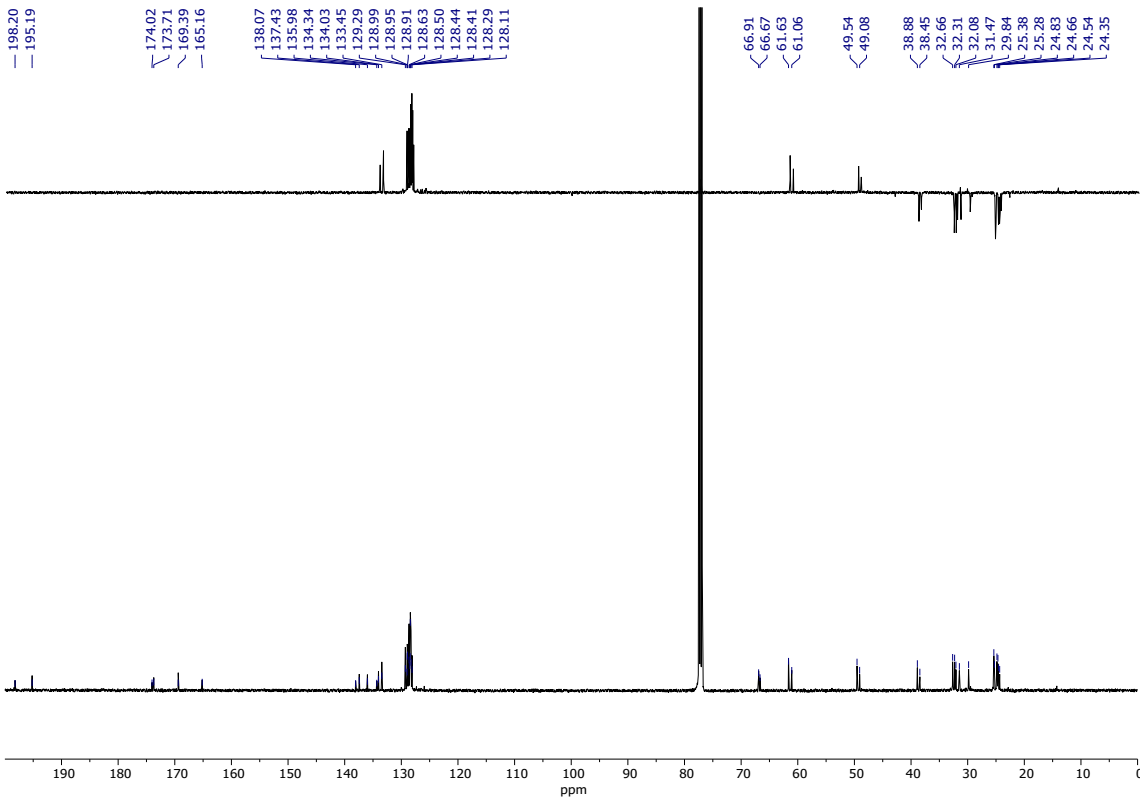


Figure S231. ^{13}C and DEPT-135 NMR spectra of **7k** (125 MHz, $CDCl_3$).

3-Benzoyl-1-cyclohexylpyrrolidin-2,5-dione (12)

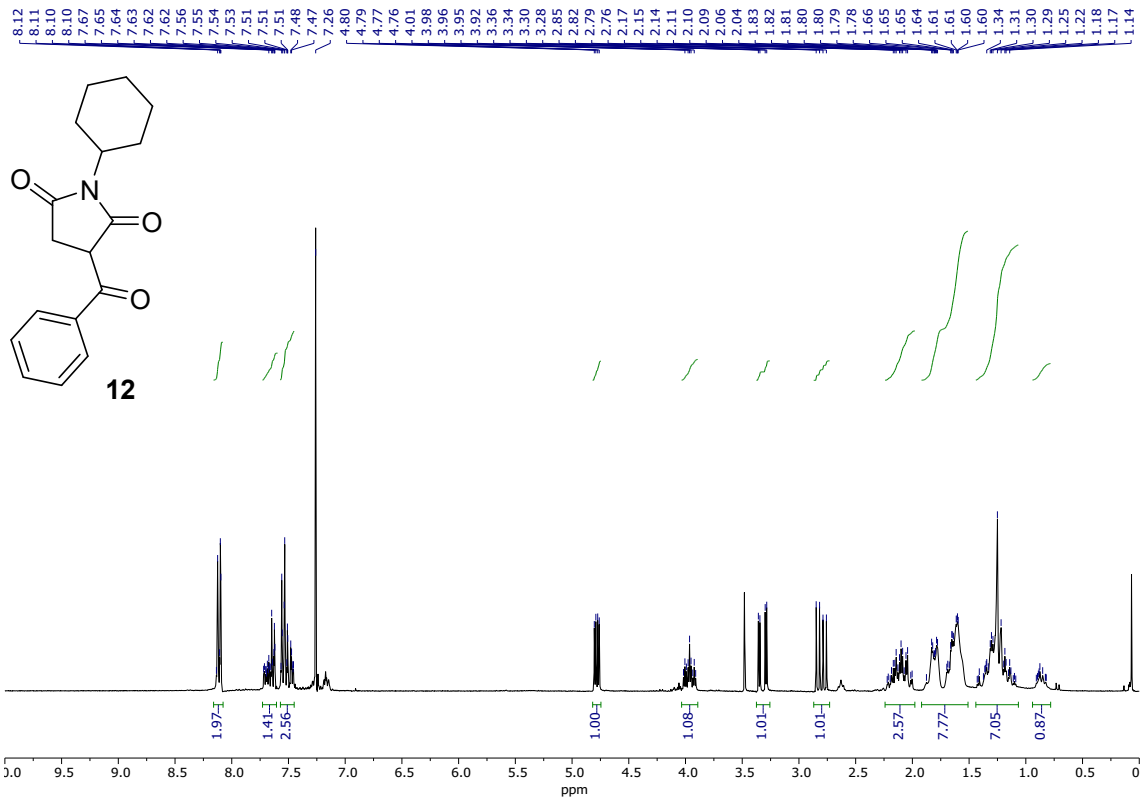


Figure S232. ^{1}H NMR spectrum of **12** (300 MHz, $CDCl_3$).

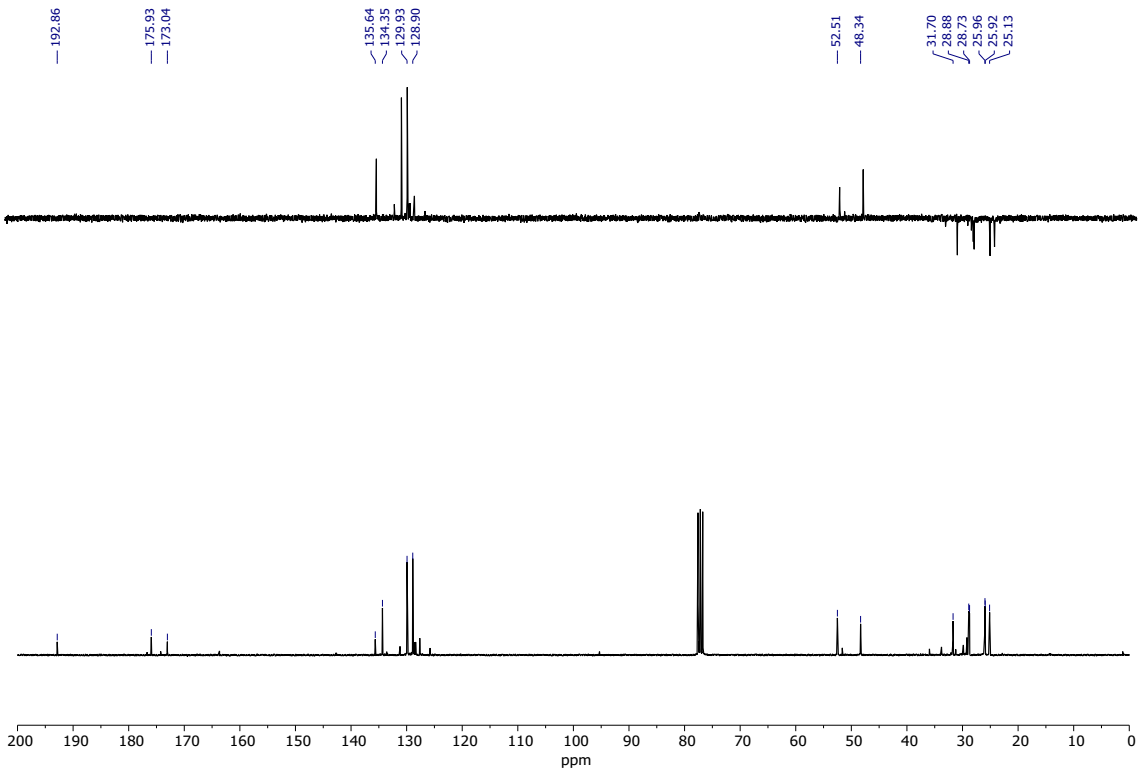


Figure S233. ^{13}C and DEPT-135 NMR spectra of **12** (75 MHz, $CDCl_3$).

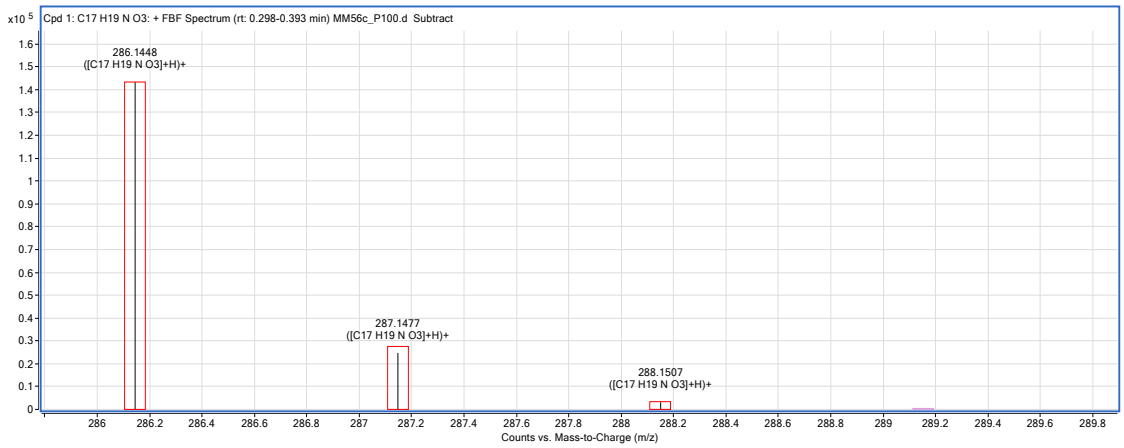


Figure S234. HRMS (+ESI) spectrum of **12**.

4. X-ray crystallographic data for compounds 6a, 7d, 7jdiast2, 8m and 9n

Table S1. Crystal data and refinement details for compounds **6a**, **7d**, **7jdiast2** and **8m**.

	6a	**7d**	**7jdiast2**	**8m**
formula	$C_{24}H_{25}N_3O_5$	$C_{25}H_{27}N_3O_5$	$C_{30}H_{28}FN_3O_5 \cdot CHCl_3$	$C_{25}H_{24}N_2O_4$
MW	435.47	449.49	648.92	416.46
crystal system	Monoclinic	Triclinic	Triclinic	Triclinic
space group	$P2_1/c$	P-1	P-1	P-1
T/K	298(2)	100(2)	230(2)	100(2)
a/Å	12.5652(2)	10.1914(11)	9.940(16)	8.9559(3)
b/Å	14.3595(3)	10.3790(11)	10.793(10)	11.0368(4)
c/Å	12.2203(2)	11.8123(13)	16.25(2)	12.1951(5)
α/deg	90	73.566(2)	108.53(4)	90.7300(10)
β/deg	100.2020(10)	67.677(2)	96.84(7)	106.0010(10)
γ/deg	90	83.029(2)	106.91(5)	100.4010(10)
V/Å^3	2170.05(7)	1108.5(2)	1538(4)	1137.18(7)
F(000)	920	476	672	440
Z	4	2	2	2
λ, Å (MoK$_\alpha$ or CuK$_\alpha$)	1.54178	0.71073	1.54184	1.54178
D_{calc}/g cm^{-3}	1.333	1.347	1.401	1.216
μ/mm^{-1}	0.777	0.095	3.129	0.673
θ range/deg	5.58–72.16	1.93–28.25	2.95–66.67	5.38–66.79
R_{int}	0.0425	0.0462	0.0900	0.0579
reflections measured	37271	13009	29480	48611
unique reflections	4231	5000	5392	3983
reflections observed	3564	3058	3218	3736
GOF on F^2	1.028	0.914	1.023	1.136
$R1$[a]	0.0421	0.0502	0.0657	0.0605
$wR2$[b]	0.1100	0.1274	0.2160	0.1716
Largest ≠ peak & hole/eÅ^{-3}	0.203 and -0.221	0.287 and -0.253	0.542 and -0.426	0.610 and -0.324

[a] $R1 = \sum \| \|F_0\| - \|Fc\| \| / \sum \|F_0\|$. [b] w$R2$ (all data) = $\{\sum[w(\| \|F_0\|^2 - \|Fc\|^2)^2] / \sum[w(F_0^4)]\}^{1/2}$

Table S2. Crystal data and refinement details for compound **9n**.

	9n
formula	$C_{13}H_{18}N_2O_3$
MW	250.29
crystal system	Monoclinic
space group	$P2_1/n$
T/K	230(2)
a/Å	10.9497(11)
b/Å	10.1546(11)
c/Å	12.5474(19)
α/deg	90
β/deg	111.425(8)
γ/deg	90
V/Å^3	1298.7(3)
F(000)	536
Z	4
λ, Å (MoK$_\alpha$ or CuK$_\alpha$)	1.54184
D_{calc}/g cm^{-3}	1.280
μ/mm^{-1}	0.751
θ range/deg	5.77–72.47
R_{int}	0.0687
reflections measured	38343
unique reflections	2560
reflections observed	2194
GOF on F^2	1.065
$R1$[a]	0.0423
$wR2$[b]	0.1093
Largest ≠ peak & hole/eÅ^{-3}	0.286 and -0.216

[a] $R1 = \sum \| \|F_0\| - \|Fc\| \| / \sum \|F_0\|$. [b] w$R2$ (all data) = $\{\sum[w(\| \|F_0\|^2 - \|Fc\|^2)^2] / \sum[w(F_0^4)]\}^{1/2}$

X-ray diffraction studies. Single crystals were obtained by slow evaporation of solutions of the isolated compounds in acetone (**6a**), methanol (**7d** and **8m**) or a 1:3 chloroform:hexane mixture (**7jdiast2** and **9n**).

Three dimensional X-ray data were collected on BRUKER SMART APEX CCD (**7d**) and BRUKER D8 VENTURE (**6a**, **8m**, **7jdiast2** and **9n**) diffractometers. For **6a**, **7jdiast2**, **8m**, and **9n**, data were corrected for absorption by semiempirical methods[1] based on symmetry-equivalent reflections; no absorption correction was carried out in the case of **7d**. Complex scattering factors were taken from the SHELXL-2016[2] (**6a**, **7d**, **7jdiast2** and **9n**) or SHELXL-2018[2] (**8m**) programs, running under the WinGX program system[3] (**6a** and **7d**) or under the Olex2 software[4] (**7jdiast2**, **8m** and **9n**). The structure of **6a** was solved with Superflip,[5] whereas that of **7d** was solved with SIR92[6] and those of **7jdiast2**, **8m** and **9n** with SHELXT;[7] all of them were refined by full-matrix least-squares on F^2. For **7d** all hydrogen atoms, except those corresponding to the NH fragments of the amide groups, which were refined freely in the final stages of the refinement, were included in calculated positions and refined in riding mode; in the case of **6a**, **7jdiast2**, **8m** and **9n** all hydrogen atoms were included in calculated positions. The molecular structure of **7d** shows positional disorder in the nitro group, with an occupation factor of 0.56 for the atoms labelled as A. EXTI correction was employed to complete the refinement of **7jdiast2** and **8m**. Finally, refinement converged with anisotropic displacement parameters for all non-hydrogen atoms for the 5 crystals. Crystal data and details on data collection and refinement are summarized in **Tables S1** and **S2**. CCDC 2193426 (**6a**), 2193428 (**7d**), 2193429 (**7jdiast1**), 2193430 (**8m**) and 2193435 (**9n**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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[1] SADABS 2016/2: Krause, L.; Herbst-Irmer, R.; Sheldrick, G. M.; Stalke, D. *J. Appl. Cryst.* **2015**, *48*, 3-10.

[2] SHELXL-2016, SHELXL-2018: Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112-122.

[3] WinGX: Farrugia, L. J. *J. Appl. Cryst*. **1999**, *32*, 837-838.

[4] Olex2: Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst*. **2009**, *42*, 339-341.

[5] SUPERFLIP: Palatinus, L.; Chapuis, G. *J. Appl. Cryst*. **2007**, *40*, 786-790.

[6] SIR92: Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Cryst.* **1994**, *27*, 435.

[7] SHELXT: Sheldrick, G. M. *Acta Cryst.* **2015**, *A71*, 3-8.

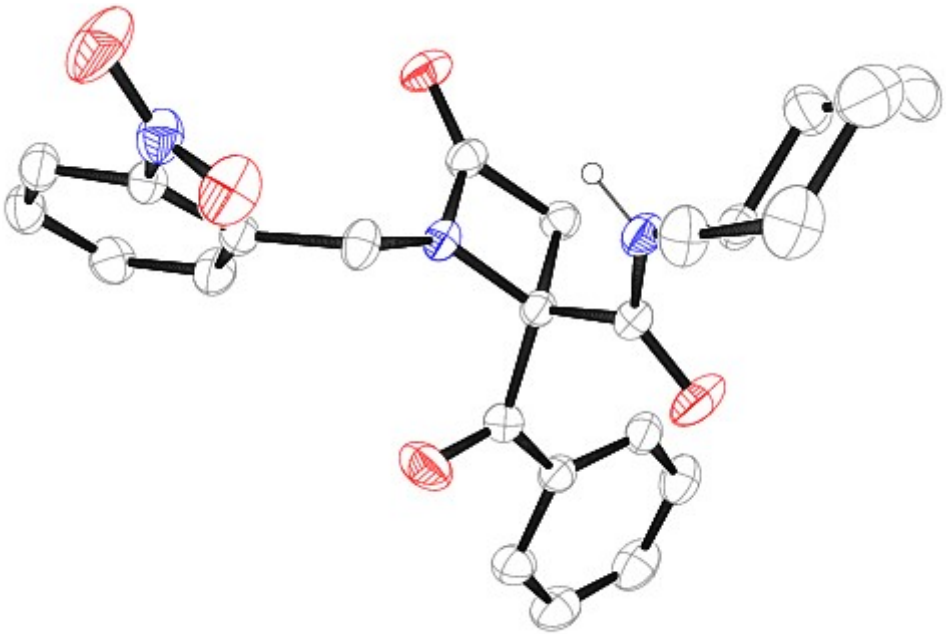

Figure S235. X-ray molecular structure of compound **6a**. Hydrogen atoms, except that of the N-H fragment, have been omitted for the sake of simplicity. The ORTEP plot is at the 30% probability level.

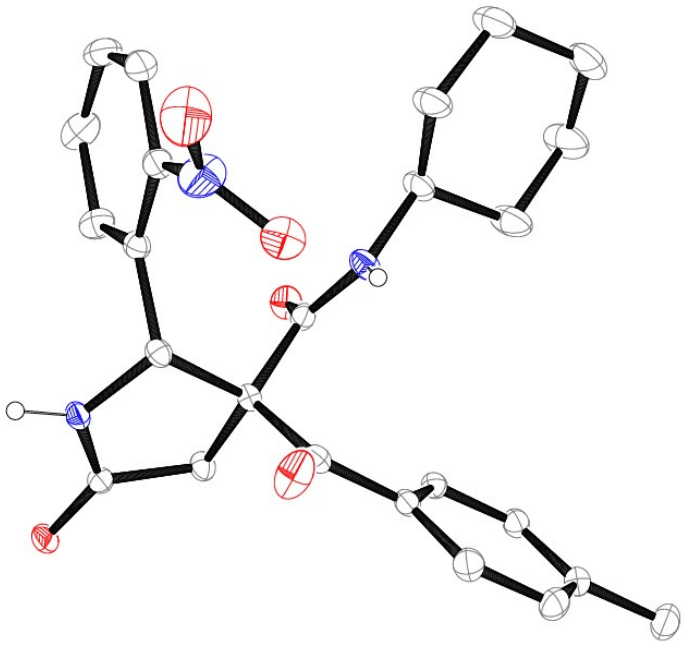

Figure S236. X-ray molecular structure of compound **7d**. The structure presents positional disorder in the nitro group, and the represented oxygen atoms correspond to those displaying the highest occupation factor. Hydrogen atoms, except those of the N-H fragments, have been omitted for the sake of simplicity. The ORTEP plot is at the 30% probability level.

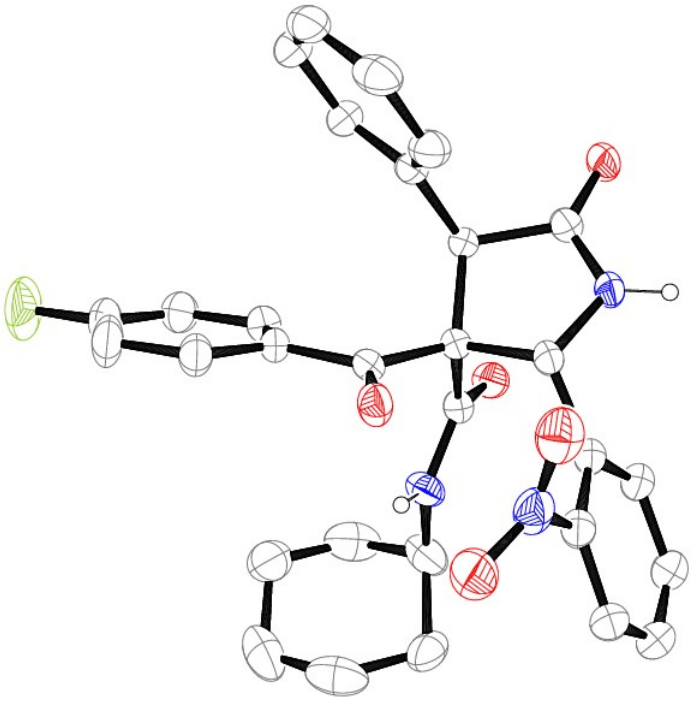

Figure S237. X-ray molecular structure of compound **7jdiast2**. Hydrogen atoms, except those of the N-H fragments, and a chloroform molecule have been omitted for the sake of simplicity. The ORTEP plot is at the 30% probability level.

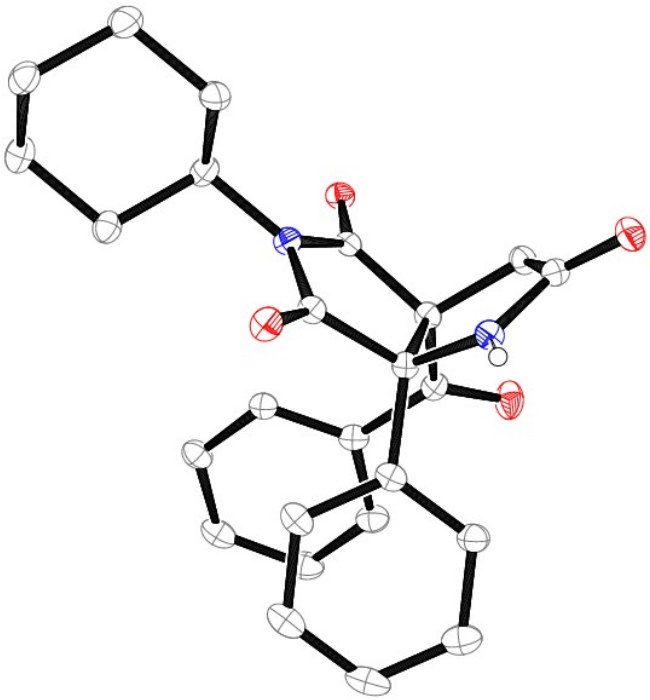

Figure S238. X-ray molecular structure of compound **8m**. Hydrogen atoms, except that of the N-H fragment, have been omitted for the sake of simplicity. The ORTEP plot is at the 30% probability level.

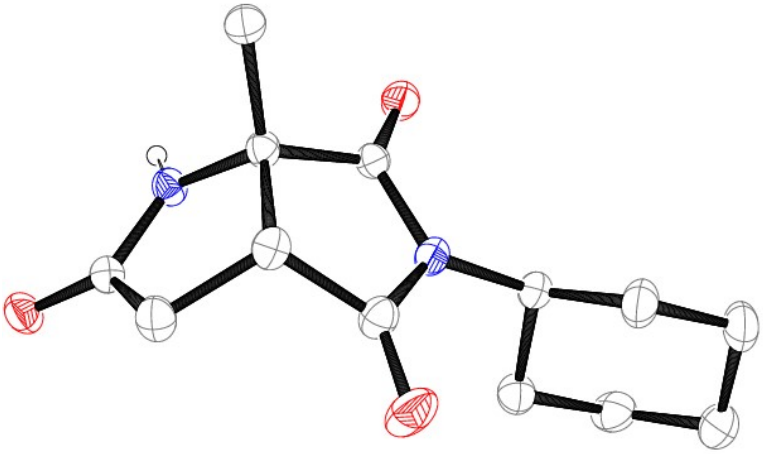

Figure S239. X-ray molecular structure of compound **9n**. Hydrogen atoms, except that of the N-H fragment, have been omitted for the sake of simplicity. The ORTEP plot is at the 30% probability level.