Supplementary Information (SI) for Organic & Biomolecular Chemistry.

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1) General Information

Unless otherwise stated, all reactions were carried out at RT under an inert (N_2 or Ar) atmosphere in oven-dried glassware. Except where stated all reagents were purchased from commercial sources and were used without furtFher purification. Anhydrous CH_2Cl_2, MeCN, and THF were obtained from the SPS laboratory system and used immediately after being dispensed. Standard grade dry MeOH and 1,4-dioxane were purchased from Sigma Aldrich and used as supplied.

^1H NMR spectra were recorded at 400 MHz on Bruker AV400 or Bruker AMX 400/JEOL ECS-400. ^{13}C NMR spectra were recorded at 101 MHz on Bruker AV 400 or Bruker AMX 400 MHz Ultra Shiled^{TM}. All spectroscopic data was acquired at 298 K (25 °C) unless stated otherwise and samples were dissolved in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm), with residual solvent peaks used for internal reference: $CDCl_3$: δ_H = 7.26, $CDCl_3$: δ_C = 77.0. The multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; dd, doublet of doublets; dt doublet of triplets; td, triplet of doublets; tt, triplet of triplets; ddd, doublet of doublets of doublets; pd, pentet of doublets; where br indicates a broad signal, and app. indicates an apparent. ^1H NMR experiments are reported as: chemical shift in ppm, quoted to the nearest 0.01 ppm, (integration, multiplicity, coupling constant and assignment (where possible)). ^{13}C NMR experiments are reported as: chemical shift in ppm, quoted to the nearest 0.1 ppm, (carbon assignment (where possible) or multiplicity, coupling constant and assignment (where applicable)).

Spectra were analysed using MestReNova 12.0.3-21384 software and values of coupling constant (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The term "overlapping" is used to describe resonance peak, which is behind another resonance peak, *i.e.*, compound resonance behind the solvent peak or combination of two resonance peaks. The systematic chemical names were generated using the IUPAC name generator tool option is included within the ChemBioFDaw Ultra 19.1 software.

Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 or Pekin Elmer Spectrum 100 spectrometer fitted with a universal Attenuated Total Reflectance (ATR) accessory; data was recorded as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$, neat or solid state by ATR-FTIR.

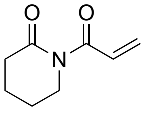
High Resolution Mass Spectra (HRMS) were obtained by the University of York Mass Spectrometry Service, recorded on a Waters XEVO G2-XS TOF, Waters Synapt G2S TOF or Bruker Micro-TOF mass spectrometer, with HRMS mode incorporating a lock-in mass into the mobile phase (leucine enkehalin) or on a Bruker Daltonics, Micro-TOF spectrometer, using Electrospray Ionisation (ESI) or Atmospheric Pressure Chemical Ionisation (APCI), positive or negative generative modes.

Thin Layer Chromatography (TLC) was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and was visualised using UV light ($\lambda = 254$ nm, short wavelength) or UV light ($\lambda = 366$ nm, long wavelength) and stained with basic aqueous potassium permanganate ($KMnO_4$), ninhydrin or vanillin solution dip. Concentration under reduced pressure or *vacuo* was performed using a Büchi® Rotavapor® R-210 evaporator with jack and water bath, 29/32 joint, 240V rotary evaporator using a mixture of acetone and dry ice or ice/water as the coolant. Flash column chromatography was conducted using Aldrich technical grade silica gel (SiO_2), 60 Å, 230-400 mesh, 40-63 µm particle size, under a light positive pressure of air, eluting with the specified solvent system.

Melting points were recorded as decomposition temperature range and measured on a Stuart SMP10 or Gallenkamp apparatus using open tubes with no corrections.

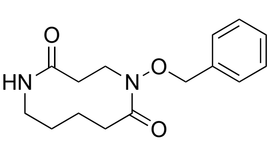
2) Compound Characterisation Data and Synthetic Procedures

1-Acryloyl-piperidin-2-one (3a)[1]



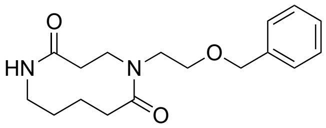
A solution of δ-valerolactam (1.02 mg, 10.3 mmol) in dry THF (36.5 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 3.65 mL, 11.0 mmol) was added using a syringe pump over 15 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (1.3 mL, 15.5 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (30 mL) and extracted with Et_2O (3 x 35 mL). The combined organics were washed with saturated $NaHCO_3$ solution (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a pale-yellow liquid (1.2 g, 72% yield); R_f 0.40 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2953, 1678, 1403, 1384, 1289, 1209, 1155, 1003, 796, 607; δ_H (400 MHz, $CDCl_3$) 6.96 (1H, dd, *J* = 16.9, 10.4 Hz, COC**H**), 6.33 – 6.29 (1H, m, C**H**H’), 5.70 – 5.66 (1H, m, CH**H’**), 3.74 – 3.71 (2H, m, C**H**$_2$), 2.57 – 2.53 (2H, m, C**H**$_2$), 1.86 – 1.83 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**O), 169.7 (**C**OCH), 132.0 (CO**C**H), 128.0 (**C**HH’), 44.7 (**C**H$_2$), 34.9 (**C**H$_2$), 22.6 (**C**H$_2$), 20.8 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_8H_{11}NNaO_2$, 176.0682. Found: [MNa]$^+$, 176.0682 (−0.1 ppm error).

5-(Benzyloxy)-1,5-diazecane-2,6-dione (7a)



To a solution of 1-acryloyl-piperidin-2-one **3a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL) was added benzyl-o-hydroxylamine (130 µL, 1.1 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (175 mg, 63% yield). In solution in $CDCl_3$, some evidence of rotameric broadening in the ^{1}H NMR data, with trace (<10%) signals for a minor rotamer; m.p. 115–117 °C; R_f 0.48 (1:9 methanol:ethyl acetate); **IR** (ATR): ν_{max}/ cm^{-1} 3313, 2930, 2871, 2240, 1650, 1531, 1441, 1379, 1312, 1175, 992, 909, 728, 699, 509; δ_H (400 MHz, $CDCl_3$) 7.38 – 7.36 (5H, m, Ar**H**), 5.55 (1H, d, *J* = 6.6 Hz, N**H**), 4.83 (2H, s, C**H**$_2$), 4.73 – 4.65 (1H , m, C**H**$_2$), 3.53 – 3.46 (1H, m, C**H**$_2$), 3.20 – 3.16 (1H, m, C**H**$_2$), 2.98 – 2.95 (1H, m, C**H**$_2$), 2.90 – 2.84 (1H, m, C**H**$_2$), 2.58 (1H, app td, *J* = 12.6, 5.5 Hz, C**H**$_2$), 2.20 – 2.16 (1H, m, C**H**$_2$), 2.07 – 1.89 (2H, m, C**H**$_2$), 1.85 – 1.72 (2H, m, C**H**$_2$), 1.44 – 1.35 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.8 (**C**O), 170.1 (**C**O), 134.4 (**C**Ar), 129.7 (Ar**C**H), 129.3 (Ar**C**H), 128.9 (Ar**C**H), 77.4 (**C**H$_2$), 45.3 (**C**H$_2$), 39.9 (**C**H$_2$), 34.5 (**C**H$_2$), 31.6 (**C**H$_2$), 27.8 (**C**H$_2$), 23.5 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{15}H_{20}N_2NaO_3$ 299.1365. Found $[MNa]^+$ 299.1366 (0.3 ppm error).

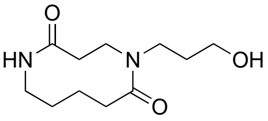
5-(2-(Benzyloxy)ethyl)-1,5-diazecane-2,6-dione (7b)



To a solution of 1-acryloyl-piperidin-2-one **3a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL) was added 2-(benzyloxy)-1-ethanamine (100 µL, 1.10 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (127 mg, 42% yield); m.p. 108–110 °C; R_f 0.26 (1:19 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3301, 2929, 2859, 1616, 1556, 1454, 1353, 1208, 1162, 1096, 1082, 1014, 734, 698; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.27 (5H, m, Ar**H**), 6.37 (1H, d, *J* = 10.2 Hz, N**H**), 4.57 – 4.50 (2H, m, C**H**$_2$), 4.25 – 4.12 (2H , m, C**H**$_2$), 3.98 – 3.91 (1H, m, C**H**$_2$), 3.69 – 3.60 (1H , m, C**H**$_2$), 3.56 – 3.51 (1H, m, C**H**$_2$), 3.20 – 3.14 (1H, m, C**H**$_2$), 3.01 – 2.94 (1H, m, C**H**$_2$), 2.53 – 2.50 (1H, m, C**H**$_2$), 2.49 – 2.45 (2H, m, C**H**$_2$), 2.15 – 2.11 (1H, m, C**H**$_2$), 2.09 – 1.97 (2H, m, C**H**$_2$), 1.57 – 1.48 (2H, m, C**H**$_2$), 1.23 – 1.12 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 171.0 (**C**O), 136.8 (**C**Ar), 128.8 (Ar**C**H), 128.5 (2 x Ar**C**H, overlapping), 73.8 (**C**H$_2$), 67.0 (**C**H$_2$), 49.4 (**C**H$_2$), 48.3 (**C**H$_2$), 38.6 (**C**H$_2$), 37.5 (**C**H$_2$), 28.7 (**C**H$_2$), 26.2 (**C**H$_2$), 24.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{17}H_{24}N_2NaO_3$, 327.1678. Found: $[MNa]^+$, 327.1679 (0.3 ppm error).

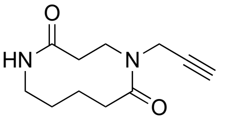
For LCMS data confirming this product has >95% purity, see SI Section 5.

5-(3-Hydroxypropyl)-1,5-diazecane-2,6-dione (7c)



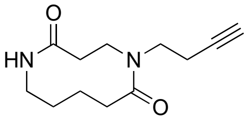
To a solution of 1-acryloyl-piperidin-2-one **3a** (77 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 3-aminopropan-1-ol (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (66 mg, 58% yield); m.p. 117−120 °C; R_f 0.46 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3286, 2930, 2860, 2236, 1609, 1176, 1060, 1040, 921, 813, 729. δ_H (400 MHz, $CDCl_3$) 5.81 (1H, d, *J* = 9.5 Hz, N**H**), 4.03 – 3.90 (2H, m, C**H**$_2$), 3.87 – 3.78 (1H, m, C**H**$_2$), 3.63 – 3.47 (2H , m, C**H**$_2$), 3.31 – 3.25 (1H , m, C**H**$_2$), 3.15 – 3.09 (1H, m, C**H**$_2$), 2.93 – 2.89 (1H, m, C**H**$_2$), 2.69 – 2.61 (1H, m, C**H**$_2$), 2.36 – 2.31 (2H , m, C**H**$_2$), 2.15 – 2.05 (2H, m, C**H**$_2$), 1.84 – 1.58 (4H, m, 2 x C**H**$_2$), 1.48 – 1.39 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.9 (**C**O), 59.0 (**C**H$_2$), 45.6 (**C**H$_2$), 43.0 (**C**H$_2$), 39.3 (**C**H$_2$), 38.1 (**C**H$_2$), 30.5 (**C**H$_2$), 28.4 (**C**H$_2$), 25.9 (**C**H$_2$), 23.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{11}H_{20}N_2NaO_3$, 251.1364. Found: $[MNa]^+$, 251.1366 (0.7 ppm error).

5-(Prop-2-yn-1-yl)-1,5-diazecane-2,6-dione (7d)



To a solution of 1-acryloyl-piperidin-2-one **3a** (77 mg, 0.50 mmol) in dry methanol (1.0 mL) was added propargylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a colourless oil (73 mg, 70% yield); R_f 0.45 (1:9 methanol:ethyl acetate); **IR** (ATR): ν_{max}/cm^{-1} 3290, 3096, 2932, 2857, 2242, 1621, 1558, 1442, 1456, 1350, 1205, 1178, 1110, 729; δ_H (400 MHz, $CDCl_3$) 5.65 – 5.63 (1H, m, N**H**), 4.68 (1H, d, *J* = 17.1 Hz, C**H**$_2$), 4.10 – 4.03 (1H, m, C**H**$_2$), 3.90 – 3.79 (2H, m, C**H**$_2$), 3.51 – 3.47 (1H, m, C**H**$_2$), 2.92 – 2.89 (1H, m, C**H**$_2$), 2.75 – 2.59 (2H, m, C**H**$_2$), 2.35 – 2.29 (2H, m, C**H** and C**H**H’), 2.16 – 2.09 (2H, m, C**H**$_2$), 1.73 – 1.60 (2H, m, C**H**$_2$), 1.55 – 1.45 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**O), 171.0 (**C**O), 80.9 (**C**CH), 72.4 (**C**H), 47.4 (**C**H$_2$), 39.4 (**C**H$_2$), 37.8 (**C**H$_2$), 36.7 (**C**H$_2$), 28.3 (**C**H$_2$), 25.7 (**C**H$_2$), 24.0 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{11}H_{16}N_2NaO_2$, 231.1109. Found [MNa]$^+$ 231.1104 (−2.1 ppm error).

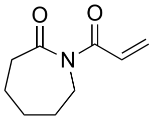
5-(But-3-yn-1-yl)-1,5-diazecane-2,6-dione (7e)



To a solution of 1-acryloyl-piperidin-2-one **3a** (77 mg, 0.50 mmol) in dry methanol (1.00 mL) was added but-3-yn-1-amine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (54 mg, 49% yield); m.p. 148 – 150 °C; R_f 0.42 (1:9 methanol:ethyl acetate); **IR** (ATR): ν_{max}/cm^{-1} 3301, 3094, 2931, 2241, 1615, 1556, 1458, 1423, 1349, 1201, 1176, 727, 645. In solution in $CDCl_3$, the product exists as a 10:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.01 (1H, s, N**H**), 4.01 – 3.94 (1H, m, C**H$_2$**), 3.82 – 3.69 (1H, m, C**H$_2$**), 3.52 – 3.49 (2H, m, C**H$_2$**), 3.36 – 3.32 (1H, m, C**H$_2$**), 2.91 – 2.87 (1H, m, C**H$_2$**), 2.74 – 2.70 (1H, m, C**H$_2$**), 2.63 – 2.55 (1H, m, C**H$_2$**), 2.47 – 2.42 (2H, m, C**H$_2$**), 2.29 – 2.26 (1H, m, C**H$_2$**), 2.07 – 1.99 (3H, m, C**H** and C**H$_2$**), 1.74 – 1.54 (2H, m, C**H$_2$**), 1.45 – 1.36 (1H, m, C**H$_2$**); δ_C (100 MHz, $CDCl_3$) 174.4 (**C**O), 171.0 (**C**O), 83.3 (**C**CH), 70.6 (**C**H), 47.3 (**C**H$_2$), 47.1 (**C**H$_2$), 39.2 (**C**H$_2$), 38.3 (**C**H$_2$), 28.6 (**C**H$_2$), 26.1 (**C**H$_2$), 24.1 (**C**H$_2$), 17.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{18}N_2O_2$, 245.1257. Found [MNa]$^+$ 245.1260 (1.2 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.89 – 5.85 (1H, m, N**H**).

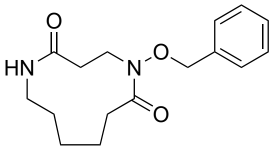
1-Acryloyl-azepan-2-one (3b)[1,2]



A solution of caprolactam (1.13 g, 10.00 mmol) in dry THF (36.5 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 3.7 mL, 11 mmol) was added dropwise using a syringe pump over 15 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (1.2 mL, 15.00 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (40 mL) and extracted with Et_2O (40 mL). The combined organics were washed with saturated aq. $NaHCO_3$ solution (2 x 40 mL), dried over

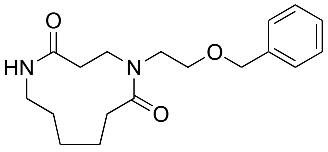
$MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a colourless liquid (1.17 g, 70% yield); R_f 0.40 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2953, 1678, 1403, 1384, 1289, 1209, 1155, 1003, 796, 607; δ_H (400 MHz, $CDCl_3$) 6.93 (1H, dd, *J* = 16.9, 10.1 Hz, C**H**CHH'), 6.33 – 6.29 (1H, m, CHC**H**H'), 5.70 – 5.67 (1H, m, CHCH**H'**), 3.92 – 3.90 (2H, m, C**H**$_2$), 2.72 – 2.70 (2H, m, C**H**$_2$), 1.78 – 1.70 (6H, m, 3 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.1 (**C**O), 169.0 (**C**O), 132.0 (**C**HCHH'), 128.1 (CH**C**HH'), 43.8 (**C**H$_2$), 39.5 (**C**H$_2$), 29.4 (**C**H$_2$), 28.7 (**C**H$_2$), 23.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_9H_{13}NNaO_2$, 190.0838. Found $[MNa]^+$, 190.0838 (−0.3 ppm error).

5-(Benzyloxyl)-1,5-diazacycloundecane-2,6-dione (8a)



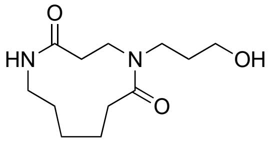
To a solution of 1-acryloyl-azepan-2-one **3b** (170 mg, 1.00 mmol) in dry methanol (2.0 mL) was added benzyl-o-hydroxylamine (130 µL, 1.10 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (189 mg, 65% yield). In solution in $CDCl_3$, some evidence of rotameric broadening in the ^{1}H NMR data, with trace (<10%) signals for a minor rotamer; R_f 0.49 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/ cm^{-1} 3301, 2933, 2871, 2234, 1645, 1539, 1441, 1405, 1350, 1226, 1190, 1169, 984, 912, 730, 699, 645, 523; δ_H (400 MHz, $CDCl_3$) 7.40 – 7.38 (5H, m, Ar**H**), 5.80 – 5.61 (1H, m, N**H**), 4.98 – 4.75 (3H, m, NOC**H**$_2$ and C**H**H'), 3.71 – 3.63 (1H , m, C**H**$_2$), 3.21 – 3.18 (1H, m, CH**H'**), 2.92 – 2.86 (1H, m, C**H**$_2$), 2.79 – 2.78 (1H, m, C**H**$_2$), 2.65 – 2.57 (1H, m, C**H**$_2$), 2.25 – 2.22 (1H, m, C**H**$_2$), 1.98 – 1.84 (2H, m, C**H**$_2$), 1.68 – 1.64 (1H, m, C**H**$_2$), 1.58 – 1.51 (2H, m, C**H**$_2$), 1.37 – 1.24 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 170.3 (**C**O), 134.2 (**C**Ar), 129.7 (Ar**C**H), 129.4 (Ar**C**H), 129.0 (Ar**C**H), 77.4 (NO**C**H$_2$), 42.2 (**C**H$_2$), 39.7 (**C**H$_2$), 34.5 (**C**H$_2$), 30.9 (**C**H$_2$), 27.0 (**C**H$_2$), 24.5 (**C**H$_2$), 24.1 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{16}H_{22}N_2NaO_3$, 313.1520. Found $[MNa]^+$ 313.1523 (0.8 ppm error).

5-(2-(Benzyloxyl)ethyl-1,5-diazacycloundecane-2,6-dione (8b)



To a solution of 1-acryloyl-azepan-2-one **3b** (167 mg, 1.00 mmol) in dry methanol (2.0 mL) was added 2-(benzyloxy)-1-ethanamine (160 µL, 1.10 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (175 mg, 55% yield); m.p. 129−130 °C; R_f 0.36 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3312, 2931, 2864, 2239, 1623, 1549, 1351, 1167, 1093, 1028, 906, 728, 698; δ_H (400 MHz, $CDCl_3$) 7.35 – 7.27 (5H, m, Ar**H**), 6.90 (1H, s, N**H**), 4.59 – 4.49 (2H, m, C**H**$_2$), 4.29 – 4.23 (1H, m, C**H**$_2$), 4.12 – 4.06 (1H, m, C**H**$_2$), 4.03 – 3.96 (1H, m, C**H**$_2$), 3.54 – 3.48 (1H, m, C**H**$_2$), 3.43 – 3.33 (1H, m, C**H**$_2$), 3.18 – 3.10 (1H, m, C**H**$_2$), 3.02 – 2.93 (1H, m, C**H**$_2$), 2.62 – 2.57 (1H, m, C**H**$_2$), 2.38 – 2.32 (1H, m, C**H**$_2$), 2.15 – 2.12 (2H, m, C**H**$_2$), 1.97 – 1.93 (2H, m, C**H**$_2$), 1.73 – 1.62 (1H, m, C**H**$_2$), 1.49 – 1.48 (2H, m, C**H**$_2$), 1.24 – 1.17 (1H, m, C**H**$_2$), 0.76 – 0.60 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 171.4 (**C**O), 136.9 (**C**Ar), 128.8 (Ar**C**H), 128.5 (Ar**C**H), 128.3 (Ar**C**H), 73.8 (**C**H$_2$), 67.5 (**C**H$_2$), 49.1 (**C**H$_2$), 48.1 (**C**H$_2$), 40.9 (**C**H$_2$), 37.1 (**C**H$_2$), 29.1 (**C**H$_2$), 25.9 (**C**H$_2$), 24.3 (**C**H$_2$), 22.6 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_{18}H_{26}N_2NaO_3$, 341.1832. Found $[MNa]^+$ 341.1836 (1.2 ppm error).

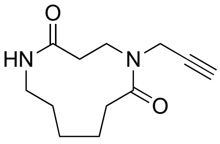
5-(3-Hydroxypropyl)-1,5-diazacycloundecane-2,6-dione (8c)



To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 3-aminopropan-1-ol (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (67.5 mg, 56% yield); m.p. 119−121 °C; R_f 0.40 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3285, 2933, 2868, 2239, 1614, 1455, 1426, 1350, 1182, 1042, 905, 727. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$)

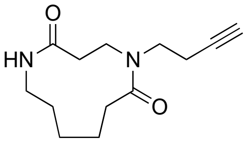
6.41 (1H, s, N**H**), 4.08 – 3.82 (2H, m, C**H**$_2$), 3.69 – 3.07 (5H , m, 2 x C**H**$_2$ and C**H**H’), 2.77 – 1.93 (6H , m, 3 x C**H**$_2$), 1.83 – 1.55 (5H , m, 2 x C**H**$_2$ and CH**H’**), 1.38 – 0.79 (2H , m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 174.9 (**C**O), 171.4 (**C**O), 58.9 (**C**H$_2$), 45.0 (**C**H$_2$), 42.2 (**C**H$_2$), 41.7 (**C**H$_2$), 37.3 (**C**H$_2$), 30.4 (**C**H$_2$), 28.5 (**C**H$_2$), 25.1 (**C**H$_2$), 24.4 (**C**H$_2$), 22.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{22}N_2NaO_3$, 265.1528. Found: [MNa]$^+$, 265.1523 (−1.9 ppm error).

5-(Prop-2-yn-1-yl)-1,5-diazacycloundecane-2,6-dione (8d)



To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (1.0 mL) was added propargylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (78.5 mg, 71% yield); m.p. 152−155 °C; R$_f$ 0.46 (1:9 methanol:ethyl acetate); **IR** (ATR): ν_{max}/cm^{-1} 3297, 3092, 2934, 2867, 2240, 1624, 1556, 1450, 1352, 1289, 1228, 730. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. δ_H (400 MHz, CDCl$_3$) 6.30 (1H, s, N**H**), 4.76 – 4.38 (1H, m, C**H**$_2$), 4.13 – 3.42 (4H, m, 2 x C**H**$_2$), 2.66 – 1.99 (7H, m, 3 x C**H**$_2$ and CC**H**), 1.75 – 1.60 (3H, m, C**H**$_2$), 1.35 – 0.79 (2H, m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 173.0 (**C**O), 171.4 (**C**O), 80.9 (**C**CH), 72.0 (C**C**H), 46.7 (**C**H$_2$), 41.9 (**C**H$_2$), 37.0 (**C**H$_2$), 35.9 (**C**H$_2$), 28.4 (**C**H$_2$), 25.3 (**C**H$_2$), 24.4 (**C**H$_2$), 22.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{18}N_2NaO_2$, 245.1262. Found [MNa]$^+$ 245.1260 (−0.5 ppm error).

5-(But-3-yn-1-yl)-1,5-diazacycloundecane-2,6-dione (8e)



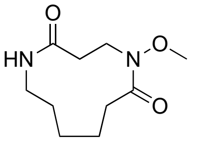
To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (1.0 mL) was added but-3-yn-1-amine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (91.6

mg, 78% yield); m.p. 125 – 127 °C; R_f 0.49 (1:9 methanol:ethyl acetate); **IR** (ATR): υ_{max}/cm^{-1} 3300, 3090, 2933, 2866, 2239, 1620, 1555, 1454, 1422, 1368, 1231, 1182, 1024, 922, 729. The ^{1}H NMR spectrum is complicated by rotameric broadening; ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 13:1:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.45 (1H, s, N**H**), 4.18 – 3.79 (1H, m, C**H**$_2$), 3.77 – 3.56 (1H, m, C**H**$_2$), 3.50 – 3.47 (2H, m, C**H**$_2$), 3.41 – 3.18 (1H, m, C**H**$_2$), 2.77 – 2.29 (6H, m, 3 x C**H**$_2$), 2.18 – 1.99 (3H, m, C**H**$_2$ and CC**H**), 1.68 – 1.57 (3H, m, C**H**$_2$), 1.36 – 1.17 (1H, m, C**H**$_2$), 1.01 – 0.68 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 171.5 (**C**O), 83.5 (**C**CH), 70.3 (C**C**H), 47.0 (**C**H$_2$), 46.8 (**C**H$_2$), 41.5 (**C**H$_2$), 37.8 (**C**H$_2$), 28.8 (**C**H$_2$), 25.4 (**C**H$_2$), 24.4 (**C**H$_2$), 22.6 (**C**H$_2$), 17.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{13}H_{20}N_2NaO_2$, 259.1418. Found $[MNa]^+$ 259.1417 (−0.5 ppm error).

Characteristic NMR data for the NH peaks of the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.19 – 6.10 (1H, m, N**H**), 5.76 – 5.72 (1H, m, N**H**).

For LCMS data confirming this product has >95% purity, see SI Section 5.

5-Methoxy-1,5-diazacycloundecane-2,6-dione (8f)

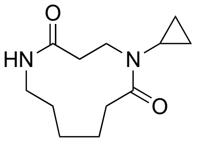


To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (1.6 mL) was added methoxyamine (63 mg, 0.75 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a yellow oil (55.8 mg, 52% yield); R_f 0.27 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3301, 3088, 2933, 2238, 1643, 1544, 1442, 1406, 1190, 1017, 922, 800, 728. In solution in $CDCl_3$, the product exists as a 5:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 5.77 – 5.76 (1H, m, N**H**), 4.79 – 4.71 (1H, m, C**H**$_2$), 3.69 (3H, s, C**H**$_3$), 3.66 – 3.59 (1H , m, C**H**$_2$), 3.33 – 3.29 (1H , m, C**H**$_2$), 2.91 – 2.80 (2H, m, C**H**$_2$), 2.62 – 2.54 (1H, m, C**H**$_2$), 2.28 – 2.25 (1H, m, C**H**$_2$), 2.10 – 2.05 (1H, m, C**H**$_2$), 1.90 – 1.83 (1H, m, C**H**$_2$), 1.68 – 1.65 (1H , m, C**H**$_2$), 1.56 – 1.53 (2H, m, C**H**$_2$), 1.41 – 1.30 (2H , m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.3 (**C**O), 170.3 (**C**O), 61.9 (**C**H$_3$), 41.0 (**C**H$_2$), 39.7 (**C**H$_2$), 34.3 (**C**H$_2$), 31.0 (**C**H$_2$), 27.0 (**C**H$_2$), 24.5 (**C**H$_2$), 24.2 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{10}H_{18}N_2NaO_3$, 237.1209. Found: $[MNa]^+$, 237.1210 (0.1 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.49 – 6.35 (1H, m, N**H**).

For LCMS data confirming this product has >95% purity, see SI Section 5.

5-Cyclopropyl-1,5-diazacycloundecane-2,6-dione (8g)

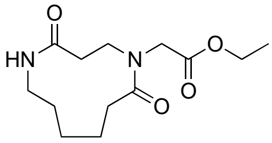


To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (1.0 mL) was added cyclopropylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (41.2 mg, 37% yield); R_f 0.22 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3288, 3088, 2932, 2869, 2236, 1631, 1547, 1441, 1409, 1260, 1227, 1153, 1032, 906, 727. In solution in $CDCl_3$, the product exists as a 6:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.07 – 6.06 (1H, m, N**H**), 4.38 (1H, ddd, *J* = 14.2, 8.5, 5.7 Hz, C**H**$_2$), 3.68 – 3.60 (1H , m, C**H**$_2$), 3.10 – 2.97 (2H , m, C**H**$_2$), 2.87 – 2.82 (1H, m, C**H**$_2$), 2.81 – 2.76 (1H, m, C**H**), 2.73 – 2.67 (1H, m, C**H**$_2$), 2.58 – 2.51 (1H, m, C**H**$_2$), 2.10 – 2.04 (1H, m, C**H**$_2$), 1.83 – 1.73 (1H, m, C**H**$_2$), 1.64 – 1.54 (4H , m, 2 x C**H**$_2$), 1.41 – 1.34 (1H, m, C**H**$_2$), 1.00 – 0.94 (1H, m, cyclopropyl C**H**$_2$), 0.85 – 0.78 (1H, m, cyclopropyl C**H**$_2$), 0.72 – 0.59 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 177.7 (**C**O), 171.0 (**C**O), 42.8 (**C**H$_2$), 39.0 (**C**H$_2$), 35.3 (**C**H$_2$), 33.8 (**C**H$_2$), 30.3 (**C**H), 26.8 (**C**H$_2$), 24.2 (**C**H$_2$), 23.7 (**C**H$_2$), 12.0 (cyclopropyl **C**H$_2$), 7.3 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{12}H_{20}N_2NaO_2$, 247.1416. Found: $[MNa]^+$, 247.1417 (0.4 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.26 – 6.20 (1H, m, N**H**).

For LCMS data confirming this product has >95% purity, see SI Section 5.

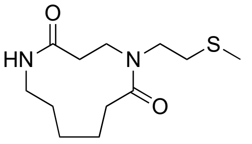
Ethyl 2-(4,11-dioxo-1,5-diazacycloundecan-1-yl)acetate (8h)



To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (1.1 mL) was added glycine ethyl ester (86.5 mg, 0.62 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (102.5 mg, 76% yield); m.p. 133 – 135 °C; R_f 0.40 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3337, 3088, 2934, 2869, 2243, 1728, 1639, 1551, 1448, 1206, 1157, 1028, 728; δ_H (400 MHz, $CDCl_3$) 8.09 (1H, s, N**H**), 4.72 (1H, d, *J* = 17.1 Hz, C**H**H'COO), 4.26 – 4.20 (2H, m, C**H**$_2$), 4.18 – 4.07 (1H, m, C**H**$_2$), 3.72 – 3.67 (1H, m, C**H**$_2$), 3.32 (1H, d, *J* = 17.1 Hz, CH**H'**COO), 3.24 – 3.20 (1H, m, C**H**$_2$), 2.61 – 2.48 (2H, m, C**H**$_2$), 2.46 – 2.42 (1H, m, C**H**$_2$), 2.26 – 2.22 (1H, m, C**H**$_2$), 2.14 – 2.01 (2H , m, C**H**$_2$), 1.76 – 1.70 (1H, m, C**H**$_2$), 1.62 – 1.55 (2H, m, C**H**$_2$), 1.30 (3H, t, *J* = 7.2 Hz, C**H**$_3$), 1.24 – 1.17 (1H, m, C**H**$_2$), 0.93 – 0.82 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 172.2 (**C**O), 171.2 (**C**O), 62.2 (**C**H$_2$), 50.8 (**C**H$_2$), 48.3 (**C**H$_2$), 41.6 (**C**H$_2$), 37.1 (**C**H$_2$), 28.0 (**C**H$_2$), 25.2 (**C**H$_2$), 24.5 (**C**H$_2$), 22.7 (**C**H$_2$), 14.2 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{13}H_{22}N_2NaO_4$, 293.1472. Found: $[MNa]^+$, 293.1472 (−0.0 ppm error).

For LCMS data confirming this product has >95% purity, see SI Section 5.

5-(2-(Methylthio)ethyl)-1,5-diazacycloundecane-2,6-dione (8i)

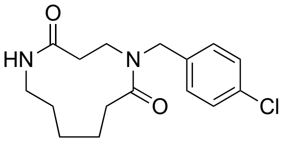


To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (1.1 mL) was added 2-(methylthio)ethylamine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a pale-yellow oil (66.9 mg, 52% yield); R_f 0.44 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3288, 2928, 1620, 1555, 1424, 1351, 1301, 1229, 1179, 921, 728. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a roughly 2:1

mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.77 (1H, s, N**H**), 4.22 – 3.90 (1H, m, C**H**$_2$), 3.78 – 3.41 (3H, m, C**H**$_2$ and C**H**H'), 3.23 – 3.19 (1H, m, CH**H'**), 3.10 – 2.85 (1H, m, C**H**$_2$), 2.74 – 2.56 (1H, m, C**H**$_2$), 2.51 – 2.45 (1H, m, C**H**$_2$), 2.41 – 2.33 (2H, m, C**H**$_2$), 2.18 (3H, s, C**H**$_3$), 2.12 – 2.00 (1H, m, C**H**$_2$), 1.77 – 1.63 (6H, m, 3 x C**H**$_2$), 1.34 – 1.16 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 171.4 (**C**O), 46.5 (**C**H$_2$), 46.2 (**C**H$_2$), 41.4 (**C**H$_2$), 37.6 (**C**H$_2$), 32.0 (**C**H$_2$), 28.7 (**C**H$_2$), 25.3 (**C**H$_2$), 24.3 (**C**H$_2$), 22.5 (**C**H$_2$), 15.5 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{12}H_{22}N_2NaO_2S$, 281.1297. Found: $[MNa]^+$, 281.1294 (−0.8 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.96 – 5.83 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 179.1 (**C**O), 42.8 (**C**H$_2$), 36.7 (**C**H$_2$), 30.6 (**C**H$_2$), 29.8 (**C**H$_2$), 23.5 (**C**H$_2$), 14.2 (**C**H$_3$).

5-(4-Chlorobenzyl)-1,5-diazacycloundecane-2,6-dione (8j)



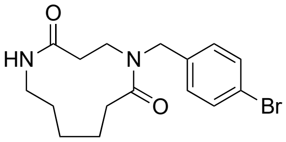
To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (2.0 mL) was added 4-chlorobenzylamine (70 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (73.6 mg, 48% yield); m.p. 158 – 160 °C; R_f 0.56 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3293, 2932, 1636, 1617, 1561, 1488, 1450, 1421, 1437, 1225, 1177, 1090, 905, 841, 798, 727, 563. The ^1H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 7:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.18 (4H, m, Ar**H**), 6.07 (1H, s, N**H**), 5.26 – 4.68 (1H, m, C**H**$_2$), 4.42 – 3.82 (2H, m, C**H**$_2$), 3.76 – 3.13 (2H, m, C**H**$_2$), 2.63 – 2.02 (6H, m, 3 x C**H**$_2$), 1.79 – 1.49 (4H, m, 2 x C**H**$_2$), 1.36 – 0.83 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 171.4 (**C**O), 136.5 (**C**Ar), 133.6 (**C**Ar), 129.6 (ArCH), 129.1 (Ar**C**H), 48.1 (**C**H$_2$), 44.8 (**C**H$_2$), 41.7 (**C**H$_2$), 36.9 (**C**H$_2$), 28.5 (**C**H$_2$), 25.2 (**C**H$_2$), 24.4 (**C**H$_2$), 22.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{16}H_{21}ClN_2NaO_2$, 331.1185. Found: $[MNa]^+$, 331.1184 (−0.4 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.89 – 5.85 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 175.3 (**C**O), 171.0 (**C**O), 135.5 (**C**Ar), 133.6 (**C**Ar), 129.1

(Ar**C**H), 128.0 (Ar**C**H), 53.5 (**C**H$_2$), 43.0 (**C**H$_2$), 37.4 (**C**H$_2$), 34.6 (**C**H$_2$), 33.8 (**C**H$_2$), 25.9 (**C**H$_2$), 23.4 (**C**H$_2$), 22.3 (**C**H$_2$).

For LCMS data confirming this product has >95% purity, see SI Section 5.

5-(4-Bromobenzyl)-1,5-diazacycloundecane-2,6-dione (8k)

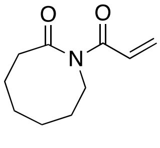


To a solution of 1-acryloyl-azepan-2-one **3b** (84 mg, 0.50 mmol) in dry methanol (2.0 mL) was added 4-bromobenzylamine (70 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:99 methanol:ethyl acetate) to afford the title compound as a white solid (112.9 mg, 64% yield); m.p. 180 – 183 °C; R$_f$ 0.54 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3296, 3089, 2933, 2239, 1625, 1556, 1487, 1452, 1404, 1351, 1182, 1070, 1011, 908, 795, 730. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in CDCl$_3$, the product exists as a 7:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, CDCl$_3$) 7.50 – 7.40 (2H, m, Ar**H**), 7.22 – 7.11 (2H, m, Ar**H**), 5.79 (1H, s, N**H**), 5.19 – 4.71 (1H, m, C**H**$_2$), 4.41 – 3.85 (2H, m, C**H**$_2$), 3.80 – 3.16 (2H, m, C**H**$_2$), 2.66 – 2.03 (6H, m, 3 x C**H**$_2$), 1.92 – 1.47 (4H, m, 2 x C**H**$_2$), 1.45 – 1.14 (1H, m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 173.6 (**C**O), 171.3 (**C**O), 137.2 (**C**Ar), 132.1 (**C**Ar), 130.0 (Ar**C**H), 121.8 (Ar**C**H), 48.3 (**C**H$_2$), 44.9 (**C**H$_2$), 41.8 (**C**H$_2$), 37.1 (**C**H$_2$), 28.6 (**C**H$_2$), 25.2 (**C**H$_2$), 24.4 (**C**H$_2$), 22.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{16}H_{21}{}^{79}BrN_2NaO_2$, 375.0686. Found: [MNa]$^+$, 377.0679 (−2.0 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_C (100 MHz, CDCl$_3$) 175.4 (**C**O), 171.0 (**C**O), 136.1 (**C**Ar), 132.1 (**C**Ar), 128.4 (ArCH), 121.7 (Ar**C**H), 53.7 (**C**H$_2$), 43.2 (**C**H$_2$), 37.4 (**C**H$_2$), 34.7 (**C**H$_2$), 33.8 (**C**H$_2$), 25.9 (**C**H$_2$), 23.3 (**C**H$_2$), 22.2 (**C**H$_2$).

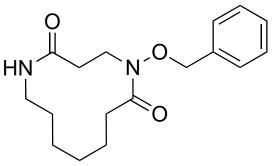
For LCMS data confirming this product has >95% purity, see SI Section 5.

1-Acryloyl-azocan-2-one (3c)[1,2]



A solution of 1-aza-2-cyclooctanone (510 mg, 4.00 mmol) in dry THF (14 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 1.4 mL) was added *via* dropwise using a syringe pump over 15 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (0.5 mL, 6.00 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (15 mL) and extracted with Et_2O (25 mL). The combined organics were washed with saturated $NaHCO_3$ solution (2 x 15 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a colourless oil (358 mg, 49% yield); R_f 0.43 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2927, 2359, 1679, 1445, 1402, 1378, 1304, 1248, 1203, 1175, 1127, 1093, 973, 797, 589 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.87 (1H, dd, *J* = 16.8, 10.5 Hz, C**H**CHH'), 6.31 (1H, dd, *J* = 16.8, 1.7 Hz, CHC**H**H'), 5.67 (1H, dd, *J* = 10.5, 1.7 Hz, CHCH**H'**), 3.93 – 3.90 (2H, m, NC**H**$_2$), 2.67 – 2.64 (2H, m, C**H**$_2$), 1.92 – 1.85 (2H, m, C**H**$_2$), 1.79 – 1.73 (2H, m, C**H**$_2$), 1.63 – 1.57 (2H, m, C**H**$_2$), 1.49 – 1.44 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.7 (**C**O), 169.2 (**C**O), 131.8 (**C**HCHH'), 127.5 (CH**C**HH'), 43.7 (N**C**H$_2$), 36.6 (**C**H$_2$), 29.8 (**C**H$_2$), 29.2 (**C**H$_2$), 26.1 (**C**H$_2$), 23.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{10}H_{15}NNaO_2$, 204.0994. Found: $[MNa]^+$, 204.0995 (0.4 ppm error).

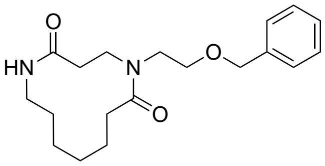
5-(Benzyloxy)-1,5-diazacyclododecane-2,6-dione (9a)



To a solution of 1-acryloyl-azocan-2-one **3c** (113 mg, 0.60 mmol) in dry methanol (1.3 mL) was added benzyl-o-hydroxylamine (80 µL, 0.7 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude product was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (117 mg, 61% yield); m.p. 125-127 °C; R_f 0.18 (1:19 methanol:ethyl acetate. **IR** (ATR): ν_{max}/cm^{-1} 3300, 2928, 2862, 2239, 1650, 1548, 1454, 1411, 1220, 1196, 978, 906, 728, 699, 645; δ_H (400 MHz, $CDCl_3$) 7.41 – 7.35 (5H, m, Ar**H**), 5.78 (1H, s, N**H**), 4.85 – 4.77 (3H, m, NOC**H**$_2$ and C**H**H'), 3.36 – 3.29 (1H , m, C**H**$_2$), 3.27 – 3.19 (1H, m, CH**H'**), 2.87 – 2.81 (1H, m, C**H**$_2$), 2.73 – 2.65 (1H, m, C**H**$_2$), 2.44 – 2.40 (1H, m, C**H**$_2$), 2.04 – 1.99 (1H, m, C**H**$_2$), 1.95 – 1.92 (1H, m, C**H**$_2$), 1.62 – 1.53 (2H, m, C**H**$_2$), 1.51 – 1.44 (2H, m, C**H**$_2$), 1.35 – 1.21 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.7 (**C**O), 169.9 (**C**O), 134.1 (**C**Ar), 129.6 (Ar**C**H), 129.4 (ArCH), 129.0 (Ar**C**H), 76.7 (NO**C**H$_2$), 40.0 (**C**H$_2$), 37.7 (**C**H$_2$), 34.4 (**C**H$_2$), 29.3 (**C**H$_2$), 25.7

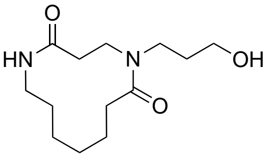
(**C**H$_2$), 25.4 (**C**H$_2$), 22.3 (**C**H$_2$), 22.0 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{17}H_{24}N_2NaO_3$, 327.1675. Found: $[MNa]^+$, 327.1679 (1.3 ppm error).

5-(2-(Benzyloxy)ethyl)-1,5-diazacyclododecane-2,6-dione (9b)



To a solution of 1-acryloyl-azocan-2-one **3c** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 2-(benzyloxy)-1-ethanamine (80 µL, 1.1 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude product was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (98 mg, 59% yield); m.p. 83 – 86 °C; R_f 0.48 (1:9 methanol:ethyl acetate. **IR** (ATR): ν_{max}/cm^{-1} 3289, 3087, 2925, 2859, 2234, 1640, 1620, 1550, 1453, 1208, 1099, 923, 732, 698. In solution $CDCl_3$, this compound exists as a roughly 1:1 mixture of rotamers. δ_H (400 MHz, $CDCl_3$) 7.36 − 7.33 (5H, m, Ar**H**), 7.32 − 7.28 (5H, m, Ar**H**), 6.44 (1H, d, *J* = 8.5 Hz, N**H**), 6.18 – 6.17 (1H, m, N**H**), 4.59 – 4.49 (6H, m, 3 x C**H**$_2$), 3.78 – 3.71 (2H , m, C**H**$_2$), 3.63 – 3.53 (4H, m, 2 x C**H**$_2$), 3.48 – 3.43 (1H, m, C**H**$_2$), 2.97 – 2.90 (1H, m, C**H**$_2$), 2.89 – 2.83 (1H, m, C**H**$_2$), 2.75 – 2.68 (1H, m, C**H**$_2$), 2.57 – 2.47 (3H, m, C**H**$_2$), 2.16 – 2.00 (5H, m, C**H**$_2$), 1.83 – 1.70 (2H, m, C**H**$_2$), 1.62 – 1.53 (3H, m, C**H**$_2$), 1.49 – 1.40 (4H, m, C**H**$_2$), 1.39 – 1.24 (8H, m, C**H**$_2$), 1.18 (2H, s, C**H**$_2$), 1.07 – 0.98 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 175.5 (**C**O), 171.3 (**C**O), 170.3 (**C**O), 137.7 (**C**Ar), 137.0 (**C**Ar), 128.9 (Ar**C**H), 128.6 (Ar**C**H), 128.5 (Ar**C**H), 128.1 (Ar**C**H), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 73.7 (**C**H$_2$), 73.5 (**C**H$_2$), 68.2 (**C**H$_2$), 68.1 (**C**H$_2$), 49.5 (**C**H$_2$), 48.4 (**C**H$_2$), 48.3 (**C**H$_2$), 41.4 (**C**H$_2$), 39.0 (**C**H$_2$), 37.2 (**C**H$_2$), 36.3 (**C**H$_2$), 35.6 (**C**H$_2$), 32.1 (2 x **C**H$_2$, overlapping), 27.4 (**C**H$_2$), 26.8 (**C**H$_2$), 26.4 (**C**H$_2$), 25.6 (**C**H$_2$), 24.0 (**C**H$_2$), 23.6 (**C**H$_2$), 22.5 (**C**H$_2$), 22.0 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{19}H_{28}N_2NaO_3$, 355.1993. Found: $[MNa]^+$, 355.1992 (−0.2 ppm error).

5-(3-Hydroxypropyl)-1,5-diazacyclododecane-2,6-dione (9c)

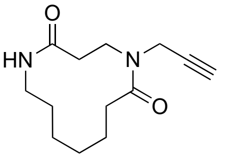


To a solution of 1-acryloyl -azocan-2-one **3c** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 3-aminopropan-1-ol (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (83.1 mg, 65% yield); R_f 0.49 (2:3 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3288, 3093, 2928, 2863, 2237, 1642, 1614, 1556, 1456, 1440, 1424, 1354, 1199, 1053, 908, 728, 645. In solution in $CDCl_3$, the product exists as a 2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.60 (1H, s, N**H**), 4.54 (1H, ddd, *J* = 14.7, 10.3, 5.0 Hz, C**H**$_2$), 3.68 – 3.59 (4H, m, 2 x C**H**$_2$), 3.40 – 3.32 (1H , m, C**H**$_2$), 2.94 – 2.83 (2H, m, C**H**$_2$), 2.74 – 2.68 (1H, m, C**H**$_2$), 2.59 – 2.47 (2H, m, C**H**$_2$), 2.16 – 2.00 (2H, m, C**H**$_2$), 1.82 – 1.70 (3H, m, C**H**$_2$), 1.60 – 1.53 (1H , m, C**H**$_2$), 1.48 – 1.41 (3H , m, C**H**$_2$), 1.39 – 1.32 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.5 (**C**O), 59.3 (**C**H$_2$), 45.4 (**C**H$_2$), 40.8 (**C**H$_2$), 39.0 (**C**H$_2$), 35.5 (**C**H$_2$), 31.9 (**C**H$_2$), 31.8 (**C**H$_2$), 27.4 (**C**H$_2$), 25.5 (**C**H$_2$), 23.5 (**C**H$_2$), 22.0 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{13}H_{24}N_2NaO_3$, 279.1678. Found: [MNa]$^+$, 279.1679 (0.3 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.36 – 6.33 (1H, m, N**H**), 3.49 – 3.46 (1H , m, C**H**$_2$), 2.41 – 2.38 (1H , m, C**H**$_2$), 1.25 – 1.20 (1H , m, C**H**$_2$), 1.07 – 0.97 (1H , m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.2 (**C**O), 171.0 (**C**O), 58.5 (**C**H$_2$), 44.4 (**C**H$_2$), 41.3 (**C**H$_2$), 37.0 (**C**H$_2$), 36.7 (**C**H$_2$), 30.7 (**C**H$_2$), 29.9 (**C**H$_2$), 26.8 (**C**H$_2$), 23.3 (**C**H$_2$), 22.5 (**C**H$_2$).

For LCMS data confirming this product has >95% purity, see SI Section 5.

5-(Prop-2-yn-1-yl)-1,5-diazacyclododecane-2,6-dione (9d)



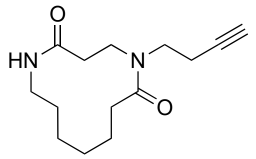
To a solution of 1-acryloyl -azocan-2-one **3c** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added propargylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (78.5

mg, 71% yield); m.p. 142 – 144 °C; R$_f$ 0.5 (1:9 methanol:ethyl acetate); **IR** (ATR): ν_{max}/cm^{-1} 3302, 3088, 2929, 2862, 2243, 1628, 1552, 1453, 1418, 1355, 1227, 1206, 907, 727, 646. In solution in CDCl$_3$, the product exists as a 2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, CDCl$_3$) 6.39 – 6.38 (1H, m, N**H**), 4.65 (1H, dt, *J* = 15.6, 8.0 Hz, C**H**$_2$), 4.13 – 4.12 (1H, m, C**H**$_2$), 3.62 – 3.53 (1H, m, C**H**$_2$), 3.00 – 2.94 (1H, m, C**H**$_2$), 2.93 – 2.88 (1H, m, C**H**$_2$), 2.68 – 2.64 (2H, m, C**H**$_2$), 2.52- 2.45 (2H, m, C**H**), 2.35- 2.34 (1H, m, C**H**$_2$), 2.16 – 2.05 (1H, m, C**H**$_2$), 1.63 – 1.55 (1H, m, C**H**$_2$), 1.49 – 1.39 (4H, m, 2 x C**H**$_2$), 1.35 – 1.29 (2H, m, C**H**$_2$), 1.14 – 1.02 (1H, m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 175.1 (**C**O), 170.0 (**C**O), 78.4 (C**C**H), 73.5 (**C**CH), 41.8 (**C**H$_2$), 38.9 (**C**H$_2$), 38.4 (**C**H$_2$), 35.6 (**C**H$_2$), 32.0 (**C**H$_2$), 27.3 (**C**H$_2$), 25.6 (**C**H$_2$), 23.0 (**C**H$_2$), 21.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{13}H_{20}N_2NaO_2$, 259.1414. Found [MNa]$^+$ 259.1417 (1.3 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, CDCl$_3$) 5.86 (1H, s, N**H**), 2.28 – 2.27 (1H, m, C**H**), 2.26 – 2.19 (2H, m, C**H**$_2$), 1.79 (2H, s, C**H**$_2$), 1.26 – 1.21 (2H, m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 174.2 (**C**O), 170.8 (**C**O), 80.9 (C**C**H), 71.6 (**C**CH), 46.7 (**C**H$_2$), 36.9 (**C**H$_2$), 36.7 (**C**H$_2$), 35.5 (**C**H$_2$), 31.2 (**C**H$_2$), 26.6 (**C**H$_2$), 23.9 (**C**H$_2$), 22.5 (**C**H$_2$).

For LCMS data confirming this product has >95% purity, see SI Section 5.

5-(But-3-yn-1-yl)-1,5-diazacyclododecane-2,6-dione (9e)

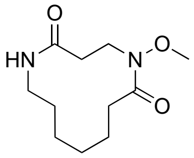


To a solution of 1-acryloyl-azocan-2-one **3c** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added but-3-yn-1-amine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (80 mg, 64% yield); m.p. 100 – 104 °C; R$_f$ 0.49 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3302, 2928, 2860, 2239, 1620, 1554, 1455, 1421, 1354, 1244, 1200, 1100, 1025, 905, 727, 646. In solution in CDCl$_3$, the product exists as a 4:2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, CDCl$_3$) 6.34 (1H, d, *J* = 8.4, N**H**), 4.50 – 4.43 (1H, m, C**H**$_2$), 3.78 – 3.64 (2H, m, C**H**$_2$), 3.45 – 3.38 (1H, m, C**H**$_2$), 3.00 (1H, dt, *J* = 14.7, 5.7 Hz, C**H**$_2$), 2.86 – 2.76 (2H, m, C**H**$_2$), 2.56 – 2.49 (2H, m, C**H**$_2$), 2.46 – 2.41 (3H, m, C**H**$_2$), 2.05 – 1.97 (2H, m, C**H** and C**H**H’), 1.63 – 1.54 (2H, m, CH**H’** and C**H**$_2$), 1.49 – 1.40 (4H, m, 2 x C**H**$_2$), 1.28 – 1.14 (1H, m, C**H**$_2$); δ_C

(100 MHz, $CDCl_3$) 175.5 (**C**O), 170.2 (**C**O), 80.3 (C**C**H), 71.2 (**C**CH), 47.2 (**C**H_2), 41.2 (**C**H_2), 39.2 (**C**H_2), 35.4 (**C**H_2), 32.4 (**C**H_2), 27.3 (**C**H_2), 25.6 (**C**H_2), 24.0 (**C**H_2), 22.3 (**C**H_2), 19.0 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{14}H_{22}N_2NaO_2$, 273.1576. Found: $[MNa]^+$, 273.1573 (−0.9 ppm error).

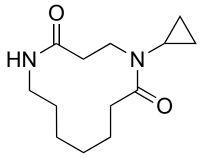
Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.03 (1H, s, N**H**), 5.88- 5.77 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 175.3 (**C**O), 171.1 (**C**O), 84.4 (C**C**H), 70.0 (**C**CH), 46.8 (**C**H_2), 42.0 (**C**H_2), 37.7 (**C**H_2), 36.7 (**C**H_2), 32.2 (**C**H_2), 31.4 (**C**H_2), 28.2 (**C**H_2), 26.8 (**C**H_2), 25.9 (**C**H_2), 24.5 (**C**H_2), 23.6 (**C**H_2), 17.4 (**C**H_2).
For LCMS data confirming this product has >95% purity, see SI Section 5.

5-Methoxy-1,5-diazacycloundecane-2,6-dione (9f)



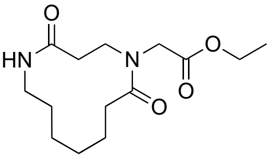
To a solution of 1-acryloyl-azocan-2-one **3c** (91 mg, 0.50 mmol) in dry methanol (1.6 mL) was added methoxyamine (63 mg, 0.75 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (52.7 mg, 46% yield); m.p. 103 – 105 °C; R_f 0.24 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3088, 2930, 2863, 2239, 1644, 1549, 1443, 1413, 1199, 1065, 995, 906, 727, 645; δ_H (400 MHz, $CDCl_3$) 5.81 (1H, s, N**H**), 4.78 – 4.70 (1H, m, C**H**$_2$), 3.68 (3H, s, C**H**$_3$), 3.34 – 3.24 (3H , m, C**H**$_2$), 2.88 – 2.81 (1H, m, C**H**$_2$), 2.69 – 2.61 (1H, m, C**H**$_2$), 2.47 – 2.43 (1H, m, C**H**$_2$), 2.12 – 2.02 (2H, m, C**H**$_2$), 1.59 – 1.54 (1H, m, C**H**$_2$), 1.52 – 1.45 (2H , m, C**H**$_2$), 1.40 – 1.21 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 169.8 (**C**O), 61.6 (**C**H_3), 39.0 (**C**H_2), 37.8 (**C**H_2), 34.3 (**C**H_2), 29.1 (**C**H_2), 25.7 (**C**H_2), 25.6 (**C**H_2), 22.4 (**C**H_2), 21.9 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{11}H_{20}N_2NaO_3$, 251.1363. Found: $[MNa]^+$, 251.1366 (1.1 ppm error).

5-Cyclopropyl-1,5-diazacycloundodecane-2,6-dione (9g)



To a solution of 1-acryloyl-azocan-2-one **3c** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added cyclopropylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (49.7 mg, 42% yield); m.p. 145 – 147 °C; R_f 0.29 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3286, 3087, 2928, 2862, 2234, 1642, 1549, 1448, 1407, 1375, 1263, 1156, 1069, 1030, 921, 727, 644; δ_H (400 MHz, CDCl$_3$) 6.36 (1H, d, *J* = 7.4 Hz, N**H**), 4.71 – 4.62 (1H, m, C**H**$_2$), 3.73 – 3.64 (1H, m, C**H**), 2.91 – 2.72 (4H , m, 2 x C**H**$_2$), 2.71 – 2.68 (1H , m, C**H**), 2.65 – 2.58 (1H , m, C**H**$_2$), 2.21 – 2.11 (2H, m, C**H**$_2$), 1.64 – 1.56 (1H, m, C**H**$_2$), 1.53 – 1.33 (5H, m, C**H**$_2$), 1.07 – 1.00 (1H, m, cyclopropyl C**H**$_2$), 0.99 – 0.91 (1H, m, C**H**$_2$), 0.90 – 0.83 (1H, m, cyclopropyl C**H**$_2$), 0.77 – 0.66 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 177.5 (**C**O), 170.3 (**C**O), 39.9 (**C**H$_2$), 38.6 (**C**H$_2$), 35.5 (**C**H$_2$), 33.0 (**C**H$_2$), 28.7 (**C**H), 27.7 (**C**H$_2$), 25.8 (**C**H$_2$), 22.5 (**C**H$_2$), 21.1 (**C**H$_2$), 11.9 (cyclopropyl **C**H$_2$), 6.8 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{13}H_{22}N_2NaO_2$, 261.1575. Found: [MNa]$^+$, 261.1573 (−0.6 ppm error).

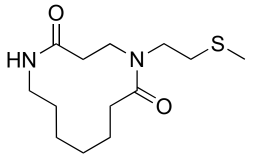
Ethyl 2-(4,12-dioxo-1,5-diazacyclododecan-1-yl)acetate (9h)



To a solution of 1-acryloyl-azocan-2-one **3c** (102 mg, 0.56 mmol) in dry methanol (1.1 mL) was added glycine ethyl ester (86.5 mg, 0.62 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (101 mg, 63% yield); m.p. 115 – 117 °C; R_f 0.45 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3087, 2928, 2861, 1738, 163, 1548, 1448, 1353, 1197, 1159, 1027, 728. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in CDCl$_3$, the product exists largely as a single rotamer, along with 2 minor rotamers. NMR data for the major rotamer only; δ$_H$ (400 MHz, CDCl$_3$) 7.18 (1H, s, N**H**), 4.23 – 4.12 (4H, m, 2 x C**H**$_2$), 3.33 – 3.28 (1H, m, C**H**$_2$), 2.43 – 2.36 (4H, m, 2 x C**H**$_2$), 1.56 – 1.55 (4H, m, 2 x C**H**$_2$), 1.32 – 1.24 (10H, m, C**H**$_3$ and C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 174.6 (**C**O), 171.8 (**C**O), 171.1 (**C**O), 61.9 (**C**H$_2$), 50.2 (**C**H$_2$COO), 48.3 (**C**H$_2$), 37.4 (**C**H$_2$), 37.2 (**C**H$_2$), 31.5 (**C**H$_2$), 26.3 (**C**H$_2$), 25.7 (**C**H$_2$), 23.1 (**C**H$_2$), 22.8 (**C**H$_2$), 14.2 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{14}H_{24}N_2NaO_4$, 307.1625. Found: [MNa]$^+$, 307.1628 (0.9 ppm error).

Characteristic NMR data for the minor rotamers can be found at; δ$_H$ (400 MHz, CDCl$_3$) 6.53 – 6.52 (1H, m, C**H**$_2$), 5.70 – 5.57 (1H, m, C**H**$_2$), 4.76 – 4.68 (1H, m, C**H**$_2$), 3.49 – 3.40 (2H, m, C**H**$_2$), 3.34 – 3.29 (2H, m, C**H**$_2$), 3.10 – 3.03 (1H, m, C**H**$_2$), 2.95 – 2.92 (1H, m, C**H**$_2$), 2.82 – 2.77 (1H, m, C**H**$_2$), 2.65 – 2.59 (1H, m, C**H**$_2$). δ_C (100 MHz, CDCl$_3$) 175.2 (**C**O), 170.4 (**C**O), 62.1 (**C**H$_2$), 51.0 (**C**H$_2$), 43.7 (**C**H$_2$), 42.0 (**C**H$_2$), 38.8 (**C**H$_2$), 35.8 (**C**H$_2$), 32.4 (**C**H$_2$), 32.2 (**C**H$_2$), 31.8 (**C**H$_2$), 28.2 (**C**H$_2$), 27.0 (**C**H$_2$), 25.8 (**C**H$_2$), 23.1 (**C**H$_2$), 21.7 (**C**H$_2$), 14.3 (**C**H$_3$).

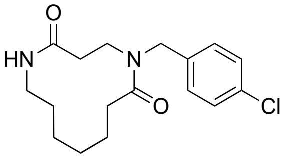
5-(2-(Methylthio)ethyl)-1,5-diazacylododecane-2,6-dione (9i)



To a solution of 1-acryloyl-azocan-2-one **3c** (91 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 2-(methylthio)ethylamine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a pale-yellow liquid (88.2 mg, 65% yield); R$_f$ 0.5 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3288, 2924, 2236, 1639, 1553, 1454, 1359, 1300, 1100, 906, 726. In solution in CDCl$_3$, the product exists as a roughly 3:1 mixture of rotamers. NMR data for both rotamers; δ$_H$ (400 MHz, CDCl$_3$) 6.56 – 6.54 (1H, m, N**H**), 4.44 – 4.37 (1H, m, C**H**$_2$), 3.70 – 3.56 (2H, m, C**H**$_2$), 3.47 – 3.43 (1H, m, C**H**$_2$), 3.29 – 3.25 (1H, m, C**H**$_2$), 2.96 – 2.90 (1H, m, C**H**$_2$), 2.83 – 2.73 (3H, m, C**H**$_2$), 2.63 – 2.57 (2H, m, C**H**$_2$), 2.48 – 2.42 (1H, m, C**H**$_2$), 2.40 – 2.34 (2H, m, C**H**$_2$), 2.09 – 2.08 (3H, m, C**H**$_3$), 1.74 – 1.71 (1H, m, C**H**$_2$), 1.56 – 1.52 (4H, m, 2 x C**H**$_2$), 1.43 – 1.40 (3H, m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 175.2 (**C**O), 170.1 (**C**O), 48.4 (**C**H$_2$), 41.5 (**C**H$_2$), 39.0 (**C**H$_2$), 35.3 (**C**H$_2$), 32.9 (**C**H$_2$), 32.3 (**C**H$_2$), 27.2 (**C**H$_2$), 25.5 (**C**H$_2$), 24.0 (**C**H$_2$), 22.3 (**C**H$_2$), 15.9 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{13}H_{24}N_2NaO_2S$, 295.1447. Found: [MNa]$^+$, 295.1451 (1.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.27 – 6.11 (1H, m, N**H**), 4.44 – 4.37 (2H, m, C**H**$_2$), 2.96 – 2.90 (2H, m, C**H**$_2$), 2.31 – 2.20 (1H, m, C**H**$_2$), 2.00 – 1.91 (2H, m, C**H**$_2$), 1.20 – 1.16 (1H, m, C**H**$_2$), 1.08 – 0.99 (1H, m, C**H**$_2$). δ_C (100 MHz, $CDCl_3$) 177.8 (**C**O), 171.0 (**C**O), 41.8 (**C**H$_2$), 32.3 (**C**H$_2$), 32.1 (**C**H$_2$), 28.1 (**C**H$_2$), 25.7 (**C**H$_2$), 24.5 (**C**H$_2$), 15.5 (**C**H$_3$).

5-(4-Chlorobenzyl)-1,5-diazacyclododecane-2,6-dione (9j)

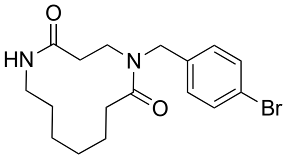


To a solution of 1-acryloyl-azocan-2-one **3c** (97 mg, 0.54 mmol) in dry methanol (2.0 mL) was added 4-chlorobenzylamine (70 µL, 0.59 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a yellow oil (51.3 mg, 29% yield); m.p. 138 – 140 °C; R_f 0.59 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3295, 2931, 2241, 1629, 1617, 1553, 1491, 1454, 1353, 1092, 906, 727. In solution in $CDCl_3$, the product exists as a 6:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.28 – 7.25 (2H, m, Ar**H**), 7.04 (2H, m, Ar**H**), 6.39 (1H, d, *J* = 8.8 Hz, N**H**), 4.81 (1H, d, *J* = 16.9 Hz, C**H**H'Ph), 4.46 – 4.39 (1H, m, C**H**$_2$), 4.35 (1H, d, *J* = 16.9 Hz, CH**H'**Ph), 3.75 – 3.66 (1H, m, C**H**$_2$), 2.86 – 2.73 (3H, m, C**H**$_2$), 2.54 – 2.40 (2H, m, C**H**$_2$), 2.12 – 1.95 (2H, m, C**H**$_2$), 1.58 – 1.52 (1H, m, C**H**$_2$), 1.49 – 1.39 (5H, m, C**H**$_2$), 1.15 – 1.07 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.2 (**C**O), 135.2 (**C**Ar), 133.7 (**C**Ar), 129.2 (Ar**C**H), 127.9 (Ar**C**H), 51.6 (**C**H$_2$), 41.3 (**C**H$_2$), 39.3 (**C**H$_2$), 35.1 (**C**H$_2$), 32.6 (**C**H$_2$), 27.3 (**C**H$_2$), 25.7 (**C**H$_2$), 24.2 (**C**H$_2$), 22.4 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{17}H_{23}ClN_2NaO_2$, 345.1330. Found: [MNa]$^+$, 345.1340 (2.9 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.46 – 5.40 (1H, m, N**H**), 4.62 – 4.57 (2H, m, C**H**$_2$), 1.77 – 1.76 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.0 (**C**O), 170.8 (**C**O), 137.5 (**C**Ar), 136.8 (**C**Ar), 129.9 (Ar**C**H), 128.9 (Ar**C**H), 48.2 (**C**H$_2$), 44.9 (**C**H$_2$), 36.8 (**C**H$_2$), 30.8 (**C**H$_2$), 26.8 (**C**H$_2$), 26.7 (**C**H$_2$), 23.5 (**C**H$_2$), 22.5 (**C**H$_2$).

For LCMS data confirming this product has >95% purity, see SI Section 5.

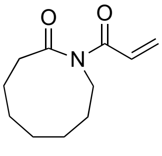
5-(4-Bromobenzyl)-1,5-diazacyclododecane-2,6-dilone (9k)



To a solution of 1-acryloyl-azocan-2-one **3c** (91.0 mg, 0.5 mmol) in dry methanol (1.0 mL) was added 4-bromobenzylamine (700 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:99 methanol:ethyl acetate) to afford the title compound as a white solid (40.4 mg, 22% yield); m.p. 150 – 152 °C; R_f 0.59 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3293, 3086, 2928, 2861, 2238, 2239, 1627, 1553, 1487, 1453, 1404, 1352, 1207, 1070, 1010, 908, 795, 727. In solution in $CDCl_3$, the product exists as a 5:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.45 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.02 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.40 (1H, s, N**H**), 4.82 (1H, d, *J* = 17.0 Hz, C**H**H'Ph), 4.48 – 4.43 (1H, m, C**H**$_2$), 4.37 (1H, d, *J* = 17.0 Hz, CH**H'**Ph), 3.77 – 3.70 (1H, m, C**H**$_2$), 2.89 – 2.77 (3H, m, C**H**$_2$), 2.57 – 2.42 (2H, m, C**H**$_2$), 2.14 – 1.96 (2H, m, C**H**$_2$), 1.61 – 1.54 (1H, m, C**H**$_2$), 1.51 – 1.42 (5H, m, C**H**$_2$), 1.18 – 1.10 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 170.3 (**C**O), 135.7 (**C**Ar), 132.2 (Ar**C**H), 128.2 (Ar**C**H), 121.7 (**C**Ar), 51.7 (**C**H$_2$), 41.3 (**C**H$_2$), 39.3 (**C**H$_2$), 35.1 (**C**H$_2$), 32.6 (**C**H$_2$), 27.3 (**C**H$_2$), 25.7 (**C**H$_2$), 24.2 (**C**H$_2$), 22.4 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{17}H_{23}{}^{79}BrN_2NaO_2$, 389.0830. Found: $[MNa]^+$, 389.0835 (1.2 ppm error).

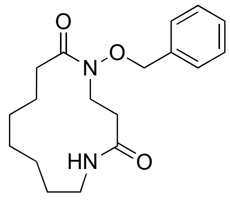
Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.50 – 5.40 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 175.0 (**C**O), 170.8 (**C**O), 137.3 (**C**Ar), 131.9 (Ar**C**H), 130.2 (Ar**C**H), 121.6 (**C**Ar), 48.3 (**C**H$_2$), 44.9 (**C**H$_2$), 36.8 (**C**H$_2$), 30.8 (**C**H$_2$), 26.8 (**C**H$_2$), 26.7 (**C**H$_2$), 23.5 (**C**H$_2$), 22.5 (**C**H$_2$).

1-Acryloylazonan-2-one (3d)



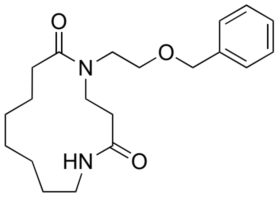
A solution of azonan-2-one (830.6 mg, 5.88 mmol) in dry THF (33 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 2.2 mL, 6.67 mmol) was added *via* dropwise using a syringe pump over 30 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (0.7 mL, 8.80 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (20 mL) and extracted with Et_2O (20 mL). The combined organics were washed with saturated $NaHCO_3$ solution (2 x 20 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether : hexane) to afford the title compound as a colourless liquid (487.6 mg, 43% yield); R_f 0.60 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} ν_{max} 2927, 2868, 1676, 1619, 1445, 1402, 1378, 1227, 1164, 1020, 975, 905, 793, 720, 570; δ_H (400 MHz, $CDCl_3$) 6.73 (1H, dd, *J* = 16.9, 10.5 Hz, C**H**CHH'), 6.32 (1H, dd, *J* = 16.9, 1.8 Hz, CHC**H**H'), 5.67 (1H, dd, *J* = 10.5, 1.8 Hz, CHCH**H'**), 3.8 – 3.84 (2H, m, NC**H**$_2$), 2.68 – 2.65 (2H, m, C**H**$_2$), 1.90 – 1.85 (2H, m, C**H**$_2$), 1.82 – 1.75 (2H, m, C**H**$_2$), 1.67 – 1.61 (2H, m, C**H**$_2$), 1.51 – 1.45 (2H, m, C**H**$_2$), 1.42 – 1.36 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 180.4 (**C**O), 168.6 (**C**O), 131.1 (**C**HCHH'), 128.0 (CH**C**HH'), 45.0 (**C**H$_2$), 38.8 (**C**H$_2$), 28.5 (**C**H$_2$), 28.1 (**C**H$_2$), 26.0 (**C**H$_2$), 25.5 (**C**H$_2$), 21.3 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{11}H_{17}NNaO_2$, 218.1152. Found [MNa]$^+$, 218.1151 (−0.3 ppm error).

5-(Benzyloxy)-1,5-diazacyclotridecane-2,6-dione (10a)



To a solution of 1-acryloylazonan-2-one **3d** (155 mg, 0.80 mmol) in dry methanol (1.6 mL) was added benzyl-o-hydroxylamine (100 µL, 0.9 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (137 mg, 54% yield); m.p. 102 – 105 °C; R_f 0.40 (1:19 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3302, 2927, 2860, 2239, 1644, 1548, 1439, 1416, 1359, 1199, 974, 729, 69. δ_H (400 MHz, $CDCl_3$) 7.40 – 7.38 (5H, m, Ar**H**), 6.38 (1H, s, N**H**), 4.83 (2H, s, **C**H$_2$), 3.37 – 3.09 (2H, m, **C**H$_2$), 2.66 – 1.89 (5H, m, **C**H$_2$), 1.76 – 1.59 (2H, m, **C**H$_2$), 1.55 – 1.49 (2H, m, **C**H$_2$), 1.38 – 1.13 (7H, m, **C**H$_2$); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 170.2 (**C**O), 134.2 (**C**Ar), 129.3 (Ar**C**H), 129.2 (Ar**C**H), 128.9 (Ar**C**H), 76.3 (**C**H$_2$), 42.0 (**C**H$_2$), 39.8 (**C**H$_2$), 34.6 (**C**H$_2$), 31.6 (**C**H$_2$), 27.6 (**C**H$_2$), 26.6 (**C**H$_2$), 26.9 (**C**H$_2$), 25.4 (**C**H$_2$), 22.5 (**C**H$_2$); **HRMS (ESI)**: calcd. for $C_{18}H_{26}N_2NaO_3$, 341.1838. Found [MNa]$^+$ 341.1836 (−0.8 ppm error).

5-(2-(Benzyloxy)ethyl)-1,5-diazacyclotridecane-2,6-dione (10b)

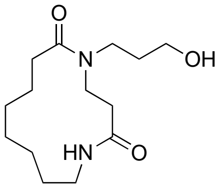


To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 2-(benzyloxy)-1-ethanamine (80 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (94 mg, 54% yield); m.p. 117 − 119 °C; R_f 0.50 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3087, 2927, 2858, 2239, 1622, 1552, 1454, 1359, 1100, 1028, 908, 733, 698, 600. In solution in $CDCl_3$, the product exists as a roughly 2:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.37 – 7.31 (5H, m, Ar**H**), 6.68 (1H, s, N**H**), 4.49 (2H, s, **C**H_2), 3.60 – 3.59 (1H, m, **C**H_2), 3.57 – 3.54 (2H, m, **C**H_2), 3.52 – 3.50 (1H, m, **C**H_2), 2.63 (2H, m, **C**H_2), 2.40 – 2.37 (2H, m, **C**H_2), 1.73 – 1.67 (2H, m, **C**H_2), 1.54 – 1.51 (2H, m, **C**H_2), 1.38 – 1.30 (6H, m, 3 x **C**H_2), 1.26 – 1.20 (4H, m, 2 x **C**H_2); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**O), 170.6 (**C**O), 137.9 (**C**Ar), 128.6 (Ar**C**H), 128.0 (Ar**C**H), 127.6 (Ar**C**H), 73.4 (NO**C**HH'), 68.0 (**C**H_2), 49.0 (**C**H_2), 42.5 (**C**H_2), 39.7 (**C**H_2), 35.2 (**C**H_2), 32.7 (**C**H_2), 27.9 (**C**H_2), 27.1 (**C**H_2), 26.9 (**C**H_2), 25.7 (**C**H_2), 23.8 (**C**H_2); **HRMS (ESI)**: calcd. for $C_{20}H_{30}N_2NaO_3$, 369.2144. Found [MNa]$^+$ 369.2149 (1.2 ppm error).

NMR data for the minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 7.29 – 7.26 (5H, m, Ar**H**), 6.33 – 6.32 (1H, m, N**H**), 4.52 (2H, s, **C**H_2), 3.84 – 3.82 (2H, m, **C**H_2), 3.60 – 3.59 (2H, m, **C**H_2), 2.94 – 2.93 (2H, m, **C**H_2), 2.31 – 2.28 (2H, m, **C**H_2); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 171.3 (**C**O), 137.2 (**C**Ar), 128.8 (Ar**C**H), 128.4 (Ar**C**H), 127.9 (Ar**C**H), 73.7 (NO**C**HH'), 68.9 (**C**H_2), 47.5 (**C**H_2), 38.2 (**C**H_2), 37.0 (**C**H_2), 30.3 (**C**H_2), 26.7 (**C**H_2), 26.5 (**C**H_2), 25.0 (**C**H_2), 24.8 (**C**H_2), 23.3 (**C**H_2).

For LCMS data confirming this product has >95% purity, see SI Section 5.

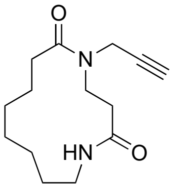
5-(3-Hydroxypropyl)-1,5-diazacyclotridecane-2,6-dione (10c)



To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 3-aminopropan-1-ol (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (73.9 mg, 55% yield); m.p. 100 – 105 °C; R_f 0.55 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3290, 2928, 2861, 1619, 1557, 1435, 1360, 1300, 1193, 1056, 701. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.94 – 6.92 (1H, m, N**H**), 3.65 – 3.62 (2H, m, C**H**$_2$), 3.50 – 3.45 (3H, m, C**H**$_2$), 2.63 (2H, s, C**H**$_2$), 2.39 – 2.31 (3H, m, C**H**$_2$), 1.81 – 1.63 (5H, m, C**H**$_2$), 1.53 – 1.50 (2H, m, C**H**$_2$), 1.38 – 1.37 (2H, m, C**H**$_2$), 1.34 – 1.28 (3H, m, C**H**$_2$), 1.25 – 1.21 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.7 (**C**O), 170.8 (**C**O), 59.4 (**C**H$_2$), 46.3 (**C**H$_2$), 42.2 (**C**H$_2$), 39.8 (**C**H$_2$), 35.1 (**C**H$_2$), 32.5 (**C**H$_2$), 31.7 (**C**H$_2$), 27.9 (**C**H$_2$), 27.1 (**C**H$_2$), 26.8 (**C**H$_2$), 25.7 (**C**H$_2$), 23.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{14}H_{26}N_2NaO_3$, 293.1839. Found: $[MNa]^+$, 293.1836 (−1.2 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.37 – 6.34 (1H, m, N**H**), 3.68 – 3.66 (2H, m, C**H**$_2$), 3.40 – 3.36 (2H, m, C**H**$_2$), 1.68 – 1.63 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.1 (**C**O), 171.3 (**C**O), 58.5 (**C**H$_2$), 43.9 (**C**H$_2$), 41.9 (**C**H$_2$), 38.1 (**C**H$_2$), 36.6 (**C**H$_2$), 30.0 (**C**H$_2$), 29.8 (**C**H$_2$), 26.6 (**C**H$_2$), 25.1 (**C**H$_2$), 24.8 (**C**H$_2$), 24.5 (**C**H$_2$), 22.6 (**C**H$_2$).
For LCMS data confirming this product has >95% purity, see SI Section 5.

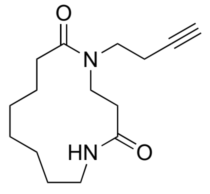
5-(Prop-2-yn-1-yl)-1,5-diazacyclotridecane-2,6-dione (10d)



To a solution of 1-acryloylazonan-2-one **3d** (123 mg, 0.63 mmol) in dry methanol (1.3 mL) was added 2-propylamine (50 µL, 0.69 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (99 mg, 63% yield); m.p. 125-128 °C; R_f 0.54 (2:3 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3304, 2929, 2860, 2243, 1631, 1552, 1441, 1418, 1372, 1359, 1287, 1229, 906, 728, 647. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.73 (1H, s, N**H**), 4.22 – 4.13 (3H, m, C**H**$_2$), 2.66 – 2.63 (2H , m, C**H**$_2$), 2.42 – 2.41 (2H, m, C**H**$_2$), 2.33 – 2.29 (1H, m, C**H**), 1.78 – 1.67 (3H, m, C**H**$_2$), 1.60 – 1.49 (4H, m, 2 x C**H**$_2$), 1.42 (2H, s, C**H**$_2$), 1.29 – 1.24 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 170.3 (**C**O), 78.4 (**C**CH), 73.0 (C**C**H), 42.4 (**C**H$_2$), 39.6 (**C**H$_2$), 38.8 (**C**H$_2$), 35.1 (**C**H$_2$), 32.9 (**C**H$_2$), 27.8 (**C**H$_2$), 27.1 (**C**H$_2$), 27.0 (**C**H$_2$), 25.5 (**C**H$_2$), 23.6 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{14}H_{22}N_2NaO_2$, 273.1567. Found: [MNa]$^+$, 273.1573 (2.4 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.05 (1H, s, N**H**); δ_C (100 MHz, $CDCl_3$) 173.1 (**C**O), 171.1 (**C**O), 80.7 (**C**CH), 71.7 (C**C**H), 45.2 (**C**H$_2$), 38.5 (**C**H$_2$), 36.7 (**C**H$_2$), 29.9 (**C**H$_2$), 26.8 (**C**H$_2$), 25.7 (**C**H$_2$), 25.0 (**C**H$_2$), 24.8 (**C**H$_2$), 22.9 (**C**H$_2$). For LCMS data confirming this product has >95% purity, see SI Section 5.

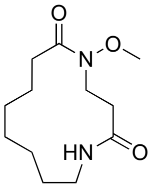
5-(But-3-yn-1-yl)-1,5-diazacyclotridecane-2,6-dione (10e)



To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added but-3-yn-1-amine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (72.3 mg, 55% yield); m.p. 115 – 118 °C; R_f 0.60 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3303, 3089, 2928, 2859, 2239, 1623, 1552, 1455, 1422, 1360, 1252, 1021, 1063, 1021, 921, 729, 644. In solution in $CDCl_3$, the product exists as a 7:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.54 (1H, s, N**H**), 3.60 (2H, s, C**H**$_2$), 2.78 – 2.65 (2H, m, C**H**$_2$), 2.44 – 2.31 (5H, m, C**H**$_2$), 2.00 – 1.99 (1H, m, C**H**), 1.76 – 1.70 (2H, m, C**H**$_2$), 1.61 – 1.52 (3H, m, C**H**$_2$), 1.37 – 1.22 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.5 (**C**O), 170.6 (**C**O), 80.4 (**C**CH), 71.1 (C**C**H), 48.1 (**C**H_2), 42.7 (**C**H_2), 39.7 (**C**H_2), 35.0 (**C**H_2), 32.7 (**C**H_2), 27.9 (**C**H_2), 27.2 (**C**H_2), 27.0 (**C**H_2), 25.9 (**C**H_2), 24.2 (**C**H_2), 18.8 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{15}H_{24}N_2NaO_2$, 287.1723. Found: $[MNa]^+$, 287.1730 (2.5 ppm error).

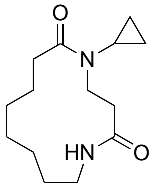
Characteristic ^{13}C NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.09 (1H, s, N**H**), 3.74 – 3.71 (2H, m, C**H₂**), 3.44 – 3.41 (2H, m, C**H₂**), 3.39 – 3.36 (2H, m, C**H₂**), 2.57 – 2.53 (2H, m, C**H₂**), 1.69 – 1.64 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 171.3 (**C**O), 83.8 (**C**CH), 69.9 (C**C**H), 46.3 (**C**H_2), 45.9 (**C**H_2), 38.1 (**C**H_2), 37.3 (**C**H_2), 29.8 (**C**H_2), 26.7 (**C**H_2), 25.4 (**C**H_2), 24.9 (**C**H_2), 24.4 (**C**H_2), 22.8 (**C**H_2), 17.7 (**C**H_2).

5-Methoxy-1,5-diazacyclotridecane-2,6-dione (10f)



To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.6 mL) was added methoxyamine (63 mg, 0.75 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (49.1 mg, 41% yield); m.p. 99 – 101 °C; R_f 0.29 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3302, 3088, 2929, 2860, 2241, 1643, 1548, 1437, 1416, 1359, 1202, 1055, 999, 905, 728. The ^1H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 6.39 – 6.38 (1H, m, N**H**), 4.31- 3.00 (7H, m, C**H₃** and 2 x C**H₂**), 2.67 – 2.20 (4H, m, 2 x C**H₂**), 1.90 – 1.63 (2H, m, C**H₂**), 1.55 – 1.49 (2H, m, C**H₂**), 1.41 (2H, s, C**H₂**), 1.35 – 1.30 (2H, m, C**H₂**), 1.28 – 1.23 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 170.2 (**C**O), 61.4 (**C**H_3), 39.8 (**C**H_2), 34.6 (**C**H_2), 31.4 (**C**H_2), 27.6 (**C**H_2), 26.74 (**C**H_2), 26.7 (**C**H_2), 25.4 (**C**H_2), 22.5 (**C**H_2), 21.9 (**C**H_2). **HRMS (ESI)**: calcd. for $C_{12}H_{22}N_2NaO_3$, 265.1522. Found: $[MNa]^+$, 265.1523 (0.4 ppm error).

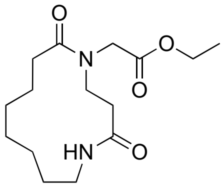
5-Cyclopropyl-1,5-diazacyclotridecane-2,6-dione (10g)



To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added cyclopropylamine (40 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (57.1 mg, 45% yield); m.p. 125 – 130 °C; R$_f$ 0.50 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3088, 2926, 2857, 2235, 1632, 1549, 1444, 1410, 1364, 1267, 1157, 1060, 1031, 922, 729, 644. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, CDCl$_3$) 6.52 (1H, s, N**H**), 3.49 – 3.13 (2H , m, C**H**$_2$), 2.75 – 2.70 (1H, m, C**H**), 2.69 – 2.66 (2H , m, C**H**$_2$), 1.95 – 1.70 (2H, m, C**H**$_2$), 1.64 – 1.62 (2H, m, C**H**$_2$), 1.59 – 1.53 (2H, m, C**H**$_2$), 1.40 – 1.19 (8H, m, 4 x C**H**$_2$), 0.97 – 0.94 (2H, m, CHC**H**$_2$), 0.77 – 0.76 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 177.3 (**C**O), 170.7 (**C**O), 42.0 (**C**H$_2$), 39.7 (**C**H$_2$), 35.2 (**C**H$_2$), 33.4 (**C**H$_2$), 30.3 (**C**H), 28.1 (**C**H$_2$), 26.8 (**C**H$_2$), 26.9 (**C**H$_2$), 26.0 (**C**H$_2$), 22.9 (**C**H$_2$), 6.7 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{14}H_{24}N_2NaO_2$, 275.1730. Found: [MNa]$^+$, 275.1730 (0.1 ppm error).

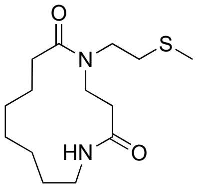
For LCMS data confirming this product has >95% purity, see SI Section 5.

Ethyl 2-(4,13-dioxo-1,5-diazacyclotridecan-1-yl)acetate (10h)



To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added glycine ethyl ester (77 mg, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a pale yellow solid (67 mg, 45% yield); m.p. 104 – 107 °C; R$_f$ 0.48 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3314, 3087, 2930, 2861, 2240, 1739, 1635, 1548, 1440, 1206, 1319, 1211, 1171, 1099, 921, 729; δ_H (400 MHz, CDCl$_3$) 7.13 (1H, s, N**H**), 3.98 – 3.95 (1H, m, CH$_2$), 3.91 – 3.85 (1H, m, C**H**$_2$), 3.76 (2H, s, C**H**$_2$), 3.58 – 3.52 (1H, m, C**H**$_2$), 3.47 – 3.40 (1H, m, C**H**$_2$), 3.20 – 3.13 (1H, m, C**H**$_2$), 2.42 – 2.33 (3H, m, C**H**$_2$), 2.32 – 2.28 (1H, m, C**H**$_2$), 1.85 – 1.77 (1H, m, C**H**$_2$), 1.61 – 1.50 (4H, m, 2 x C**H**$_2$), 1.47 – 1.46 (3H, m, C**H**$_3$), 1.41 – 1.37 (2H, m, C**H**$_2$), 1.33 – 1.30 (4H, m, 2 x C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 173.5 (**C**O), 172.8 (**C**O), 171.0 (**C**O), 55.4 (**C**H$_2$), 52.8 (**C**H$_2$COO), 44.0 (**C**H$_2$), 39.1 (**C**H$_2$), 37.2 (**C**H$_2$), 30.1 (**C**H$_2$), 26.2 (**C**H$_2$), 26.1 (**C**H$_2$), 25.0 (**C**H$_2$), 24.4 (**C**H$_2$), 22.5 (**C**H$_2$), 13.9 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{15}H_{26}N_2NaO_4$, 321.1786. Found: [MNa]$^+$, 321.1785 (−0.5 ppm error).

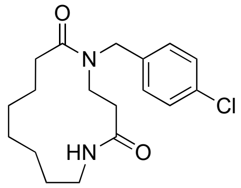
5-(2-(Methylthio)ethyl)-1,5-diazacyclotridecane-2,6-dione (10i)



To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 2-(methylthio)ethylamine (50 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (77.9 mg, 54% yield); m.p. 101 – 105 °C; R$_f$ 0.54 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3299, 2922, 2859, 1623, 1552, 1428, 1359, 1299, 1231, 729. In solution in CDCl$_3$, the product exists as a 6:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, CDCl$_3$) 6.51 (1H, s, N**H**), 3.69 – 3.37 (4H, m, 2 x C**H**$_2$), 2.66 – 2.61 (4H, m, 2 x C**H**$_2$), 2.34 – 2.30 (2H, m, C**H**$_2$), 2.13 (3H, s, C**H**$_3$), 1.78 – 1.71 (2H, m, C**H**$_2$), 1.55 – 1.52 (2H, m, C**H**$_2$), 1.38 – 1.22 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 175.3 (**C**O), 174.0 (**C**O), 49.2 (**C**H$_2$), 42.9 (**C**H$_2$), 39.7 (**C**H$_2$), 35.2 (**C**H$_2$), 32.8 (**C**H$_2$), 32.5 (**C**H$_2$), 28.0 (**C**H$_2$), 27.2 (**C**H$_2$), 26.9 (**C**H$_2$), 25.9 (**C**H$_2$), 24.1 (**C**H$_2$), 16.0 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{14}H_{26}N_2NaO_2S$, 309.1607. Found: [MNa]$^+$, 309.1607 (0.0 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, CDCl$_3$) 6.21 – 6.20 (1H, m, N**H**); δ_C (100 MHz, CDCl$_3$) 170.5 (**C**O), 171.3 (**C**O), 46.4 (**C**H$_2$), 45.8 (**C**H$_2$), 38.1 (**C**H$_2$), 37.3 (**C**H$_2$), 32.0 (**C**H$_2$), 29.8 (**C**H$_2$), 26.7 (**C**H$_2$), 25.5 (**C**H$_2$), 24.9 (**C**H$_2$), 24.4 (**C**H$_2$), 22.9 (**C**H$_2$), 15.6 (**C**H$_3$).

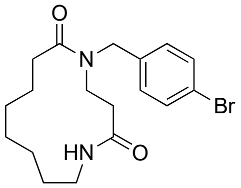
5-(4-Chlorobenzyl)-1,5-diazacyclotridecane-2,6-dione (10j)



To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 4-chlorobenzylamine (70 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (128.6 mg, 76% yield); m.p. 149 – 152 °C; R_f 0.66 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3299, 2929, 2859, 2238, 1628, 1553, 1491, 1443, 1407, 1359, 1091, 1014, 915, 729. In solution in $CDCl_3$, the product exists as a 8:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.33 – 7.29 (2H, m, Ar**H**), 7.09 – 7.06 (2H, m, Ar**H**), 6.59 (1H, s, N**H**), 4.65 – 4.57 (2H, m, C**HH'**Ph), 3.69 – 3.20 (3H, m, C**H**$_2$), 2.88 – 2.72 (3H, m, C**H**$_2$), 2.54 – 2.40 (2H, m, C**H**$_2$), 2.67 (2H, s, C**H**$_2$), 2.31 – 2.24 (2H, m, C**H**$_2$), 1.78 – 1.71 (2H, m, C**H**$_2$), 1.58 – 1.53 (2H, m, C**H**$_2$), 1.43 – 1.29 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 170.6 (**C**O), 135.3 (**C**Ar), 133.6 (**C**Ar), 129.2 (Ar**C**H), 127.8 (Ar**C**H), 52.4 (**C**H$_2$), 42.8 (**C**H$_2$), 39.7 (**C**H$_2$), 35.0 (**C**H$_2$), 32.8 (**C**H$_2$), 27.9 (**C**H$_2$), 27.3 (**C**H$_2$), 27.1 (**C**H$_2$), 25.9 (**C**H$_2$), 24.2 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{18}H_{25}ClN_2NaO_2$, 359.1492. Found: $[MNa]^+$, 359.1497 (1.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.45 – 5.43 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 171.0 (**C**O), 137.0 (**C**Ar), 133.5 (**C**Ar), 129.8 (Ar**C**H), 128.9 (Ar**C**H), 48.6 (**C**H$_2$), 44.4 (**C**H$_2$), 38.3 (**C**H$_2$), 36.7 (**C**H$_2$), 29.9 (**C**H$_2$), 26.8 (**C**H$_2$), 25.4 (**C**H$_2$), 25.2 (**C**H$_2$), 24.7 (**C**H$_2$), 22.9 (**C**H$_2$).

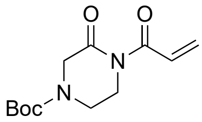
5-(4-Bromobenzyl)-1,5-diazacyclotridecane-2,6-dione (10k)



To a solution of 1-acryloylazonan-2-one **3d** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 4-bromobenzylamine (700 µL, 0.55 mmol). The reaction was stirred for 4 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (101.7 mg, 53% yield); m.p. 159 – 162 °C; R_f 0.66 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3088, 2929, 2860, 1633, 1554, 1488, 1446, 1359, 1230, 1071, 1011, 919, 797, 731. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 8:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.45 – 7.39 (2H, m, Ar**H**), 6.70 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.76 – 6.74 (1H, m, N**H**), 4.63 – 4.53 (2H, m, C**H**$_2$), 4.00 – 2.97 (4H, m, 2 x C**H**$_2$), 2.84 – 2.49 (2H, m, C**H**$_2$), 2.28 – 2.25 (2H, m, C**H**$_2$), 1.75 – 1.69 (2H, m, C**H**$_2$), 1.61 – 1.51 (2H, m, C**H**$_2$), 1.39 – 1.28 (6H, m, 3 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 170.6 (**C**O), 135.9 (**C**Ar), 132.1 (Ar**C**H), 128.1 (Ar**C**H), 121.5 (**C**Ar), 52.6 (**C**H$_2$), 43.0 (**C**H$_2$), 39.6 (**C**H$_2$), 34.8 (**C**H$_2$), 32.8 (**C**H$_2$), 27.9 (**C**H$_2$), 27.2 (**C**H$_2$), 27.1 (**C**H$_2$), 25.9 (**C**H$_2$), 24.3 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{18}H_{25}{}^{79}BrN_2NaO_2$, 403.0993. Found: $[MNa]^+$, 403.0992 (−0.3 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.79 – 5.76 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 173.8 (**C**O), 171.1 (**C**O), 137.3 (**C**Ar), 131.8 (Ar**C**H), 130.1 (Ar**C**H), 121.4 (**C**Ar), 48.4 (**C**H$_2$), 44.2 (**C**H$_2$), 38.2 (**C**H$_2$), 36.5 (**C**H$_2$), 29.9 (**C**H$_2$), 26.7 (**C**H$_2$), 25.3 (**C**H$_2$), 25.2 (**C**H$_2$), 24.7 (**C**H$_2$), 22.8 (**C**H$_2$).

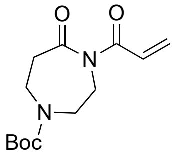
***tert*-Butyl 4-acryloyl-3-oxopiperazine-1-carboxylate (3e)**



To a stirring solution of *tert*-butyl 3-oxopiperazine-1-carboxylate (1.00 g, 5.00 mmol) in dry THF (18 mL) cooled to 0 °C was added a solution of MeMgBr (3M in diethyl ether, 1.8 mL, 5.5 mmol) *via* dropwise using a syringe pump over 30 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (0.6 mL, 7.5 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (35 mL) and extracted with Et_2O (35 mL). The combined organics were washed with saturated aq. $NaHCO_3$ solution (2 x 35 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether:hexane) to afford the title compound as a colourless oil (905 mg, 71% yield); R_f 0.51 (1:1 diethyl ether:hexane). **IR** (ATR): ν_{max}/cm^{-1} 2977, 2934, 1686, 1477, 1407, 1390, 1305, 1366, 1243, 1163, 1133, 1022, 919, 864, 796, 769 609; δ_H (400 MHz, $CDCl_3$) 7.14 (1H, dd, *J* = 16.9, 10.4 Hz, NCOC**H**CHH’), 6.42 (1H, dd,

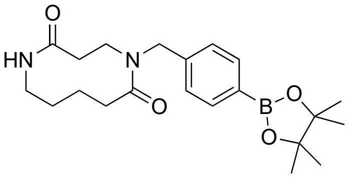
J = 16.9, 1.5 Hz, NCOCHC**H**H’), 5.81 (1H, dd, J = 10.4, 1.5 Hz, CHCH**H**’), 4.23 (2H, s, C**H**$_2$), 3.90 – 3.87 (2H, m, C**H**$_2$), 3.64 – 3.62 (2H, m, C**H**$_2$), 1.47 (9H, s, 3 x CH$_3$); δ_C (100 MHz, CDCl$_3$) 168.8 (**C**O), 168.1 (**C**O), 153.7 (*t*-BuO-**C**O), 131.1 (**C**HCHH’), 130.3 (CH**C**HH’), 81.3 (COO**C**), 49.2 (**C**H$_2$), 42.3 (**C**H$_2$), 40.8 (**C**H$_2$), 28.4 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{12}H_{18}N_2NaO_4$, 277.1159. Found: [MNa]$^+$, 277.1159 (0.1 ppm error).

***tert*-Butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate (3f)**



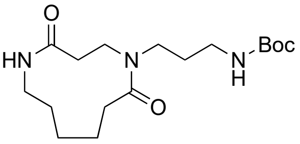
A solution of *tert*-butyl 5-oxo-1,4-diazepane-1-carboxylate (2.0 g, 9.3 mmol) in dry THF (34 mL) was cooled to 0 °C and a solution of MeMgBr (3M in diethyl ether, 3.4 mL, 10.3 mmol) was added *via* dropwise using a syringe pump over 30 min. The reaction was stirred for 10 min at 0 °C, then acryloyl chloride (1.2 mL, 14.0 mmol) was added and the reaction was stirred 30 min at 0 °C. The reaction was quenched with saturated aq. NH_4Cl solution (30 mL) and extracted with Et_2O (30 mL). The combined organics were washed with saturated $NaHCO_3$ solution (2 x 30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified with flash column chromatography (1:1 diethyl ether:hexane → 2:1 diethyl ether:hexane) to afford the title compound as a white solid (1.9 gram, 76% yield); m.p. 70 – 74 °C; R_f 0.36 (2:1 diethyl ether:hexane). **IR** (ATR): ν_{max} /cm^{-1} 3357, 2977, 2933, 1682, 1561, 1420, 1405, 1366, 1329, 1242, 1161, 1116, 1042, 957, 864, 795, 770, 585; δ_H (400 MHz, CDCl$_3$) 6.93 (1H, dd, J = 16.8, 10.3 Hz, C**H**CHH’), 6.40 (1H, dd, J = 16.8, 1.5 Hz, CHC**H**H’), 5.73 (1H, dd, J = 10.3, 1.5 Hz, CHCH**H**’), 4.00 – 3.98 (2H, m, C**H**$_2$), 3.67 – 3.59 (4H, m, 2 x C**H**$_2$), 2.84 – 2.81 (2H, m, C**H**$_2$), 1.45 (9H, s, 3 x CH$_3$); δ_C (100 MHz, CDCl$_3$) 176.0 (**C**O), 168.5 (**C**O), 154.6 (*t*-BuO-**C**O), 131.3 (**C**HCHH’), 129.1 (CH**C**HH’), 80.9 (**C**CH$_3$), 47.5 (**C**H$_2$), 44.1 (**C**H$_2$), 41.4 (2 x **C**H$_2$, overlapping), 28.4 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{13}H_{20}N_2NaO_4$, 291.1310. Found: [MNa]$^+$, 291.1315 (1.7 ppm error).

5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,5-diazecane-2,6-dione (7l)



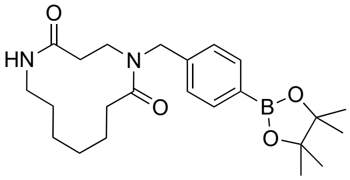
To a solution of 1-acryloyl-piperidin-2-one **3a** (77 mg, 0.50 mmol) in dry methanol (1.0 mL) was added (4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (128 mg, 0.55 mmol). The reaction was stirred for 18 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (139.6 mg, 72% yield); m.p. 180–186 °C; R_f 0.62 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3298, 3093, 2978, 2932, 2176, 1613, 1561, 1444, 1405, 1360, 1272, 1209, 1143, 1088, 963, 859, 727, 659; δ_H (400 MHz, $CDCl_3$) 7.74 – 7.72 (2H, m, Ar**H**), 7.30 – 7.22 (2H, m, Ar**H**), 5.71 – 5.52 (1H, m, N**H**), 4.90 – 4.83 (1H, m, C**H**H'Ph), 4.46 – 4.33 (1H, m, CH**H'**Ph), 3.93 – 3.86 (1H, m, C**H**$_2$), 3.74 (1H, s, C**H**$_2$), 3.39 – 3.20 (1H, m, C**H**$_2$), 2.90 – 2.81 (1H, m, C**H**$_2$), 2.74 – 2.62 (1H, m, C**H**$_2$), 2.13 – 1.94 (4H, m, 2 x C**H**$_2$), 1.72 – 1.45 (3H, m, C**H**$_2$), 1.30 – 1.29 (12H, m, 4 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 171.1 (**C**O), 141.3 (**C**Ar), 135.4 (ArCH), 127.5 (Ar**C**H), 126.1 (**C**Ar), 83.9 (**C**CH$_3$), 49.5 (**C**HH'Ph), 45.4 (**C**H$_2$), 39.2 (**C**H$_2$), 37.5 (**C**H$_2$), 28.2 (**C**H$_2$), 25.9 (**C**H$_2$), 24.9 (**C**H$_3$), 23.9 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{21}H_{31}BN_2NaO_4$, 409.2275. Found: [MNa]$^+$, 409.2269 (−0.6 ppm error).

tert-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate (8m)



To a solution of 1-acryloylazepan-2-one **xx** (1.47 g, 8.8 mmol) in dry methanol (17.5 mL) was added *N*-Boc-1,3-diaminopropane (1.68 g, 9.7 mmol). The reaction was stirred for 18 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a off-white solid (2.50 g, 83% yield); m.p. 108 – 111 °C; R_f 0.60 (1:4 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3305, 2934, 1690, 1623, 1454, 1365, 1250, 1169. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 6.92 – 6.90 (1H, m, N**H**), 5.27 (1H, s, N**H**), 3.72 – 3.42 (2H, m, C**H**$_2$), 3.33 – 2.90 (5H, m, C**H**$_2$), 2.60 – 2.32 (4H, m, 2 x C**H**$_2$), 2.09 – 1.95 (1H, m, C**H**$_2$), 1.73 – 1.62 (6H, m, 3 x C**H**$_2$), 1.38 (11H, m, C**H**$_2$ and 3 x C**H**$_3$); δ_C (100 MHz, CDCl$_3$) 174.1 (**C**O), 171.7 (**C**O), 156.4 (**C**O), 79.3 (**C**CH$_3$), 45.7 (**C**H$_2$), 43.5 (**C**H$_2$), 41.4 (**C**H$_2$), 37.9 (overlapping, 2 x **C**H$_2$), 29.0 (**C**H$_2$), 28.5 (overlapping **C**H$_2$ and **C**H$_3$), 25.3 (**C**H$_2$), 24.3 (**C**H$_2$), 22.5 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{17}H_{31}N_3NaO_4$, 364.2204. Found: [MNa]$^+$, 364.2207 (0.8 ppm error).

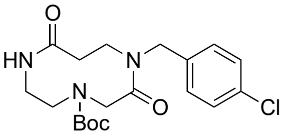
5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,5-diazacyclododecane-2,6-dione (9l)



To a solution of 1-acryloylazonan-2-one **3c** (98 mg, 0.50 mmol) in dry methanol (1.0 mL) was added (4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (128 mg, 0.55 mmol). The reaction was stirred for 18 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate) to afford the title compound as a white solid (120.1 mg, 58% yield). In solution in CDCl$_3$, this compound exists as a 6:1 mixture of 2 rotamers; m.p. 77 – 80 °C; R$_f$ 0.61 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3085, 2978, 2931, 1645, 1614, 1556, 1456, 1406, 1361, 1273, 1214, 1144, 1089, 1021, 963, 859, 657; NMR data for the major rotamer only: δ_H (400 MHz, CDCl$_3$) 7.78 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.14 (2H, d, *J* = 7.9 Hz, Ar**H**), 6.44 – 6.42 (1H, m, N**H**), 4.90 (1H, d, *J* = 17.1 Hz, C**H**H'Ph), 4.53 (1H, ddd, *J* = 14.2, 9.3, 5.1 Hz, C**H**$_2$), 4.42 (1H, d, *J* = 17.1 Hz, CH**H'**Ph), 3.79 – 3.70 (1H, m, C**H**$_2$), 2.89 – 2.83 (2H, m, C**H**$_2$), 2.80 – 2.74 (1H, m, C**H**$_2$), 2.60 – 2.53 (1H, m, C**H**$_2$), 2.49 – 2.43 (1H, m, C**H**$_2$), 2.14 – 2.03 (2H, m, C**H**$_2$), 1.61 – 1.41 (6H, m, 3 x C**H**$_2$), 1.33 (12H, s, 4 x C**H**$_3$), 1.17 – 1.12 (1H, m, C**H**$_2$); δ_C (100 MHz, CDCl$_3$) 176.1 (**C**O), 170.3 (**C**O), 139.7 (**C**Ar), 135.5 (**C**Ar), 128.0 (Ar**C**H), 125.8 (Ar**C**H), 84.0 (**C**CH$_3$), 52.0 (**C**HH'Ph), 41.1 (**C**H$_2$), 39.2 (**C**H$_2$), 35.2 (**C**H$_2$), 32.5 (**C**H$_2$), 27.4 (**C**H$_2$), 25.8 (**C**H$_2$), 25.0 (**C**H$_3$), 23.9 (**C**H$_2$), 22.2 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{23}H_{35}BN_2NaO_4$, 437.2592. Found: [MNa]$^+$, 437.2582 (−1.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, CDCl$_3$) 175.0 (**C**O), 170.9 (**C**O), 141.9 (**C**Ar), 135.3 (**C**Ar), 127.2 (Ar**C**H), 49.6 (**C**H$_2$), 45.6 (**C**H$_2$), 37.1 (**C**H$_2$), 36.8 (**C**H$_2$), 31.0 (**C**H$_2$), 26.8 (**C**H$_2$), 24.7 (**C**H$_3$), 23.6 (**C**H$_2$), 22.6 (**C**H$_2$).

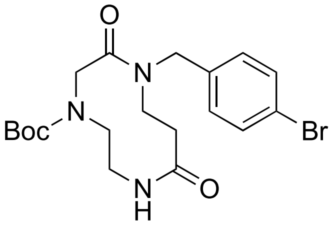
tert-Butyl 1-(4-chlorobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (11j)



To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylayte **3e** (127 mg, 0.50 mmol) in dry methanol (1.0 mL) was added 4-chlorobenzylamine (78 mg, 0.55 mmol). The reaction was stirred for 18 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:99 methanol: ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (167.8 mg, 69% yield); m.p. 77 – 80 °C; R_f 0.60 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3086, 2977, 2246, 1653, 1547, 1406, 1366, 1245, 1160, 1128, 1091, 726, 646. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. The ratio could not be determined due to the presence of a complex mixture of rotamers. NMR data for the major rotamer only: δ_H (400 MHz, $CDCl_3$) 7.26 – 7.24 (2H, m Ar**H**), 7.10 – 7.08 (2H, m, Ar**H**), 5.85 – 5.83 (1H, m, N**H**), 5.08 (1H, d, *J* = 16.5 Hz, C**H**H'), 4.99 – 4.95 (1H, m, C**H**$_2$), 4.22 – 4.16 (2H, m, C**H**$_2$), 4.10 – 4.06 (1H, m, CH**H'**), 3.72 – 3.68 (1H, m, C**H**$_2$), 3.25 – 3.21 (1H, m, C**H**$_2$), 3.02 – 2.99 (1H, m, C**H**$_2$), 2.96 – 2.91 (1H, m, C**H**$_2$), 2.84 – 2.80 (1H, m, C**H**$_2$), 2.76 – 2.69 (1H, m, C**H**$_2$), 2.47 – 2.40 (1H, m, C**H**$_2$), 1.47 (9H, s, 3 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 170.7 (**C**O), 155.1 (*t*-BuO-**C**O), 135.5 (**C**Ar), 133.4 (**C**Ar), 129.0 (Ar**C**H), 128.5 (ArCH), 81.4 (**C**CH$_3$), 52.3 (**C**H$_2$), 51.6 (**C**H$_2$), 49.2 (**C**H$_2$), 41.7 (**C**H$_2$), 38.8 (**C**H$_2$), 35.1 (**C**H$_2$), 28.3 (3 x **C**H$_3$). **HRMS (ESI)**: calcd. for $C_{19}H_{26}ClN_3NaO_4$, 418.1496. Found: [MNa]$^+$, 418.1504 (1.9 ppm error).

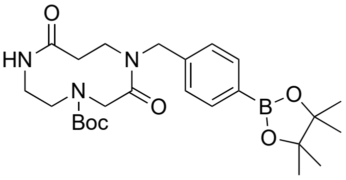
Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 171.8 (**C**O), 154.0 (**C**O), 153.9 (**C**O), 134.9 (**C**Ar), 133.8 (**C**Ar), 129.6 (Ar**C**H), 129.2 (Ar**C**H), 129.1 (ArCH), 128.0 (Ar**C**H), 80.9 (**C**CH$_3$), 52.4 (**C**H$_2$), 42.2 (**C**H$_2$), 41.1 (**C**H$_2$), 38.5 (**C**H$_2$), 34.8 (**C**H$_2$), 28.3 (**C**H$_3$).

***tert*-Butyl 1-(4-bromobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (11k)**



To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylate **3e** (100 mg, 0.393 mmol) in dry methanol (1.0 mL) was added 4-bromobenzylamine (80.5 mg, 0.433 mmol) in a single portion. The reaction mixture was allowed to stir for 4 hours at RT and then the solvent was removed in vacuo. Purification by column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → 3:1 dichloromethane : acetone) afforded the title compound as a white solid (140 mg, 81%). In solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with evidence of 2 minor rotamers also present (≈10:1:1); R_f = 0.27 (3:1 dichloromethane : acetone); m.p. 128–131 °C; vmax/cm–1 (thin film) 1650, 1548, 1405, 1366, 1245, 1161, 1128, 1070, 733; ^1H and ^{13}C NMR data for the major rotamer: δ_H (400 MHz, $CDCl_3$) 7.44 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**, minor rotamer), 7.40 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**, major rotamer), 7.10 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**, minor rotamer), 7.03 (2H, d, *J* = 8.0 Hz, 2 x Ar**H**, major rotamer), 5.84 (1H, d, *J* = 10.5 Hz, N**H**, major rotamer), 5.06 (1H, d, *J* = 16.5 Hz, C$\mathbf{H_2}$, major rotamer), 4.96 (1H, d, *J* = 14.0 Hz, C$\mathbf{H_2}$, major rotamer), 4.28 – 4.10 (2H, m, C$\mathbf{H_2}$, major rotamer), 4.07 (1H, d, *J* = 16.5 Hz, C$\mathbf{H_2}$, major rotamer), 3.69 (1H, dt, *J* = 14.0, 2.5 Hz, C$\mathbf{H_2}$, major rotamer), 3.22 (1H, d, *J* = 14.0 Hz, C$\mathbf{H_2}$, major rotamer), 3.10 – 2.58 (4H, m, 2 x C$\mathbf{H_2}$, both rotamers), 2.43 (1H, ddd, J = 13.0, 8.5, 4.5 Hz, C$\mathbf{H_2}$, major rotamer), 1.47 (9H, s, 3 × C$\mathbf{H_3}$, major rotamer), 1.42 (9H, s, 3 × C$\mathbf{H_3}$, minor rotamer), 1.34 (9H, s, 3 × C$\mathbf{H_3}$, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 172.6 (**C**O), 170.7 (**C**O), 155.1 (**C**O), 136.1 (Ar**C**), 131.9 (Ar**C**), 128.8 (2 × Ar**C**H), 121.5 (2 × Ar**C**H), 81.3 (**C**(CH_3)), 52.3 (**C**H_2), 51.6 (**C**H_2), 49.2 (**C**H_2), 41.7 (**C**H_2), 38.7 (**C**H_2), 35.1 (**C**H_2), 28.3 (3 × **C**H_3); HRMS (ESI) calcd.for $C_{19}H_{27}{}^{79}BrN_3O_4$, 440.1179. Found: $[MNa]^+$, 440.1185 (−1.3 ppm error).

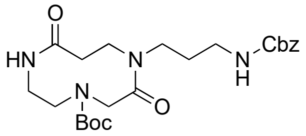
tert-Butyl 2,8-dioxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-7-triazecane-4-carboxylate (11l)



To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylayte **3e** (127 mg, 0.50 mmol) in dry methanol (1.0 mL) was added benzyl(3-aminopropyl)carbamate (156 mg, 0.75 mmol). The reaction was stirred for 18 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:99 methanol: ethyl acetate) to afford the title compound as a white solid (167.8 mg, 69% yield). In solution in $CDCl_3$, this compound exists as a 1:3 mixture of rotamers; m.p. 77 – 80 °C; R_f 0.66 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3085, 2978, 2934, 2247, 1657, 1547, 1488, 1456, 1400, 1359, 1246, 1162, 1143, 1088, 962, 911, 859, 729, 657; NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.73 – 7.71 (2H, m Ar**H**), 7.16 – 7.14 (2H, m, Ar**H**), 5.84 (1H, s, N**H**), 5.15 – 4.97 (2H, m, C**H**$_2$), 4.30 – 4.04 (3H, m, C**H**$_2$), 3.69 – 3.65 (1H, m, C**H**$_2$), 3.27 – 3.24 (1H, m, C**H**$_2$), 3.07 – 2.98 (1H, m, C**H**$_2$), 2.93 – 2.82 (2H, m, C**H**$_2$), 2.70 – 2.69 (1H, m, C**H**$_2$), 2.43 – 2.41 (1H, m, C**H**$_2$), 1.47 – 1.42 (9H, m, 3 x C**H**$_3$), 1.28 (12H, s, 4 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 170.8 (**C**O), 155.1 (*t*-BuO-**C**O), 140.0 (**C**Ar), 135.4 (Ar**C**H), 135.3 (**C**Ar), 126.5 (Ar**C**H), 83.8 (**C**CH$_3$), 81.2 (COO**C**), 52.0 (**C**H$_2$), 51.5 (**C**H$_2$), 49.1 (**C**H$_2$), 41.6 (**C**H$_2$), 38.7 (**C**H$_2$), 35.0 (**C**H$_2$), 28.3 (3 x **C**H$_3$), 24.9 (4 x **C**H$_3$). **HRMS (ESI)**: calcd. for $C_{25}H_{38}BN_3NaO_6$, 510.2760. Found: $[MNa]^+$, 510.2746 (−2.0 ppm error).

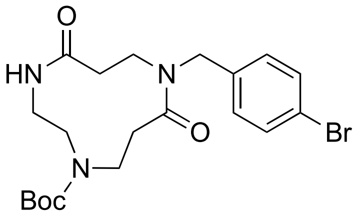
Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 171.8 (**C**O), 154.1 (**C**O), 139.5 (**C**Ar), 83.9 (**C**CH$_3$), 81.3 (COO**C**), 52.3 (**C**H$_2$), 42.2 (**C**H$_2$), 41.0 (**C**H$_2$), 38.4 (**C**H$_2$), 34.8 (**C**H$_2$), 28.3 (**C**H$_3$).

tert-Butyl1-(3-(((benzyloxy)carbonyl)aminopropyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (11n)



To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylayte **3e** (127 mg, 0.50 mmol) in dry methanol (1.0 mL) was added (4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) methanamine (128 mg, 0.55 mmol). The reaction was stirred for 18 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a colourless oil (135.4 mg, 59% yield); R$_f$ 0.40 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3316, 2975, 2935, 2246, 1659, 1536, 1454, 1433, 1405, 1366, 1244, 1157, 911, 728, 697; δ_H (400 MHz, $CDCl_3$) 7.33 – 7.32 (5H, m Ar**H**), 5.63 (1H, s, N**H**), 5.61 (1H, s, N**H**), 5.09 – 5.07 (2H, m, C**H**$_2$), 4.90 (1H, d, *J* = 14.2 Hz, C**H**H'), 4.27 – 4.24 (1H, m, C**H**$_2$), 4.05 – 4.02 (1H, m, C**H**$_2$), 3.77 – 3.69 (2H, m, C**H**$_2$), 3.32 – 3.25 (2H, m, C**H**$_2$), 3.22 – 3.18 (1H, d, *J* = 14.2 Hz, CH**H'**), 3.06 – 3.00 (2H, m, C**H**$_2$), 2.98 – 2.94 (1H, m, C**H**$_2$), 2.86 – 2.82 (1H, m, C**H**$_2$), 2.77 – 2.70 (1H, m, C**H**$_2$), 2.47 – 2.40 (1H, m, C**H**$_2$), 1.80 – 1.75 (1H, m, C**H**$_2$), 1.71 – 1.65 (1H, m, C**H**$_2$), 1.45 (9H, s, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.1 (**C**O), 170.8 (**C**O), 156.7 (**C**O), 155.4 (**C**O), 136.8 (**C**Ar), 128.6 (Ar**C**H), 128.5 (**C**Ar), 128.1 (ArCH), 81.7 (**C**CH$_3$), 66.6 (**C**H$_2$), 51.8 (**C**H$_2$), 49.1 (**C**H$_2$), 47.0 (**C**H$_2$), 42.1 (**C**H$_2$), 38.9 (**C**H$_2$), 38.5 (**C**H$_2$), 35.2 (**C**H$_2$), 29.2 (**C**H$_2$), 28.3 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{23}H_{34}N_4NaO_6$, 485.2377. Found: [MNa]$^+$, 485.2371 (−1.4 ppm error).

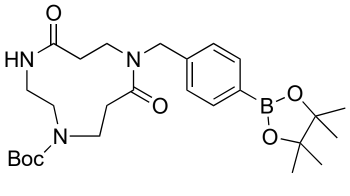
tert-Butyl 8-(4-bromobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (12k)



To a solution of *tert*-butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate **3f** (100 mg, 0.373 mmol) in dry methanol (1.0 mL), was added 4-bromobenzylamine (76.3 mg, 0.410 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed in vacuo. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate:

hexane → 2:1 ethyl acetate: hexane → 3:1 dichloromethane : acetone) afforded the title compound as a white solid (158 mg, 92%). In solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with 2 minor rotamers also evident in the NMR spectra; R_f = 0.21 (3:1 dichloromethane : acetone); m.p. 132–136 °C; vmax/cm–1 (thin film) 3336, 2930, 1641, 1555, 1481, 1455, 1406, 1366, 1352, 1246, 1166, 1139, 1071, 1011, 797, 730; δ_H (400 MHz, $CDCl_3$) 7.50 – 7.36 (2H, m, 2 x Ar**H**, both rotamers), 7.14 (1H, d, *J* = 8.0 Hz, Ar**H**, major rotamer), 7.02 (1H, d, *J* = 8.0 Hz, Ar**H**, minor rotamer), 6.98 (1H, d, *J* = 8.0 Hz, Ar**H**, major rotamer), 5.99 (1H, d, *J* = 10.5 Hz, N**H**, major rotamer), 4.92 – 4.66 (1H, m, C**H₂**, both rotamers), 4.43 – 4.09 (2H, m, C**H₂**, both rotamers), 3.75 (1H, dt, *J* = 13.0, 3.5 Hz, C**H₂**, major rotamer), 3.66 – 3.42 (2H, m, C**H₂**, both rotamers), 3.37 – 3.16 (2H, m, C**H₂**, both rotamers), 2.95 (1H, dt, *J* = 13.5, 7.5 Hz, C**H₂**, major rotamer), 2.90 – 2.70 (2H, m, C**H₂**, major rotamer), 2.45 – 2.35 (1H, m, C**H₂**, major rotamer), 2.30 – 2.17 (1H, m, C**H₂**, major rotamer), 2.09 (1H, dt, *J* = 13.5, 3.5 Hz, C**H₂**, major rotamer), 1.55 – 1.38 (9H, m, 3 x C**H₃**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.7 (**C**O), 171.4 (**C**O), 170.4 (**C**O), 156.5 (Ar**C**), 132.1 (Ar**C**), 129.9 (2 × Ar**C**H), 121.8 (2 x Ar**C**H), 80.4 (**C**(CH_3)), 53.2 (**C**H_2), 52.8 (**C**H_2), 51.8 (**C**H_2), 43.0 (**C**H_2), 39.0 (**C**H_2), 35.3 (**C**H_2), 32.7 (**C**H_2), 28.4 (3 × **C**H_3); HRMS (ESI): calcd. for $C_{20}H_{29}{}^{79}BrN_3O_4$, 454.1336. Found: $[MNa]^+$, 456.1310 (–1.0 ppm error).

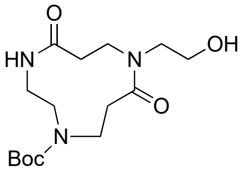
tert-Butyl 5,9-dioxo-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-8-triazacycloundecane-1-carboxylate (12l)



To a solution of *tert*-butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylayte (134 mg, 0.50 mmol) in dry methanol (1.00 mL) was added (4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (128 mg, 0.55 mmol). The reaction was stirred for 18h at rt and then concentrated in *vacuo*. The crude was purified by column chromatography (1:99 methanol: ethyl acetate) to give the title compound as a white solid (180.5 mg, 72% yield); m.p. 54 – 60 °C; R_f 0.66 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3318, 2979, 2933, 2249, 1646, 1548, 1478, 1405, 1359, 1247, 1166, 1142, 906, 858, 726, 648. The ^1H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 5:3:2 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.71 – 7.69 (2H, m, Ar**H**), 7.28 – 7.24 (2H, m, Ar**H**), 6.10 – 6.08 (1H, m, N**H**), 4.90 – 4.74 (1H, m, C**H**$_2$), 4.64 (1H, s, C**H**$_2$), 4.28 – 4.16 (2H, m, C**H**$_2$), 3.59 – 3.51 (2H, m, C**H**$_2$), 3.25 – 3.21 (3H, m, C**H**$_2$), 2.94 – 2.75 (3H, m, C**H**$_2$), 2.15 – 2.07 (2H, m, C**H**$_2$), 1.27 (22H, s, C**H**$_2$ and C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.6 (**C**O), 170.4 (**C**O), 156.4 (*t*-BuO-**C**O), 139.8 (**C**Ar), 135.4 (Ar**C**H), 135.3 (**C**Ar), 125.8 (ArCH), 83.9 (**C**CH$_3$), 79.8 (OO**C**CH$_3$), 53.1 (**C**H$_2$), 53.0 (**C**H$_2$), 51.5 (**C**H$_2$), 42.6 (**C**H$_2$), 38.9 (CH$_2$), 35.2 (**C**H$_2$), 32.6 (**C**H$_2$), 28.3 (**C**H$_3$), 24.8 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{26}H_{40}BN_3NaO_6$, 524.2902. Found: $[MNa]^+$, 524.2916 (−1.7 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.94 – 5.92 (1H, m, N**H**), 5.80 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.5 (**C**O), 156.0 (**C**O), 155.8 (**C**O), 141.7 (**C**Ar), 141.2 (**C**Ar), 139.5 (Ar**C**H), 135.1 (**C**Ar), 127.4 (Ar**C**H), 125.7 (Ar**C**H), 83.8 (**C**CH$_3$), 80.6 (OO**C**CH$_3$), 80.4 (OO**C**CH$_3$), 52.4 (**C**H$_2$), 50.7 (**C**H$_2$), 49.7 (**C**H$_2$), 49.2 (**C**H$_2$), 48.3 (**C**H$_2$), 46.8 (**C**H$_2$), 45.5 (**C**H$_2$), 45.0 (**C**H$_2$), 42.2 (**C**H$_2$), 38.8 (**C**H$_2$), 36.8 (**C**H$_2$), 33.7 (**C**H$_2$), 31.4 (**C**H$_2$), 28.4 (**C**H$_3$).

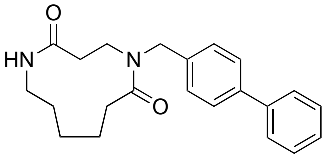
***tert*-Butyl 8-(2-hydroxyethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (12o)**



To a solution of *tert*-butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate **3f** (268 mg, 1.00 mmol) in dry methanol (2.0 mL) was added ethanolamine (70 µL, 1.1 mmol). The reaction was stirred for 18 hours at RT and then concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a yellow oil (155.3 mg, 47% yield). ; R_f 0.47 (1:4 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3299, 2978, 2933, 2864, 2248, 1642, 1476, 1408, 1351, 1247, 1163, 1067, 906, 725, 646; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$) 7.56 (1H, s, N**H**), 4.42 – 4.04 (2H, m, C**H**$_2$), 3.91 – 3.45 (5H , m, C**H**$_2$), 3.38 – 3.23 (3H , m, C**H**$_2$), 3.11 – 2.91 (2H, m, C**H**$_2$), 2.79 – 2.41 (2H, m, C**H**$_2$), 2.33 – 1.98 (2H, m, C**H**$_2$), 1.46 (9H, s, 3 x C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 172.0 (**C**O), 156.5 (**C**O), 80.0 (**C**CH$_3$), 61.4 (**C**H$_2$), 60.5 (**C**H$_2$), 53.1 (**C**H$_2$), 52.7 (**C**H$_2$), 44.2

(**C**H$_2$), 39.0 (**C**H$_2$), 36.8 (**C**H$_2$), 31.9 (**C**H$_2$), 28.5 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{15}H_{27}N_3NaO_5$, 352.1828. Found: [MNa]$^+$, 352.1843 (4.3 ppm error).

5-([1,1'-Biphenyl]-4-ylmethyl)-1,5-diazacycloundecane-2,6-dione (13a)

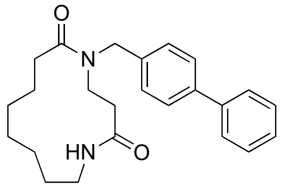


5-(4-Bromobenzyl)azacycloundecane-2,6-dione **8k** (71.0 mg, 0.2 mmol) and phenylboronic acid (37.0 mg, 0.3 mmol) were dissolved in 1,4-dioxane (2.0 mL) then Na_2CO_3 (64.0 mg, 0.6 mmol) was dissolved in water (1.0 mL), was added while stirring subsequently. Pd(dppf)Cl_2(CH_2Cl_2) (8.0 mg, 0.05 mmol) was added, and the reaction was heated to 50 °C and stirred for 18 hours. The reaction was then cooled to RT and quenched with H_2O (15 mL) and extracted with DCM (3 x 15 mL). The combined organics dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (54.1 mg, 77% yield); m.p. 180 –184 °C; R$_f$ 0.45 (1:49 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 3087, 2933, 2866, 1624, 1560, 1488, 1453, 1293, 1229, 1183, 1152, 758, 699. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 7:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.56 – 7.54 (4H, m, Ar**H**), 7.44 – 7.41 (2H, m, Ar**H**), 7.37 – 7.33 (3H, m, Ar**H**), 6.06 – 6.05 (1H, m, N**H**), 5.21 – 4.83 (1H, m, C**H**$_2$), 4.50 – 4.21 (1H, m, C**H**$_2$), 4.13 – 3.19 (3H, m, C**H**$_2$), 2.69 – 2.40 (2H, m, C**H**$_2$), 2.27 – 2.06 (4H, m, 2 x C**H**$_2$), 1.70 – 1.64 (3H, m, C**H**$_2$), 1.39 – 0.95 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 171.5 (**C**O), 140.8 (**C**Ar), 140.5 (**C**Ar), 137.2 (**C**Ar), 129.0 (Ar**C**H), 128.7 (Ar**C**H), 127.6 (Ar**C**H), 127.5 (Ar**C**H), 127.1 (Ar**C**H), 48.6 (N**C**H$_2$), 45.0 (**C**H$_2$), 41.7 (**C**H$_2$), 37.0 (**C**H$_2$), 28.5 (**C**H$_2$), 25.3 (**C**H$_2$), 24.4 (**C**H$_2$), 22.8 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{22}H_{26}N_2NaO_2$, 373.1883. Found: [MH]$^+$, 373.1886 (1.0 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.95 – 5.93 (1H, s, N**H**), δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 171.1 (**C**O), 140.8 (**C**Ar), 136.0 (**C**Ar), 53.8 (**C**H$_2$), 43.0 (**C**H$_2$), 37.5 (**C**H$_2$), 34.7 (**C**H$_2$), 33.8 (**C**H$_2$), 26.0 (**C**H$_2$), 23.5 (**C**H$_2$), 22.4 (**C**H$_2$).

For LCMS data confirming this product has >95% purity, see SI Section 5.

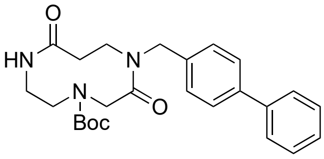
3-([1,1'-Biphenyl]-4-ylmethyl)-1,3-diazacyclotridecane-2,6-dione (13b)



To a solution of 5-(4-bromobenzyl)-1,5-diazacyclotridecane-2,6-dione **10k** (60 mg, 0.16 mmol) and phenylboronic acid (29.0 mg, 0.24 mmol) were dissolved in 1,4-dioxane (2.0 mL) then Na_2CO_3 (64 mg, 0.6 mmol) was dissolved in water (1.0 mL) and the solution added while stirring. $Pd(dppf)Cl_2(CH_2Cl_2)$ (6.5 mg, 0.008 mmol) was added, and the reaction mixture was heated to 50 °C and stirred for 18 hours. The reaction mixture was cooled to RT and quenched with H_2O (10 mL) and extracted with DCM (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a yellow solid (48.3 mg, 80% yield); m.p. 127 – 131 °C; R_f 0.56 (1:49 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3289, 2977, 2931, 1612, 1561, 1404, 1359, 1271, 1143, 1088, 962, 859, 732, 658; The ^1H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, this compound exists as a 9:1:1 mixture of 3 rotamers. NMR data for the major rotamer: δ_H (400 MHz, $CDCl_3$) 7.58 – 7.54 (4H, m, Ar**H**), 7.47 – 7.32 (4H, m, Ar**H**), 7.21 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.84 (1H, s, N**H**), 4.88 – 4.58 (2H, m, C**H**$_2$), 4.03 – 2.91 (4H, m, 2 x C**H**$_2$), 2.85 – 2.53 (2H, m, C**H**$_2$), 2.45 – 2.32 (2H, m, C**H**$_2$), 1.79 – 1.77 (2H, m, C**H**$_2$), 1.59 (2H, s, C**H**$_2$), 1.45 (2H, s, C**H**$_2$), 1.41 – 1.36 (2H, m, C**H**$_2$), 1.33 – 1.32 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.1 (CO), 170.7 (**C**O), 140.7 (**C**Ar), 140.5 (**C**Ar), 135.6 (**C**Ar), 128.9 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 127.1 (Ar**C**H), 126.8 (Ar**C**H), 52.4 (**C**H$_2$), 42.5 (**C**H$_2$), 39.7 (**C**H$_2$), 35.0 (**C**H$_2$), 33.0 (**C**H$_2$), 27.9 (**C**H$_2$), 27.2 (**C**H$_2$), 27.0 (**C**H$_2$), 25.7 (**C**H$_2$), 24.1 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{24}H_{30}N_2NaO_2$, 401.2201. Found: $[MNa]^+$, 401.2199 (−0.3 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 173.8 (**C**O), 171.1 (**C**O), 137.6 (**C**Ar), 135.9 (**C**Ar), 132.1 (**C**Ar), 128.1 (Ar**C**H), 127.5 (Ar**C**H), 52.5 (**C**H$_2$), 48.9 (**C**H$_2$), 44.7 (**C**H$_2$), 42.9 (**C**H$_2$), 38.4 (**C**H$_2$), 36.7 (**C**H$_2$), 32.8 (**C**H$_2$), 30.0 (**C**H$_2$), 29.8 (**C**H$_2$), 26.8 (**C**H$_2$), 25.9 (**C**H$_2$), 25.3 (**C**H$_2$), 24.8 (**C**H$_2$), 24.3 (**C**H$_2$), 23.0 (**C**H$_2$).

tert-Butyl 1-([1,1'-biphenyl]-4-ylmethyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (13c)



Method 1

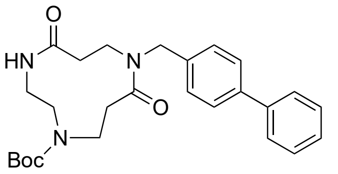
tert-Butyl 1-(4-bromobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate **11k** (60 mg, 0.136 mmol) and phenylboronic acid (24.9 mg, 0.204 mmol) were dissolved in 1,4-dioxane (2.0 mL). Then Na_2CO_3 (43.3 mg, 0.409 mmol) which dissolved in water (1.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (5.5 mg, 0.007 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 hexane : ethyl acetate → ethyl acetate → 3:1 dichloromethane : acetone) to afford the title compound (53.6 mg, 90%) as a yellow solid.

Method 2

tert-Butyl 2,8-dioxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-7-triazecane-4-carboxylate **11l** (209 mg, 0.43 mmol) and bromobenzene (0.07 mL, 0.64 mmol) were dissolved in 1,4-dioxane (4.0 mL). Then Na_2CO_3 (136.7 mg, 1.29 mmol) was dissolved in water (2.0 mL), and was added while stirring. $Pd(dppf)Cl_2(CH_2Cl_2)$ (17.4 mg, 0.02 mmol) was added, and the reaction mixture was heated to 50 °C and stirred for 18 hours. The reaction mixture was cooled to RT and quenched with H_2O (15 mL) and extracted with DCM (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (116 mg, 62% yield);

Data for **13c**: R_f = 0.25 (3:1 dichloromethane : acetone); m.p. 145–149 °C; ν_{max}/cm^{-1} (thin film) 3314, 2975, 1648, 1554, 1455, 1435, 1408, 1366, 1247, 1162, 1129, 1071, 950, 759, 698; In solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with 2 minor rotamers also evident in the NMR spectra; δ_H (400 MHz, $CDCl_3$) 7.60 – 7.51 (4H, m, 4 x Ar**H**, both rotamers), 7.42 (2H, m, 2 x Ar**H**, both rotamers), 7.33 (1H, m, Ar**H**, both rotamers), 7.29 – 7.21 (2H, m,2 x Ar**H**, both rotamers), 5.79 (1H, d, J = 8.5 Hz, N**H**, major rotamer), 5.19 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 5.07 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 4.35 – 4.23 (1H, m, C**H₂**, both rotamers), 4.19 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 3.73 (1H, dt, *J* = 14.0, 2.5 Hz, C**H₂**, major rotamer), 3.43 – 3.34 (1H, m, C**H₂**, major rotamer), 3.31 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 3.16 – 2.97 (2H, m, C**H₂**, major rotamer), 2.88 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 2.78 (1H, ddd, *J* = 13.0, 8.5, 6.0 Hz, C**H₂**, major rotamer), 2.50 (1H, ddd, *J* = 13.0, 8.5, 4.5 Hz, C**H₂**, major rotamer), 1.52 (9H, s, 3 x C**H₃**, major rotamer), 1.49 (9H, s, 3 x C**H₃**, minor rotamer), 1.46 (9H, s, 3 x C**H₃**, minor rotamer), 1.40 (9H, s, 3 x C**H₃**, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 172.7 (**C**O), 170.9 (**C**O), 155.2 (**C**O), 140.7 (Ar**C**), 136.0 (Ar**C**), 128.9 (Ar**C**), 128.8 (Ar**C**H), 127.6 (Ar**C**H), 127.6 (Ar**C**H), 127.4 (Ar**C**H), 127.1 (Ar**C**), 80.2 (O**C**(CH_3)$_3$), 52.6 (**C**H_2), 51.6 (**C**H_2), 49.1 (**C**H_2), 41.7 (**C**H_2), 38.8 (**C**H_2), 35.2 (**C**H_2), 28.3 (3 x **C**H_3); HRMS (ESI) calcd. for $C_{25}H_{31}N_3NaO_4^+$, 460.2207. Found: $[MH]^+$ 460.2214 (−1.6 ppm error).

***tert*-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (13d)**



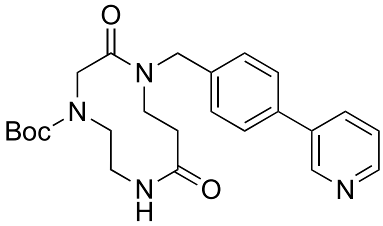
Method 1

tert-Butyl 8-(4-bromobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **12k** (100 mg, 0.220 mmol) and phenylboronic acid (40.2 mg, 0.330 mmol) were dissolved in 1,4-dioxane (2.0 mL). Then Na_2CO_3 (70.0 mg, 0.660 mmol) which dissolved in water (1.0 mL) was added followed by Pd(dppf)$Cl_2 \cdot CH_2Cl_2$ (8.9 mg, 0.011 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, 1:1 hexane : ethyl acetate → ethyl acetate → 3:1 dichloromethane : acetone) to afford the title compound (78.5 mg, 79%) as a yellow solid.

Method 2

tert-Butyl-5,9-dioxo-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-8-triazacycloundecane-1-carboxylate (1.65 g, 3.3 mmol) and bromobenzene (0.7 mL, 6.6 mmol) were dissolved in 1,4-dioxane (22 mL). Then Na_2CO_3 (1.05 g, 9.9 mmol) was dissolved in water (10 mL), was added while stirring. Pd(dppf)$Cl_2(CH_2Cl_2)$ (133.7 mg, 0.17 mmol) was added, and the reaction mixture was heated to 50 °C and stirred overnight. The reaction mixture was then cooled to room temperature and quenched with H_2O (100 mL) and extracted with DCM (3 x 100 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to give the title compound as a solid (1.05 g, 70% yield); R_f 0.64 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3308, 2975, 2931, 1649, 1551, 1479, 1408, 1366, 1247, 1167, 759, 731, 699. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) δ_H (400 MHz, $CDCl_3$) 7.56 – 7.53 (6H, m, Ar**H**), 7.44 – 7.40 (3H, m, Ar**H**), 6.10 – 6.07 (1H, m, N**H**), 4.94 – 4.87 (1H, m, C**H**$_2$), 4.77 – 4.64 (1H, m, C**H**$_2$), 4.35 – 4.26 (2H, m, C**H**$_2$), 3.66 – 3.52 (2H, m, C**H**$_2$), 3.35 – 3.28 (2H, m, C**H**$_2$), 2.96 – 2.86 (2H, m, C**H**$_2$), 2.23 – 2.16 (3H, m, C**H**$_2$), 1.57 – 1.46 (11H, m, C**H**$_2$ and C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.8 (**C**O), 170.6 (**C**O), 156.5 (*t*-BuO-**C**O), 140.9 (**C**Ar), 140.6 (**C**Ar), 135.8 (**C**Ar), 128.9 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 127.5 (Ar**C**H), 127.1 (Ar**C**H), 80.8 (COO**C**), 53.1 (**C**H$_2$), 52.9 (**C**H$_2$), 51.7 (**C**H$_2$), 42.8 (**C**H$_2$), 39.1 (**C**H$_2$), 35.3 (**C**H$_2$), 32.8 (**C**H$_2$), 28.4 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{26}H_{33}N_3NaO_4$, 474.2359. Found: $[MNa]^+$, 474.2363 (0.9 ppm error).

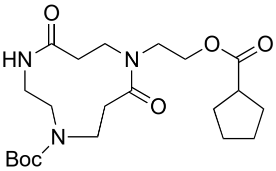
tert-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate (13e)



tert-Butyl 1-(4-bromobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate **11k** (60 mg, 0.136 mmol) and pyridine boronic acid (25.1 mg, 0.204 mmol) were dissolved in 1,4-dioxane (2.0

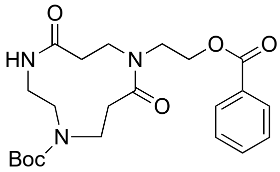
mL). Then Na_2CO_3 (43.3 mg, 0.409 mmol) which dissolved in water (1.0 mL) was added followed by $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (5.5 mg, 0.007 mmol) and the resulting mixture was purged with argon for 10 minutes. The mixture was stirred and heated at 50 °C for 18 hours under argon. After being allowed to cool to RT, water (10 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, ethyl acetate → 1:1 dichloromethane : acetone → 1:3 dichloromethane : acetone) to afford the title compound (31.2 mg, 52%) as a yellow solid. R_f = 0.33 (1:3 dichloromethane : acetone); m.p. 134–138 °C; ν_{max}/cm^{-1} (thin film) 3303, 2972, 2928, 1649, 1453, 1430, 1402, 1366, 1246, 1161, 1128, 1070, 1002, 798, 731, 711; δ_H (400 MHz, $CDCl_3$) 8.92 – 8.76 (1H, m, Ar**H**, both rotamers), 8.67 – 8.53 (1H, m, Ar**H**, both rotamers), 7.95 – 7.79 (1H, m, Ar**H**, both rotamers), 7.61 – 7.51 (2H, m, 2 x Ar**H**, both rotamers), 7.44 – 7.29 (3H, m, 3 x Ar**H**, both rotamers), 5.63 (1H, d, *J* = 10.5 Hz, N**H**, major rotamer), 5.23 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 5.07 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 4.39 – 4.24 (2H, m, C**H₂**, both rotamers), 4.20 (1H, d, *J* = 16.5 Hz, C**H₂**, major rotamer), 3.85 – 3.72 (1H, m, C**H₂**, major rotamer), 3.31 (1H, d, *J* = 14.0 Hz, C**H₂**, major rotamer), 3.13 – 2.98 (2H, m, C**H₂**, both rotamers), 2.93 – 2.75 (2H, m, C**H₂**, major rotamer), 2.52 (1H, ddd, *J* = 13.5, 9.0, 5.0 Hz, C**H₂**, major rotamer), 1.67 (9H, s, 3 x C**H₃**, minor rotamer), 1.54 (9H, s, 3 x C**H₃**, major rotamer), 1.51 (9H, s, 3 x C**H₃**, minor rotamer), 1.50 (9H, s, 3 x C**H₃**, minor rotamer), 1.42 (9H, s, 3 x C**H₃**, minor rotamer); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 172.8 (**C**O), 170.9 (**C**O), 155.2 (**C**O), 148.5(ArCH), 148.2(Ar**C**H), 137.3(Ar**C**), 137.1 (Ar**C**), 136.4 (Ar**C**H), 134.8 (Ar**C**), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 127.1 (Ar**C**), 123.9 (Ar**C**H), 81.5 (O**C**(CH_3)$_3$), 52.7 (**C**H₂), 51.7 (**C**H₂), 49.3 (**C**H₂), 41.9 (**C**H₂), 38.9 (**C**H₂), 35.4 (**C**H₂), 28.4 (3 x **C**H₃); HRMS (ESI) calcd. for $C_{24}H_{31}N_4O_4^+$, 439.2340. Found: $[MH]^+$ 439.2340 (0.1 ppm error).

***tert*-butyl 8-(2-((Cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (13f)**



To a solution of *tert*-butyl 8-(2-hydroxyethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **12o** (224 mg, 0.68 mmol) was dissolved in dry DCM (15 mL), was cooled to 0 ℃ and dry triethylamine (0.3 mL, 3.00 mmol) was added dropwise. Next, cyclopentane carbonyl chloride (0.1 mL, 0.85 mmol) and DMAP (8.3 mg, 0.068 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (239.2 mg, 83% yield); R_f 0.50 (1:9 methanol:ethyl acetate). In solution in $CDCl_3$, the product exists as a 4:1.1:1 mixture of 3 rotamers based on NH peaks. All ^1H and ^{13}C signals are broadened due to rotamer interconversion; δ_H (400 MHz, $CDCl_3$) 6.66 (1H, s, N**H**, minor rotamer), 6.60 (1H, s, N**H**, minor rotamer), 6.23 – 6.21 (1H, m, N**H**, major rotamer), 4.12 – 3.71 (8H, m, C**H**$_2$), 3.64 – 3.60 (1H, m, C**H**$_2$), 3.53 – 3.50 (1H, m, C**H**$_2$), 3.46 – 3.42 (2H, m, C**H**$_2$), 3.33 – 3.02 (8H, m, 2 x C**H** and 3 x C**H**$_2$), 2.98 – 2.81 (3H, m, C**H**$_2$), 2.75 – 2.63 (2H, m, C**H**$_2$), 2.56 – 2.49 (2H, m, C**H**$_2$), 2.30 – 2.23 (3H, m, C**H**$_2$), 1.97 – 1.91 (1H, m, C**H**$_2$), 1.89 – 1.86 (1H, m, C**H**$_2$), 1.72 – 1.68 (4H, m, C**H**$_2$), 1.61 – 1.50 (9H, m, C**H**$_2$), 1.43 – 1.39 (4H, m, C**H**$_2$), 1.32 (7H, m, C**H**$_3$), 1.30 (9H, m, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 179.2 (**C**O), 177.1 (**C**O), 176.2 (**C**O), 176.1 (**C**O), 174.1 (**C**O), 173.6 (**C**O), 170.3 (**C**O), 156.2 (**C**O), 80.3 (**C**CH$_3$), 80.2 (**C**CH$_3$), 79.5 (**C**CH$_3$), 61.9 (**C**H$_2$), 61.5 (**C**H$_2$), 52.7 (**C**H$_2$), 51.2 (**C**H$_2$), 48.0 (**C**H$_2$), 45.3 (**C**H), 43.5 (**C**H), 43.4 (**C**H), 42.8 (**C**H$_2$), 38.7 (**C**H$_2$), 36.7 (**C**H$_2$), 34.9 (**C**H$_2$), 32.3 (**C**H$_2$), 31.4 (**C**H$_2$), 30.3 (**C**H$_2$), 29.8 (**C**H$_2$), 29.7 (**C**H$_2$), 28.1 (**C**H$_3$), 28.0 (**C**H$_3$), 25.5 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{21}H_{35}N_3NaO_6$, 448.2429. Found: $[MNa]^+$, 448.2418 (−2.4 ppm error).

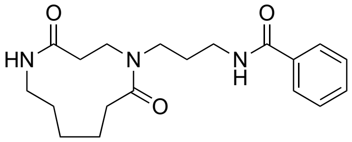
tert-Butyl 8-(2-(benzoyloxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (13g)



To a solution of *tert*-butyl 8-(2-hydroxyethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **12o** (213.8 mg, 0.65 mmol) was dissolved in dry DCM (14 mL), was cooled to 0 ℃ and dry triethylamine (0.27 mL, 1.95 mmol) was added dropwise. Next, benzyl chloride (90 µL, 0.81 mmol) and DMAP (7.9 mg, 0.065 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (15 mL) washed with saturated brine solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a colourless oil (247.1 mg, 88% yield); R_f 0.50 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3315, 2975, 1644, 1547, 1365, 1161, 1114, 1026, 857, 710. The ^{1}H NMR spectrum is complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 2.5:1.2:1 mixture of rotamers; δ_H (400 MHz, $CDCl_3$) 7.89 – 7.86 (2H, m, Ar**H**, major rotamer), 7.49 – 7.43 (1H , m, Ar**H**, major roatmer), 7.37 – 7.31 (2H , m, Ar**H**, major rotamer), 6.53 (1H, s, N**H**, major rotamer), 4.44 – 4.37 (3H, m, C**H**$_2$, major rotamer), 4.21 – 4.09 (3H, m, C**H**$_2$, major rotamer), 3.54 – 3.46 (3H, m, C**H**$_2$, major rotamer), 3.19 – 3.07 (4H, m, C**H**$_2$, major rotamer), 2.85 – 2.71 (3H, m, C**H**$_2$, major rotamer), 1.40 – 1.39 (20H, m, C**H**$_3$, major and minor rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.3 (**C**O), 170.4 (**C**O), 166.3 (**C**O), 166.0 (**C**O), 156.4 (**C**Ar), 133.3 (ArCH), 129.4 (Ar**C**H), 128.5 (ArCH), 80.5 (**C**CH$_3$), 62.1 (**C**H$_2$), 52.9 (**C**H$_2$), 51.5 (**C**H$_2$), 48.4 (**C**H$_2$), 43.1 (**C**H$_2$), 38.8 (**C**H$_2$), 34.9 (**C**H$_2$), 32.3 (**C**H$_2$), 28.1 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{22}H_{31}N_3NaO_6$, 456.2108. Found: [MNa]$^+$, 456.2105 (−0.6 ppm error).

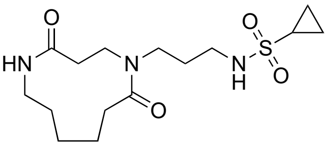
Diagnostic NMR data for minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 7.98 – 7.96 (2H, m, Ar**H**), 6.28 – 6.26 (1H, m, N**H**), 6.22 – 6.19 (1H, m, N**H**), 4.05 – 3.98 (1H, m, C**H**$_2$), 3.72 – 3.69 (1H, m, C**H**$_2$), 3.39 – 3.33 (1H, m, C**H**$_2$), 2.40 – 2.34 (1H, m, C**H**$_2$), 2.27 (1H, s, C**H**$_2$), 2.04 – 2.00 (1H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 79.7 (**C**CH$_3$), 62.8 (**C**H$_2$), 60.2 (**C**H$_2$), 53.4 (**C**H$_2$), 50.6 (**C**H$_2$), 28.3 (**C**H$_3$).

***N*-(3-(4,11-Dioxo-1,5-diazacycloundecan-1-yl)propyl)benzamide (13h)**



tert-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate **11k** (171 mg, 0.5 mmol) was dissolved in 4 M HCl in 1,4-dioxane (4.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (11 mL), was cooled to 0 ℃ and dry triethylamine (0.4 mL, 3.0 mmol) was added dropwise. Next, benzoyl chloride (70 µL, 0.63 mmol) and DMAP (6 mg, 0.05 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (15 mL) washed with saturated brine solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a white solid (80.6 mg, 47% yield); m.p. 171 – 175 °C; R_f 0.53 (1:4 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3296, 2934, 1631, 1545, 1453, 1304, 703; The ^1H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$) 7.84 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.53 – 7.49 (1H, m, Ar**H**), 7.47 – 7.40 (2H, m, Ar**H**), 6.87 – 6.86 (1H, m, N**H**), 4.20 – 2.86 (8H, m, 4 x C**H**$_2$), 2.70 – 2.28 (4H, m, 2 x C**H**$_2$), 2.21 – 1.95 (2H, m, C**H**$_2$), 1.79 (2H, s, C**H**$_2$), 1.66 (2H, s, C**H**$_2$), 1.42 – 1.04 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 171.7 (**C**O), 167.6 (**C**O), 134.4 (**C**Ar), 131.6 (Ar**C**H), 128.7 (Ar**C**H), 127.2 (Ar**C**H), 45.5 (**C**H$_2$), 43.1 (**C**H$_2$), 41.5 (**C**H$_2$), 37.8 (**C**H$_2$), 37.0 (**C**H$_2$), 28.6 (**C**H$_2$), 28.2 (**C**H$_2$), 25.3 (**C**H$_2$), 24.3 (**C**H$_2$), 22.7 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{19}H_{27}N_3NaO_3$, 368.1957. Found: $[MNa]^+$, 368.1945 (−3.5 ppm error).

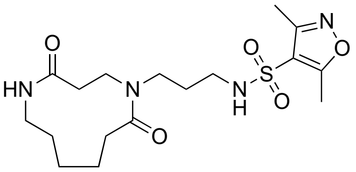
***N*-(3-(4,11-Dioxo-1,5-diazacycloundecan-1-yl)propyl)cyclopropanesulfonamide (13i)**



tert-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate **8m** (146 mg, 0.43 mmol) was dissolved in 4 M HCl in 1,4-dioxane (4.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (12 mL), was cooled to 0 °C and dry triethylamine (0.18 mL, 1.29 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (0.05 mL, 0.54 mmol) and DMAP (5.3 mg, 0.043 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (76.9 mg, 52% yield); m.p. 86 – 90 °C; R_f 0.24 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3281, 2934, 1616, 1553, 1437, 1323, 1299, 1142, 1041, 892, 727, 645; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$) 7.28 (1H, s, N**H**), 6.29 – 6.26 (1H, m, N**H**), 4.31 – 3.71 (2H, m, C**H**$_2$), 3.65 – 2.67 (6H, m, 3 x C**H**$_2$), 2.63 – 2.17 (5H, m, C**H** and 2 x C**H**$_2$), 2.06 – 1.58 (8H, m, 4 x C**H**$_2$), 1.07 (2H, s, cyclopropyl C**H**$_2$), 0.93 – 0.92 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 171.9 (**C**O), 44.9 (**C**H$_2$), 43.1 (**C**H$_2$), 41.1 (**C**H$_2$), 40.8 (**C**H$_2$), 36.8 (**C**H$_2$), 29.7 (**C**H), 28.3 (**C**H$_2$), 27.1 (**C**H$_2$), 25.2 (**C**H$_2$), 24.3 (**C**H$_2$), 22.3 (**C**H$_2$), 5.2 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{15}H_{27}N_3NaO_4S$, 368.1623. Found: [MNa]$^+$, 368.1614 (−2.2 ppm error).

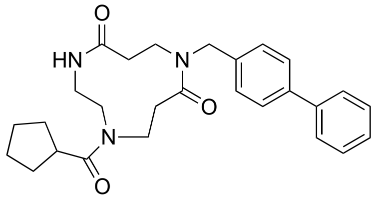
For LCMS data confirming this product has >95% purity, see SI Section 5.

N-(3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)-3,5-dimethylisoxazole-4-sulfonamide (13j)



tert-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate **8m** (171 mg, 0.5 mmol) was dissolved in 4 M HCl in 1,4-dioxane (3.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (10 mL), was cooled to 0 °C and dry triethylamine (0.20 mL, 1.5 mmol) was added dropwise. Next, 3,5-dimethylisoxazole-4-sulfonyl chloride (123.2 mg, 0.63 mmol) and DMAP (6 mg, 0.05 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (15 mL) washed with saturated brine solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a yellow oil (145.8 mg, 73% yield); R_f 0.50 (1:9 methanol:ethyl acetate). **IR** (ATR): υ_{max}/cm^{-1} 3286, 2936, 2249, 1619, 1455, 1332, 1261, 1178, 1124, 906, 725, 646, 573. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 7.34 – 7.33 (1H, m, N**H**), 7.07 – 7.04 (1H, m, N**H**), 4.29 – 3.85 (2H, m, C**H**$_2$), 3.63 – 2.76 (8H, m, 4 x C**H**$_2$), 2.60 – 2.56 (3H, m, C**H**$_3$), 2.40 – 2.36 (3H, m, C**H**$_3$), 2.04 – 1.98 (2H, m, C**H**$_2$), 1.71 – 1.57 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (CH_3**C**O), 172.6 (**C**O), 171.7 (**C**O), 157.7 (CH_3**C**N), 116.0 (OOS**C**), 44.8 (**C**H$_2$), 43.0 (**C**H$_2$), 41.1 (**C**H$_2$), 40.1 (**C**H$_2$), 36.6 (**C**H$_2$), 28.2 (**C**H$_2$), 26.2 (**C**H$_2$), 25.2 (**C**H$_2$), 24.2 (**C**H$_2$), 22.2 (**C**H$_2$), 12.6 (**C**H$_3$), 10.6 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{17}H_{28}N_4NaO_5S$, 423.1670. Found: [MNa]$^+$, 423.1673 (0.6 ppm error).

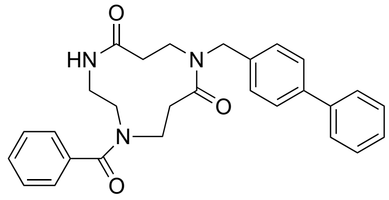
5-([1,1'-Biphenyl]-4-ylmethyl)-9-(cyclopentanecarbonyl)-1,5-diazacycloundecane-2,6-dione (14a)



tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **13d** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6 mL), was cooled to 0 ℃ and dry triethylamine (0.18 mL, 1.32 mmol) was added dropwise. Next, cyclopentane carbonyl chloride (0.04 mL, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction zmixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (10 mL) washed with saturated brine solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:99 methanol:ethyl acetate → 1:49 methanol:ethyl acetate) to afford the title compound as a white solid (84.6 mg, 86% yield over 2 steps); m.p. 89 – 93 °C; R_f 0.58 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3294, 2944, 2868, 2244, 1628, 1554, 1457, 1412, 1356, 1212, 1149, 1075, 1007, 908, 728, 698, 646. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. δ_H (400 MHz, $CDCl_3$) 7.54 – 7.52 (4H, m Ar**H**), 7.43 – 7.39 (2H, m, Ar**H**), 7.34 – 7.27 (3H, m, Ar**H**), 6.07 – 6.05 (1H, m, N**H**), 4.94 – 4.91 (1H, m, C**H**$_2$), 4.54 (1H, s, C**H**$_2$), 4.35 (1H, s, C**H**$_2$), 3.96 – 3.95 (1H, m, C**H**$_2$), 3.72 – 3.62 (2H, m, C**H** and C**H**H'), 3.50 (2H, s, C**H**$_2$), 3.33 – 3.11 (2H, m, C**H**$_2$), 2.99 – 2.80 (2H, m, CH**H'** and C**H**$_2$), 2.26 – 2.23 (3H, m, C**H**$_2$), 2.05 – 1.60 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 178.9 (**C**O), 171.8 (**C**O), 171.4 (**C**O), 140.9 (**C**Ar), 140.4 (**C**Ar), 136.7 (**C**Ar), 128.9 (ArCH), 128.4 (Ar**C**H), 127.7 (ArCH), 127.5 (Ar**C**H), 127.1 (Ar**C**H), 49.0 (**C**H$_2$), 46.2 (**C**H$_2$), 45.6 (**C**H$_2$), 45.2 (**C**H$_2$), 41.1 (**C**H), 38.7 (**C**H$_2$), 36.7 (**C**H$_2$), 31.4 (**C**H$_2$), 29.6 (**C**H$_2$), 26.3 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{27}H_{33}N_3NaO_3$, 470.2422. Found: [MNa]$^+$, 470.2414 (−1.7 ppm error).

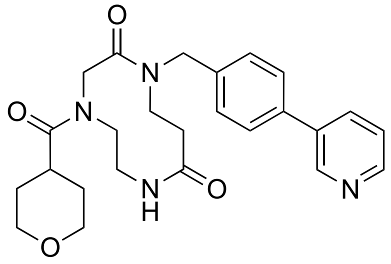
For LCMS data confirming this product has >95% purity, see SI Section 5.

8-([1,1'-Biphenyl]-4-ylmethyl)-1-benzoyl-1,4,8-triazacycloundecane-5,9-dione (14b)



tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **13d** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (5.0 mL), was cooled to 0 °C and dry triethylamine (0.18 mL, 1.32 mmol) was added dropwise. Next, benzyl chloride (0.03 mL, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (10 mL) washed with saturated brine solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (87 mg, 87% yield over 2 steps); m.p. 93 – 97 °C; R_f 0.53 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3296, 3004, 1624, 1551, 1411, 1355, 1272, 1216, 1146, 1075, 1007, 908, 750, 703, 666. The ^1H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product; δ_H (400 MHz, $CDCl_3$) 7.53 – 7.50 (7H, m Ar**H**), 7.41 – 7.37 (5H, m, Ar**H**), 7.27 – 7.24 (2H, m, Ar**H**), 6.74 (1H, s, N**H**), 4.26 – 4.13 (1H, m, C**H**$_2$), 3.94 – 2.89 (10H, m, 5 x C**H**$_2$), 2.38 – 2.09 (3H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.9 (**C**O), 171.1 (**C**O), 140.7 (**C**Ar), 140.4 (**C**Ar), 137.0 (**C**Ar), 136.6 (**C**Ar), 129.3 (Ar**C**H), 128.8 (Ar**C**H), 128.5 (Ar**C**H), 128.3 (Ar**C**H), 127.5 (Ar**C**H), 127.45 (Ar**C**H), 127.0 (Ar**C**H), 126.7 (Ar**C**H), 48.2 (**C**H$_2$), 47.5 (**C**H$_2$), 47.1 (**C**H$_2$), 44.3 (**C**H$_2$), 38.6 (**C**H$_2$), 36.3 (**C**H$_2$), 31.5 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{28}H_{29}N_3NaO_3$, 478.2111. Found: $[MNa]^+$, 478.2101 (−2.1 ppm error).

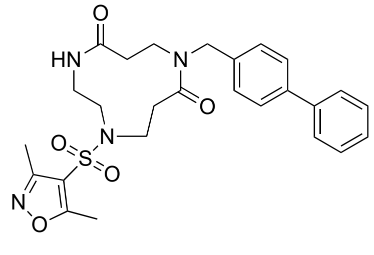
1-(4-(Pyridin-3-yl)benzyl)-4-(tetrahydro-2H-pyran-4-carbonyl)-1,4,7-triazecane-2,8-dione (14c)



tert-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate **13e** (50 mg, 0.114 mmol) was dissolved in 4 M HCl in dioxane (3.0 mL). The solution was stirred at room temperature for 10 min, after which the solution was concentrated in vacuo to yield the salt product. This salt was dissolved in anhydrous DCM (3.0 mL) at room temperature and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.05 mL, 0.342 mmol) was added dropwise, followed by tetrahydro-*2H*-pyran-4-carbonyl chloride (21.2 mg, 0.143 mmol) and DMAP (1.4 mg, 0.011 mmol). The solution was allowed to gradually warm to room temperature while being stirred for 18 hours. The solution was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulfate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, ethyl acetate → 50:1 dichloromethane : methanol → 20:1 dichloromethane : methanol) to afford the title compound (38.0 mg, 74%) as a yellow solid. In solution in $CDCl_3$, this product exists as a complex mixture of rotamers. R_f = 0.45 (20:1 dichloromethane : methanol); m.p. 159–162 °C; ν_{max}/cm^{-1} (thin film) 3318, 2930, 1641, 1479, 1408, 1365, 1353, 1245, 1165, 1138, 759, 731, 698; δ_H (400 MHz, $CDCl_3$) data for the major rotamer only: 8.88 – 8.81 (1H, m, Ar**H**), 8.65 – 8.59 (1H, m, Ar**H**), 7.93 – 7.86 (1H, m, Ar**H**), 7.60 – 7.49 (2H, m,2 x Ar**H**), 7.45 – 7.36 (2H, m, 2 x Ar**H**), 7.35 – 7.27 (1H, m, Ar**H**), 6.45 – 6.19 (1H, m, N**H**), 4.27 – 4.20 (1H, m, C**H**), 4.13 – 3.81 (4H, m, 2 x C**H₂**), 3.70 – 3.59 (1H, m, C**H₂**), 3.53 – 3.29 (4H, m,2 x C**H₂**), 3.16 (1H, t, *J* = 7.5 Hz, C**H₂**), 3.02 (1H, ddd, *J* = 14.0, 9.0, 5.5 Hz, C**H₂**), 2.85 – 2.71 (1H, m, C**H₂**), 2.37 – 2.20 (1H, m, C**H₂**), 2.04 – 1.80 (2H, m, C**H₂**), 1.70 (2H, td, *J* = 9.0, 4.0 Hz, C**H₂**), 1.61 – 1.50 (1H, m, C**H₂**), 0.93 – 0.75 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.0 (**C**O), 171.9 (**C**O), 167.6 (**C**O), 148.4 (Ar**C**H), 148.0 (Ar**C**H), 135.2 (Ar**C**), 129.2 (Ar**C**), 129.0 (Ar**C**H), 128.0 (Ar**C**), 127.8 (Ar**C**), 127.7 (Ar**C**H), 124.1 (Ar**C**H), 67.3

(**C**H), 54.1 (**C**H$_2$), 50.9 (**C**H$_2$), 48.6 (**C**H$_2$), 46.3 (**C**H$_2$), 44.9 (**C**H$_2$), 42.1 (**C**H$_2$), 38.9 (**C**H$_2$), 34.8 (**C**H$_2$), 29.7 (**C**H$_2$), 29.2 (**C**H$_2$); HRMS (ESI) calcd. for $C_{25}H_{31}N_4O_4^+$, 451.2340. Found: $[MH]^+$ 451.2371 (−6.8 ppm error).

8-([1,1'-Biphenyl]-4-ylmethyl)-1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-1,4,8-triazacycloundecane-5,9-dione (14d)

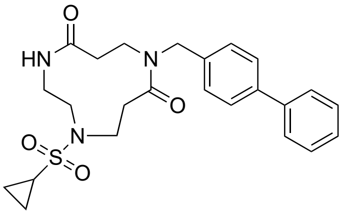


tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **13d** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6.0 mL), was cooled to 0 °C and dry triethylamine (0.18 mL, 1.32 mmol) was added dropwise. Next, 3,5-dimethylisoxazole-4-sulfonyl chloride (54 mg, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:49 methanol:ethyl acetate → 1:19 methanol:ethyl acetate) to afford the title compound as a white solid (45.5 mg, 41% yield over 2 steps); m.p. 85 – 90 °C; R_f 0.84 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3295, 2930, 1643, 1586, 1454, 1408, 1263, 1121, 985, 922, 863, 760, 706, 623, 572. The ^{1}H NMR spectrum is complicated by rotameric broadening; ^{13}C NMR data is most useful for determining the identity and purity of the product. In solution in $CDCl_3$, this compound exists as a 3:1 mixture of rotamers. Data for the major rotamer; δ_H (400 MHz, $CDCl_3$) 7.57 – 7.55 (4H, m Ar**H**), 7.45 – 7.35 (5H, m, Ar**H**), 6.63 – 6.56 (1H, m, N**H**), 5.21 – 5.00 (1H, m, C**H**$_2$), 4.59 – 4.27 (2H, m, C**H**$_2$), 3.69 – 3.61 (1H, m, C**H**$_2$), 3.52 – 3.42 (2H, m, C**H**$_2$), 3.38 – 3.15 (5H, m, C**H**$_2$), 2.69 – 2.68 (3H, m, C**H**$_3$), 2.46 (3H, s, C**H**$_3$), 1.43 – 1.39 (1H, m, C**H**$_2$), 1.29 – 1.25 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (CH$_3$**CO**), 172.2 (**C**O), 170.2 (**C**O), 157.9 (CH$_3$**CN**), 141.0 (**C**Ar), 140.6 (**C**Ar), 136.8 (**C**Ar), 128.9 (Ar**C**H), 128.9

(Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 127.2 (Ar**C**H), 114.1 (OOS**C**), 49.0 (**C**H$_2$), 47.1 (**C**H$_2$), 45.8 (**C**H$_2$), 45.0 (**C**H$_2$), 41.1 (**C**H$_2$), 36.7 (**C**H$_2$), 30.2 (**C**H$_2$), 13.4 (**C**H$_3$), 11.8 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{26}H_{30}N_4NaO_5S$, 533.1836. Found: $[MNa]^+$, 533.1829 (−1.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 135.6 (**C**Ar), 49.4 (**C**H$_2$), 43.2 (**C**H$_2$), 38.6 (**C**H$_2$), 29.8 (**C**H$_2$), 13.1 (**C**H$_3$), 11.3 (**C**H$_3$).

8-([1,1'-Biphenyl]-4-ylmethyl)-1-(cyclopropylsulfonyl)-1,4,8-triazacycloundecane-5,9-dione (14e)

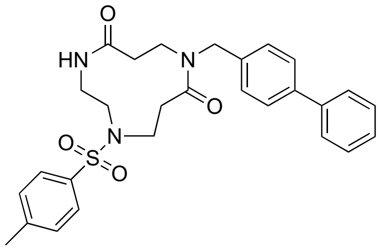


tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (100 mg, 0.22 mmol) **13d** was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6.0 mL), was cooled to 0 °C and dry triethylamine (0.09 mL, 0.66 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (0.03 mL, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a brown solid (80.2 mg, 80% yield over 2 steps); m.p. 85 – 89 °C; R_f 0.48 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3299, 2931, 2250, 1641, 1547, 1334, 1193, 1149, 1074, 1041, 986, 723, 647, 540. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 3:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.53 – 7.50 (4H, m Ar**H**), 7.41 – 7.38 (2H, m, Ar**H**), 7.34 – 7.31 (3H, m, Ar**H**), 6.86 (1H, s, N**H**), 3.63 – 3.49 (2H, m, C**H**$_2$), 3.43 – 3.14 (6H, m, 3 x C**H**$_2$), 2.52 – 2.25 (5H, m, 2 x C**H**$_2$ and C**H**), 1.19 (2H, s, cyclopropyl C**H**$_2$), 1.02 (2H, s, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.2 (**C**O), 170.5 (**C**O), 140.6 (**C**Ar), 140.5 (**C**Ar), 136.9

(**C**Ar), 128.8 (Ar**C**H), 128.6 (Ar**C**H), 127.5 (Ar**C**H), 127.4 (Ar**C**H), 127.0 (Ar**C**H), 48.6 (**C**H$_2$), 47.1 (**C**H$_2$), 46.2 (**C**H$_2$), 44.7 (**C**H$_2$), 41.3 (**C**H$_2$), 36.5 (**C**H$_2$), 30.4 (**C**H$_2$), 26.5 (**C**H), 5.0 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{24}H_{29}N_3NaO_4S$, 478.1773. Found: $[MNa]^+$, 478.1771 (−0.4 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.21 (1H, s, N**H**), 5.03 (1H, d, *J* = 16.6 Hz, C**H**H'), 4.48 (1H, d, *J* = 16.6 Hz, CH**H'**), 3.74 – 3.71 (2H, m, C**H**$_2$), 2.18 – 2.15 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$)) 172.6 (**C**O), 171.0 (**C**O), 140.8 (**C**Ar), 140.3 (**C**Ar), 135.9 (**C**Ar), 128.8 (Ar**C**H), 127.7 (Ar**C**H), 127.2 (Ar**C**H), 52.6 (**C**H$_2$), 51.4 (**C**H$_2$), 50.9 (**C**H$_2$), 43.3 (**C**H$_2$), 39.4 (**C**H$_2$), 35.9 (**C**H$_2$), 34.9 (**C**H$_2$), 25.6 (**C**H), 4.84 (cyclopropyl **C**H$_2$).

8-([1,1'-Biphenyl]-4-ylmethyl)-1-tosyl-1,4,8-triazacycloundecane-5,9-dione (14f)

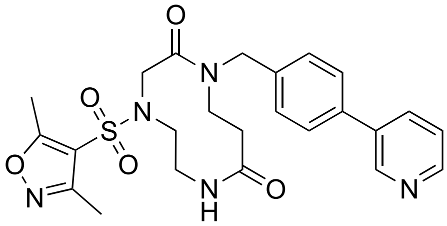


tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **13d** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 min, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6.0 mL), was cooled to 0 °C and dry triethylamine (0.09 mL, 0.66 mmol) was added dropwise. Next, 4-methylbenzenesulfonyl chloride (53.4 mg, 0.28 mmol) and DMAP (2.7 mg, 0.022 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (100% ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (100.5 mg, 90% yield over 2 steps); m.p. 92 – 95 °C; R_f 0.64 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3295, 2929, 2247, 1640, 1547, 1360, 1337, 1196, 1159, 986, 907, 864, 815, 726, 694, 644, 548. The ^1H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer only;

δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.52 – 7.49 (3H, m, Ar**H**), 7.41 – 7.30 (8H, m, Ar**H**), 7.21 – 7.18 (1H, m, N**H**), 5.33 – 5.06 (1H, m, C**H**$_2$), 4.55 – 4.38 (1H, m, C**H**$_2$), 4.31 – 4.07 (1H, m, C**H**$_2$), 4.03 – 3.77 (1H, m, C**H**$_2$), 3.70 – 3.22 (5H, m, C**H**$_2$), 3.09 – 3.05 (2H, m, C**H**$_2$), 2.56 – 2.50 (1H, m, C**H**$_2$), 2.44 – 2.36 (5H, m, C**H**$_3$ and C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.3 (**C**O), 170.3 (**C**O), 143.7 (**C**Ar), 140.6 (**C**Ar), 140.4 (**C**Ar), 137.0 (**C**Ar), 133.6 (Ar**C**H), 129.8 (Ar**C**H), 128.8 (Ar**C**H), 128.7 (Ar**C**H), 127.8 (Ar**C**H), 127.4 (Ar**C**H), 127.0 (Ar**C**H), 48.5 (**C**H$_2$), 47.5 (**C**H$_2$), 46.5 (**C**H$_2$), 44.6 (**C**H$_2$), 41.5 (**C**H$_2$), 36.4 (**C**H$_2$), 30.1 (**C**H$_2$), 21.5 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{28}H_{31}N_3NaO_4S$, 528.1944. Found: $[MNa]^+$, 528.1927 (−3.1 ppm error).

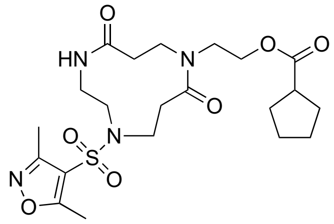
Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.41 – 6.39 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 171.1 (**C**O), 144.2 (**C**Ar), 140.7 (**C**Ar), 140.4 (**C**Ar), 136.1 (**C**Ar), 133.3 (Ar**C**H), 130.0 (Ar**C**H), 128.8 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**H), 127.3 (Ar**C**H), 127.2 (Ar**C**H), 52.9 (**C**H$_2$), 51.3 (**C**H$_2$), 51.0 (**C**H$_2$), 43.4 (**C**H$_2$), 39.7 (**C**H$_2$), 35.9 (**C**H$_2$), 35.0 (**C**H$_2$), 21.6 (**C**H$_3$).

4-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-2,8-dione (14g)



tert-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate **13e** (50 mg, 0.114 mmol) was dissolved in 4 M HCl in dioxane (3.0 mL). The solution was stirred at room temperature for 10 minutes, after which the solution was concentrated in vacuo to yield the salt product. This salt was dissolved in anhydrous DCM (3.0 mL) at room temperature and the solution was cooled to 0 °C using an ice bath. Triethylamine (0.05 mL, 0.342 mmol) was added dropwise, followed by 3,5-dimethylisoxazole-4-sulfonyl chloride (28.0 mg, 0.143 mmol) and DMAP (1.4 mg, 0.011 mmol). The solution was allowed to gradually warm to room temperature while being stirred for 18 hours. The solution was diluted with ethyl acetate (10 mL) and washed with brine (10 mL). The aqueous layer was then extracted with ethyl acetate (3 x 10 mL). The organic layers were then combined, dried with magnesium sulphate, filtered and concentrated in vacuo to give the crude product. The product was purified by column chromatography (SiO_2, ethyl acetate → 50:1 dichloromethane:methanol → 20:1 dichloromethane:methanol) to afford the title compound (30.1 mg, 53%) as a brown solid, as a mixture of 2 rotamers. R_f = 0.35 (20:1 dichloromethane : methanol); m.p. 173–177 °C; ν_{max}/cm^{-1} (thin film) 2926, 1647, 1432, 1337, 1262, 1176, 1125, 798, 755; δ_H (400 MHz, $CDCl_3$) 8.82 (1H, br s), 8.59 (1H, br s), 7.86 (1H, ddd, *J* = 8.0, 5.0, 3.0 Hz, Ar**H**), 7.61 – 7.56 (1H, m, Ar**H**), 7.56 – 7.49 (1H, m, Ar**H**), 7.42 – 7.29 (3H, m, 3 x Ar**H**), 6.27 (1H, d, *J* = 8.0 Hz, N**H**), 5.32–5.20 (1H, m, C**H₂**), 4.51 – 4.42 (1H, m, C**H₂**), 4.22 – 4.05 (1H, m, C**H₂**), 3.92 – 3.77 (1H, m, C**H₂**), 3.70 – 3.49 (1H, m, C**H₂**), 3.43 – 3.15 (3H, m, C**H₃**), 3.10 – 2.97 (1H, m, C**H₂**), 2.62 and 2.61 (2 x s, C**H₃**, 2 rotamers), 2.58 – 2.00 (4H, m, C**H₂**, overlapping the CH_3 signals), 2.37 and 2.16 (3H, d, *J* = 15.5 Hz, C**H₃**, 2 rotamers), 2; δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.4 (**C**O), 170.9 (**C**O), 157.5 (Ar**C**), 148.8 (Ar**C**H), 148.2 (Ar**C**H), 137.7(Ar**C**), 136.5 (Ar**C**), 134.4 (ArCH), 129.1 (Ar**C**), 127.9 (Ar**C**H), 127.7 (Ar**C**H), 127.5 (Ar**C**), 123.8 (Ar**C**H), 113.8 (Ar**C**) 53.9 (**C**H₂), 53.1 (**C**H₂), 43.1 (**C**H₂), 35.2 (**C**H₂), 29.4 (**C**H₂), 28.4 (**C**H₂), 13.3 (**C**H₃), 11.7 (**C**H₃); HRMS (ESI) calcd. for $C_{24}H_{28}N_5O_5S^+$, 498.1806. Found: $[MH]^+$ 498.1788 (3.5 ppm error).

2-(1-((3,5-Dimethylisoxazol-4-yl)sulfonyl-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (14h)

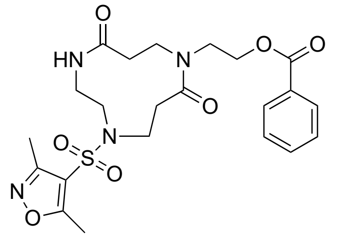


tert-Butyl 8-(2-((cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **13f** (70 mg, 0.16 mmol) was dissolved in 4 M HCl in 1,4-dioxane (1.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (5 mL), was cooled to 0 °C and dry triethylamine (70 µL, 0.48 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (39 mg, 0.20 mmol) and DMAP (2 mg, 0.016 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (10 mL) washed with saturated brine solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:9 methanol:ethyl acetate) to afford the title compound as a white solid (70.4 mg, 91% yield);

m.p. 85 – 90 °C; R_f 0.23 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3300, 2955, 2871, 2247, 1728, 1641, 1262, 1174, 1120, 985, 915, 727, 704, 621, 571. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the compoud exists predominantly as a single rotamer, with trace amount of a minor rotamer evident in the ^{13}C NMR spectrum. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.93 (1H, s, N**H**), 4.48 – 3.23 (10H, m, 5 x C**H**$_2$), 3.15 (2H, s, C**H**$_2$), 2.72 – 2.66 (1H, m, C**H**), 1.89 – 1.81 (2H, m, C**H**$_2$), 1.77 – 1.69 (2H, m, C**H**$_2$), 1.68 – 1.62 (2H, m, C**H**$_2$), 1.60 – 1.50 (2H, m, C**H**$_2$), 2.64 (3H, s, C**H**$_3$), 2.38 (3H, s, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 176.6 (CH_3**C**O), 174.0 (**C**O), 172.2 (**C**O), 170.1 (**C**O), 157.8 (CH_3**C**N), 114.1 (OOS**C**), 62.2 (**C**H$_2$), 46.8 (**C**H$_2$), 46.7 (**C**H$_2$), 45.6 (**C**H$_2$), 43.8 (**C**H), 41.1 (**C**H$_2$), 37.2 (**C**H$_2$), 30.2 (**C**H$_2$), 30.1 (**C**H$_2$), 13.2 (**C**H$_3$), 11.6 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{21}H_{32}N_4NaO_7S$, 507.1874. Found: $[MNa]^+$, 507.1884 (2.0 ppm error).

Diagnostic NMR data for minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 6.29 – 6.18 (1H, m, N**H**), 4.72 – 4.64 (1H, m, C**H**$_2$).

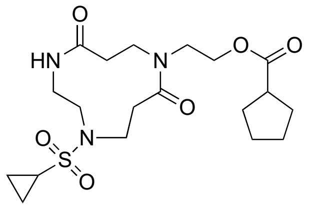
2-(1-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl benzoate (14i)



tert-Butyl 8-(2-(benzoyloxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **13g** (209 mg, 0.48 mmol) was dissolved in 4 M HCl in 1,4-dioxane (2.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (10 mL), was cooled to 0 ℃ and dry triethylamine (0.2 mL, 1.44 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (118 mg, 0.60 mmol) and DMAP (6 mg, 0.048 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (15 mL) washed with saturated brine solution (15 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a white solid (170.4 mg, 72% yield); m.p. 182 – 185 °C; R_f 0.36 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3378, 2938, 1715, 1627, 1540, 1405, 1269, 1172, 1025, 983, 917, 859, 706, 621, 570; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the compoud exists as a 2:1 mixture of rotamers. NMR data for the major rotamer; δ_H (400 MHz, $CDCl_3$) 7.89 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.49 – 7.45 (1H , m, Ar**H**), 7.36 – 7.32 (2H , m, Ar**H**), 6.70 – 6.56 (1H, m, N**H**), 4.45 – 4.42 (2H, m, C**H**$_2$), 4.20 – 3.72 (3H, m, C**H**$_2$), 3.65 – 2.98 (7H, m, C**H**$_2$), 2.72 – 2.16 (10H, m, 2 x C**H**$_3$ and 2 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.9 (CH_3**CO**), 173.9 (**C**O), 172.5 (**C**O), 170.5 (**C**O), 166.5 (**C**Ar), 157.8 (CH_3**CN**), 133.3 (Ar**C**H), 129.5 (ArCH), 128.5 (Ar**C**H), 114.0 (OOS**C**), 62.8 (**C**H$_2$), 46.4 (**C**H$_2$), 46.37 (**C**H$_2$), 46.0 (**C**H$_2$), 45.6 (**C**H$_2$), 41.0 (**C**H$_2$), 36.9 (**C**H$_2$), 30.0 (**C**H$_2$), 13.2 (**C**H$_3$), 11.6 (**C**H$_3$). **HRMS (ESI)**: calcd. for $C_{22}H_{28}N_4NaO_7S$, 515.1589. Found: $[MNa]^+$, 515.1571 (−3.5 ppm error).

Diagnostic NMR data for minor rotamer can be found at; δ_H (400 MHz, $CDCl_3$) 7.01 – 6.88 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 172.4 (**C**O), 157.5 (CH_3**CN**), 133.5 (Ar**C**H), 129.6 (ArCH), 128.6 (Ar**C**H), 114.3 (OOS**C**), 62.7 (**C**H$_2$), 13.3 (**C**H$_3$), 11.7 (**C**H$_3$).

2-(1-(Cyclopropylsulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (14j)



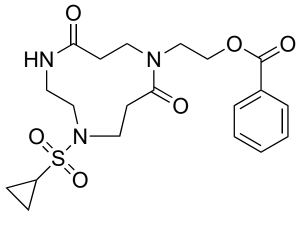
tert-Butyl 8-(2-((cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **13f** (245.7 mg, 0.58 mmol) was dissolved in 4 M HCl in 1,4-dioxane (2.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (17 mL), was cooled to 0 °C and dry triethylamine (0.24 mL, 1.73 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (70 µL, 0.72 mmol) and DMAP (7.1 mg, 0.058 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated brine solution

(20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a yellow oil (166 mg, 67% yield); R_f 0.49 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3315, 2952, 1726, 1636, 1549, 1454, 1332, 1147, 889, 725, 541. The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 6.78 (1H, s, N**H**), 4.31 (2H, s, C**H**$_2$), 3.74 – 3.12 (10H, m, 5 x C**H**$_2$), 2.72 – 2.67 (1H, m, C**H**), 2.53 – 2.49 (1H, m, C**H**), 2.47 – 2.29 (3H, m, C**H**$_2$), 1.89 – 1.84 (2H, m, C**H**$_2$), 1.77 – 1.65 (5H, m, C**H**$_2$), 1.59 – 1.54 (2H, m, C**H**$_2$), 1.24 – 1.18 (2H, m, cyclopropyl C**H**$_2$), 1.04 – 0.95 (2H, m, cyclopropyl C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.7 (**C**O), 172.1 (**C**O), 170.9 (**C**O), 62.3 (**C**H$_2$), 47.0 (**C**H$_2$), 46.9 (**C**H$_2$), 46.8 (**C**H$_2$), 46.0 (**C**H$_2$), 43.8 (**C**H), 41.3 (**C**H$_2$), 37.2 (**C**H$_2$), 30.6 (**C**H$_2$), 30.2 (**C**H$_2$), 27.1 (**C**H), 25.9 (**C**H$_2$), 5.2 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{19}H_{31}N_3NaO_6S$, 452.1828. Found: [MNa]$^+$, 452.1826 (−0.4 ppm error).

Diagnostic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.11 – 6.08 (1H, m, N**H**); δ_C (100 MHz, $CDCl_3$) 176.6 (**C**O), 172.6 (**C**O), 170.9 (**C**O), 62.1 (**C**H$_2$), 52.8 (**C**H$_2$), 51.0 (**C**H$_2$), 47.0 (**C**H$_2$), 43.7 (**C**H$_2$), 43.2 (**C**H), 39.5 (**C**H$_2$), 36.0 (**C**H$_2$), 34.8 (**C**H$_2$), 30.1 (**C**H$_2$), 25.7 (**C**H$_2$), 4.9 (cyclopropyl **C**H$_2$).

For LCMS data confirming this product has >95% purity, see SI Section 5.

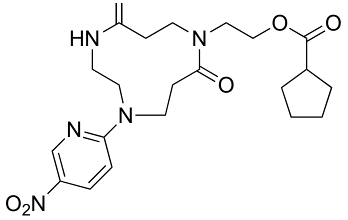
2-(1-(Cyclopropylsulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl benzoate (14k)



tert-Butyl 8-(2-(benzoyloxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **13g** (88 mg, 0.20 mmol) was dissolved in 4 M HCl in 1,4-dioxane (1.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was then dissolved in dry DCM (6 mL), was cooled to 0 °C and dry triethylamine (80 µL, 0.60 mmol) was added dropwise. Next, cyclopronesulfonyl chloride (30 µL, 0.25 mmol) and DMAP (2.4 mg, 0.02 mmol) were added and the reaction mixture was allowed to warm to RT while being stirred for 18 hours. The reaction mixture was diluted with ethyl acetate (10 mL) washed with saturated brine solution (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude was purified by column chromatography (1:9 methanol:ethyl acetate → 1:4 methanol:ethyl acetate) to afford the title compound as a white solid (78.5 mg, 90% yield); m.p. 85 – 90 °C; R_f 0.24 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3287, 2932, 2247, 1716, 1638, 1544, 1451, 1332, 1271, 1147, 1112, 1026, 987, 915, 711, 540. The ^1H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. NMR data for the major rotamer; δ_H (400 MHz, $CDCl_3$) 7.96 – 7.94 (2H, m, Ar**H**), 7.56 – 7.52 (1H , m, Ar**H**), 7.43 – 7.39 (2H , m, Ar**H**), 6.99 – 6.98 (1H, m, N**H**), 4.52 – 4.50 (2H, m, C**H**$_2$), 4.26 – 3.80 (3H, m, C**H**$_2$), 3.62 – 3.08 (8H, m, 4 x C**H**$_2$), 2.48 – 2.36 (3H, m, C**H** and C**H**$_2$), 1.23 – 1.14 (3H, m, C**H**$_2$), 1.00 – 0.91 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 170.7 (**C**O), 166.6 (**C**O), 133.4 (ArCH), 129.7 (**C**Ar), 129.6 (Ar**C**H), 128.6 (Ar**C**H), 63.0 (**C**H$_2$), 46.7 (**C**H$_2$), 46.5 (**C**H$_2$), 46.3 (**C**H$_2$), 46.0 (**C**H$_2$), 41.2 (**C**H$_2$), 37.2 (**C**H$_2$), 30.4 (**C**H$_2$), 26.8 (**C**H), 13.2 (cyclopropyl **C**H$_2$). **HRMS (ESI)**: calcd. for $C_{20}H_{27}N_3NaO_6S$, 460.1526. Found: $[MNa]^+$, 460.1513 (−3.0 ppm error).

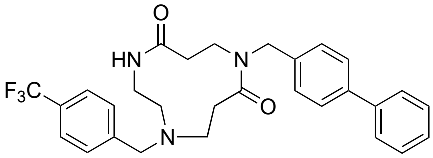
Diagnostic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 6.27 (1H, s, N**H**); δ_C (100 MHz, $CDCl_3$) 166.3 (**C**O), 133.4 (ArCH), 129.4 (**C**Ar), 62.7 (**C**H$_2$), 52.6 (**C**H$_2$), 50.8 (**C**H$_2$), 43.0 (**C**H$_2$), 43.2 (**C**H), 39.6 (**C**H$_2$), 35.8 (**C**H$_2$), 34.6 (**C**H$_2$), 25.6 (**C**H$_2$).

2-(1-(5-Nitropyridin-2-yl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (14l)



tert-Butyl 8-(2-((cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **xx** (81.4 mg, 0.19 mmol) was dissolved in 4 M HCl in 1,4-dioxane (2.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was dissolved in dry MeCN to which was added -2-chloro-5-nitropyridine (37.2 mg, 0.23 mmol) followed by K_2CO_3 (158 mg, 1.14 mmol) and the reaction stirred at 80 °C for 18 hours. The reaction mixture was allowed to cool to RT, and then concentrated *in vacuo*. The crude was purified by column chromatography (1:9 methanol:ethyl acetate) to afford the title compound as a yellow solid (71.6 mg, 84% yield); m.p. 102 – 105 °C; R_f 0.49 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3301, 2954, 1730, 1642, 1515, 1333, 1293, 1164, 1119, 1001; The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. δ_H (400 MHz, DMSO-*d*$_6$) 8.95 (1H, d, *J* = 2.8 Hz, Ar**H**), 8.21 (1H, dd, *J* = 9.6, 2.8 Hz, Ar**H**), 8.09 – 8.06 (1H, m, Ar**H**), 7.25 – 7.23 (1H, m, N**H**), 4.12 – 4.09 (2H, m, C**H**$_2$), 3.36 (12H, m, 6 x C**H**$_2$), 2.74 – 2.66 (1H, m, C**H**), 1.85 – 1.76 (2H, m, C**H**$_2$), 1.70 – 1.49 (8H, m, 4 x C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 175.6 (**C**O), 171.2 (**C**O), 171.0 (**C**O), 161.0 (**C**Ar), 145.3 (Ar**C**H), 134.4 (Ar**C**H), 131.8 (Ar**C**H), 108.1 (**C**Ar), 61.3 (**C**H$_2$), 54.9 (**C**H$_2$), 47.8 (**C**H$_2$), 45.1 (**C**H$_2$), 44.0 (**C**H$_2$), 43.0 (**C**H), 36.6 (**C**H$_2$), 35.9 (**C**H$_2$), 30.1 (**C**H$_2$), 29.4 (**C**H$_2$), 25.3 (**C**H$_2$). **HRMS (ESI)**: calcd. for $C_{21}H_{29}N_5NaO_6$, 470.2016. Found: [MNa]$^+$, 470.2010 (−1.4 ppm error).

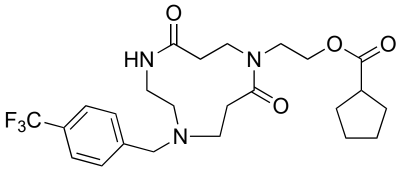
8-([1,1'-Biphenyl]-4-ylmethyl)-1-(4-(trifluoromethyl)benzyl)-1,4,8-triazacycloundecane-5,9-dione (14m)



tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **xx** (100 mg, 0.22 mmol) was dissolved in 4 M HCl in dioxane (4.0 mL). The solution was stirred at RT for 10 minutes, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was dissolved in dry THF to which was added 1-(bromomethyl)-4-(trifluoromethyl) benzene (65.7 mg, 0.28 mmol) followed by dry Et_3N (0.09 mL, 0.66 mmol) and the reaction stirred at 70 °C for 18 hours. The reaction mixture was allowed to cool to RT, and then concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate) to afford the title compound as a liquid (87.2 mg, 78% yield over 2 steps); R_f 0.60 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3312, 2930, 2830, 2243, 1632, 1324, 1160, 1107, 1120, 1065, 1018, 907, 822,728, 698, 646. In solution in $CDCl_3$, the product exists as a 3:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.60 – 7.55 (7H, m Ar**H**), 7.47 – 7.42 (6H, m, Ar**H**), 5.70 (1H, s, N**H**), 4.93 – 4.90 (1H, m, C**H**$_2$), 4.64 – 4.61 (1H, m, C**H**$_2$), 4.08 – 4.01 (1H, m, C**H**$_2$), 3.96 – 3.90 (1H, m, C**H**$_2$), 3.75 – 3.71 (1H, m, C**H**$_2$), 3.47 – 3.44 (1H, m, C**H**$_2$), 3.37 – 3.34 (2H, m, C**H**$_2$), 2.93 – 2.87 (1H, m, C**H**$_2$), 2.69 – 2.64 (1H, m, C**H**$_2$), 2.60 – 2.54 (1H, m, C**H**$_2$), 2.46 – 2.41 (1H, m, C**H**$_2$), 2.30 – 2.23 (2H, m, C**H**$_2$), 2.09 – 2.02 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.6 (**C**O), 171.5 (**C**O), 140.8 (**C**Ar), 140.4 (**C**Ar), 137.4 (**C**Ar), 129.7 (Ar**C**H), 129.5 (Ar**C**H), 128.9 (Ar**C**H), 128.8 (Ar**C**H), 127.6 (Ar**C**H), 127.1 (Ar**C**H), 126.9 (Ar**C**H), 125.3 (Ar**C**H, q, $J_{F\text{-}C}$ = 3.7 Hz), 62.3 (**C**H$_2$), 53.7 (**C**H$_2$), 51.4 (**C**H$_2$), 49.3 (**C**H$_2$), 45.6 (**C**H$_2$), 40.3 (**C**H$_2$), 36.9 (**C**H$_2$), 31.4 (**C**H$_2$). The two ^{13}C NMR signals closest to the fluorine groups were not observed. **HRMS (ESI)**: calcd. for $C_{29}H_{31}F_3N_3O_2$, 510.2374. Found: $[MH]^+$, 510.2363 (−2.1 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 7.37 – 7.33 (1H, m, Ar**H**), 7.18 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.18 – 6.17 (1H, m, N**H**), 4.72 (1H, d, *J* = 16.7 Hz, C**H**$_2$), 4.41 – 4.34 (2H, m, C**H**$_2$), 3.96 – 3.93 (1H, m, C**H**$_2$), 3.56 – 3.53 (1H, m, C**H**$_2$), 3.04 – 2.96 (2H, m, C**H**$_2$), 2.76 – 2.70 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.8 (**C**O), 143.9 (**C**Ar), 143.2 (**C**Ar), 140.8 (**C**Ar), 135.7 (**C**Ar), 58.4 (**C**H$_2$), 53.0 (**C**H$_2$), 52.8 (**C**H$_2$), 50.9 (**C**H$_2$), 43.1 (**C**H$_2$), 37.7 (**C**H$_2$), 34.8 (**C**H$_2$), 34.0 (**C**H$_2$).

2-(5,9-Dioxo-1-(4-(trifluoromethyl)benzyl)-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (14n)



tert-Butyl 8-(2-((cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate **xx** (73 mg, 0.17 mmol) was dissolved in 4 M HCl in 1,4-dioxane (2.0 mL). The solution was stirred at RT for 1 hours, after which the solution was concentrated *in vacuo* to yield the salt product. The salt product was dissolved in dry THF to which was added 1-(bromomethyl)-4-(trifluoromethyl) benzene (51.3 mg, 0.21 mmol) followed by dry Et_3N (0.07 mL, 0.51 mmol) and the reaction stirred at 70 °C for 18 hours. The reaction mixture was allowed to cool to RT, and then concentrated *in vacuo*. The crude was purified by column chromatography (1:19 methanol:ethyl acetate → 1:9 methanol:ethyl acetate) to afford the title compound as a yellow oil (57.8 mg, 70% yield); R_f 0.51 (1:9 methanol:ethyl acetate). **IR** (ATR): ν_{max}/cm^{-1} 3314, 2958, 1729, 1640, 1543, 1454, 1323, 1158, 1119, 1065, 1017, 852, 822, 732. In solution in $CDCl_3$, the product exists as a roughly 5:1 mixture of rotamers. NMR data for the major rotamer only; δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.34 (2H, d, *J* = 7.9 Hz, Ar**H**), 6.29 (1H, s, N**H**), 4.47 – 4.44 (2H, m, C**H**$_2$), 4.24 – 4.15 (1H, m, C**H**$_2$), 4.03 – 3.98 (1H, m, C**H**$_2$), 3.82 – 3.79 (1H, m, C**H**$_2$), 3.64 – 3.61 (1H, m, C**H**$_2$), 3.39 – 3.32 (2H, m, C**H**$_2$), 3.28 – 3.22 (1H, m, C**H**$_2$), 2.92 – 2.79 (2H, m, C**H**$_2$), 2.66 – 2.58 (2H, m, C**H** and C**H**H'), 2.51 – 2.48 (2H, m, C**H**$_2$), 2.44 – 2.38 (1H, m, CH**H'**), 2.30 – 2.27 (1H, m, C**H**$_2$), 2.01 (2H, m, C**H**$_2$), 1.87 – 1.81 (2H, m, C**H**$_2$), 1.72 – 1.66 (4H, m, 2 x C**H**$_2$), 1.55 – 1.53 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.6 (**C**O), 173.2 (**C**O), 171.6 (**C**O), 143.9 (**C**Ar), 129.3 (Ar**C**H), 125.3 (Ar**C**H, q, $J_{F\text{-}C}$ = 3.7 Hz), 62.6 (**C**H$_2$), 62.4 (**C**H$_2$), 53.8 (**C**H$_2$), 52.0 (**C**H$_2$), 48.0 (**C**H$_2$), 47.5 (**C**H$_2$), 43.7 (**C**H), 40.2 (**C**H$_2$), 37.1 (**C**H$_2$), 31.6 (**C**H$_2$), 30.2 (**C**H$_2$), 25.9 (**C**H$_2$). The two ^{13}C NMR signals closest to the fluorine groups were not observed. **HRMS (ESI)**: calcd. for $C_{24}H_{32}F_3N_3NaO_4$, 506.2240. Found: $[MNa]^+$, 506.2237 (−0.6 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 7.37 – 7.33 (1H, m, Ar**H**), 7.18 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.18 – 6.17 (1H, m, N**H**), 4.72 (1H, d, *J* = 16.7 Hz, C**H**$_2$), 4.41 – 4.34 (2H, m, C**H**$_2$), 3.96 – 3.93 (1H, m, C**H**$_2$), 3.56 – 3.53 (1H, m, C**H**$_2$), 3.04 – 2.96 (2H, m, C**H**$_2$), 2.76 – 2.70 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.7 (**C**O), 171.8 (**C**O), 135.7 (**C**Ar), 133.4 (**C**Ar), 125.3 (Ar**C**H), 58.4 (**C**H$_2$), 53.0 (**C**H$_2$), 52.8 (**C**H$_2$), 50.9 (**C**H$_2$), 43.1 (**C**H$_2$), 37.7 (**C**H$_2$), 34.8 (**C**H$_2$), 34.0 (**C**H$_2$).

3) Bioassay Information

To assess the antibacterial activity of the compounds at the single concentration, single dose response antibacterial activity assay was performed against Gram-positive S*taphylococcus aureus* and Gram-negative *Escherichia coli.* The compounds were diluted in Mueller-Hinton (MH) medium to a final concentration of 100 µM. Unfortunately, none of the compounds exhibited significant bacterial growth inhibition.

Single Dose Response Antibacterial Activity

A single colony of S*taphylococcus aureus* (CCUG 19434) was grown in Tryptic Soy Broth (TSB) and *Escherichia coli* (NCTC 13476) in Luria-Bertani (LB) medium overnight at 37 °C. Stock solutions of the test compounds were prepared at 5 mM in DMSO and diluted achieve a final concentration of 100 µM in Mueller-Hinton (MH) medium. The overnight culture was diluted in the same growth medium and incubated until OD_{600} reached 0.6–1.0. The bacteria concentration was measured by measuring the optical density at 600 nm and diluted to a OD_{600} of 0.022 in MH medium. 10 µL of the diluted bacterial solution was used to inoculate 300 µL of the sample solutions in individual wells of 96 well plates (Starlab 96-well Cytoone plate, non-treated). The plates were then incubated at 37 °C for 16 hours. For each replica, a control of broth only and a growth control of broth with bacterial inoculum without antibiotics were included in two columns of the plate. Polymyxin B (PMB) and vancomycin (VCM) were used at 20 µg/mL as control antibiotics for *E. coli,* and *S. aureus.* The absorbance values were measured with a TECAN well plate reader instrument M1000.The growth was measured by analysing the absorbance of the bacterial suspension at 600 nm. Each experiment was repeated in triplicate.

Compound	*S.aureus*	*E. coli*	Compound	*S.aureus*	*E. coli*
7a	103.1 ± 7.0	99.6 ± 6.9	**10d**	87.5 ± 2.1	103.2 ± 3.4
7b	97.8 ± 6.8	95.3 ± 8.7	**10e**	89.8 ± 2.5	104.4 ± 2.4
7c	99.0 ± 8.9	91.8 ± 10.9	**10g**	92.2 ± 3.3	103.0 ± 1.9
7d	96.9 ± 9.3	92.4 ± 10.3	**10f**	95.0 ± 5.1	102.6 ± 2.1
7e	95.8 ± 9.3	95.4 ± 7.2	**10h**	96.4 ± 3.9	99.9 ± 3.3
8a	96.7 ± 10.3	98.0 ± 5.5	**10i**	103.9 ± 10.3	102.7 ± 3.6
8b	99.3 ± 12.8	97.2 ± 7.6	**10j**	97.9 ± 3.7	103.6 ± 6.0
8c	100.1 ± 11.9	95.9 ± 5.9	**10k**	93.6 ± 3.6	101.7 ± 6.0
8d	103.0 ± 13.0	94.0 ± 4.9	**13a**	95.8 ± 4.1	101.5 ± 6.6
8e	102.8 ± 11.8	97.6 ± 6.2	**13b**	92.4 ± 4.1	104.4 ± 4.6
8f	106.6 ± 13.7	99.8 ± 4.7	**41**	84.1 ± 4.0	101.8 ± 5.8
8g	107.9 ± 14.9	102.7 ± 3.8	**14m**	73.1 ± 7.1	128.0 ± 4.4
8h	99.1 ± 5.0	106.2 ± 5.8	**14a**	92.0 ± 2.7	104.4 ± 2.6
8i	92.6 ± 3.9	102.0 ± 5.7	**14e**	93.5 ± 1.9	104.6 ± 2.7
8j	93.8 ± 4.8	99.5 ± 7.1	**14d**	92.5 ± 5.0	104.4 ± 3.1
8k	91.9 ± 4.5	99.3 ± 7.3	**14b**	95.8 ± 4.1	103.7 ± 2.1
9a	90.1 ± 5.1	100.4 ± 4.9	**14f**	88.9 ± 9.8	126.6 ± 12.9
9b	89.2 ± 3.6	100.9 ± 5.9	**14j**	99.8 ± 5.7	99.5 ± 3.5
9c	91.3 ± 4.2	100.7 ± 5.3	**14i**	98.2 ± 3.6	99.5 ± 6.0
9d	91.1 ± 5.0	100.6 ± 5.0	**13i**	93.0 ± 4.7	102.4 ± 5.9
9e	95.1 ± 4.9	99.7 ± 3.3	**13h**	92.3 ± 4.3	103.6 ± 5.2
9g	97.5 ± 6.3	100.9 ± 3.1	**13j**	90.5 ± 3.5	103.5 ± 4.6
9f	98.8 ± 5.3	101.2 ± 5.3	**12l**	87.6 ± 4.4	104.1 ± 3.9
9h	105.8 ± 13.0	102.1 ± 4.0	**11j**	94.8 ± 4.9	105.1 ± 5.1
9i	96.5 ± 5.0	104.5 ± 5.7	**7l**	86.8 ± 5.6	107.1 ± 2.7
9j	95.5 ± 4.1	102.8 ± 3.1	**13d**	92.1 ± 7.1	107.7 ± 4.7
9k	94.0 ± 6.1	101.6 ± 4.9	**13c**	94.6 ± 7.8	107.9 ± 3.1
10a	89.3 ± 4.0	102.1 ± 6.5	**14k**	98.4 ± 2.7	101.3 ± 5.6
10b	89.0 ± 4.1	101.1 ± 6.6	**14h**	96.1 ± 3.2	102.6 ± 5.9
10c	88.4 ± 2.7	101.3 ± 6.5	**14l**	92.2 ± 3.1	102.7 ± 5.4

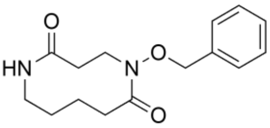
Table S1. Viability of *S. aureus* and *E. coli* in % relative to growth control after treatment with 100 µM of the corresponding compounds.

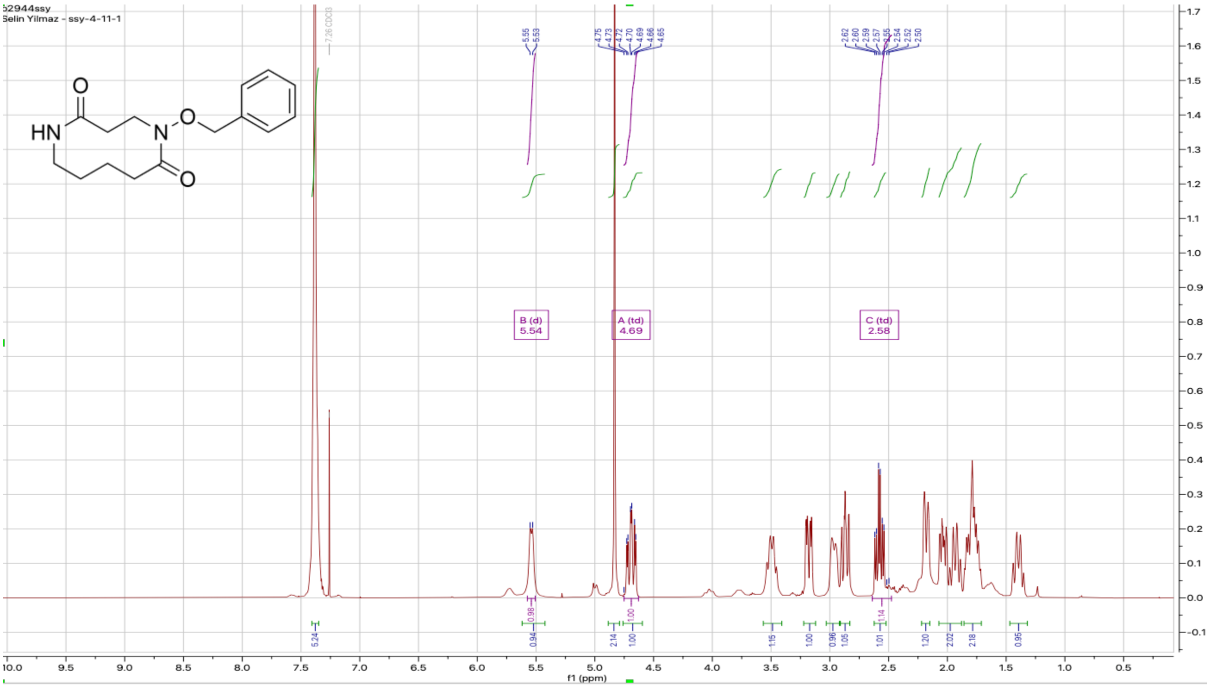
VCM	12.2 ± 1.9
PMB	14.3 ± 0.6

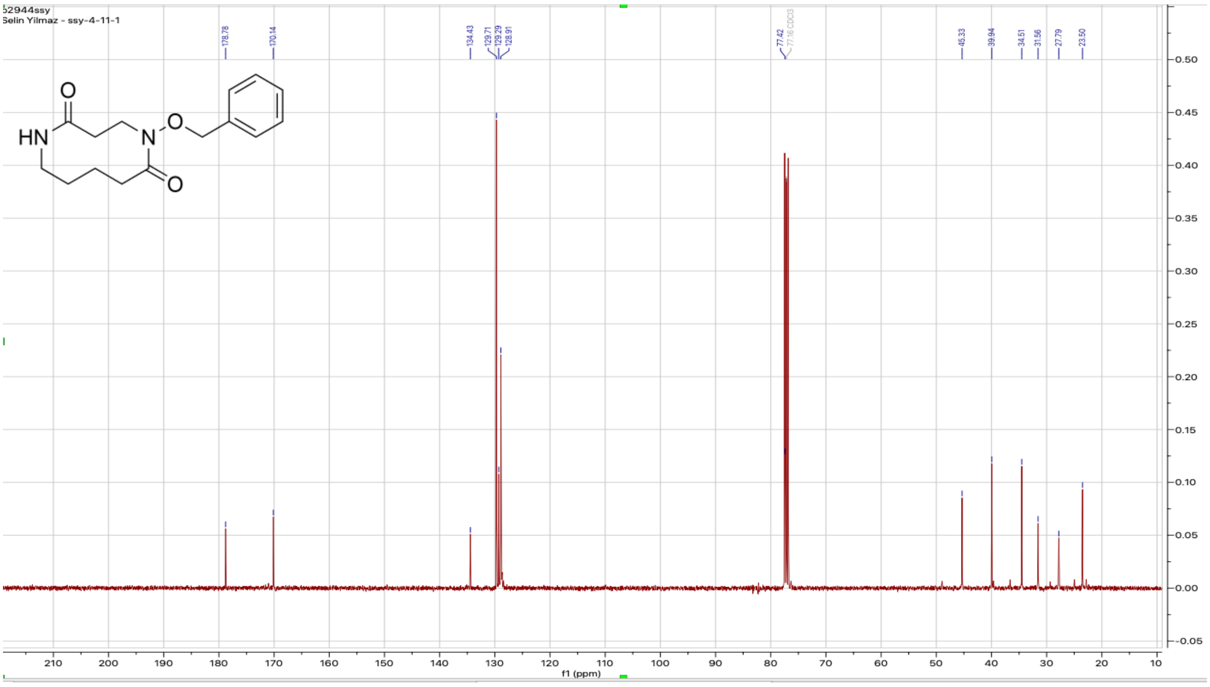
Table S2. Viability of *S. aureus* and *E. coli* respectively, in % relative to growth control after treatment with 20 µg/mL of the control antibiotics.

4. ^{1}H and ^{13}C NMR Spectra

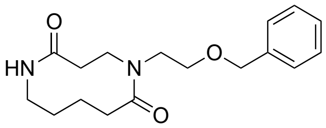
5-(Benzyloxy)-1,5-diazecane-2,6-dione (7a)- Evidence of rotameric broadening in the ^{1}H NMR data, with trace (<10%) signals for a minor rotamer.

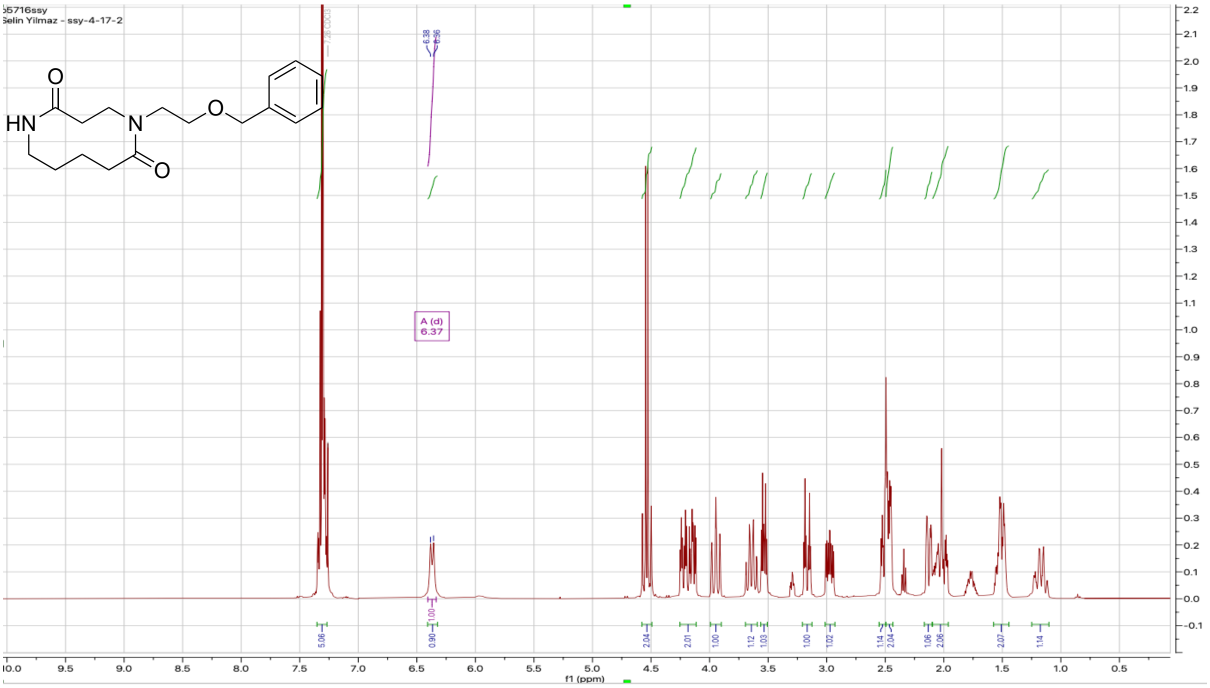


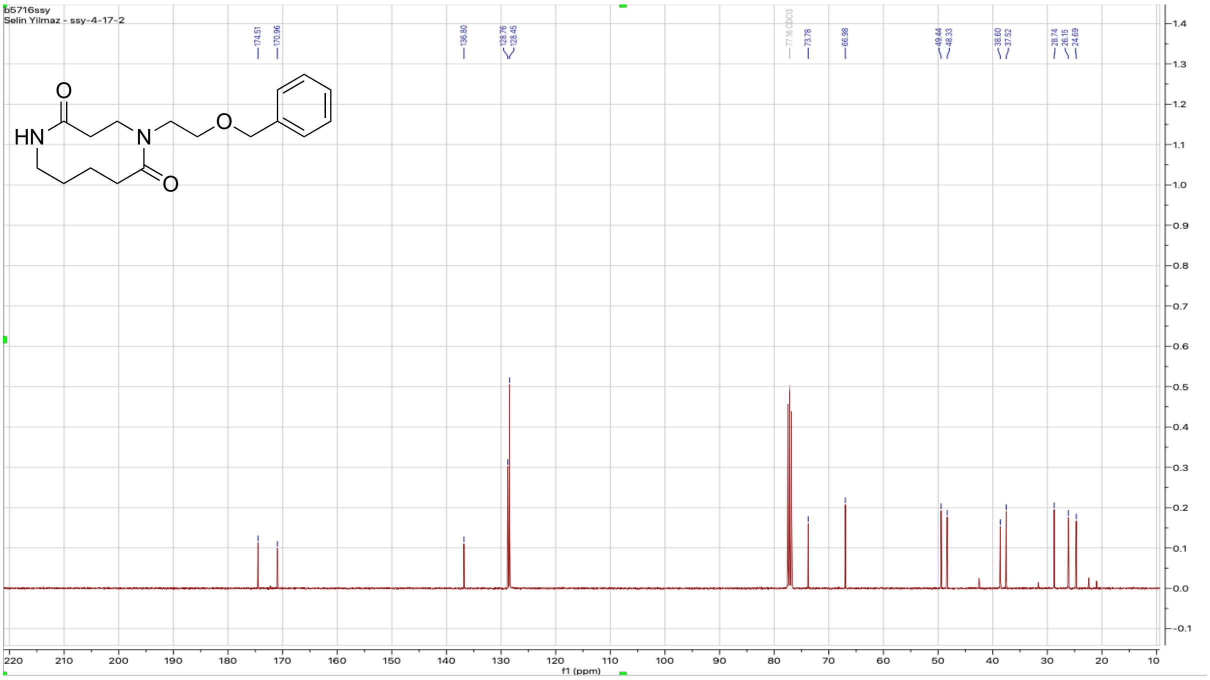




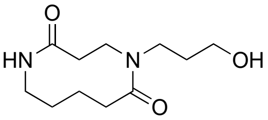
5-(2-(Benzyloxy)ethyl)-1,5-diazecane-2,6-dione (7b)

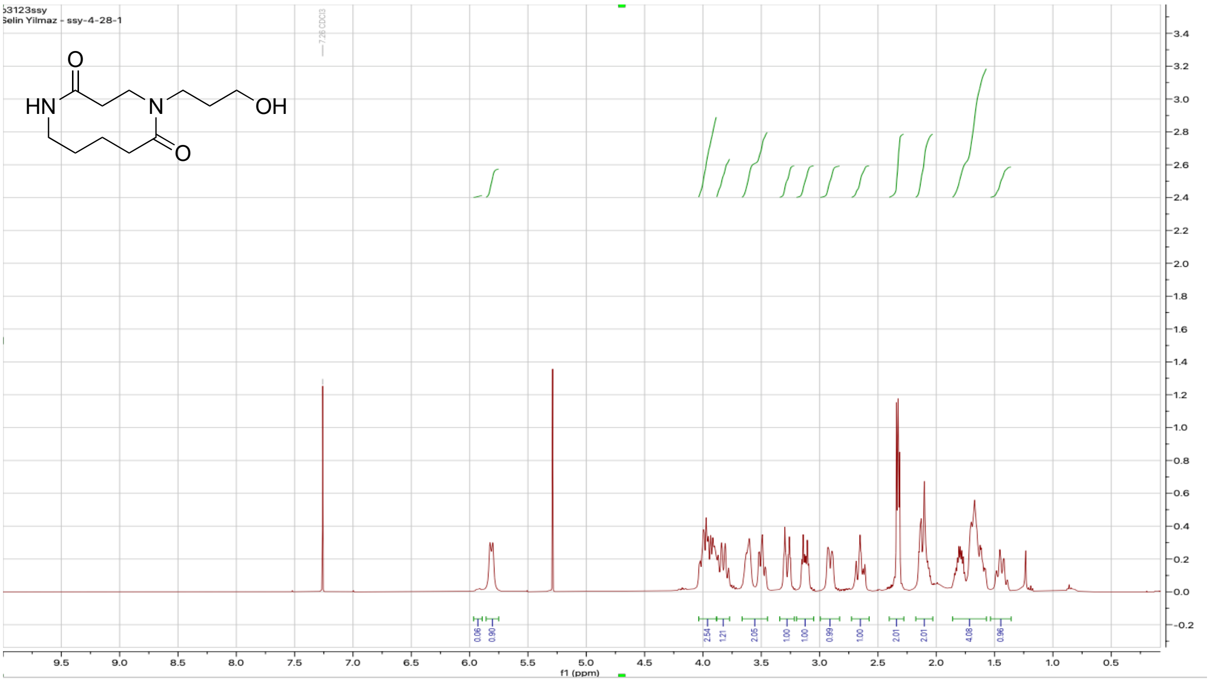


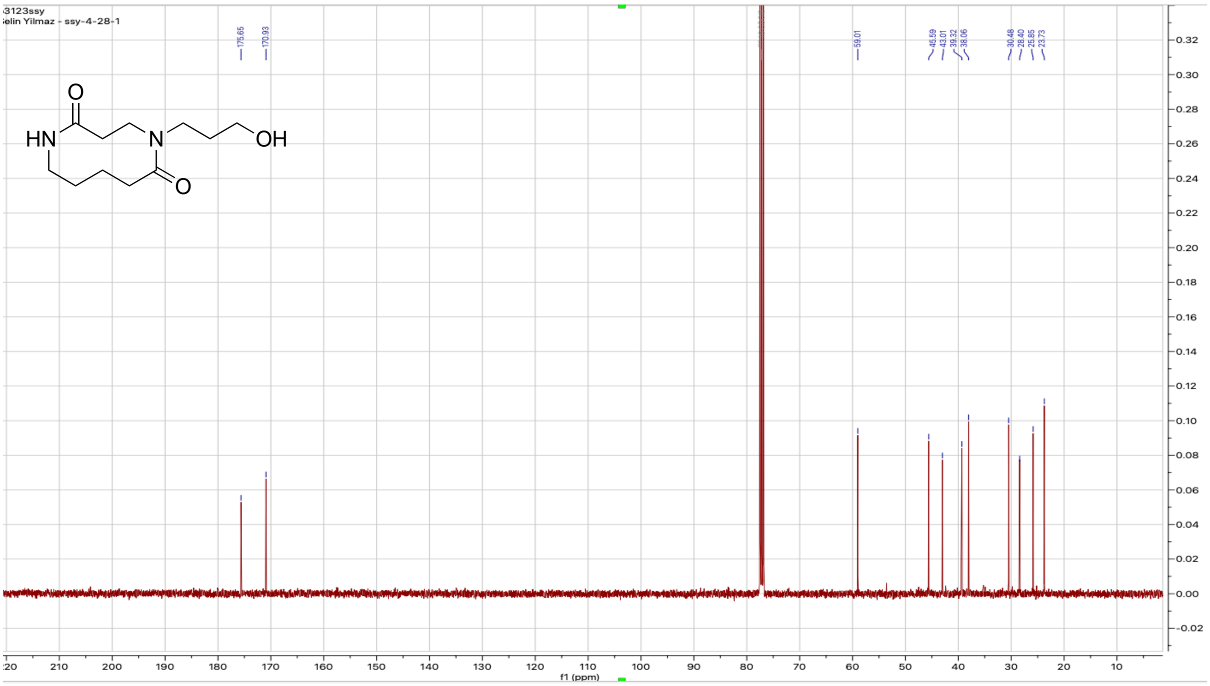




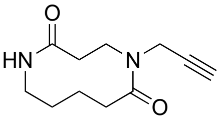
5-(3-Hydroxypropyl)-1,5-diazecane-2,6-dione (7c)

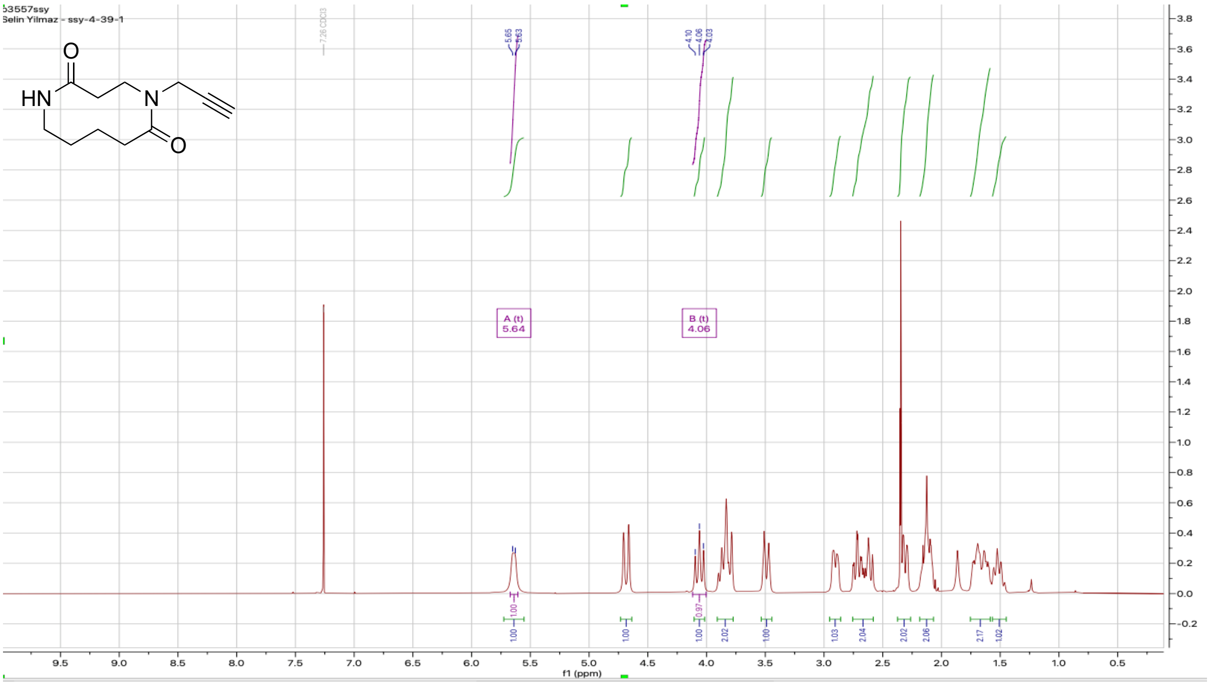


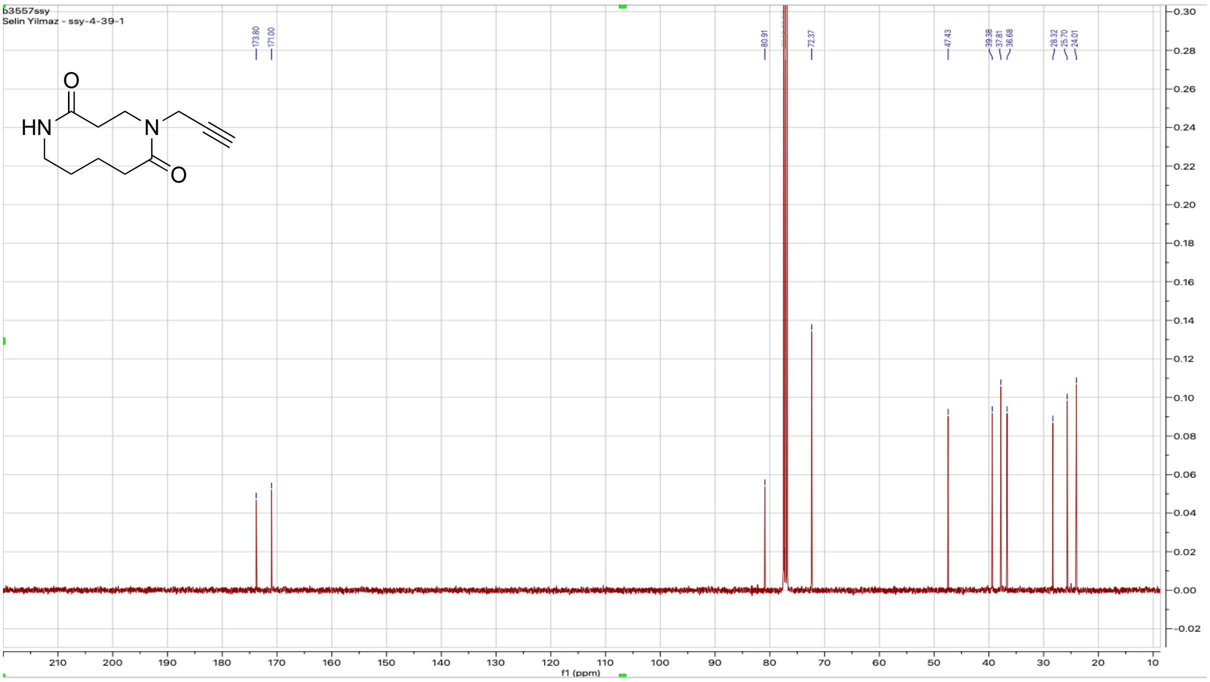




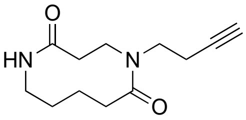
5-(Prop-2-yn-1-yl)-1,5-diazecane-2,6-dione (7d)

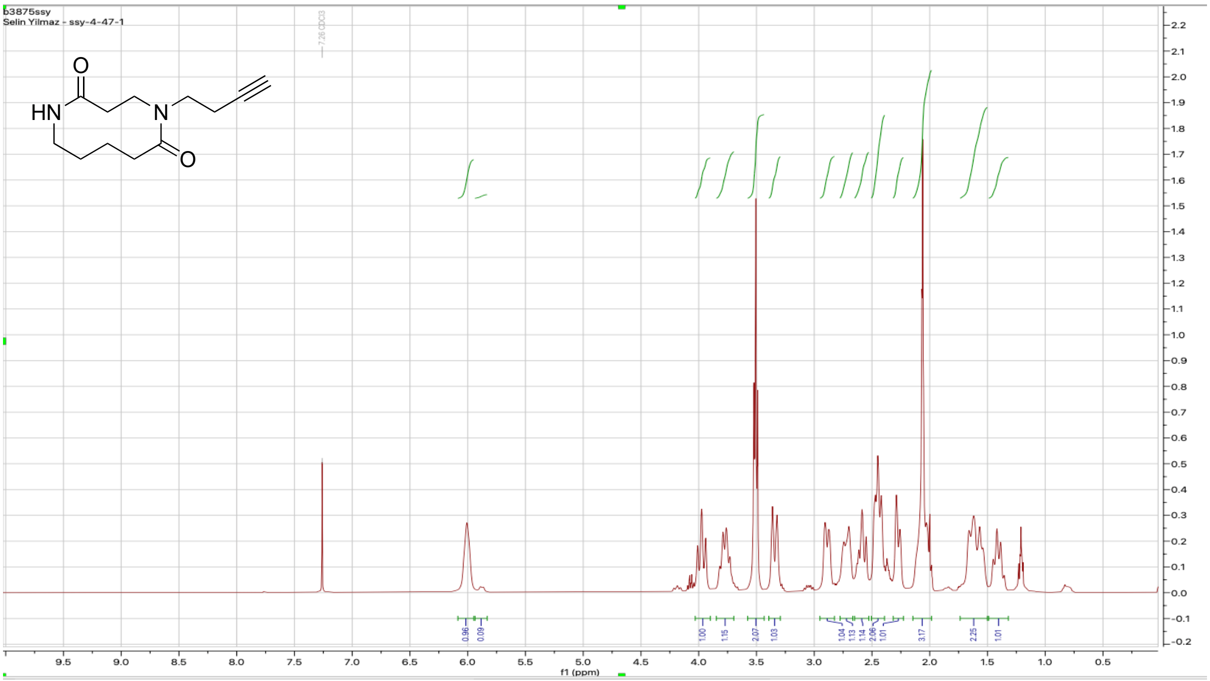


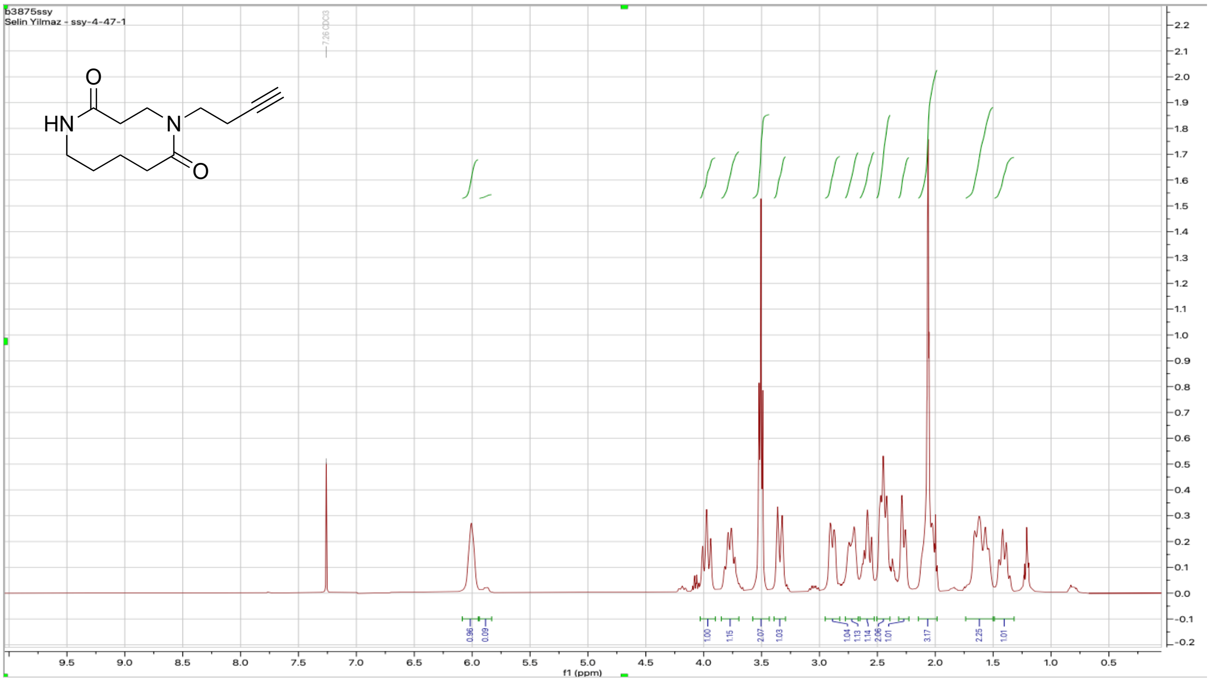




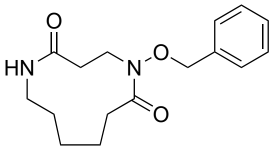
5-(But-3-yn-1-yl)-1,5-diazecane-2,6-dione (7e) – 10:1 mixture of rotamers

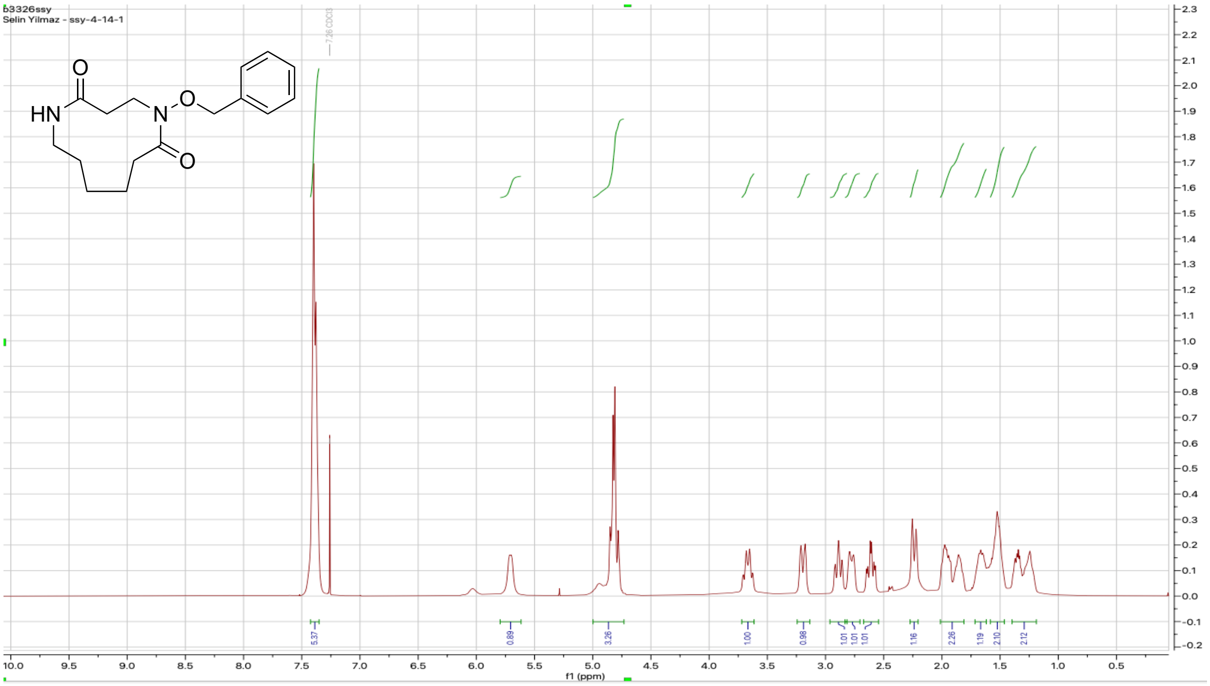


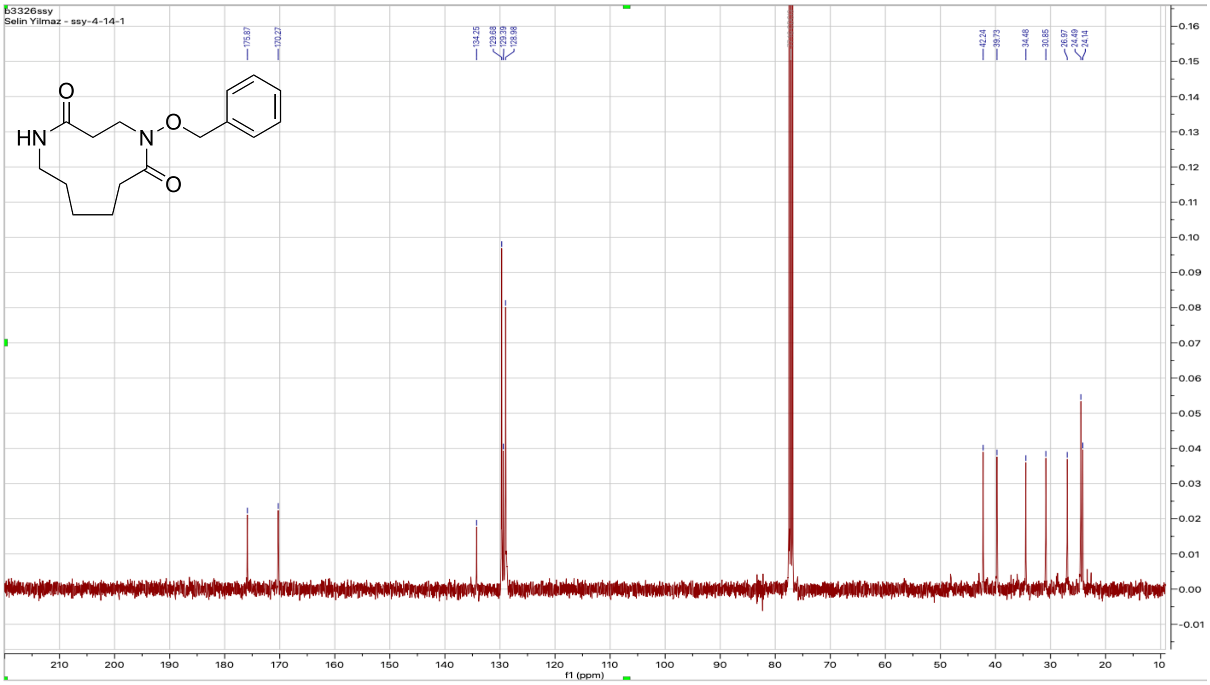




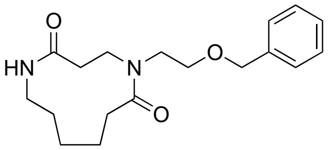
5-(Benzyloxyl)-1,5-diazacycloundecane-2,6-dione (8a) - evidence of rotameric broadening in the ^{1}H NMR data, with trace (<10%) signals for a minor rotamer

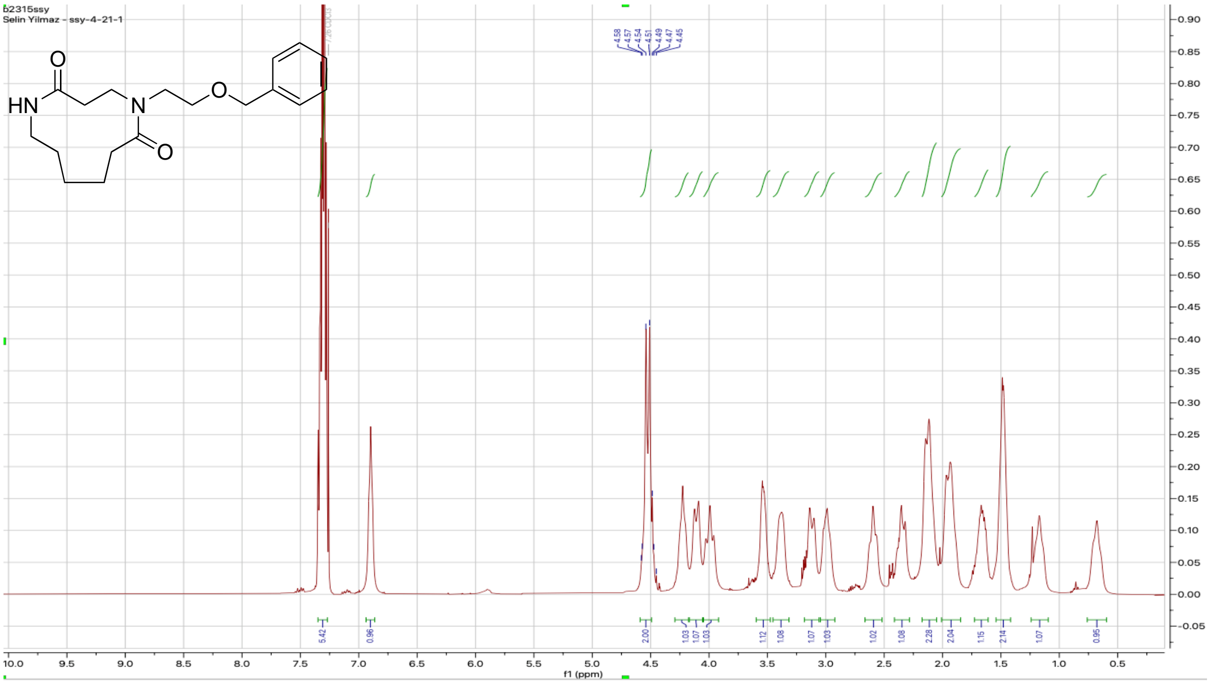


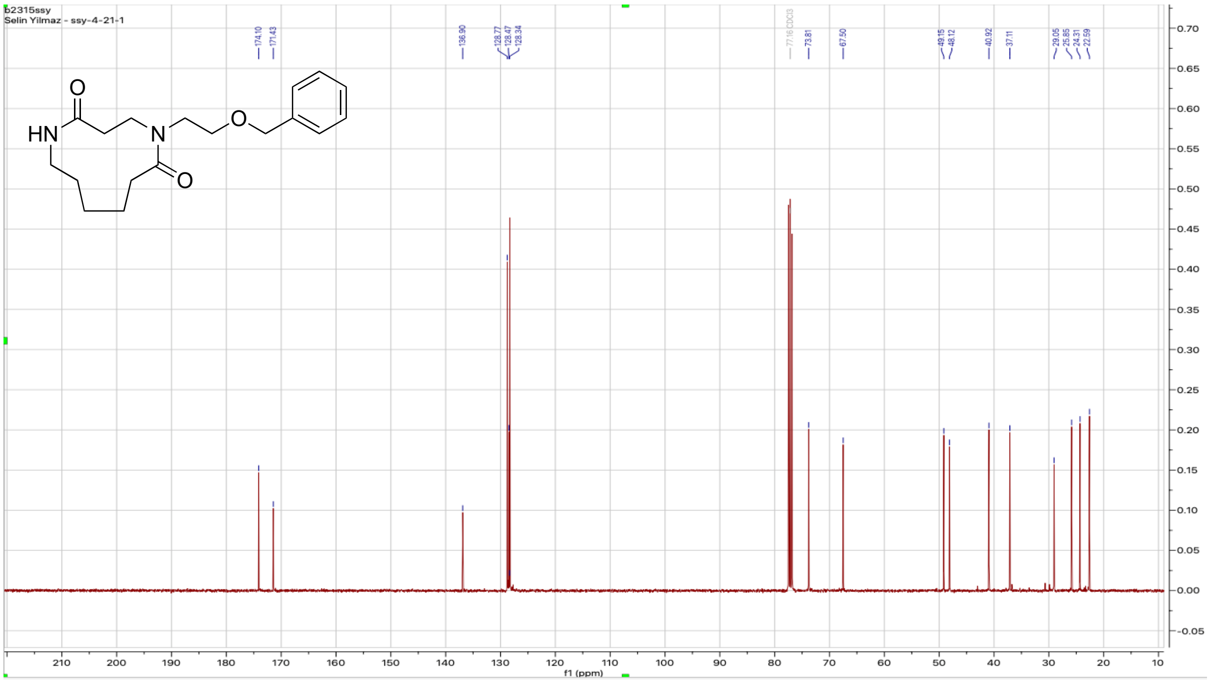




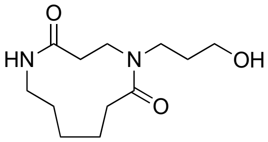
5-(2-(Benzyloxyl)ethyl-1,5-diazacycloundecane-2,6-dione (8b)

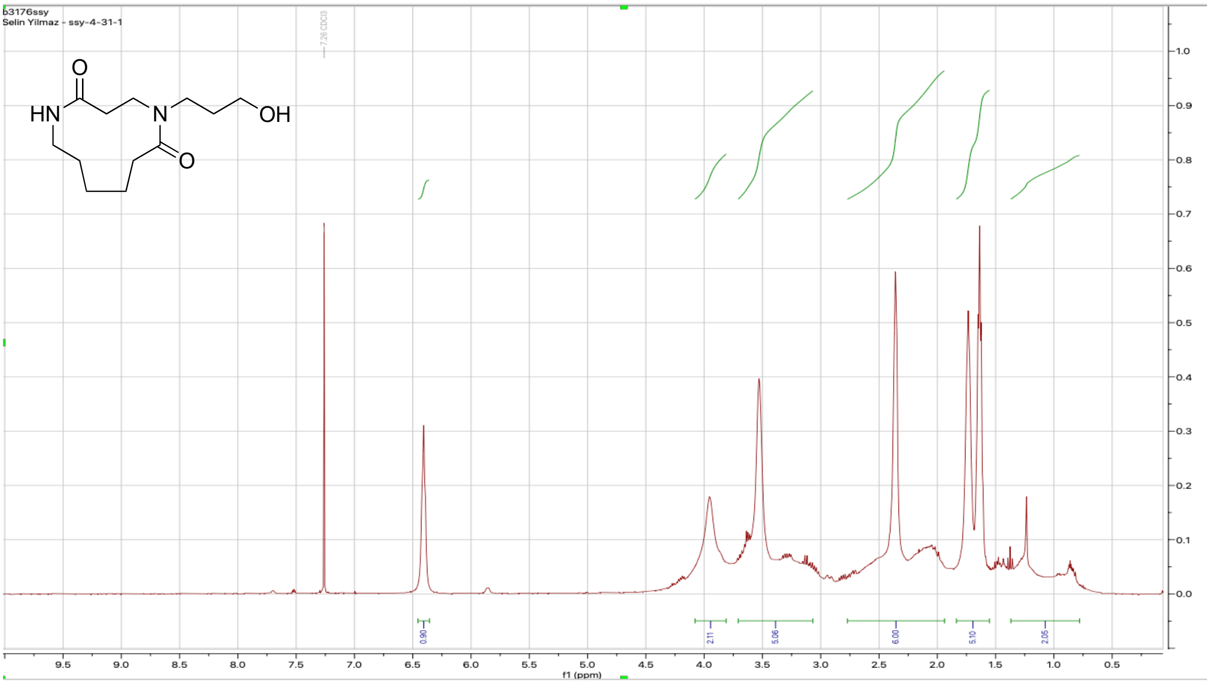


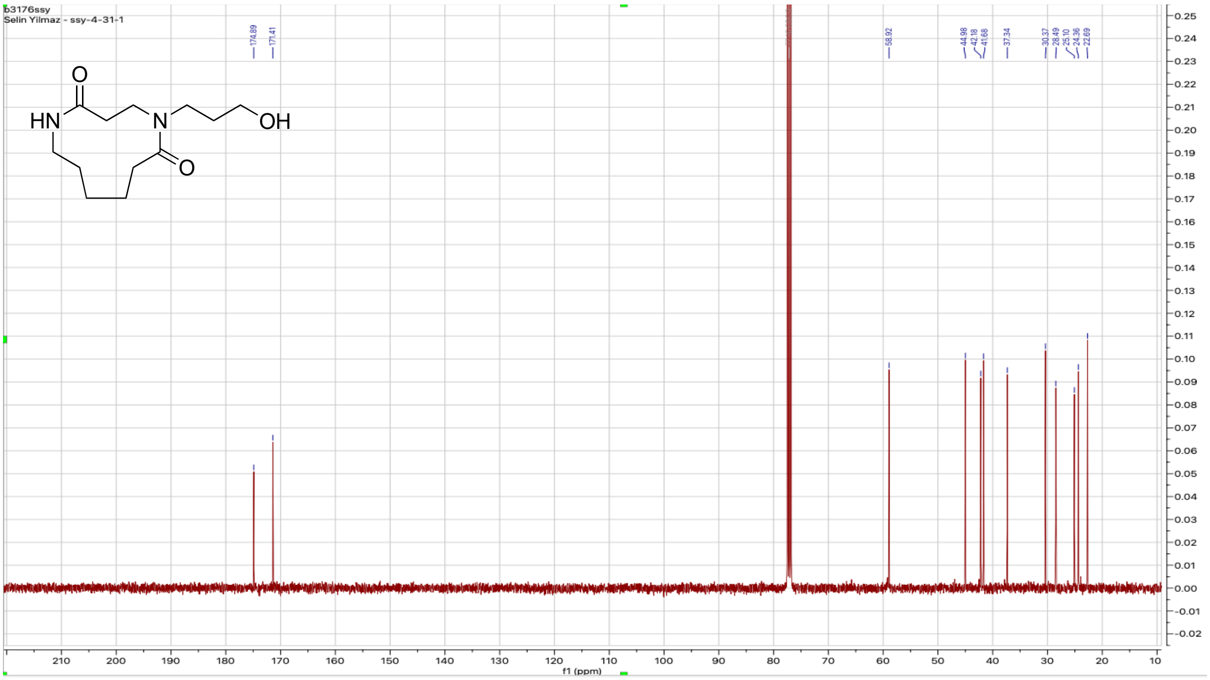




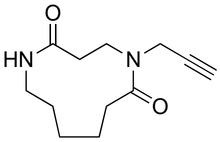
5-(3-Hydroxypropyl)-1,5-diazacycloundecane-2,6-dione (8c) - the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product

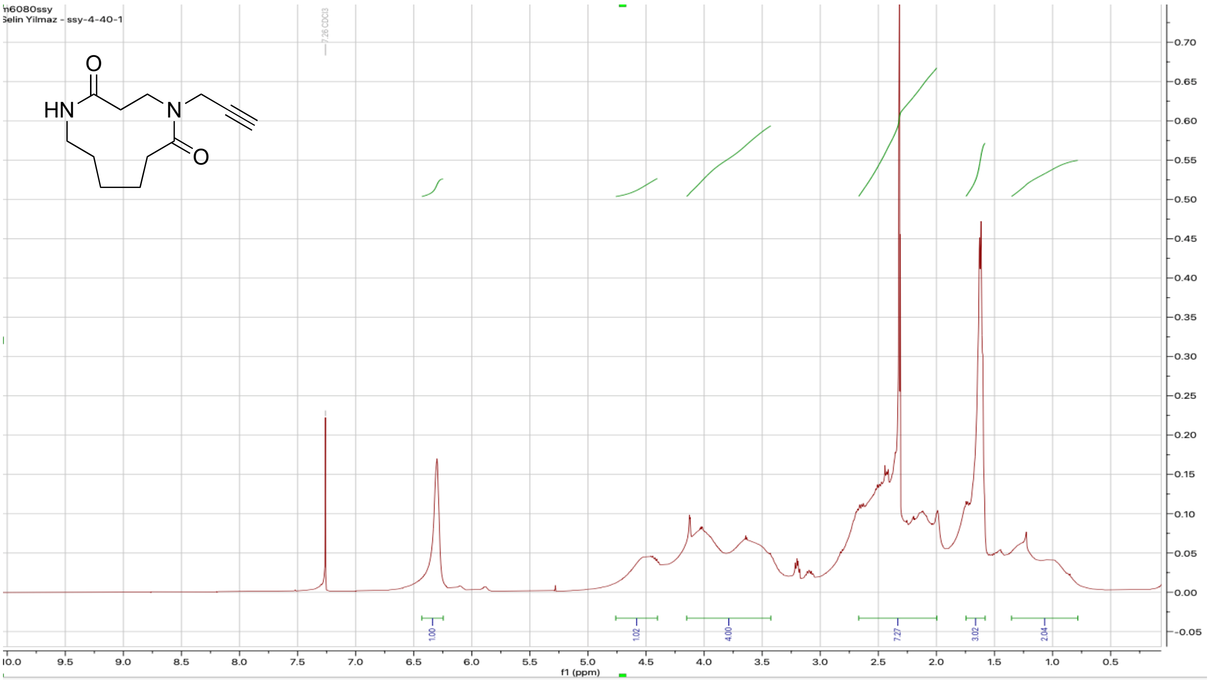


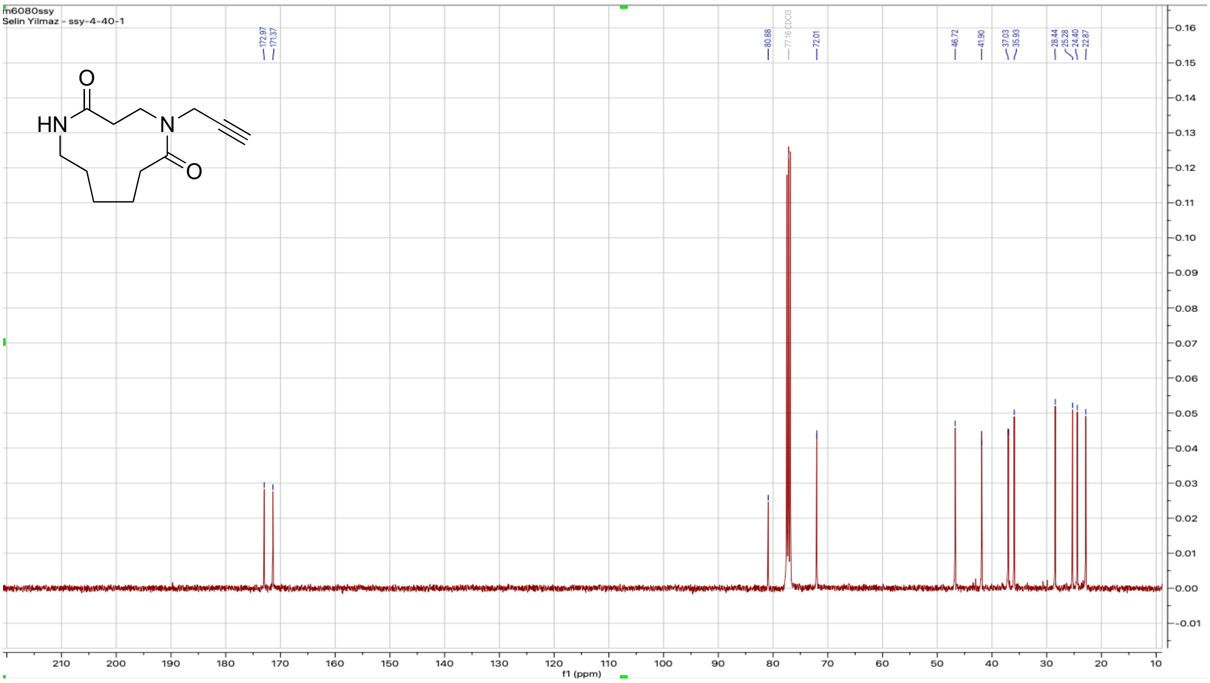




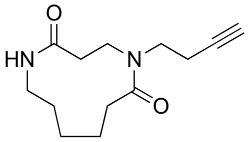
5-(Prop-2-yn-1-yl)-1,5-diazacycloundecane-2,6-dione (8d) - the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product

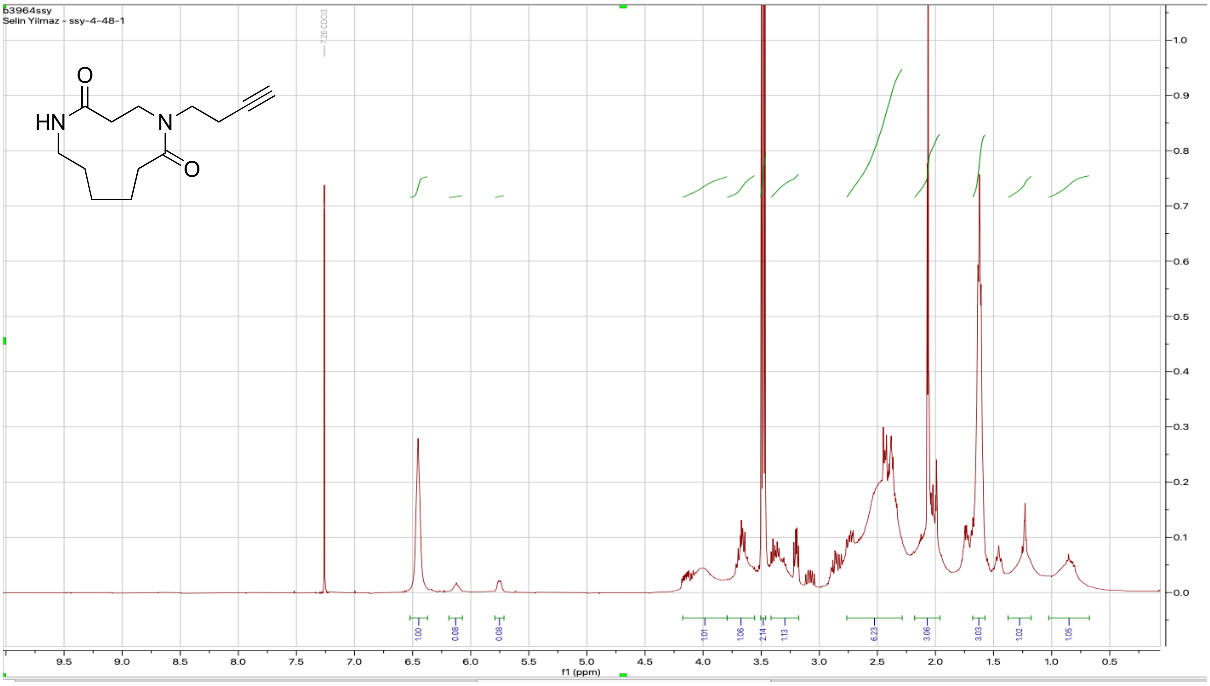


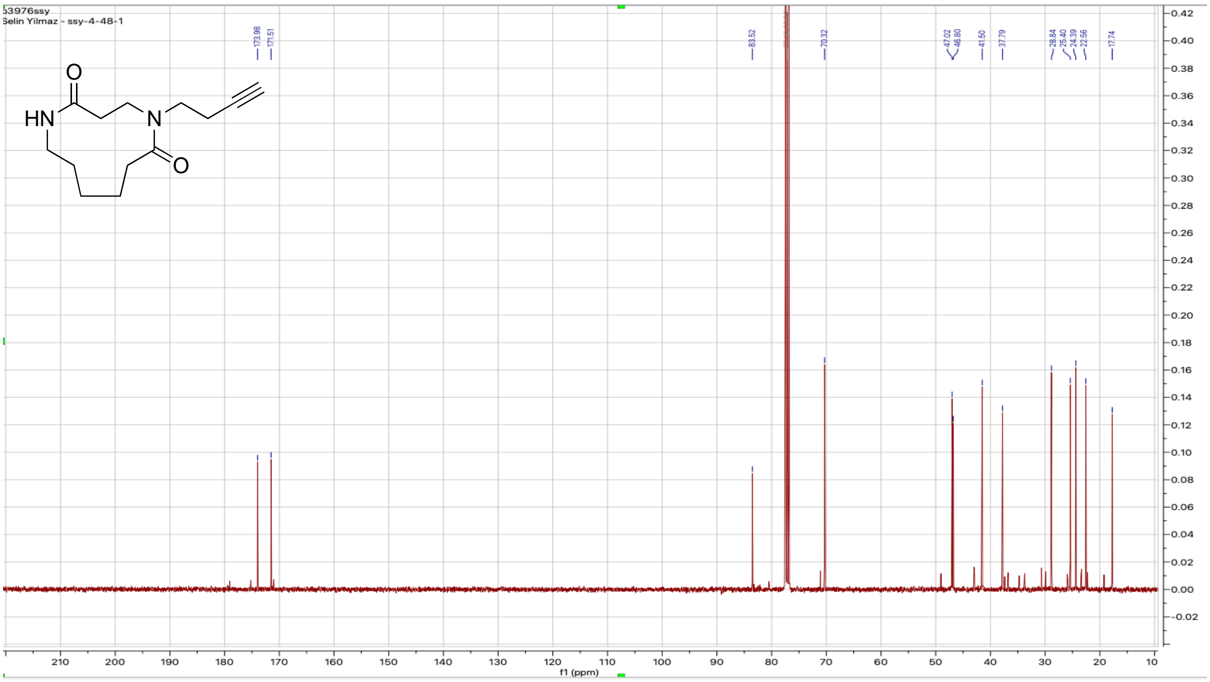




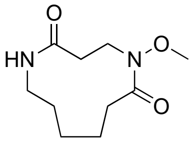
5-(But-3-yn-1-yl)-1,5-diazacycloundecane-2,6-dione (8e) - the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. In solution in CDCl$_3$, the product exists as a 13:1:1 mixture of rotamers.

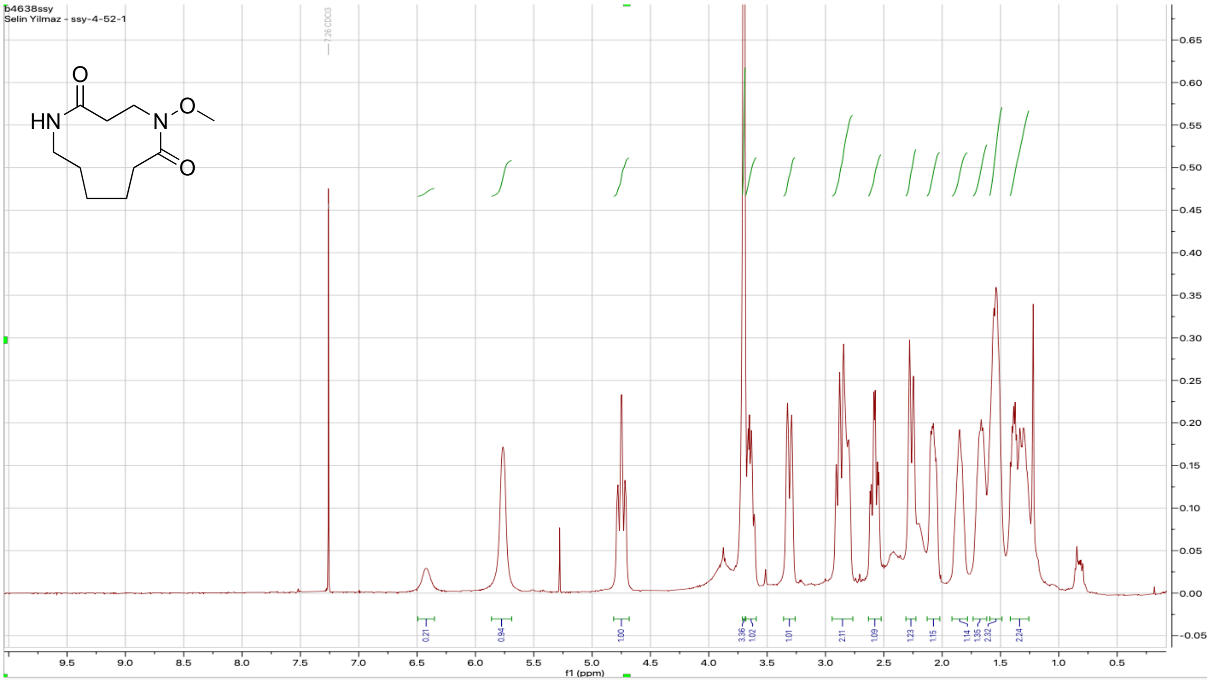


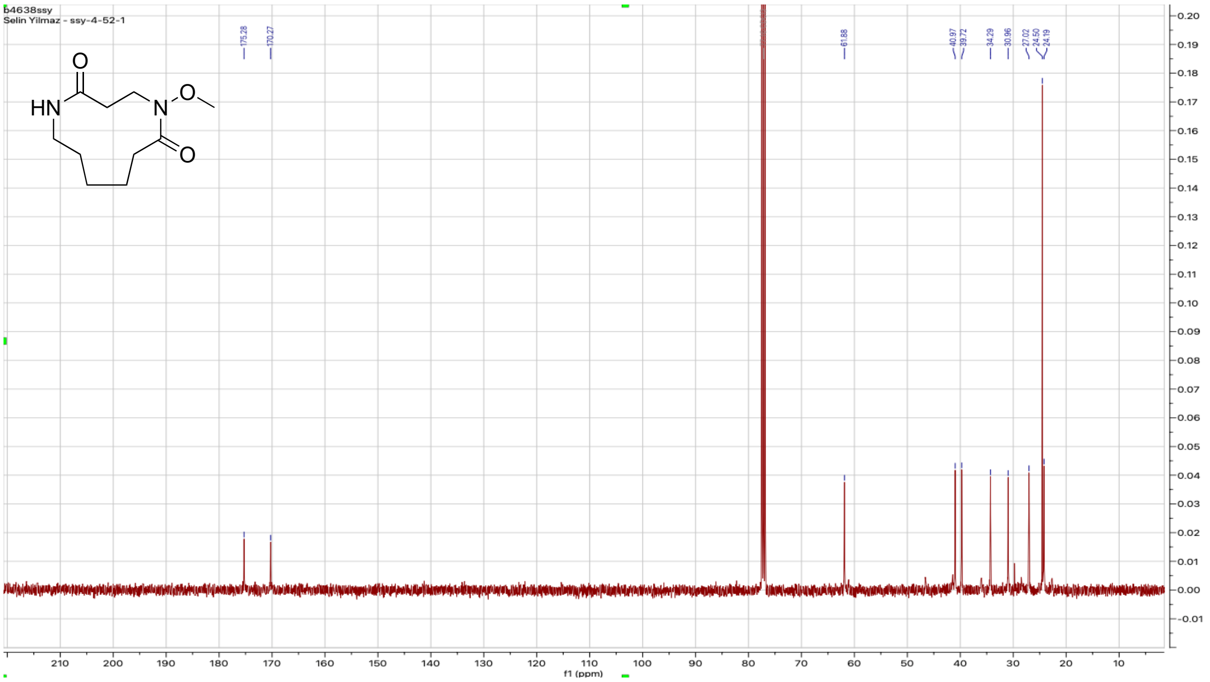




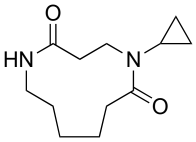
5-Methoxy-1,5-diazacycloundecane-2,6-dione (8f) - 5:1 mixture of rotamers

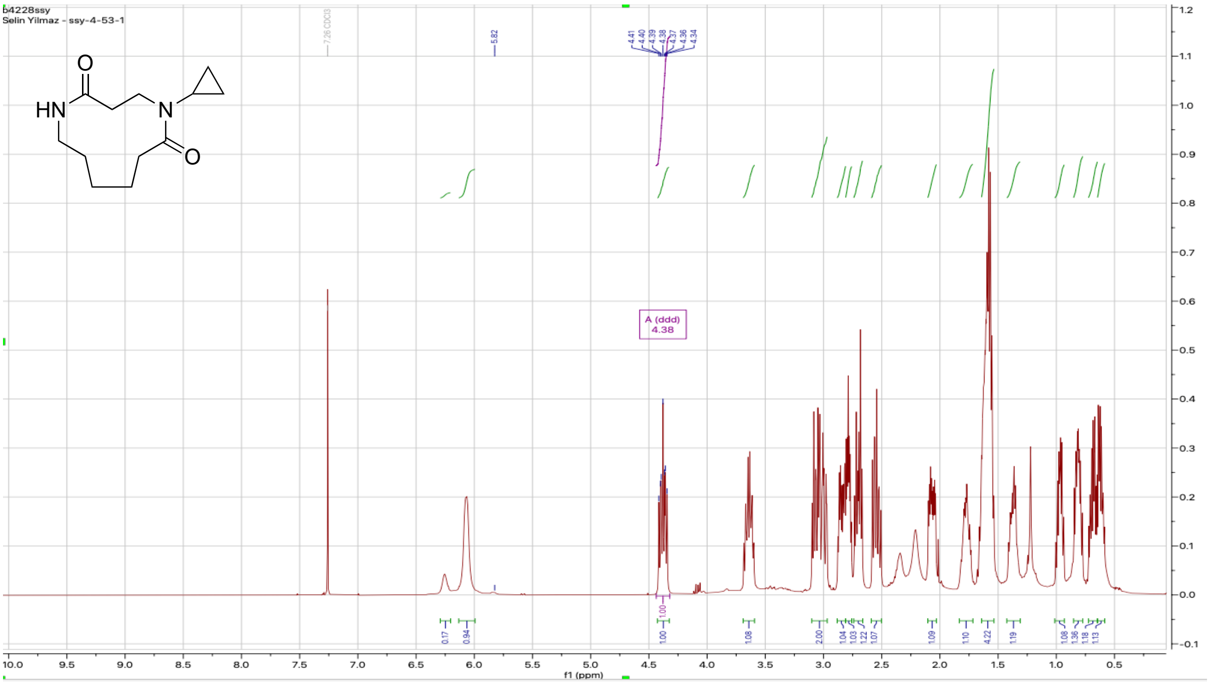


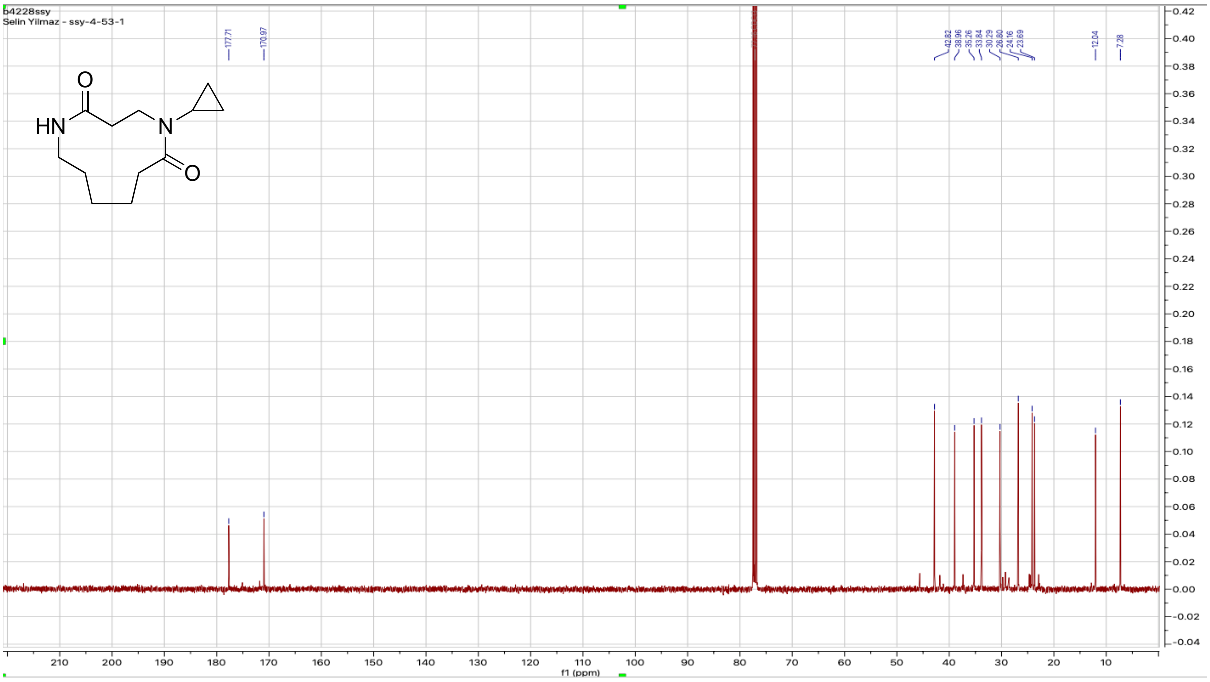




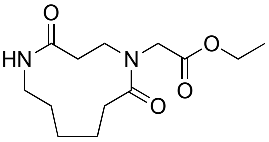
5-Cyclopropyl-1,5-diazacycloundecane-2,6-dione (8g) - 6:1 mixture of rotamers

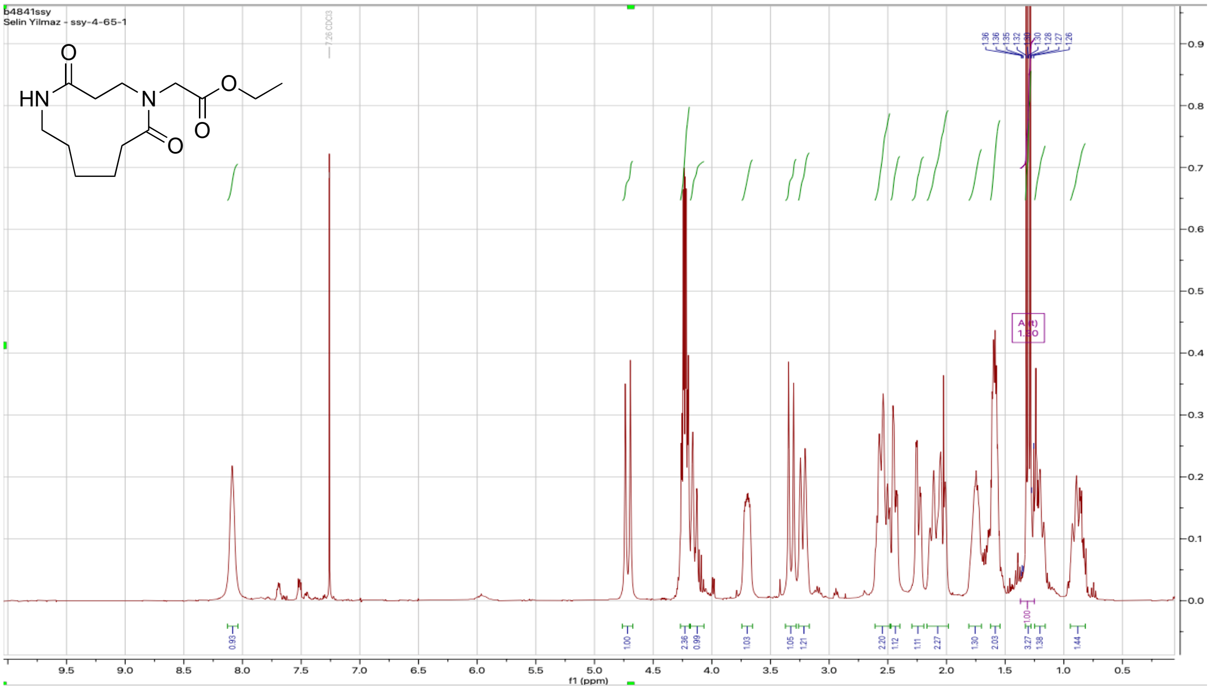


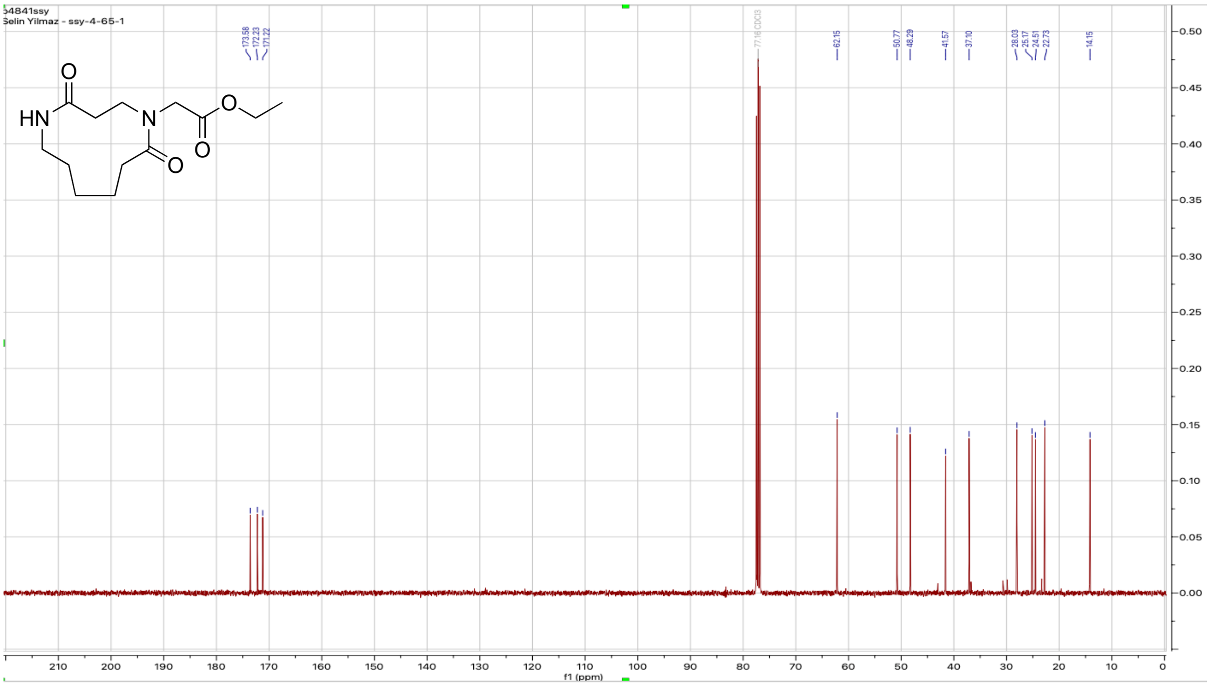




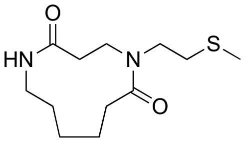
Ethyl 2-(4,11-dioxo-1,5-diazacycloundecan-1-yl)acetate (8h)

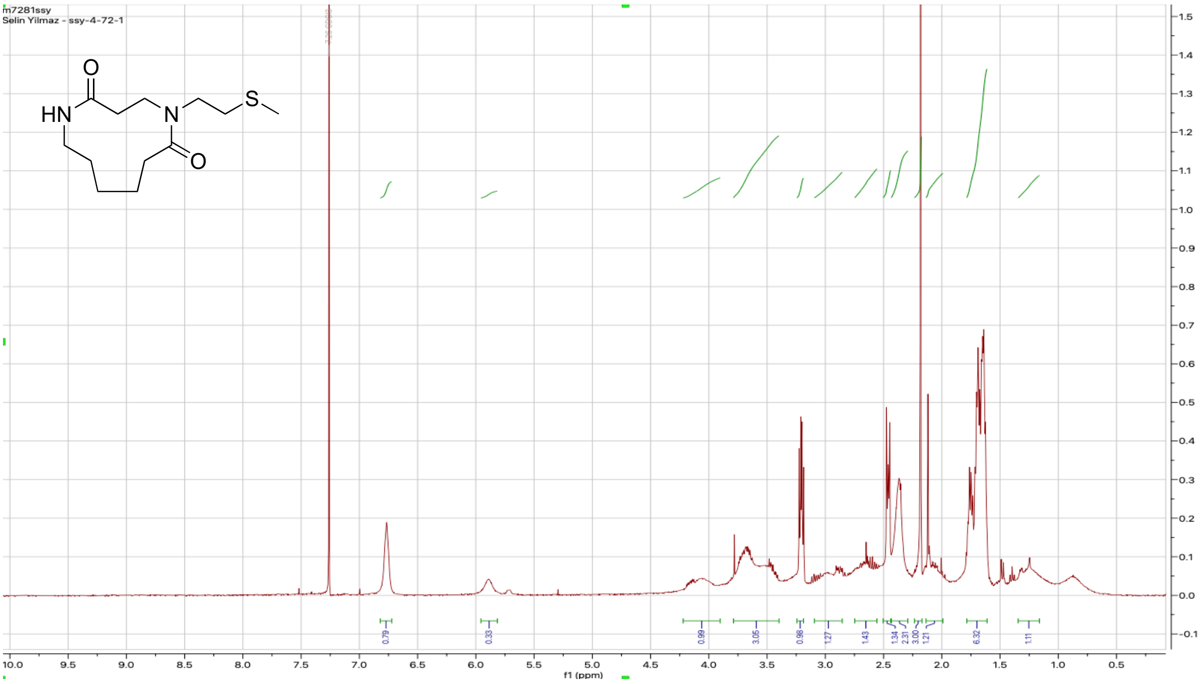


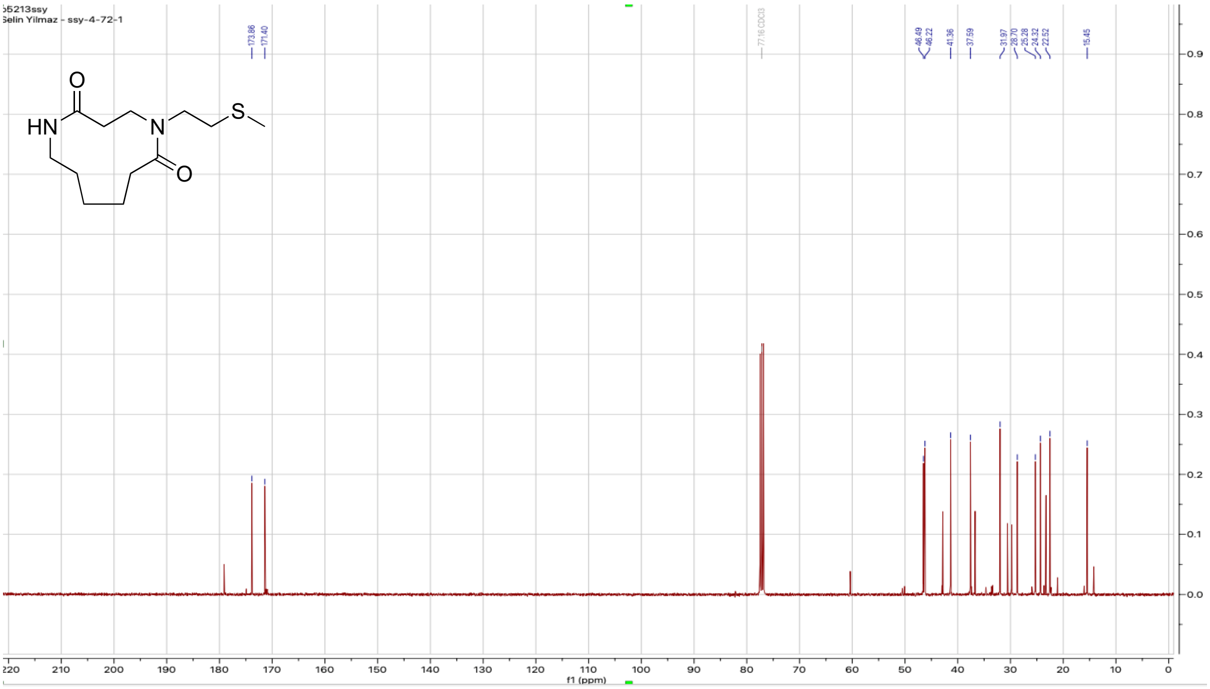




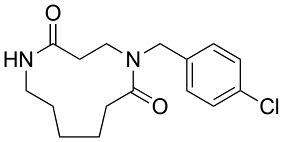
5-(2-(Methylthio)ethyl)-1,5-diazacycloundecane-2,6-dione (8i) the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. 2:1 mixture of rotamers.

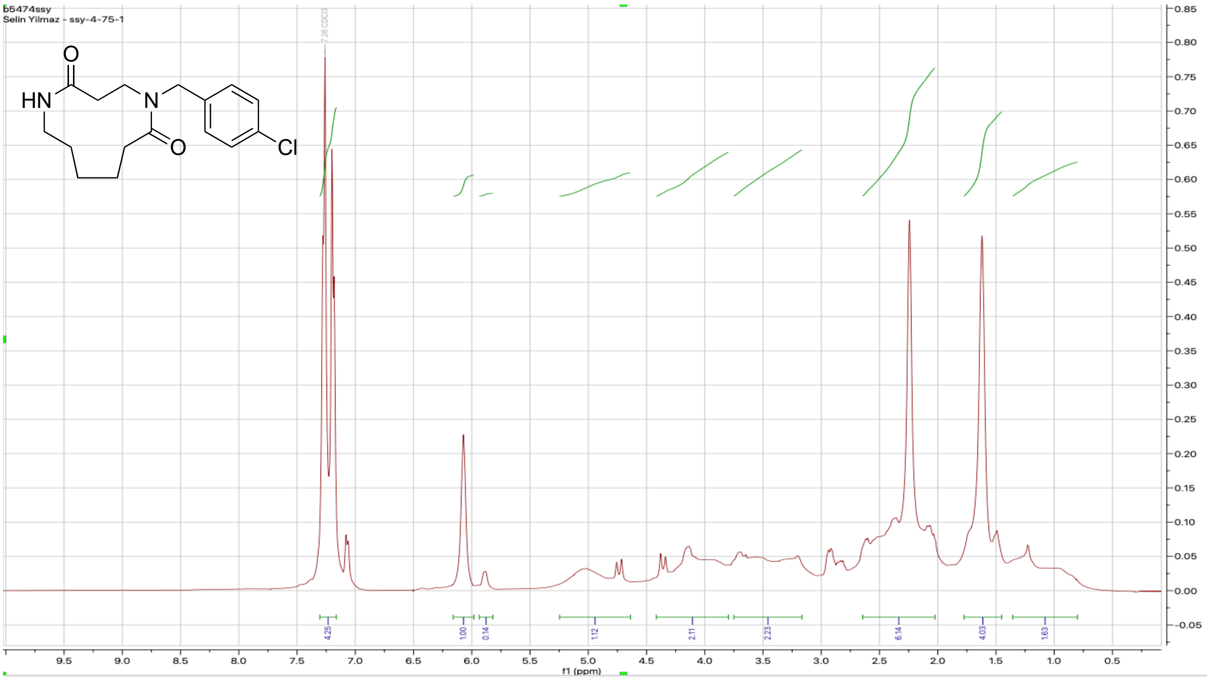


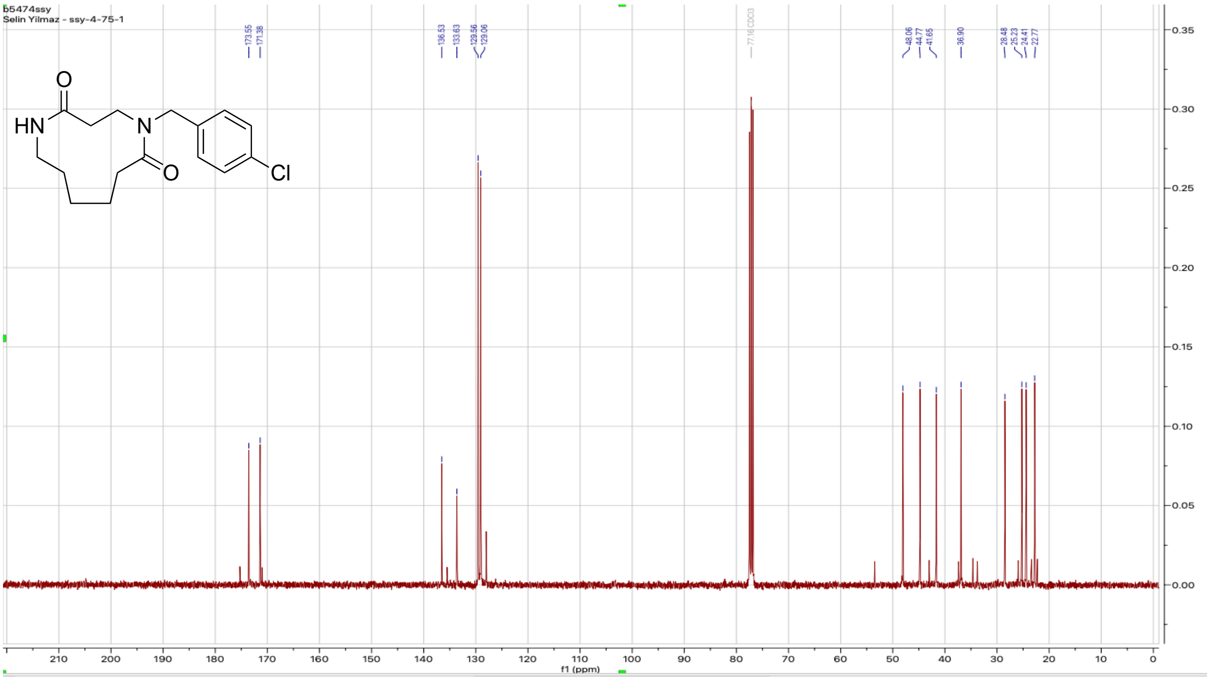




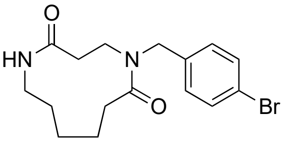
5-(4-Chlorobenzyl)-1,5-diazacycloundecane-2,6-dione (8j) the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. 7:1 mixture of rotamers.

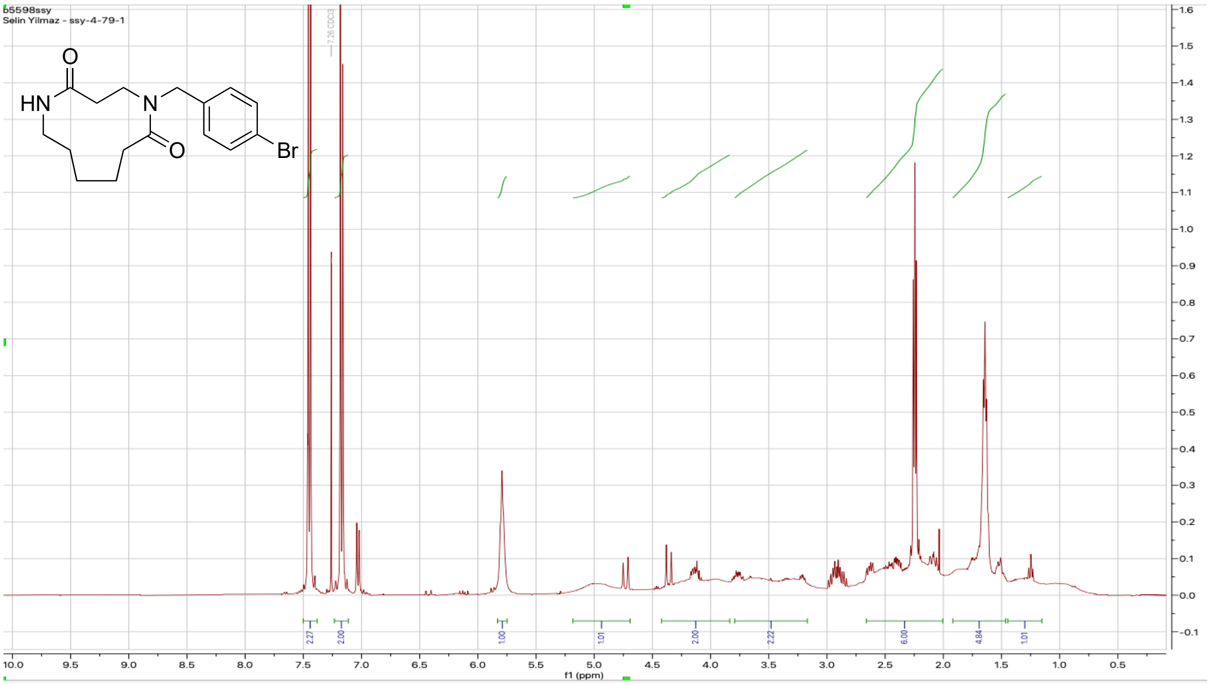


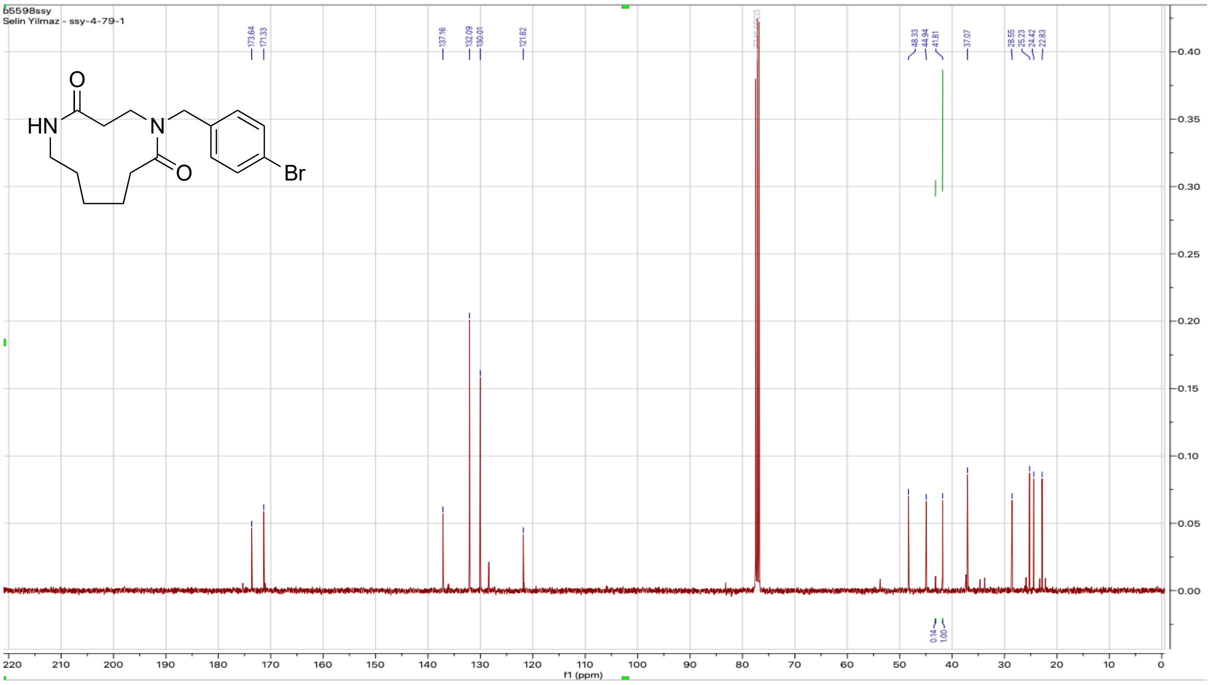




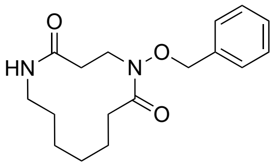
5-(4-Bromobenzyl)-1,5-diazacycloundecane-2,6-dione (8k) - the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. 1:7 mixture of rotamers.

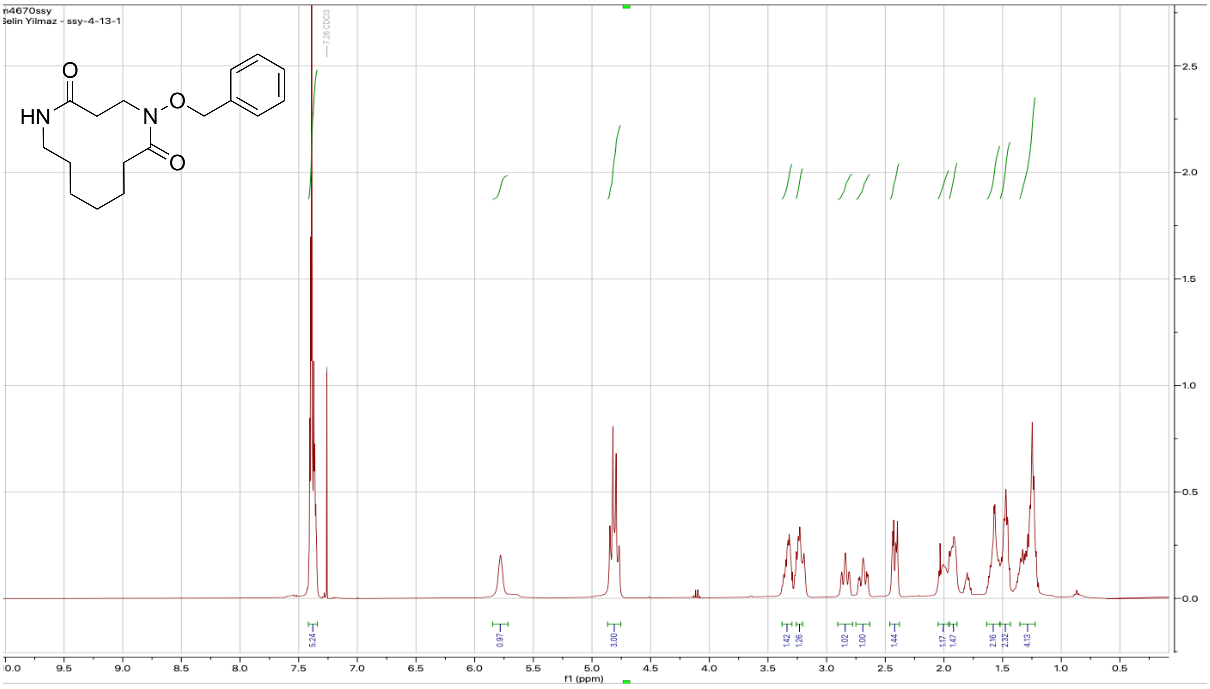


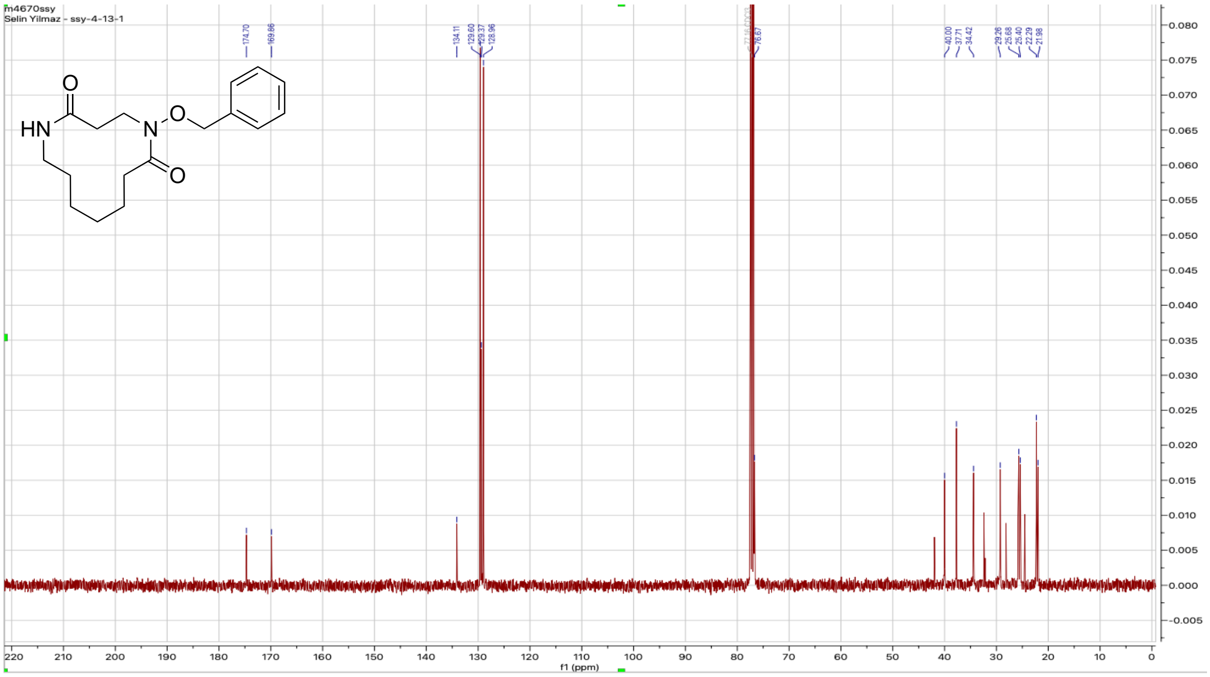




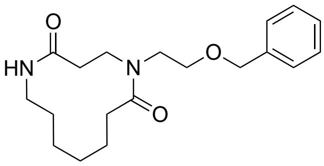
5-(Benzyloxy)-1,5-diazacyclododecane-2,6-dione (9a)

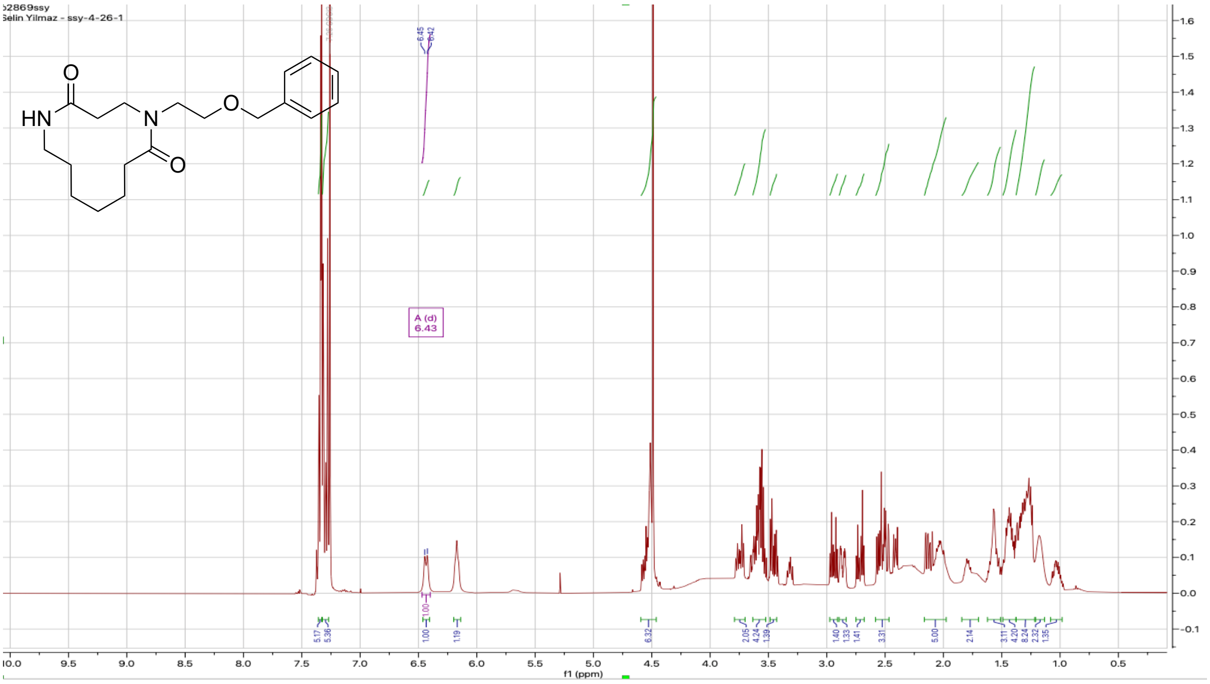


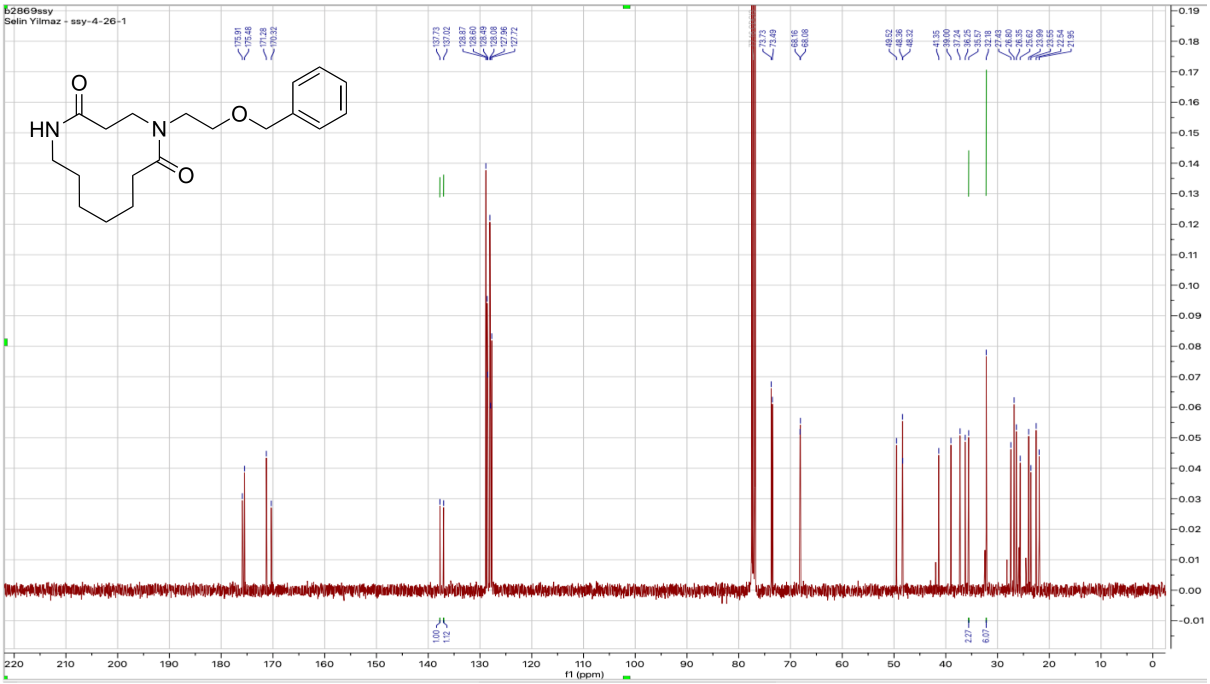




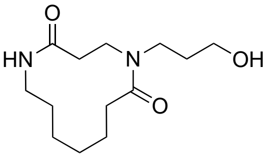
5-(2-(Benzyloxy)ethyl)-1,5-diazacyclododecane-2,6-dione (9b) – 1:1 mixture of rotamers

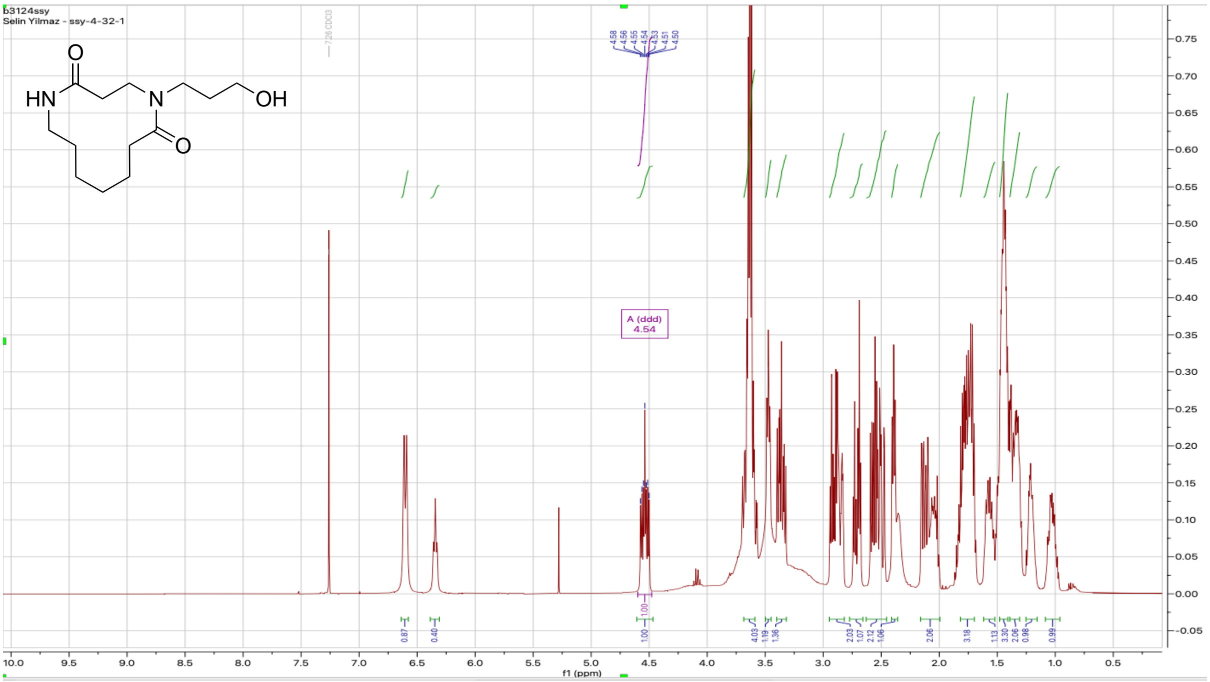


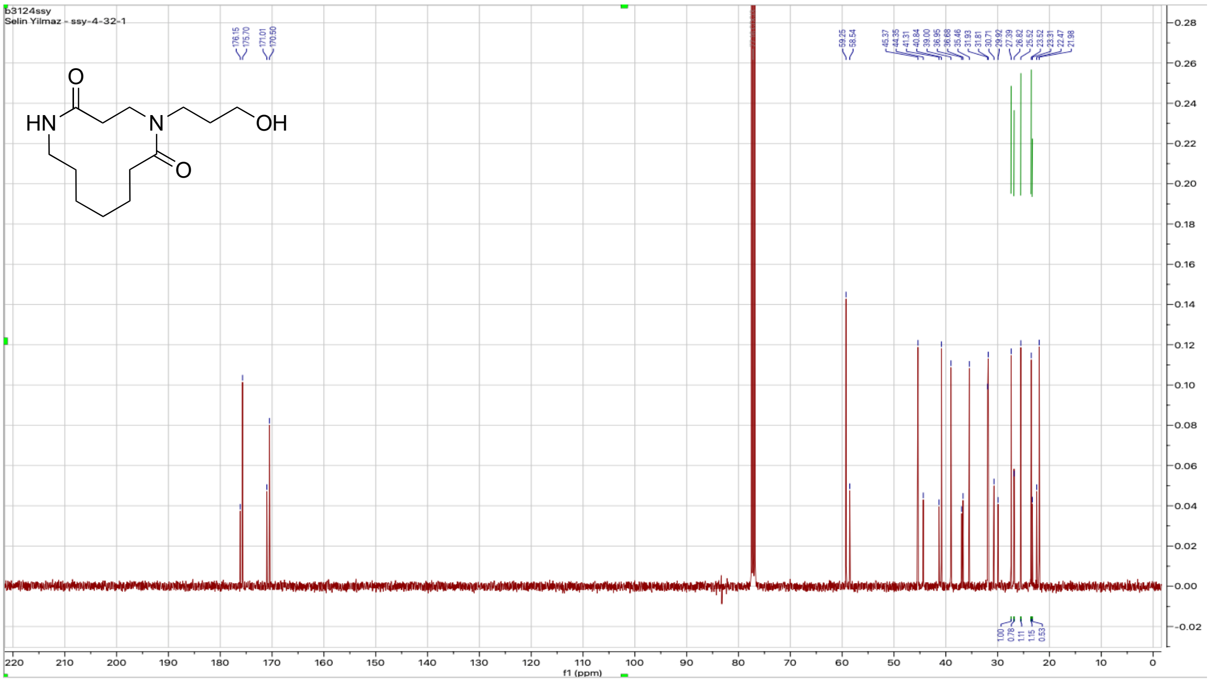




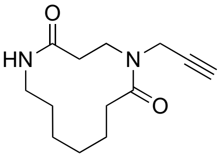
5-(3-Hydroxypropyl)-1,5-diazacyclododecane-2,6-dione (9c) – 2:1 mixture of rotamers

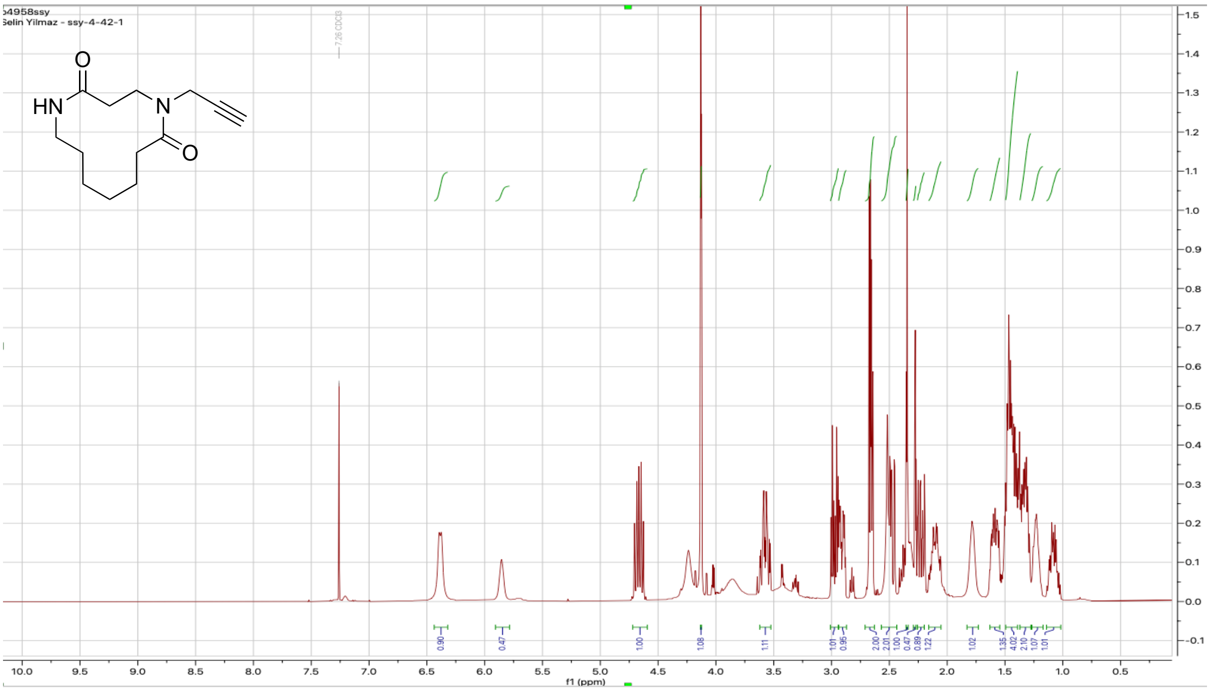


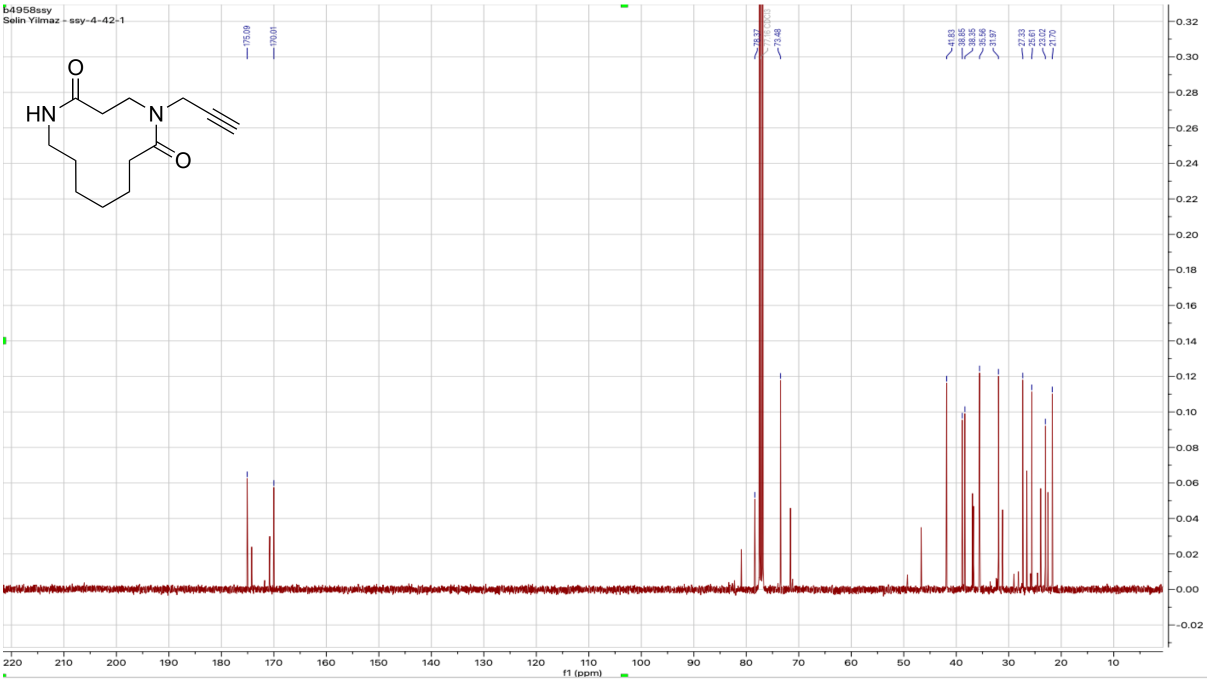




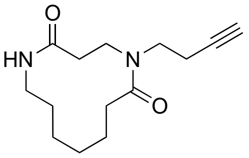
5-(Prop-2-yn-1-yl)-1,5-diazacyclododecane-2,6-dione (9d) – 2:1 mixture of rotamers

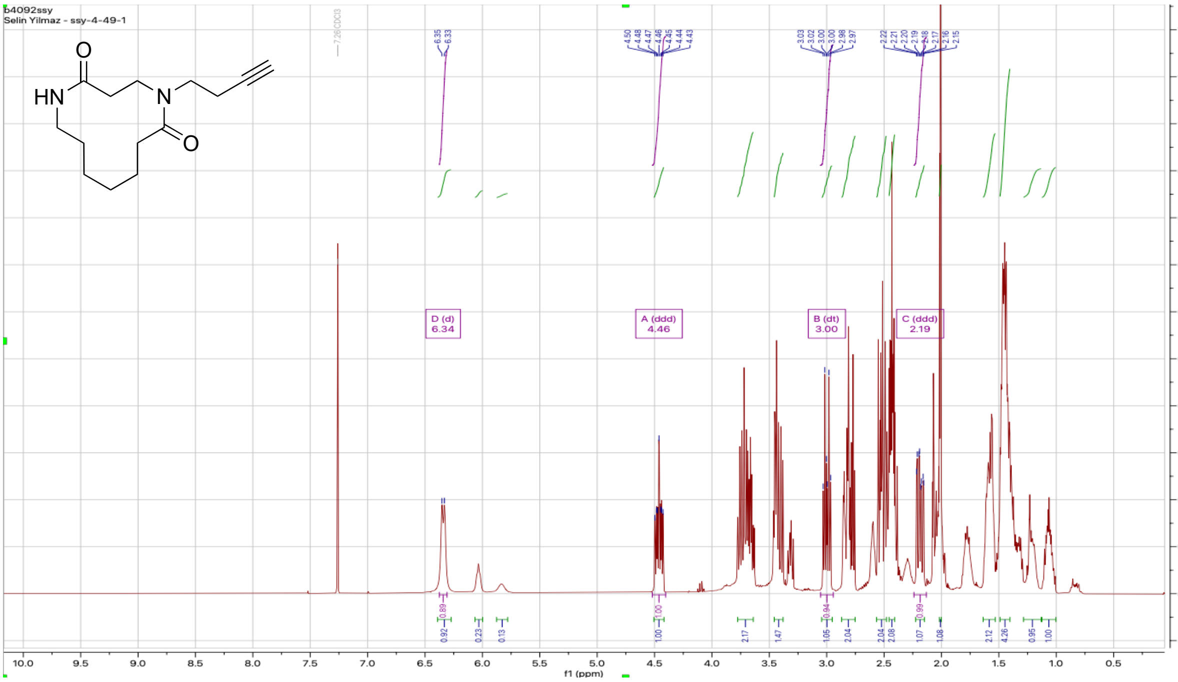


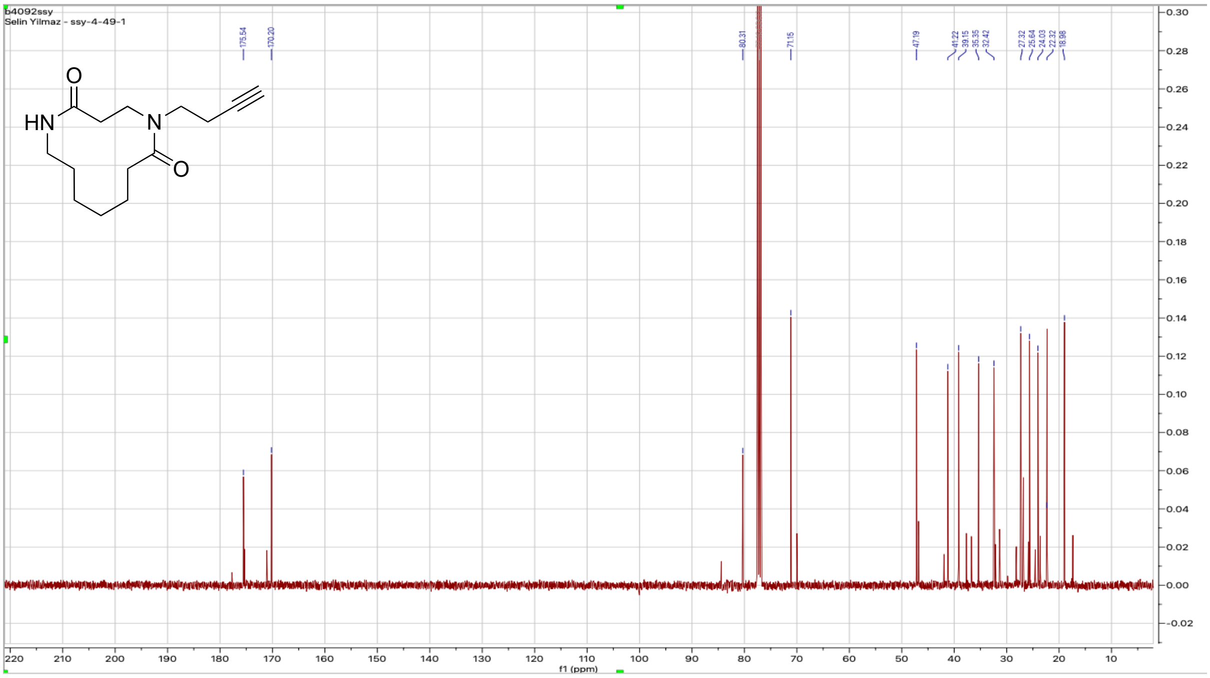




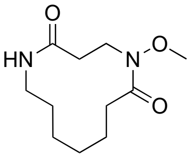
5-(But-3-yn-1-yl)-1,5-diazacyclododecane-2,6-dione (9e) – 4:2:1 mixture of rotamers

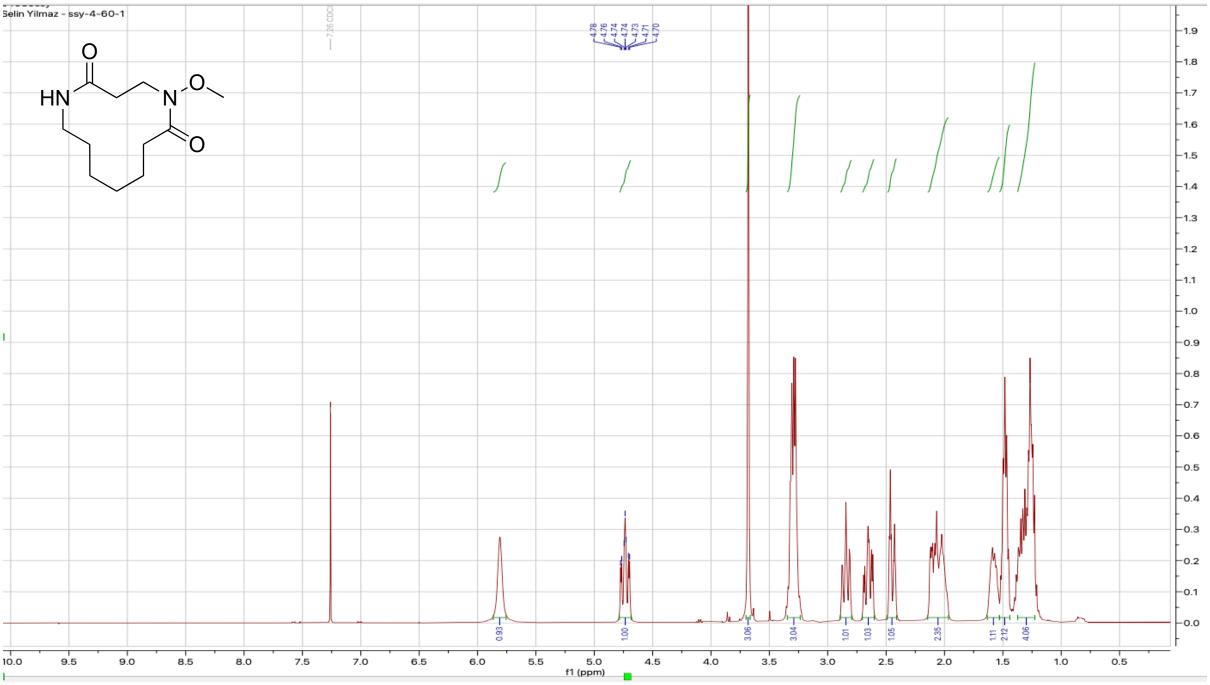


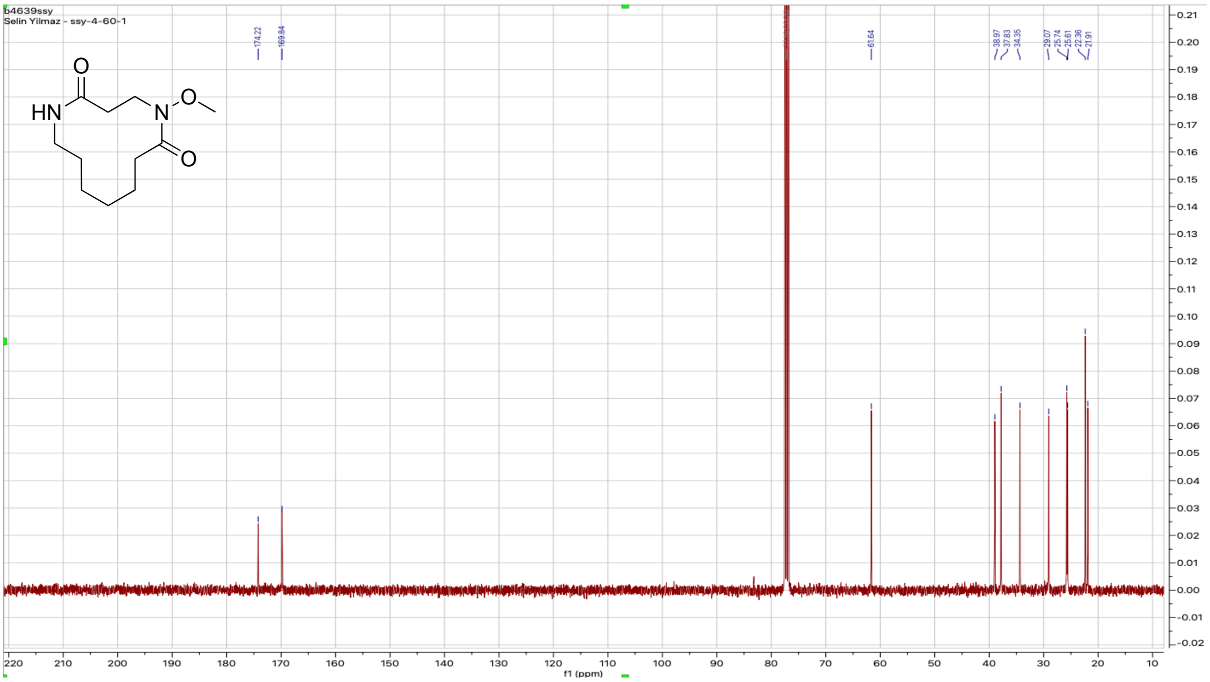




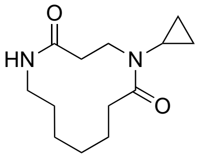
5-Methoxy-1,5-diazacycloundecane-2,6-dione (9f)

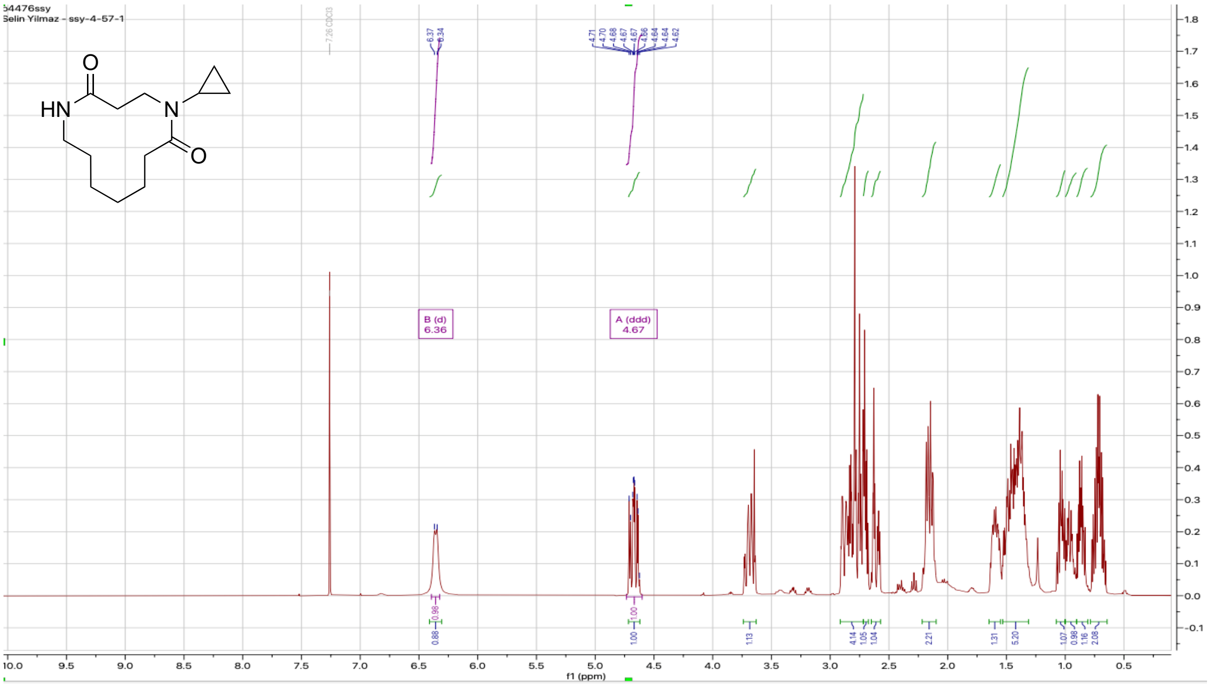


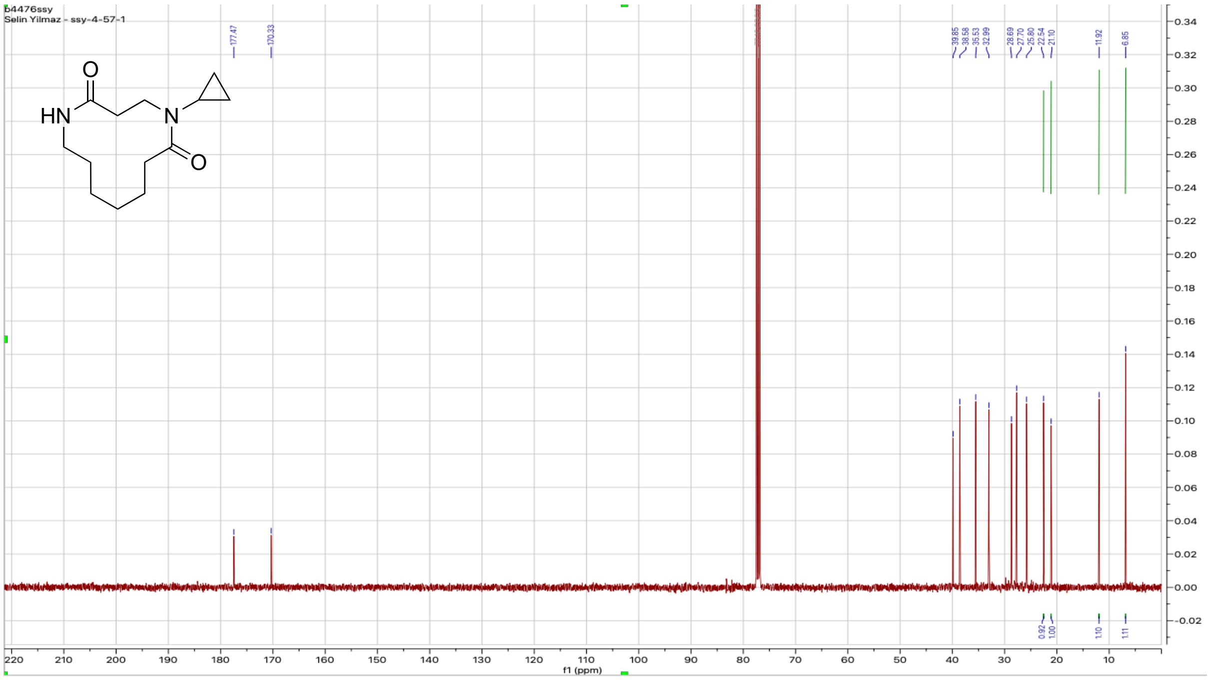




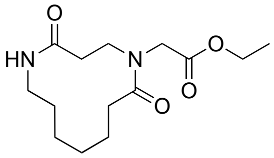
5-Cyclopropyl-1,5-diazacycloundodecane-2,6-dione (9g)

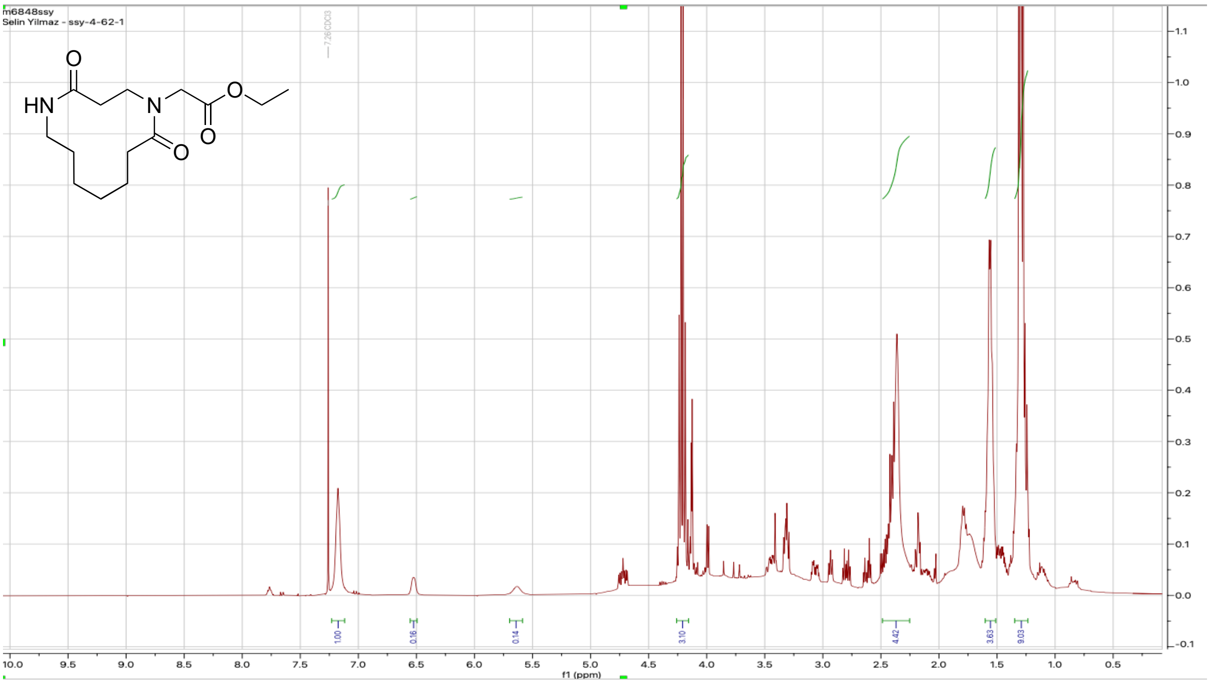


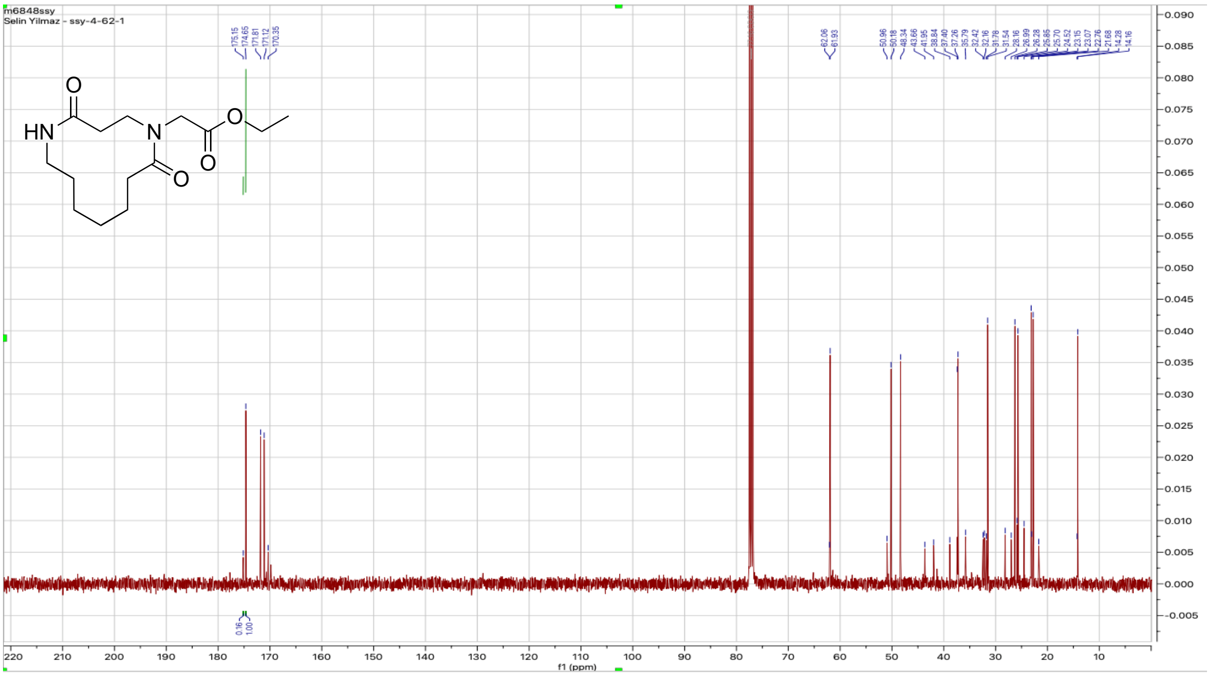




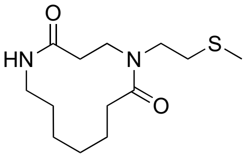
Ethyl 2-(4,12-dioxo-1,5-diazacyclododecan-1-yl)acetate (9h) - the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. 7:1 mixture of rotamers.

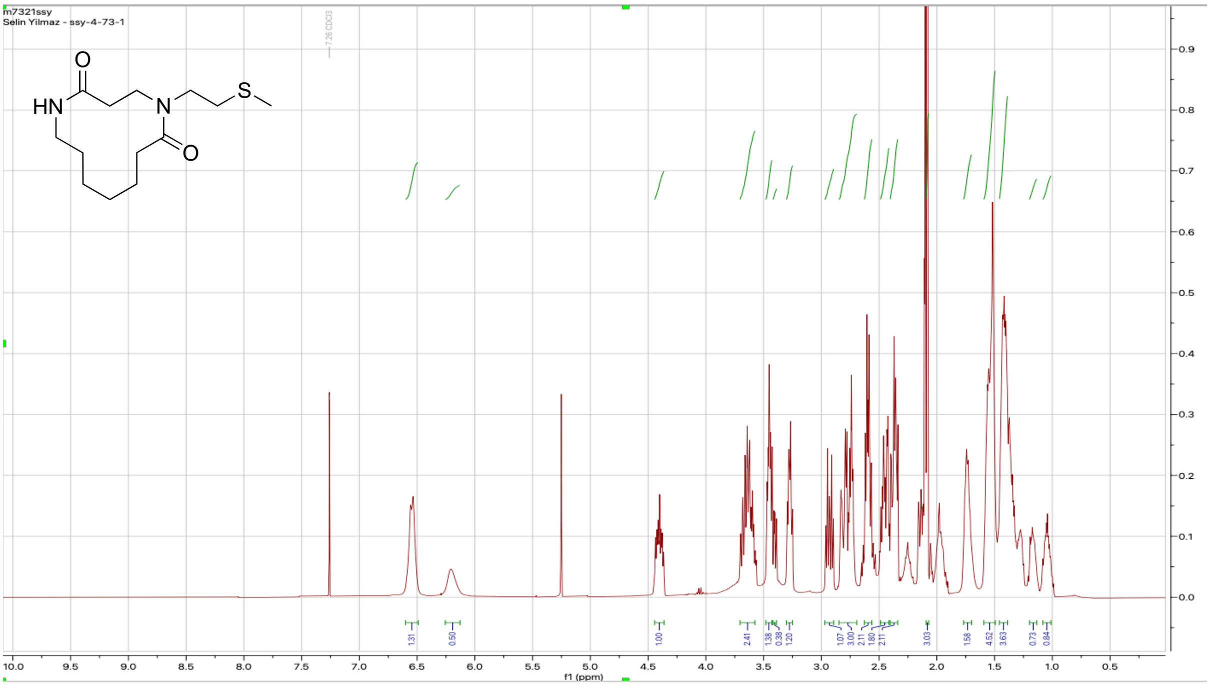


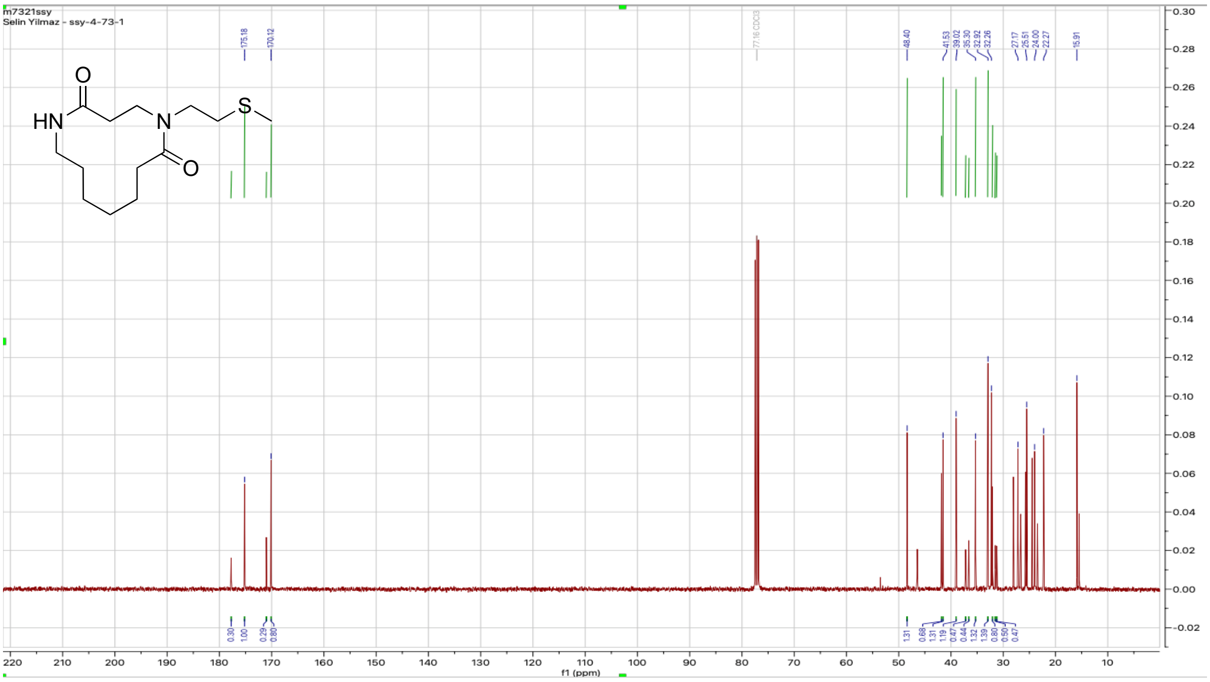




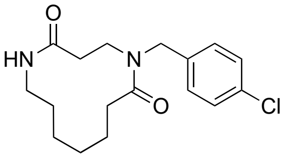
5-(2-(Methylthio)ethyl)-1,5-diazacylododecane-2,6-dione (9i) – 3:1 mixture of rotamers

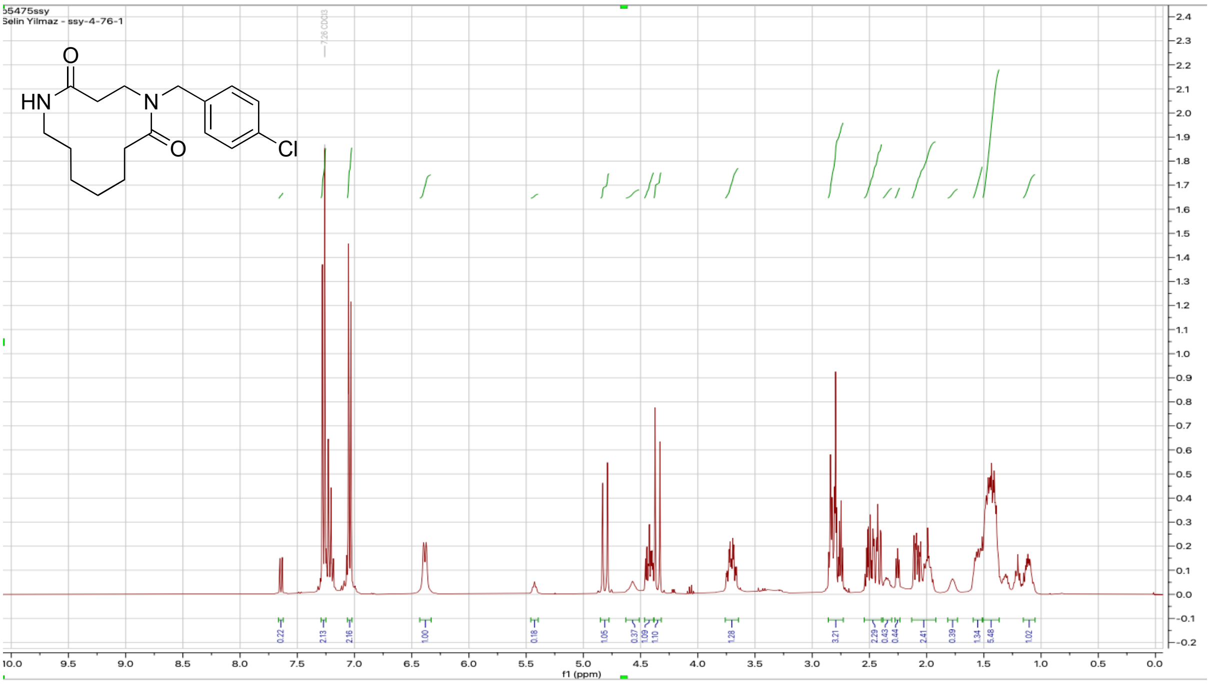


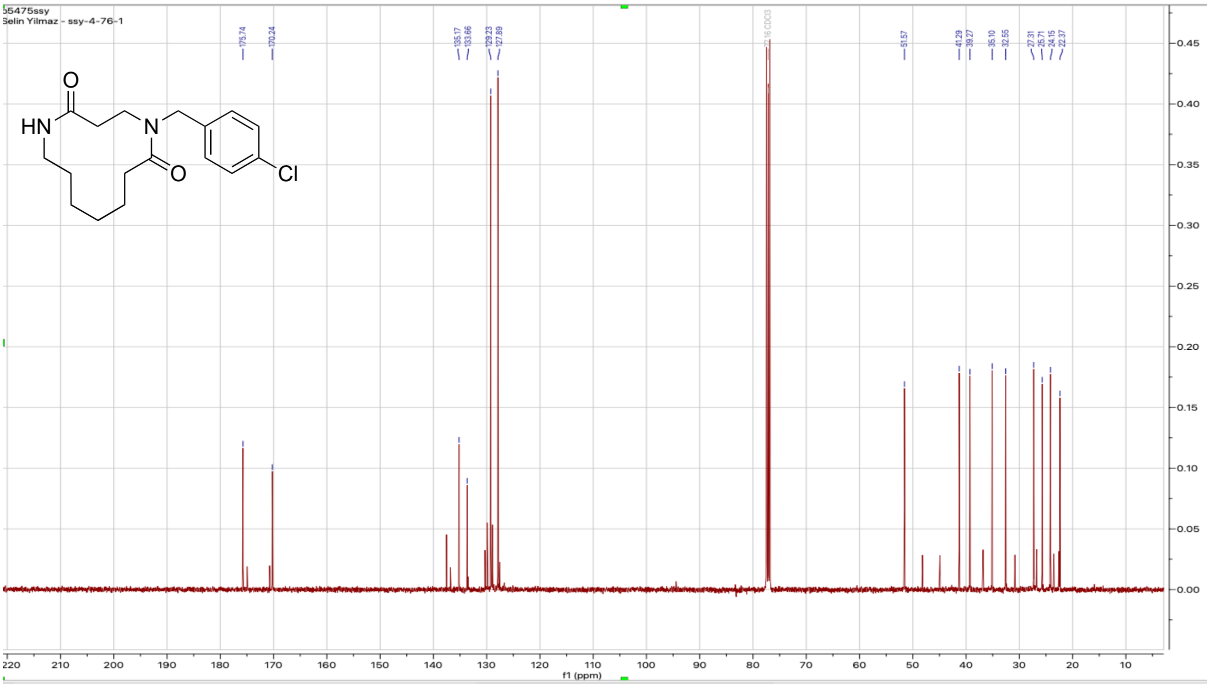




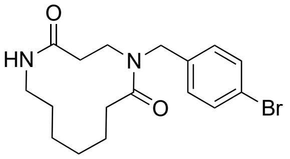
5-(4-Chlorobenzyl)-1,5-diazacyclododecane-2,6-dione (9j) – 6:1 mixture of rotamers

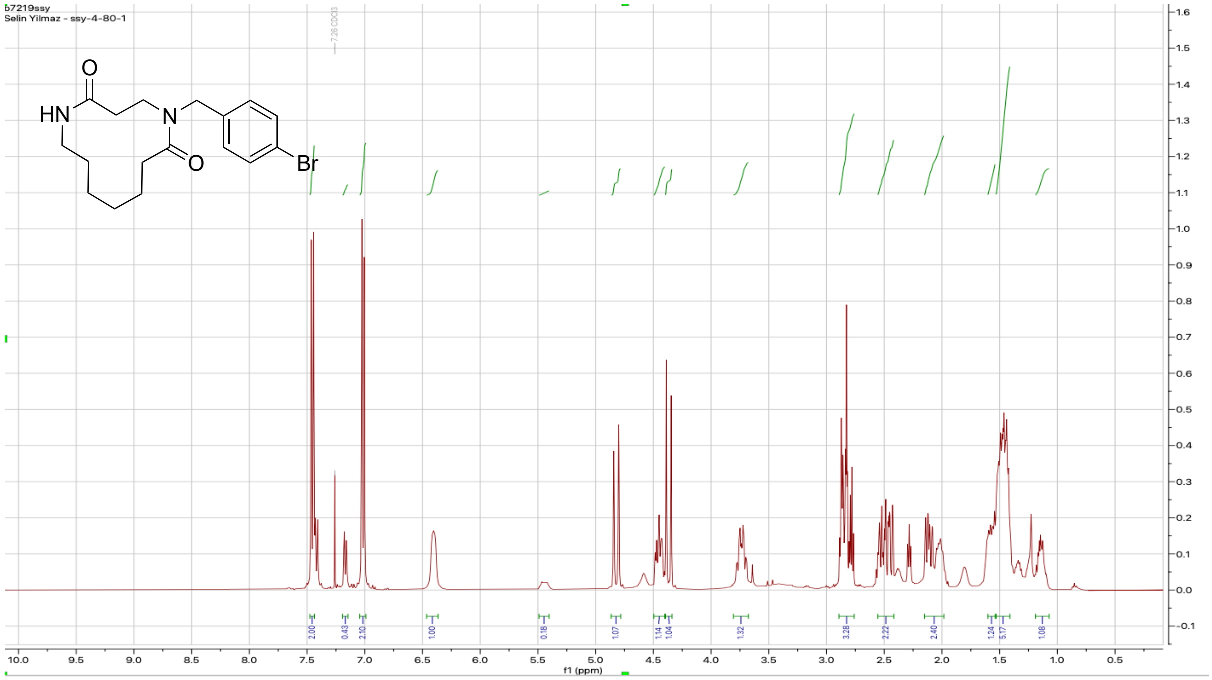


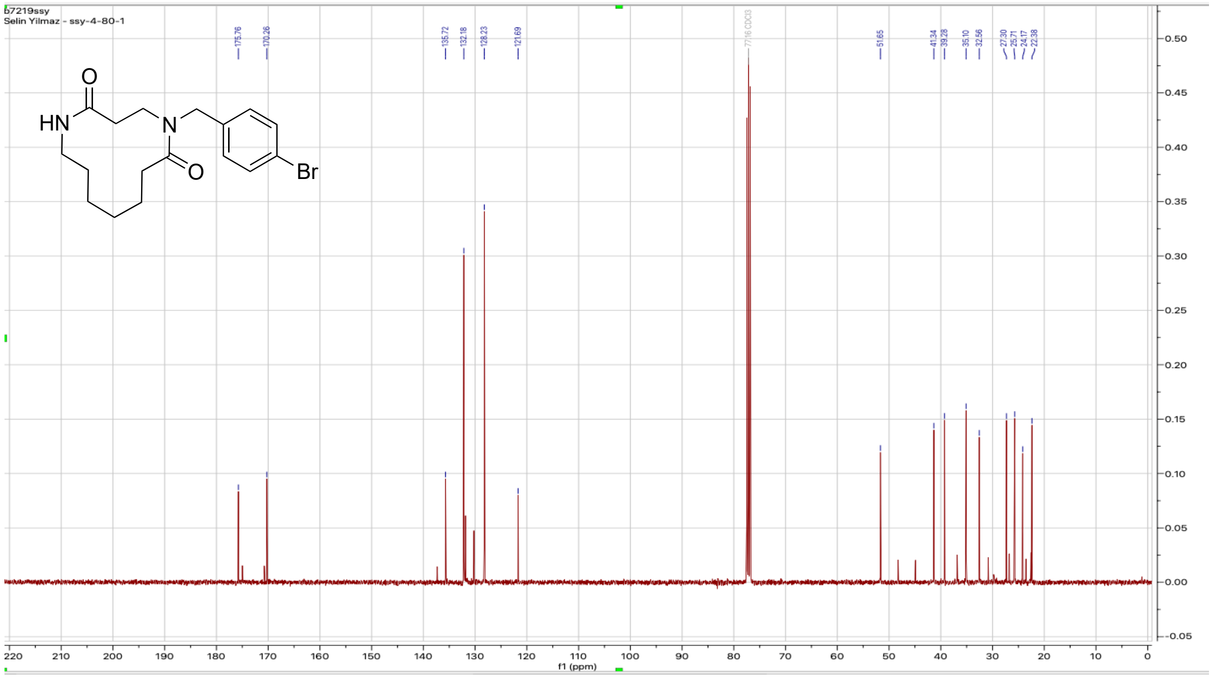




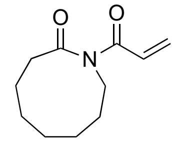
5-(4-Bromobenzyl)-1,5-diazacyclododecane-2,6-dilone (9k) – 5:1 mixture of rotamers

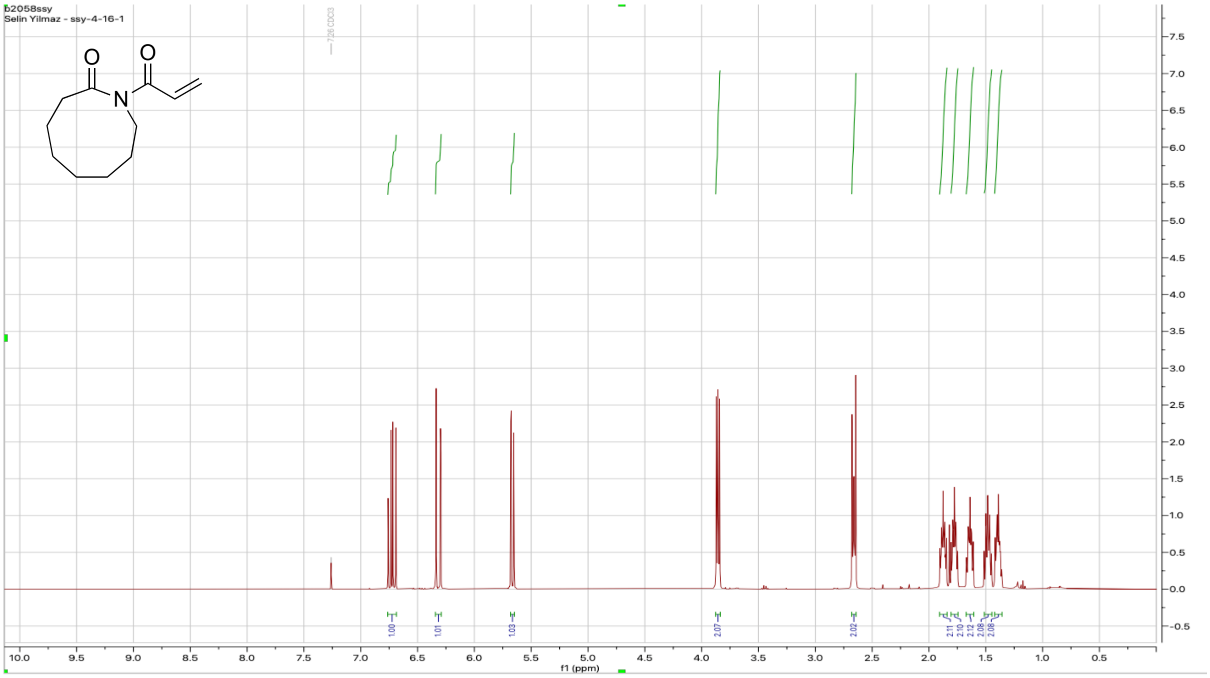


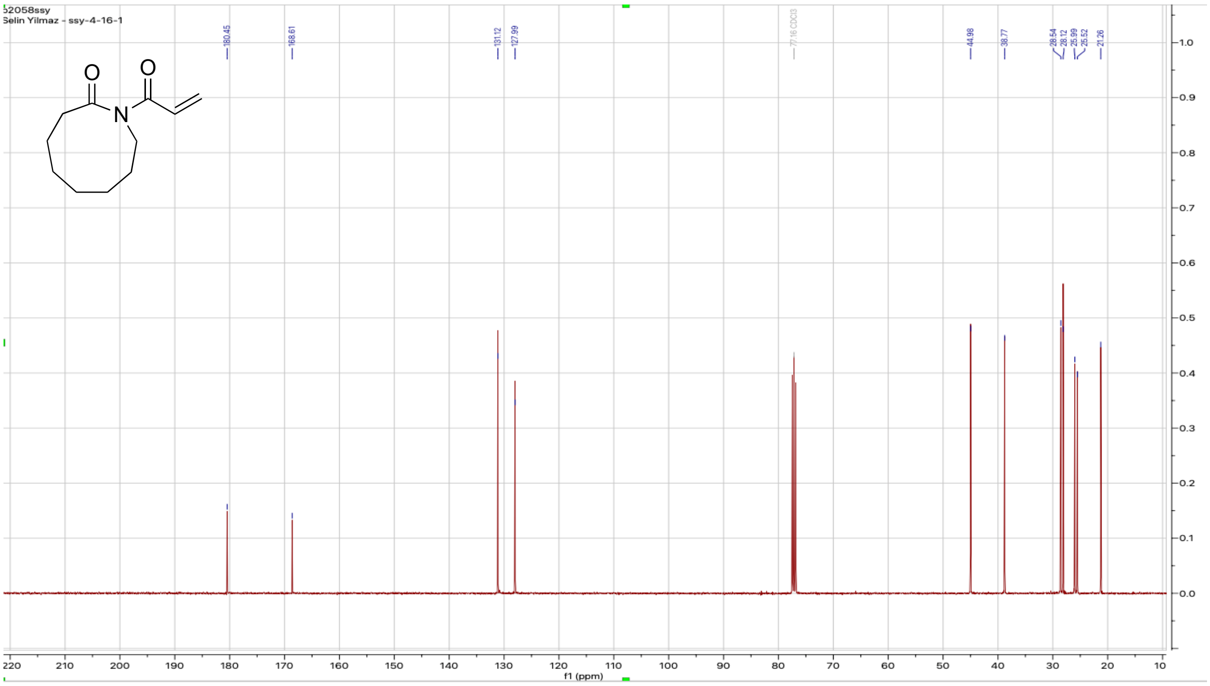




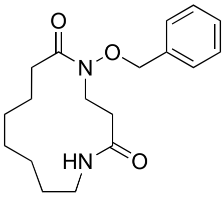
1-Acryloylazonan-2-one (3d)

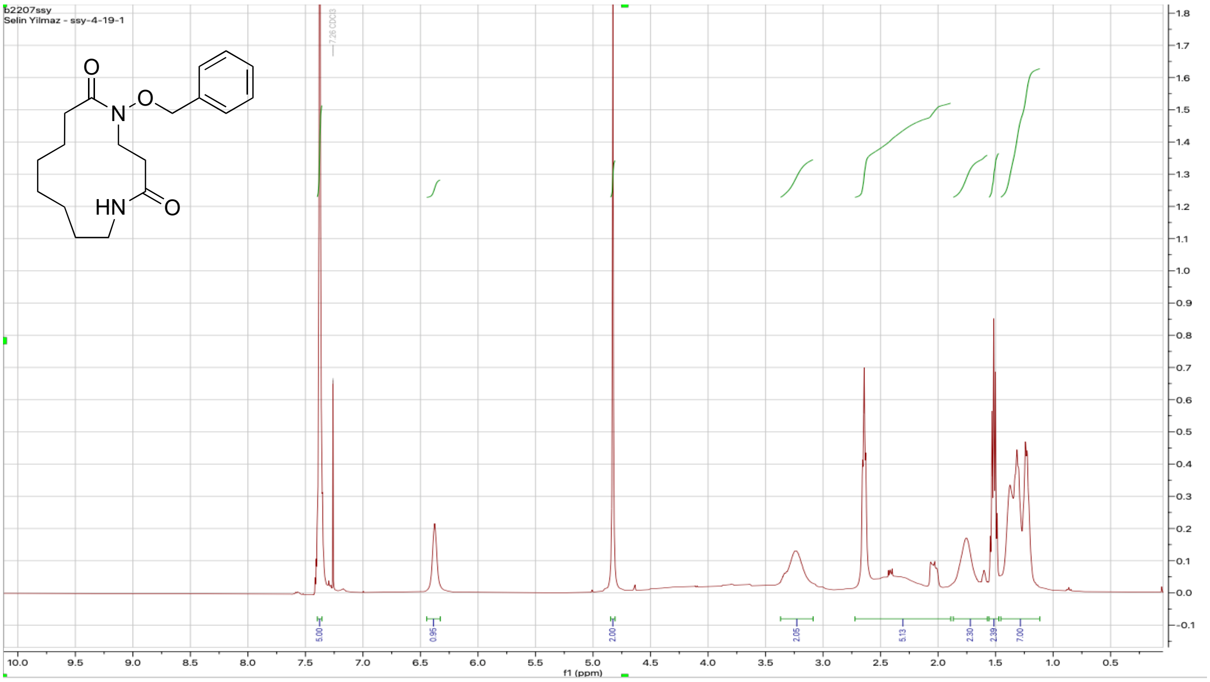


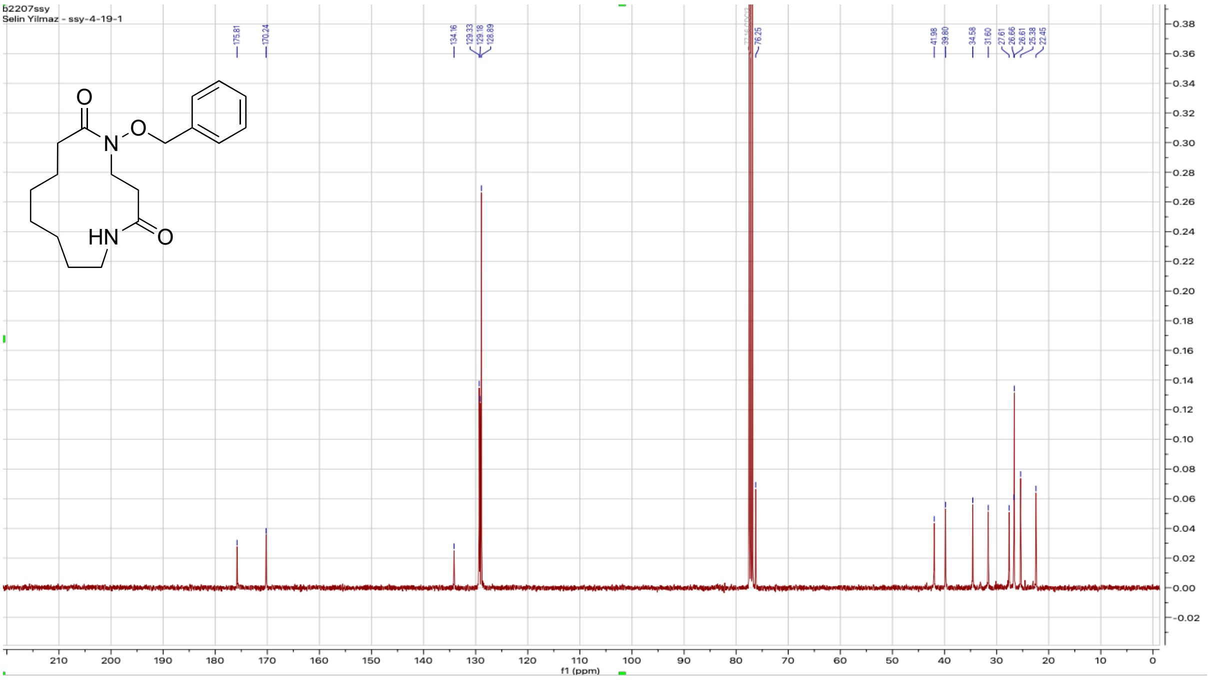




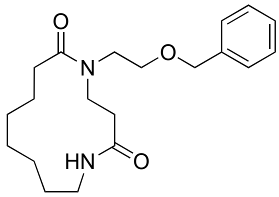
5-(Benzyloxy)-1,5-diazacyclotridecane-2,6-dione (10a)

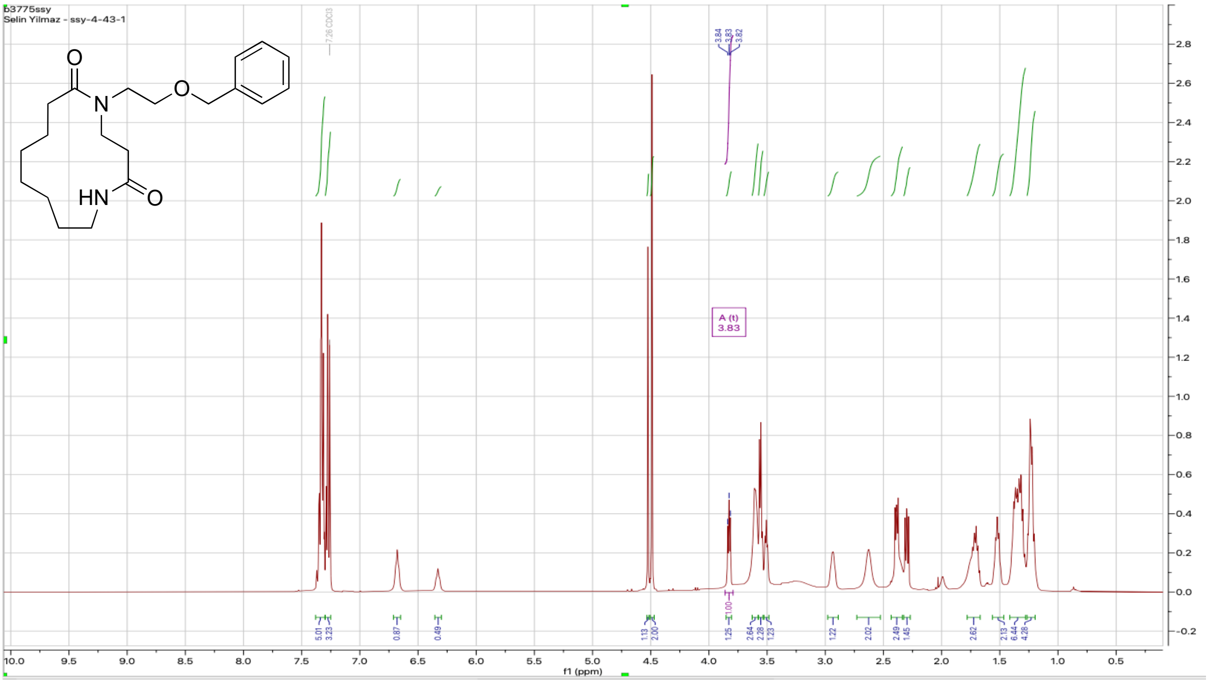


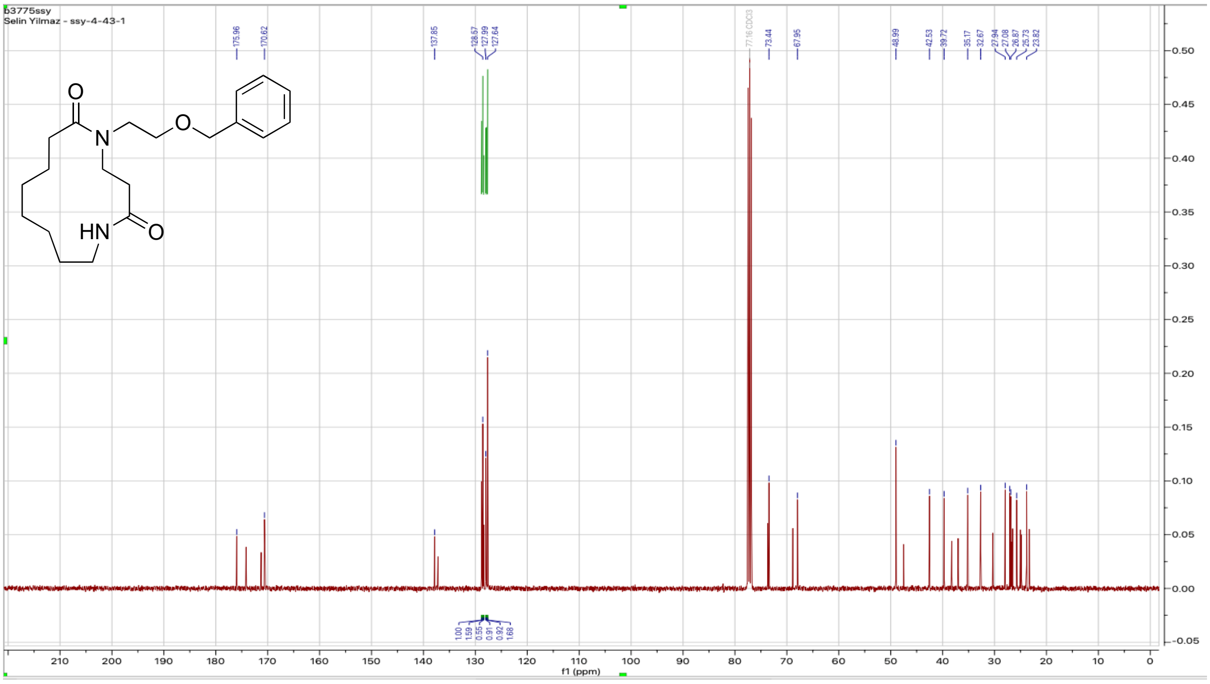




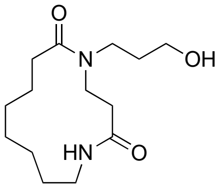
5-(2-(Benzyloxy)ethyl)-1,5-diazacyclotridecane-2,6-dione (10b) – 2:1 mixture of rotamers

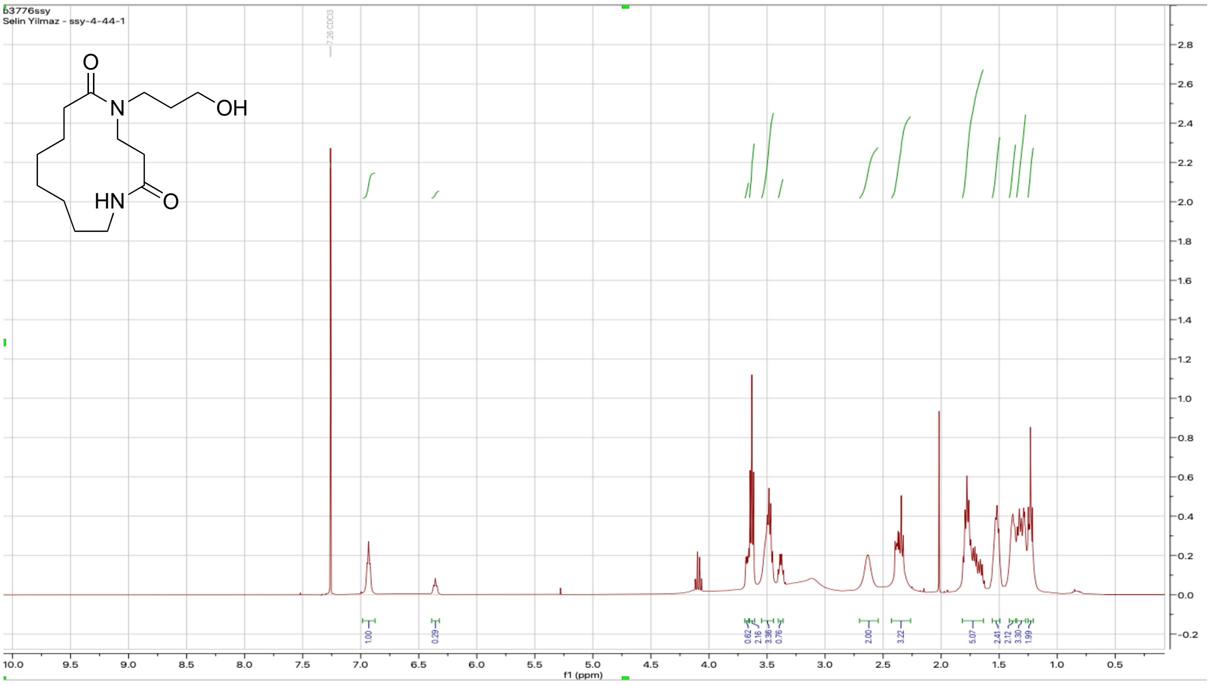


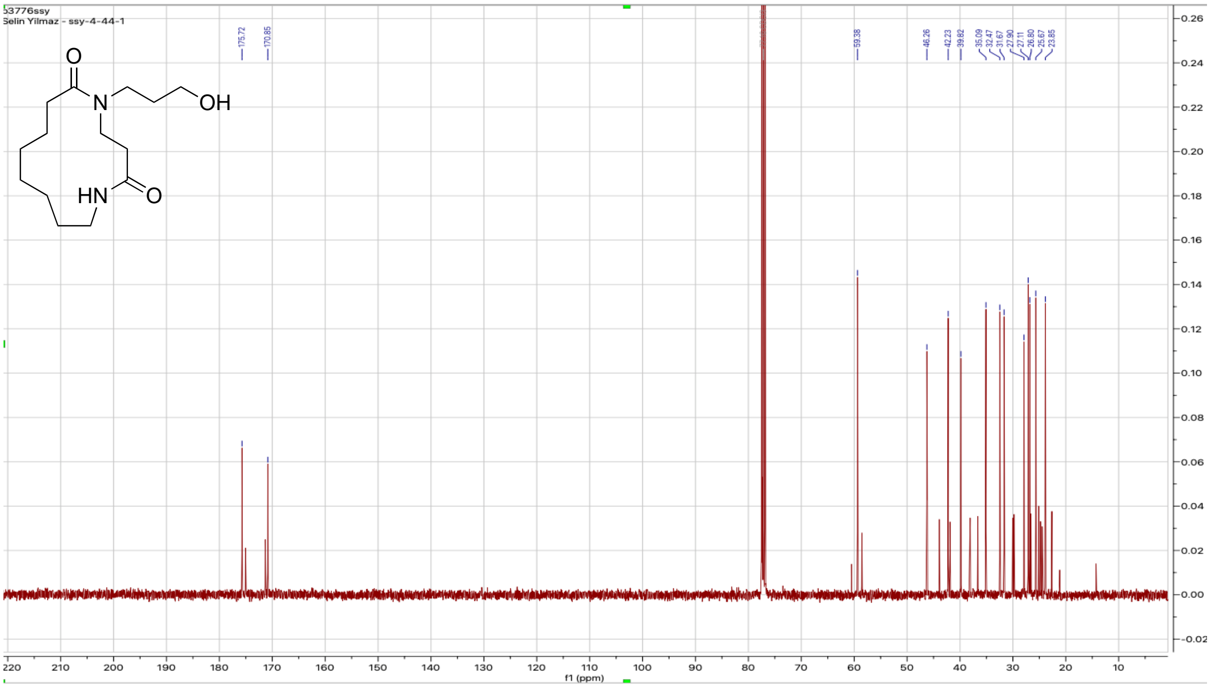




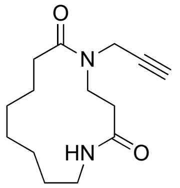
5-(3-Hydroxypropyl)-1,5-diazacyclotridecane-2,6-dione (10c) – 4:1 mixture of rotamers

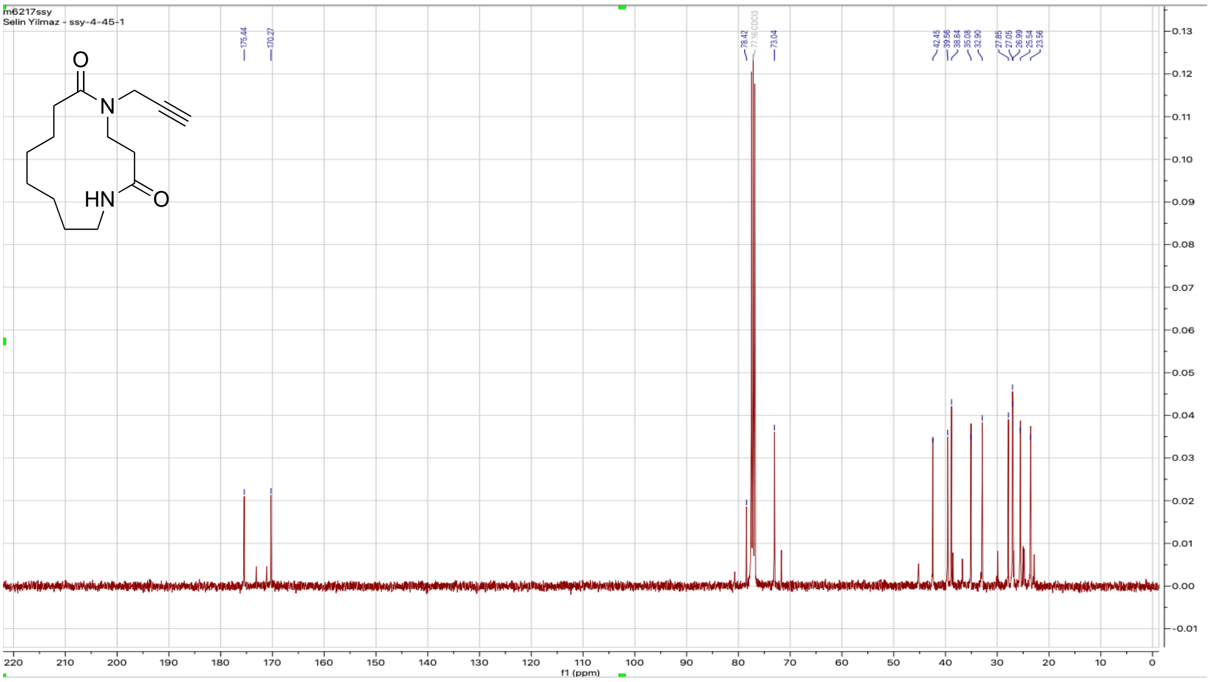




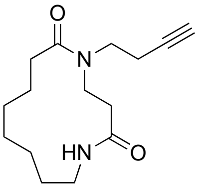


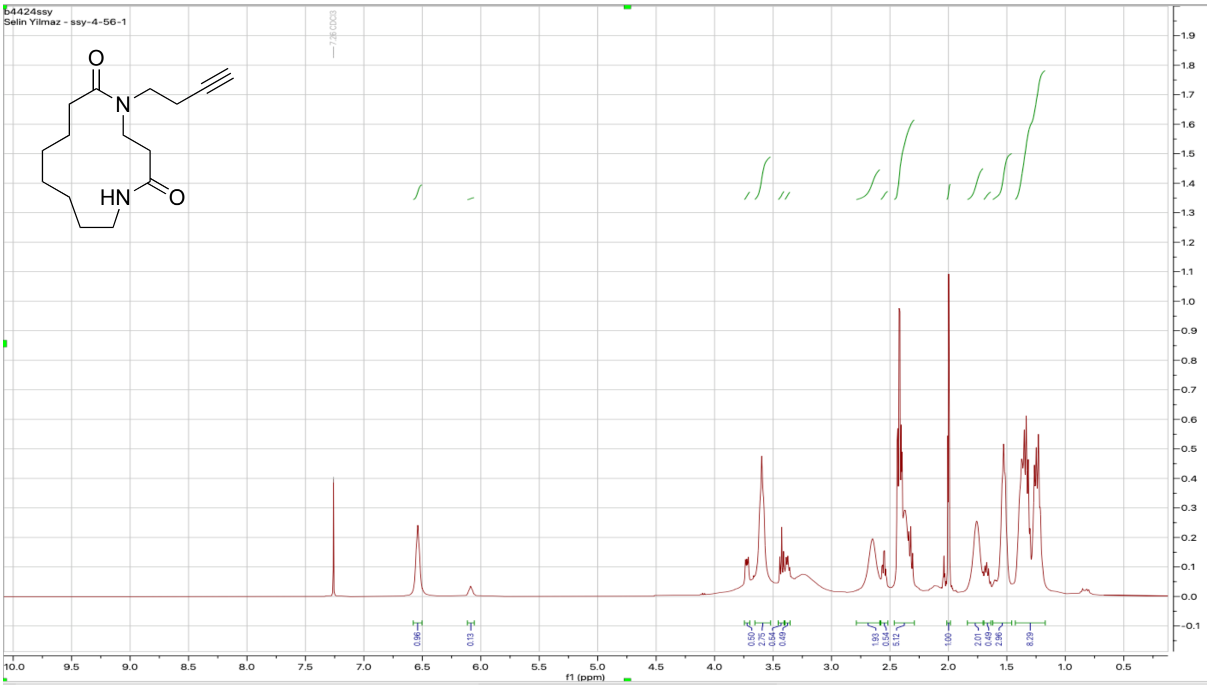
5-(Prop-2-yn-1-yl)-1,5-diazacyclotridecane-2,6-dione (10d) the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. 4:1 mixture of rotamers.

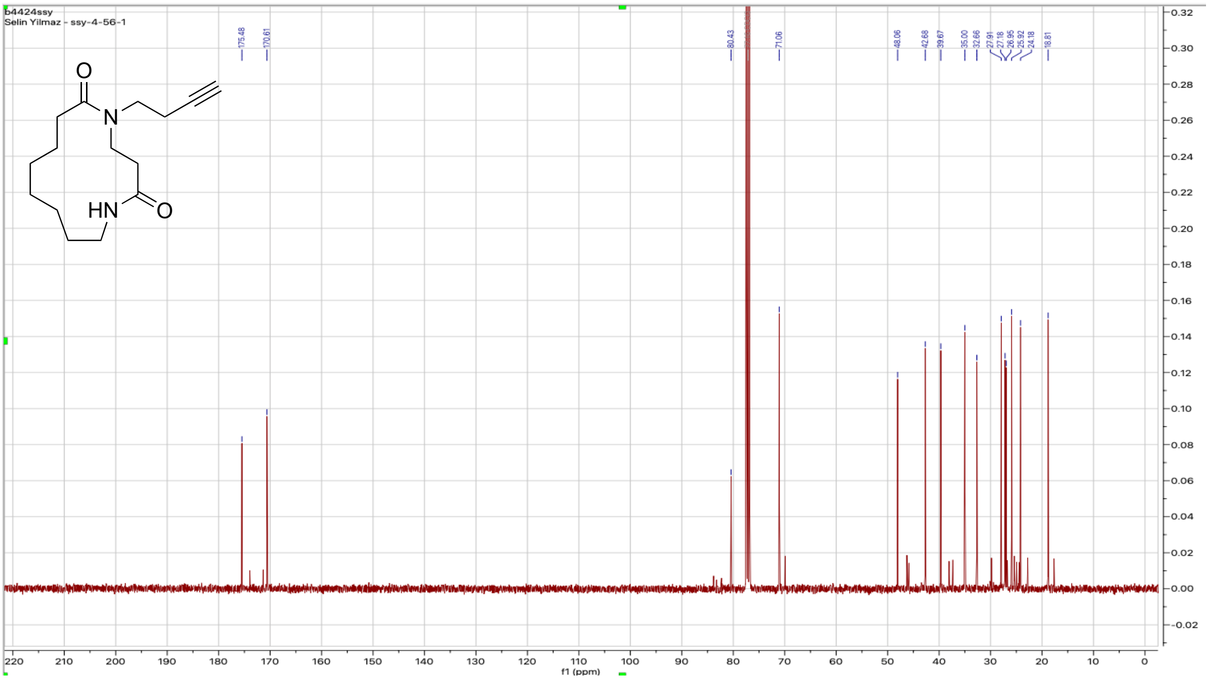




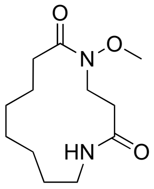
5-(But-3-yn-1-yl)-1,5-diazacyclotridecane-2,6-dione (10e) – 7:1 mixture of rotamers

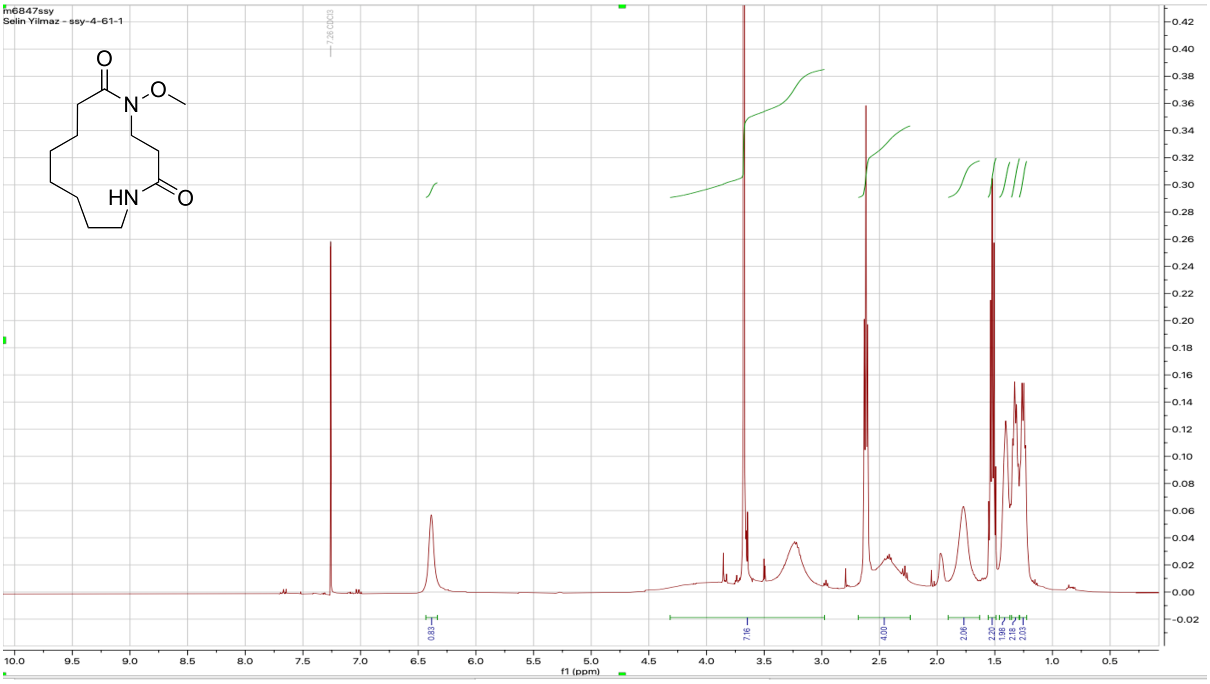


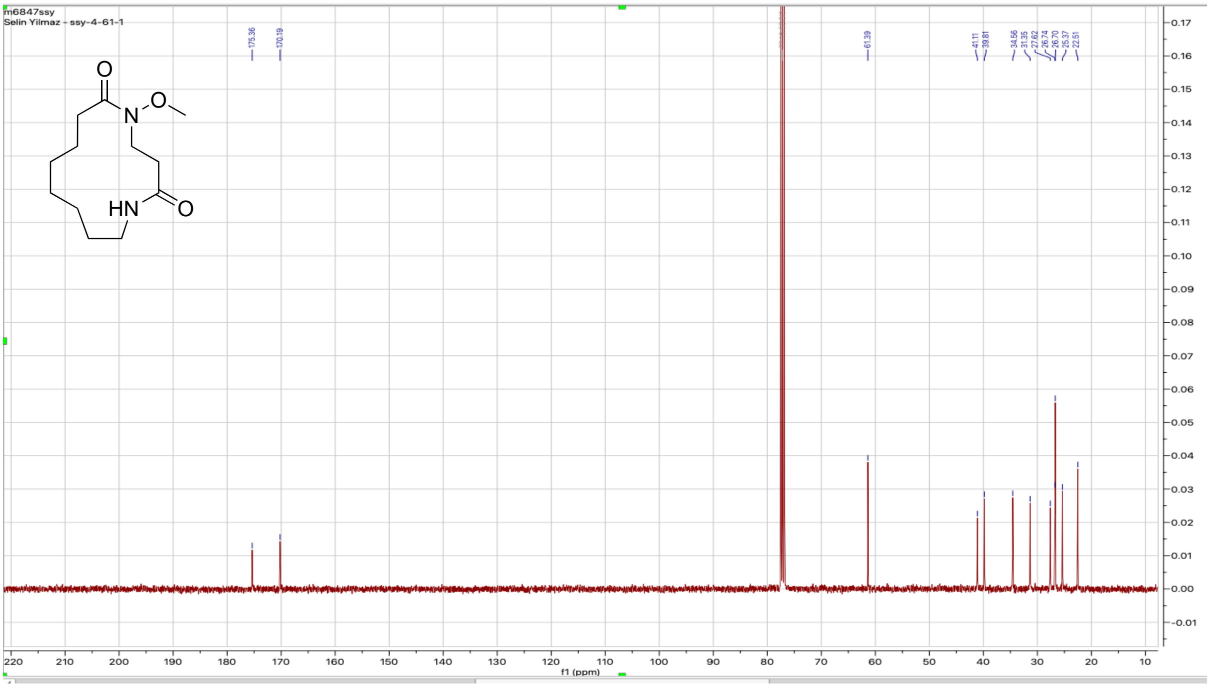




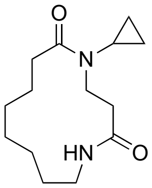
5-Methoxy-1,5-diazacyclotridecane-2,6-dione (10f) the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product.

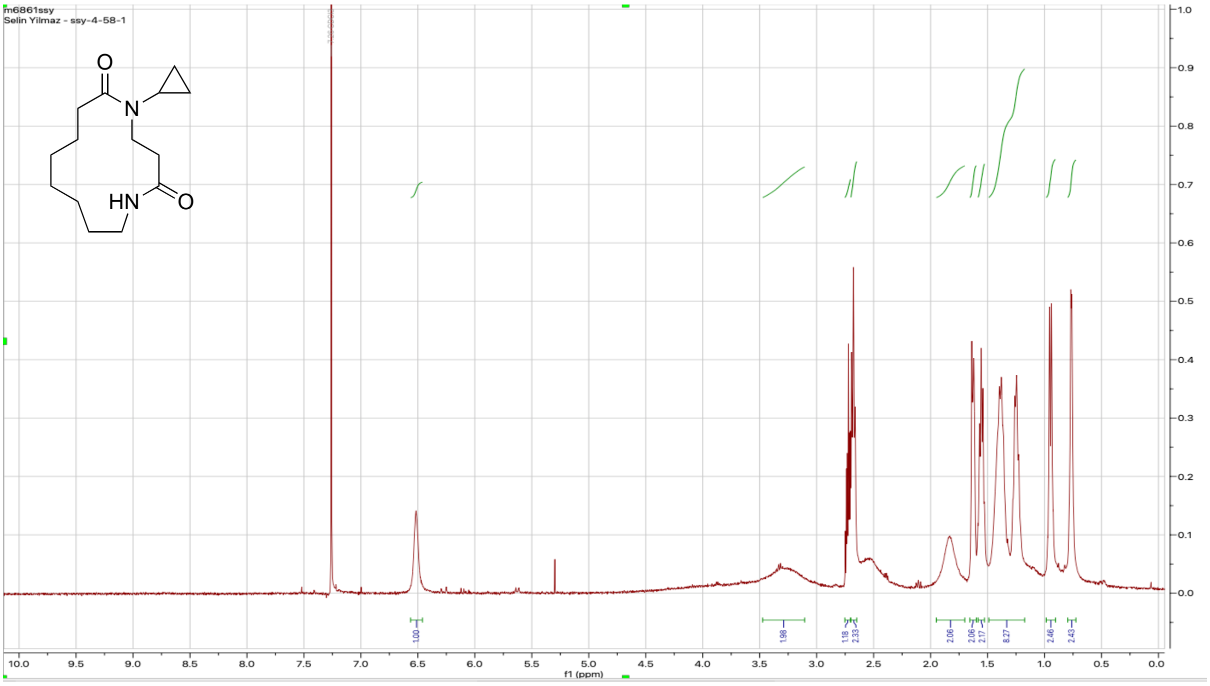


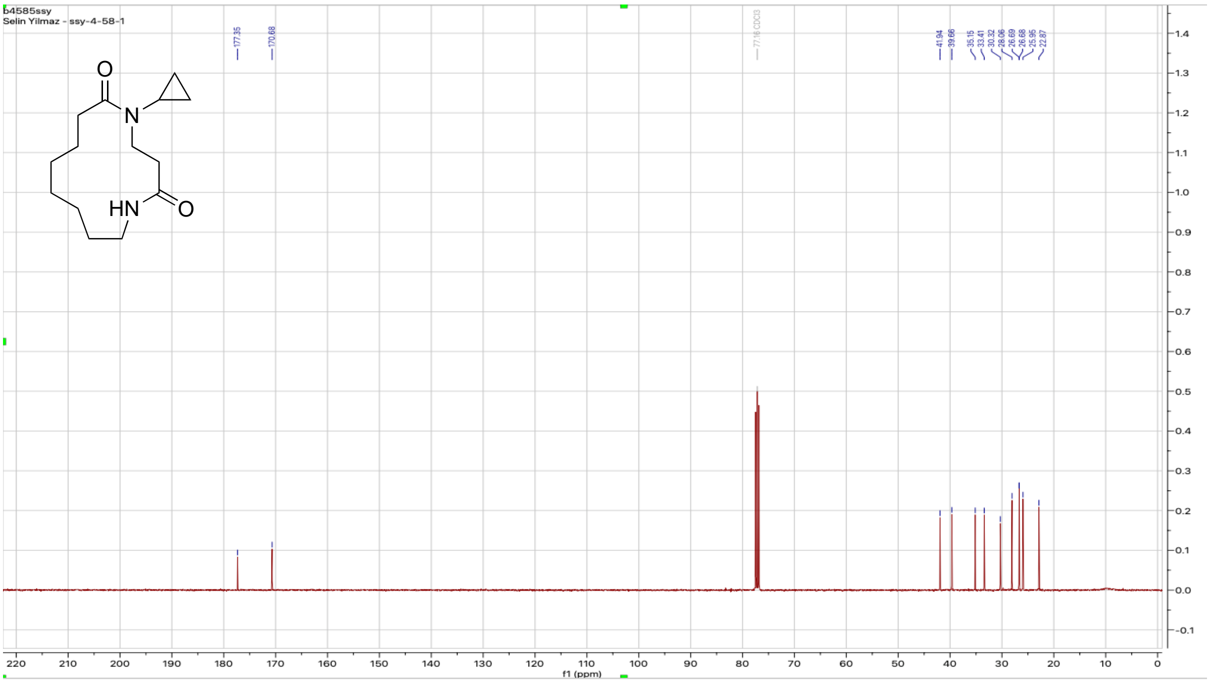




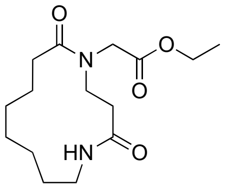
5-Cyclopropyl-1,5-diazacyclotridecane-2,6-dione (10g) - the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product.

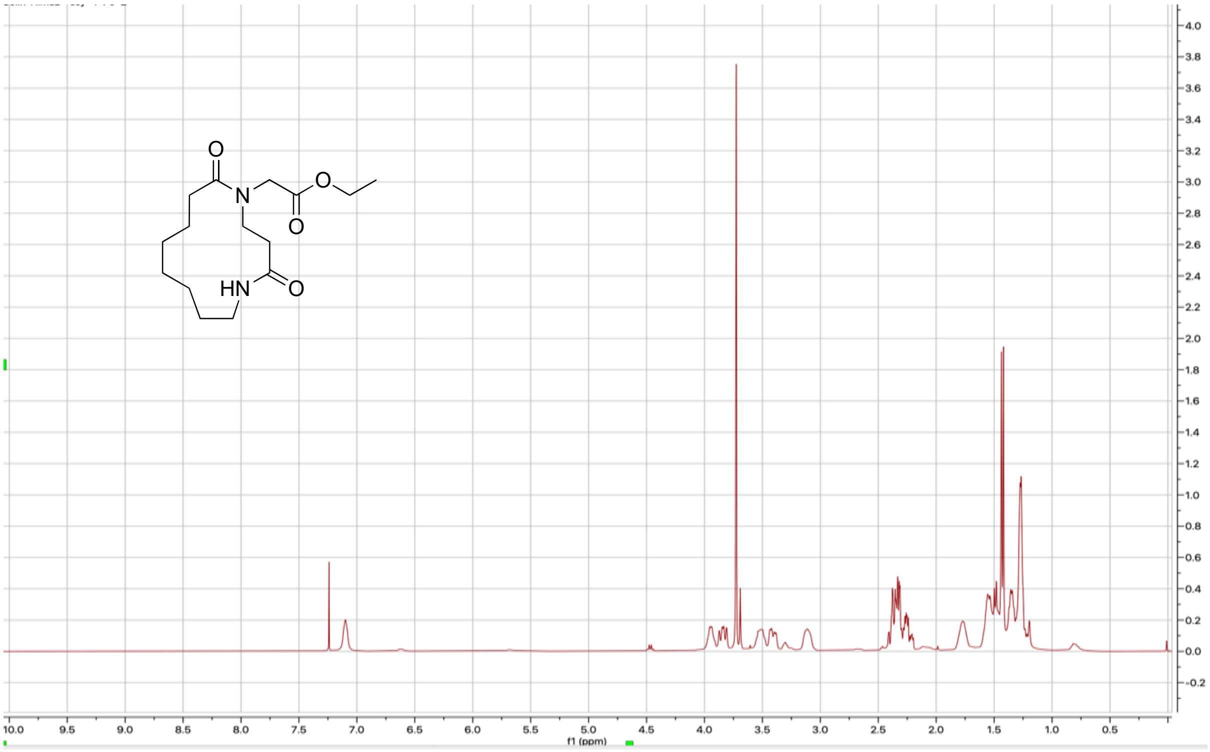


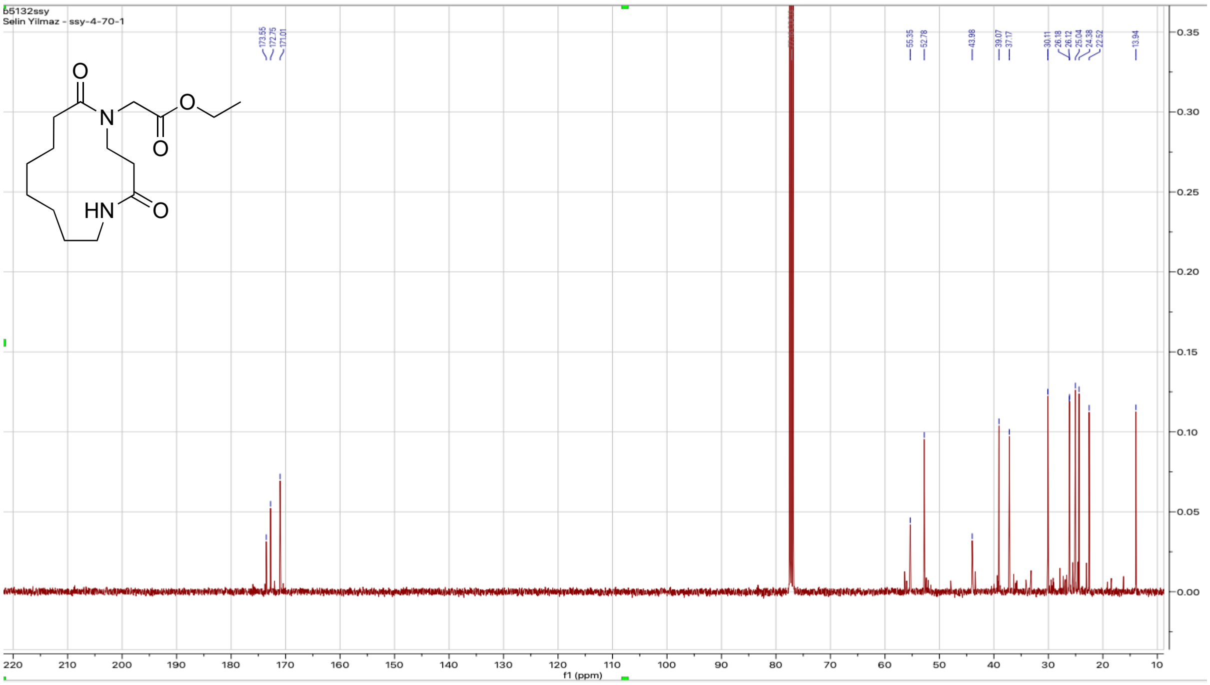




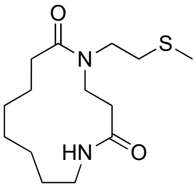
Ethyl 2-(4,13-dioxo-1,5-diazacyclotridecan-1-yl)acetate (10h)

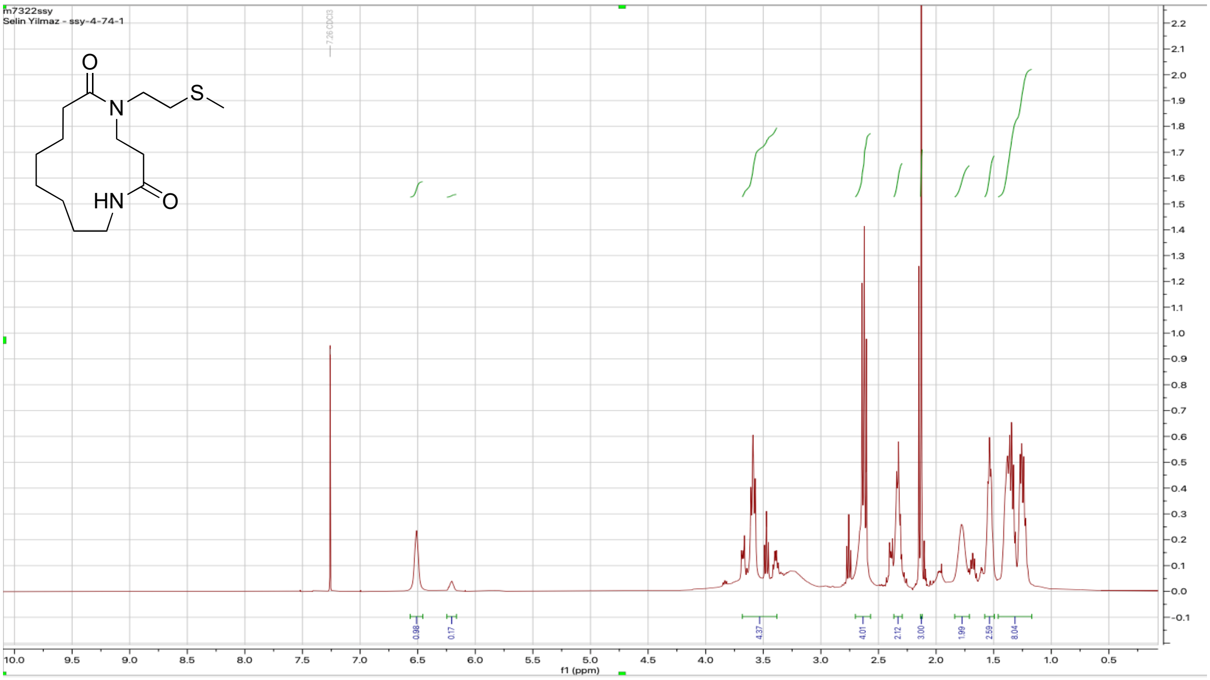


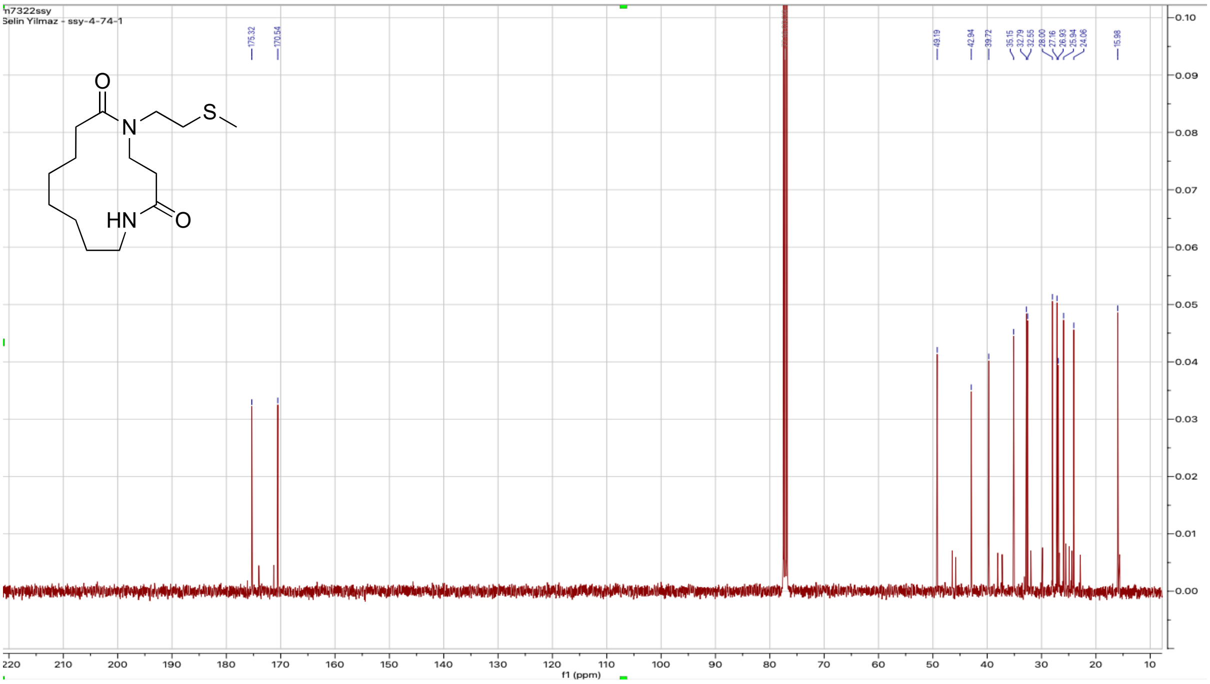




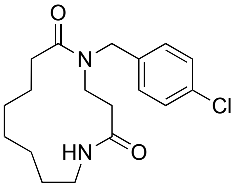
5-(2-(Methylthio)ethyl)-1,5-diazacyclotridecane-2,6-dione (10i) – 6:1 mixture of rotamers

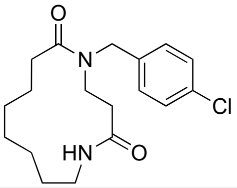


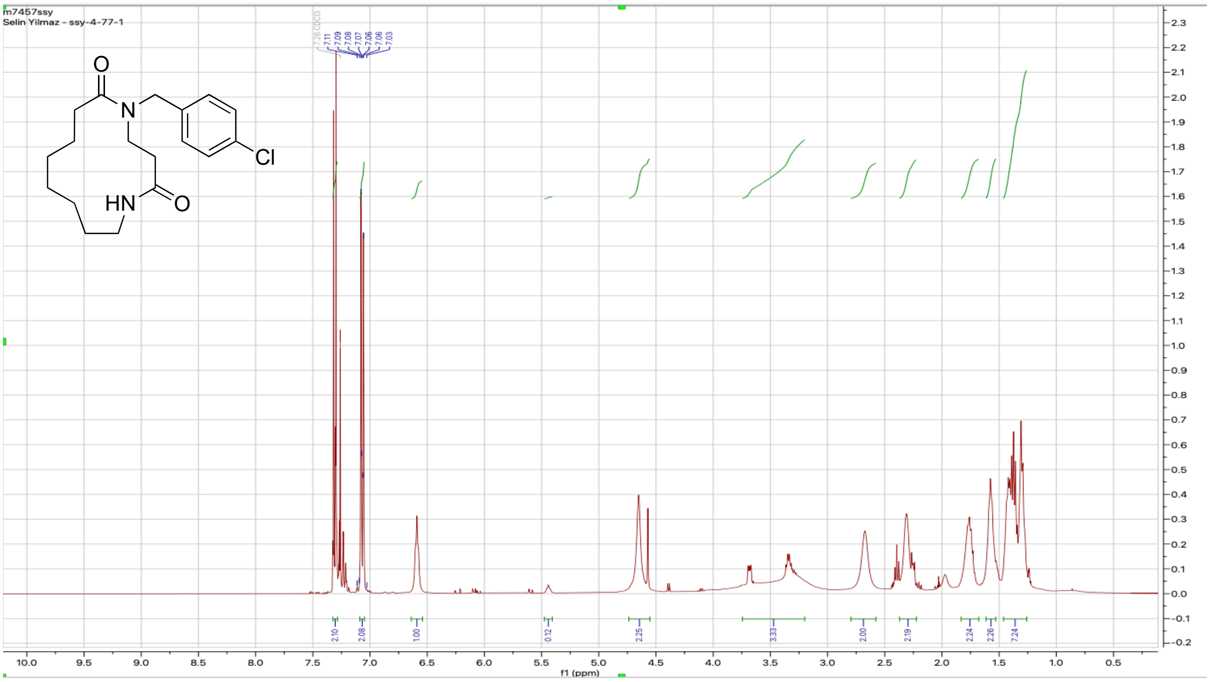


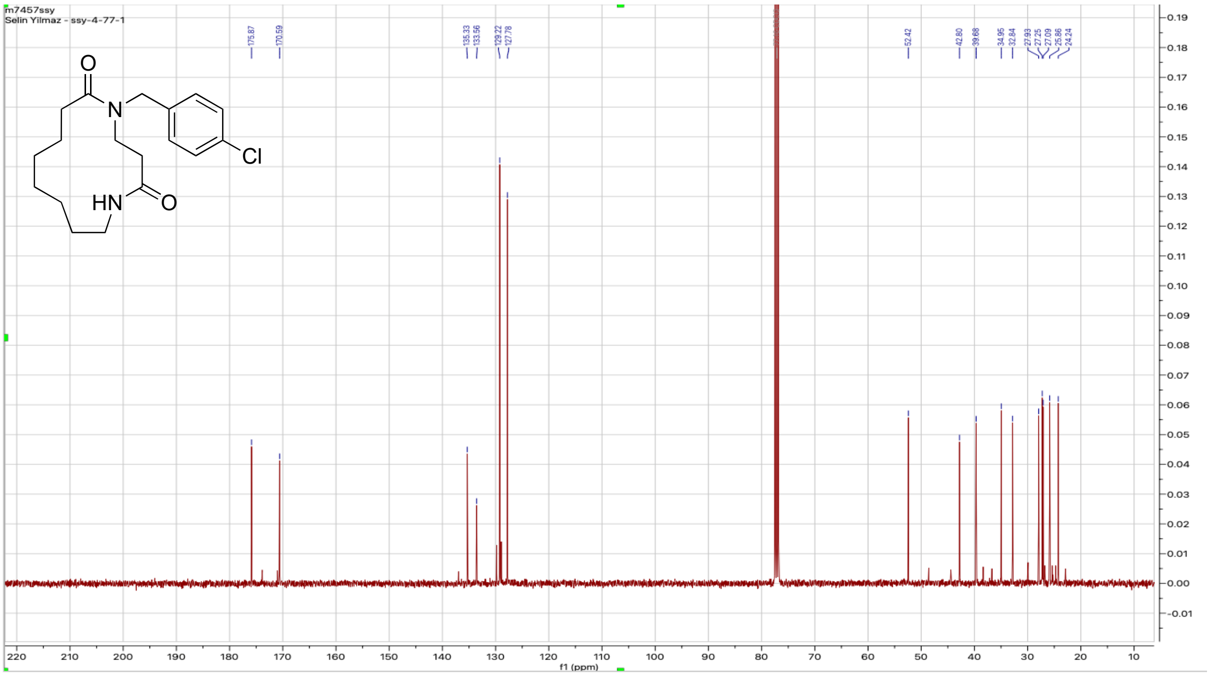


5-(4-Chlorobenzyl)-1,5-diazacyclotridecane-2,6-dione (10j) – 8:1 mixture of rotamers

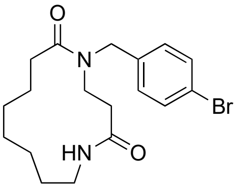


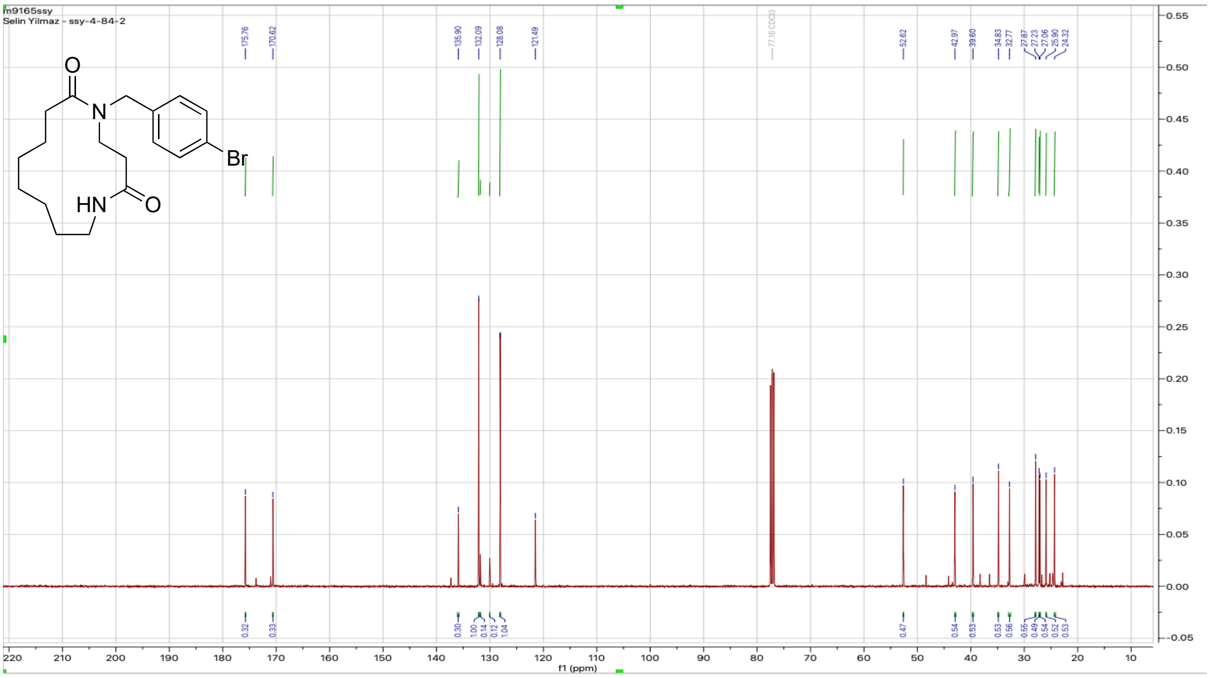




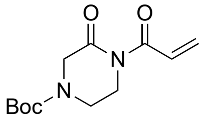


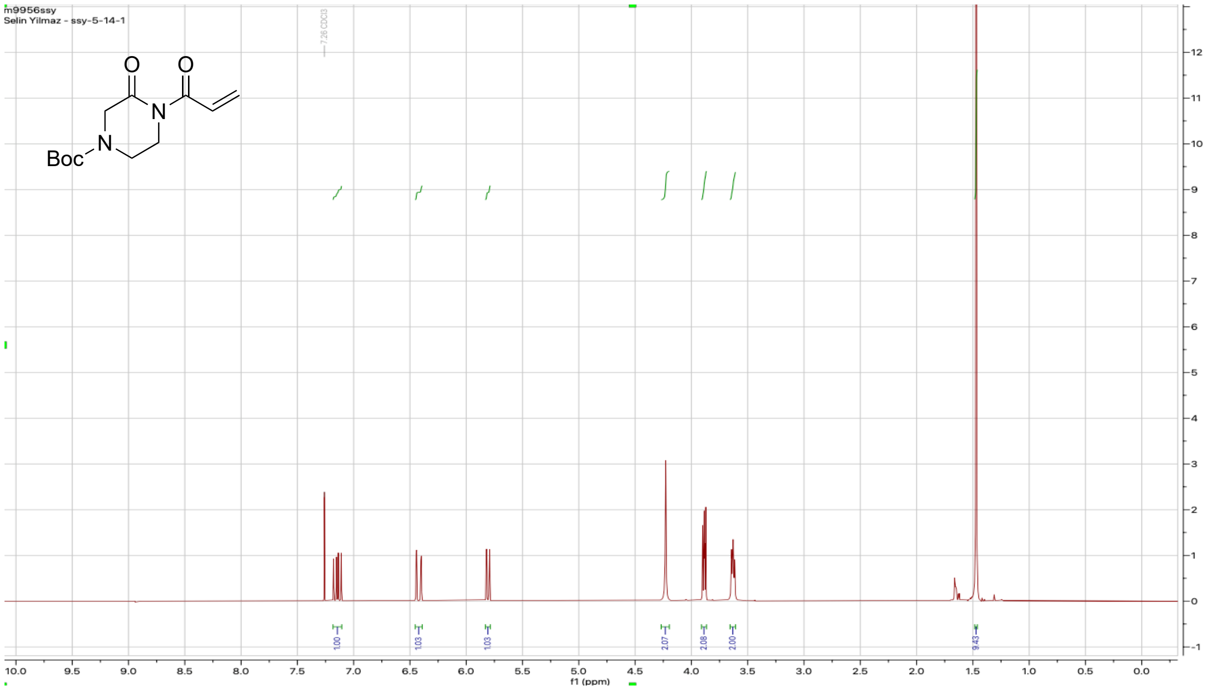
5-(4-Bromobenzyl)-1,5-diazacyclotridecane-2,6-dione (10k) - the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. 8:1 mixture of rotamers.

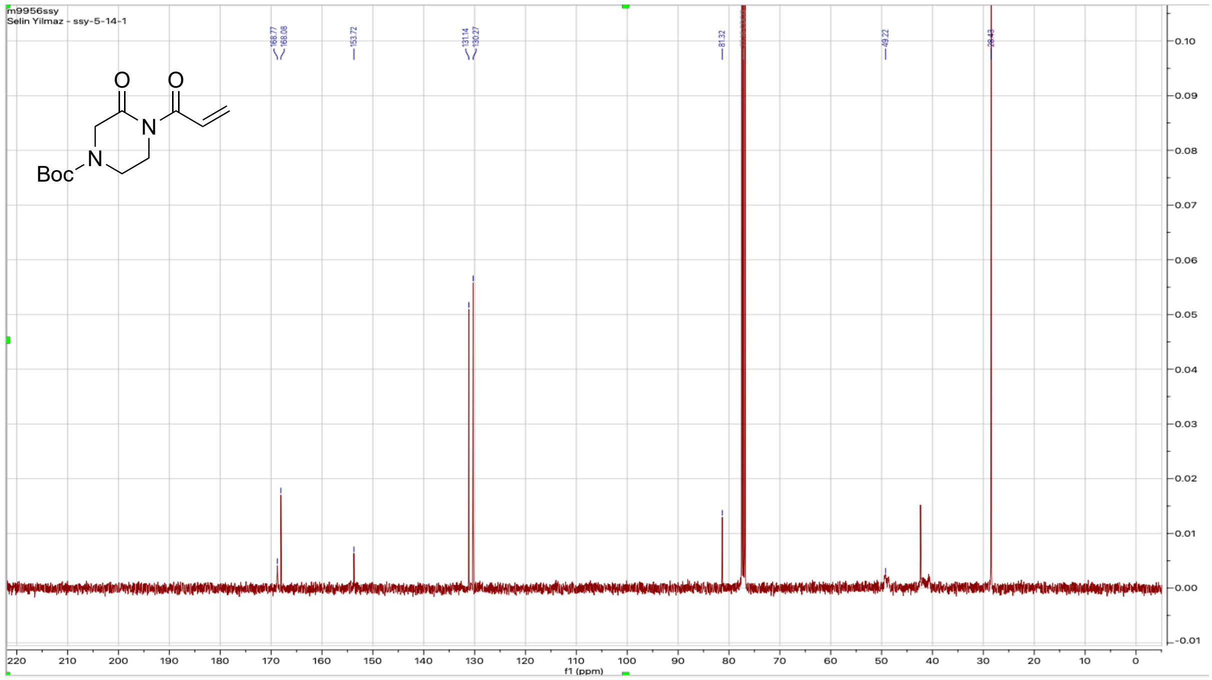




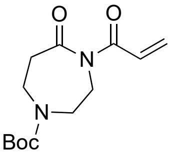
tert-Butyl 4-acryloyl-3-oxopiperazine-1-carboxylate (3e)

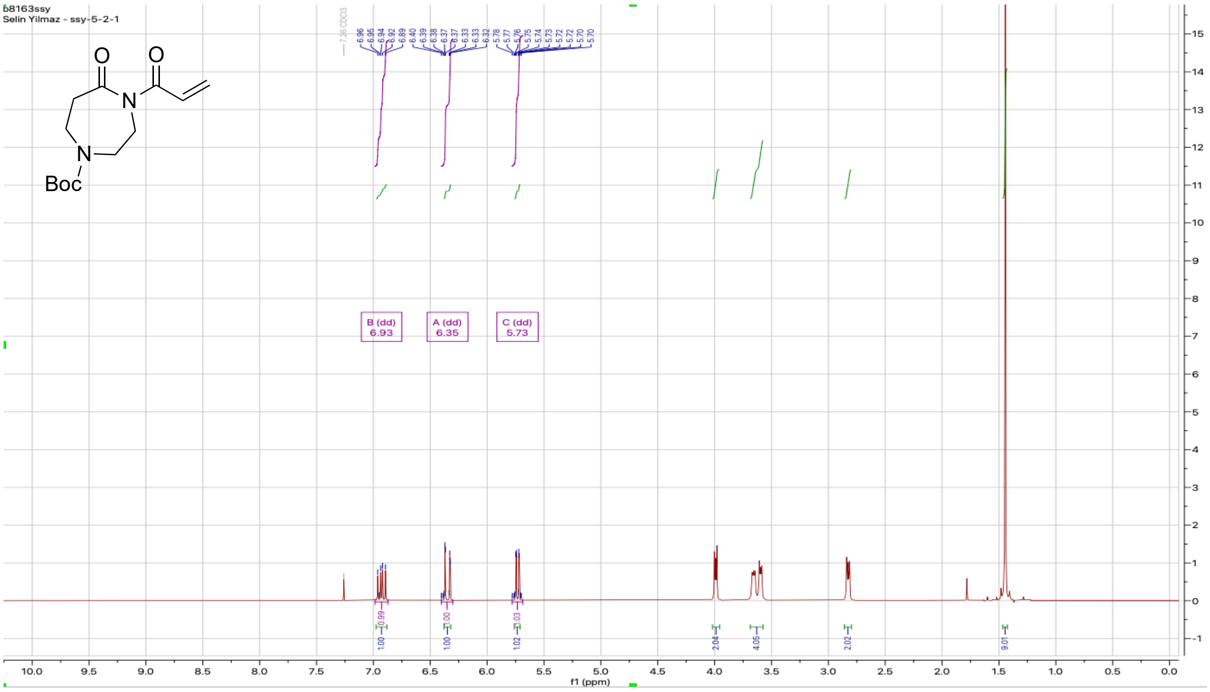


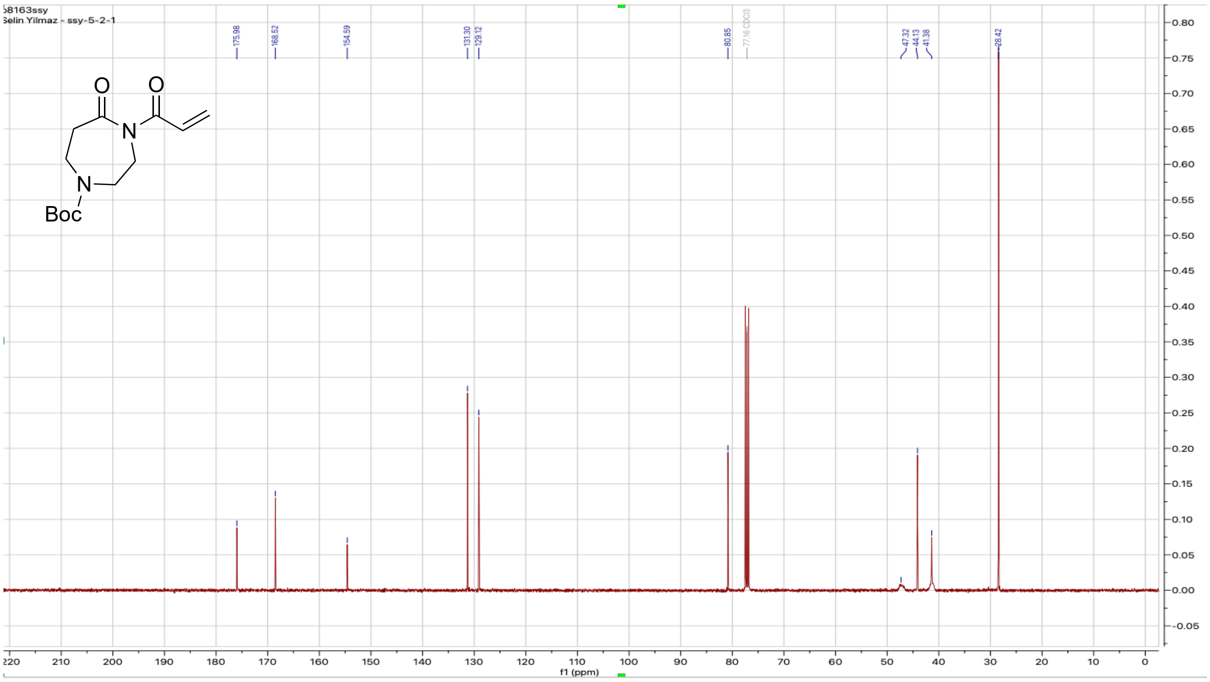




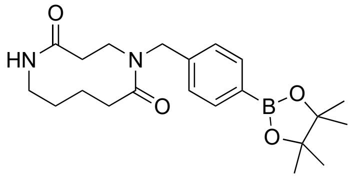
tert-Butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate (3f)

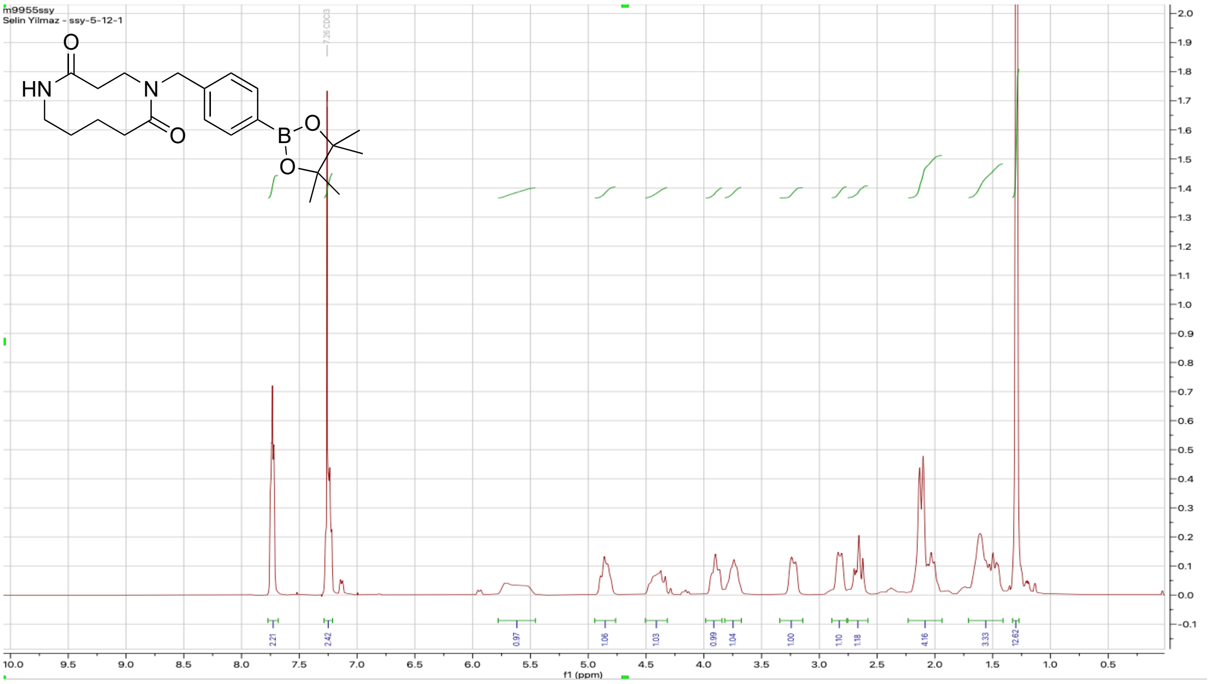


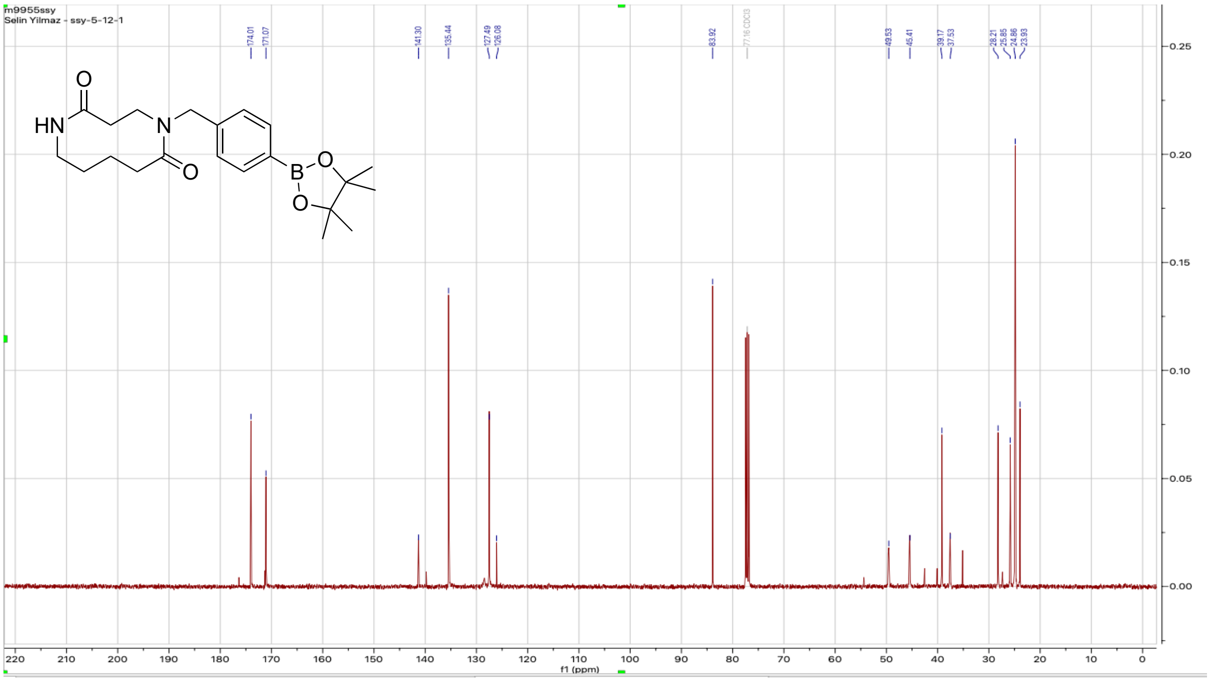




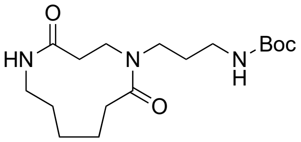
5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,5-diazecane-2,6-dione (7l)

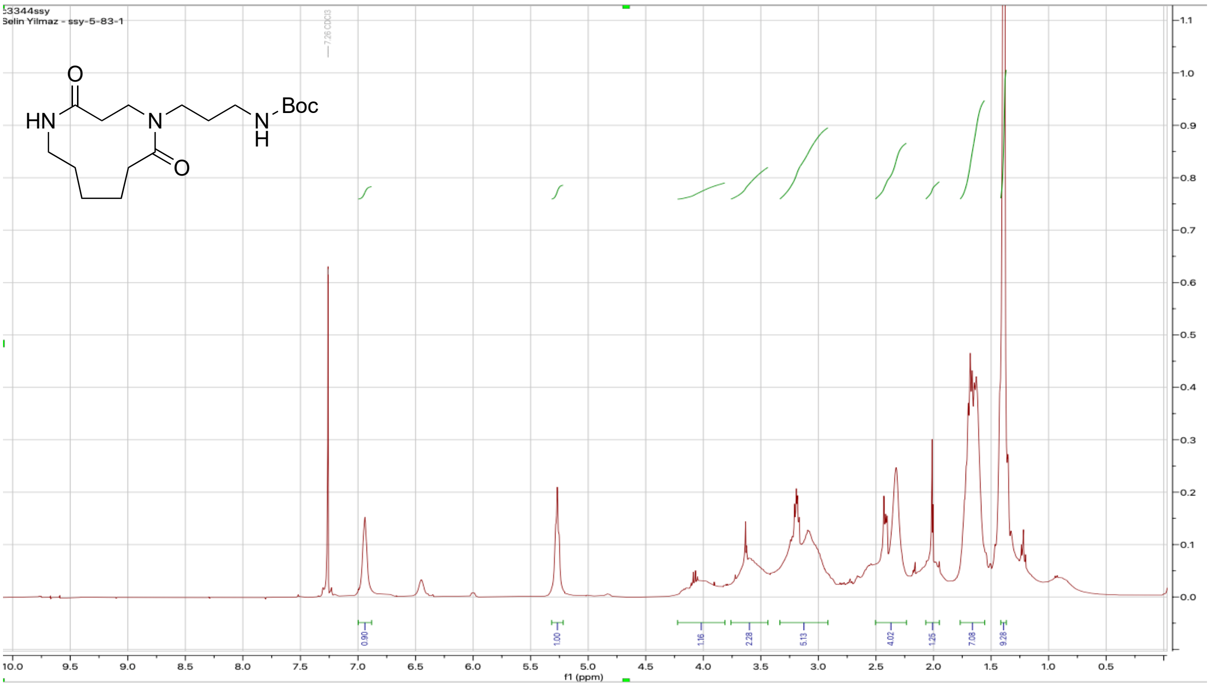


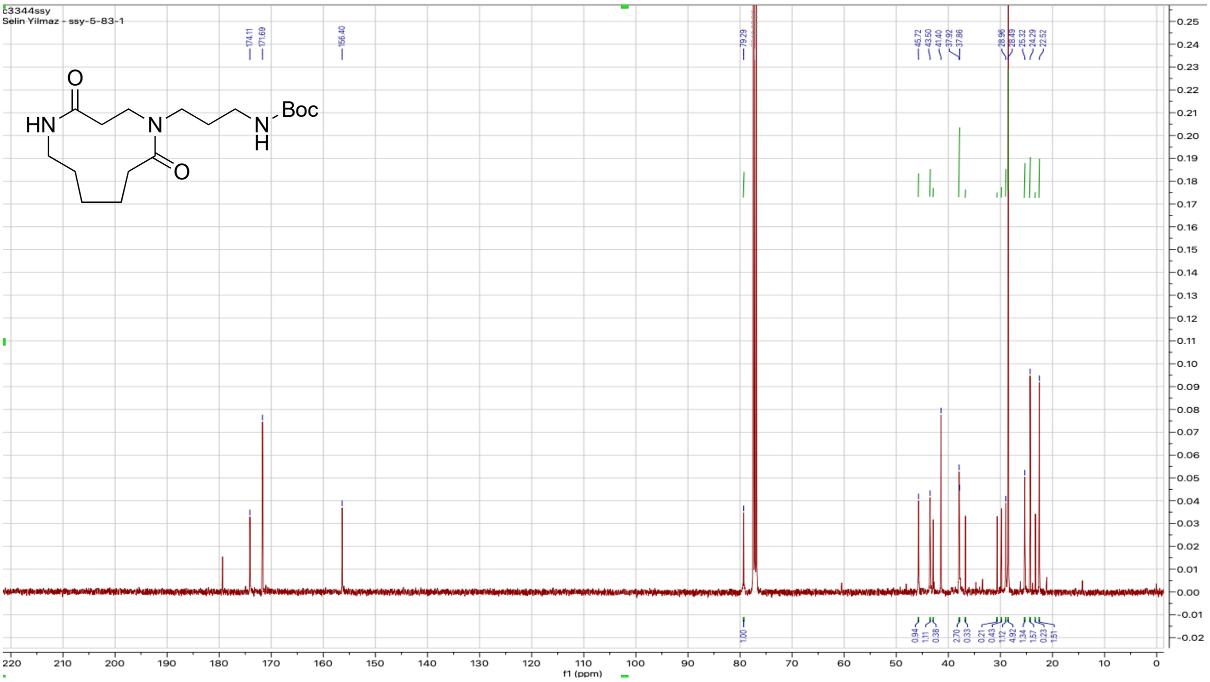




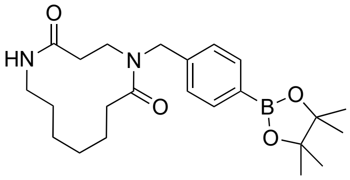
***tert*-Butyl (3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)carbamate (8m) -** the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product.

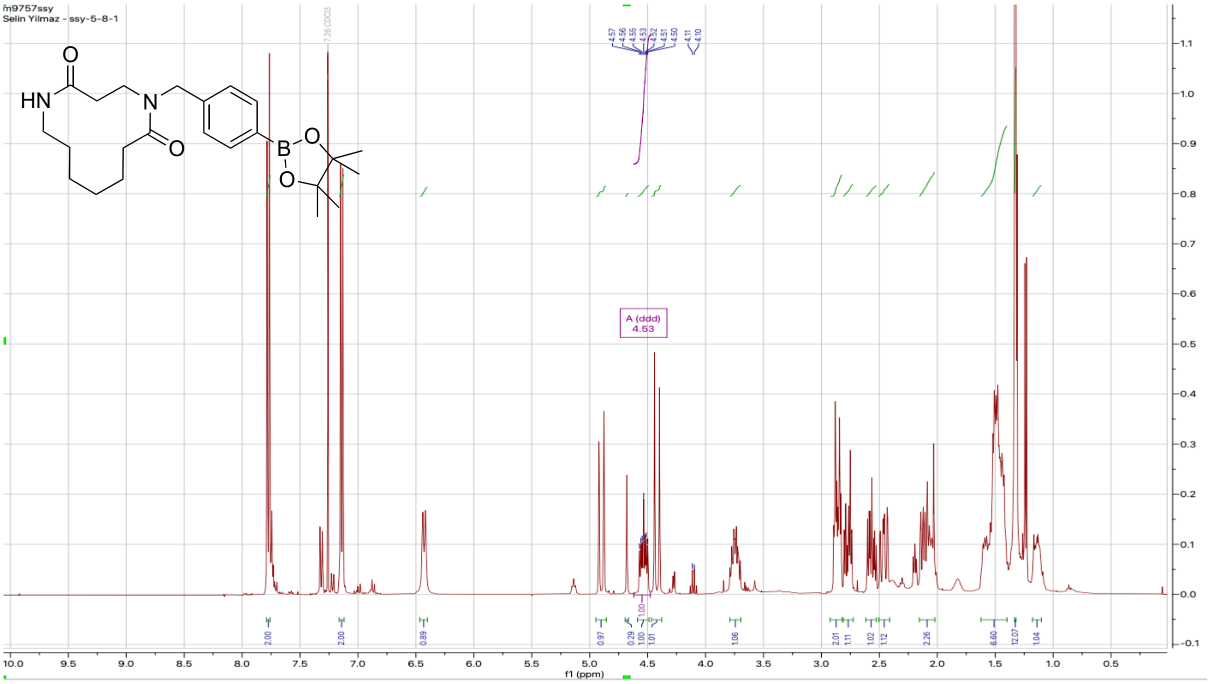


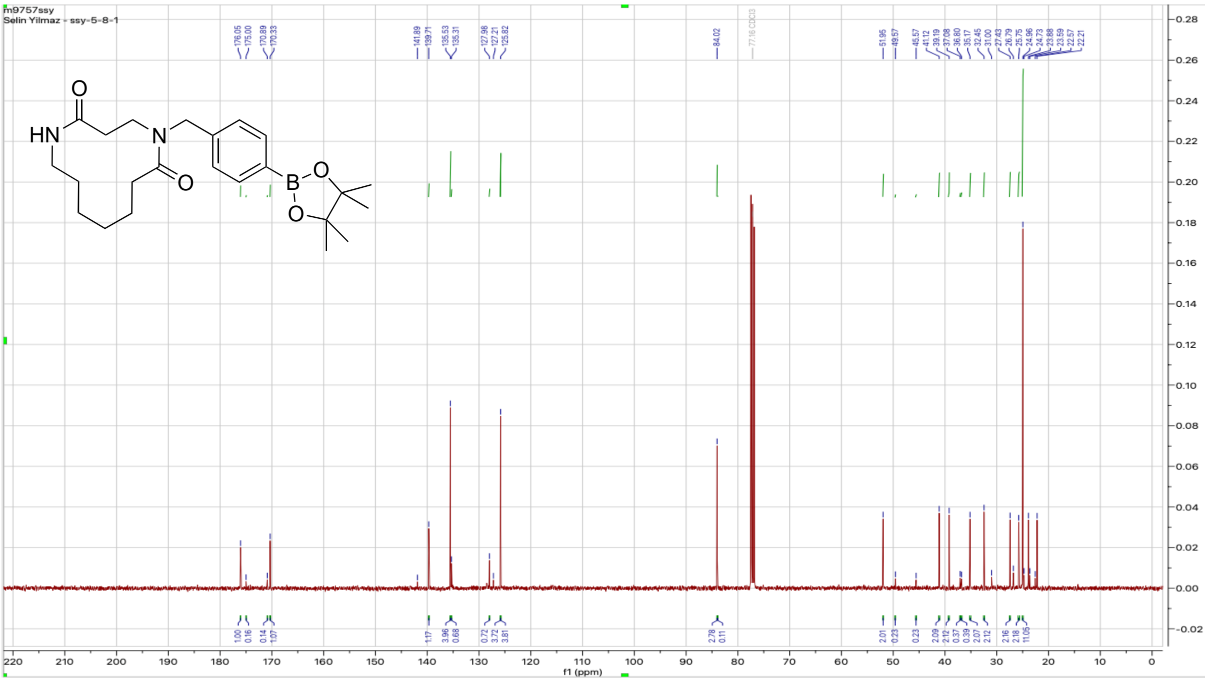




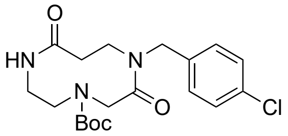
5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,5-diazacyclododecane-2,6-dione (9l) – 1:6 mixture of rotamers

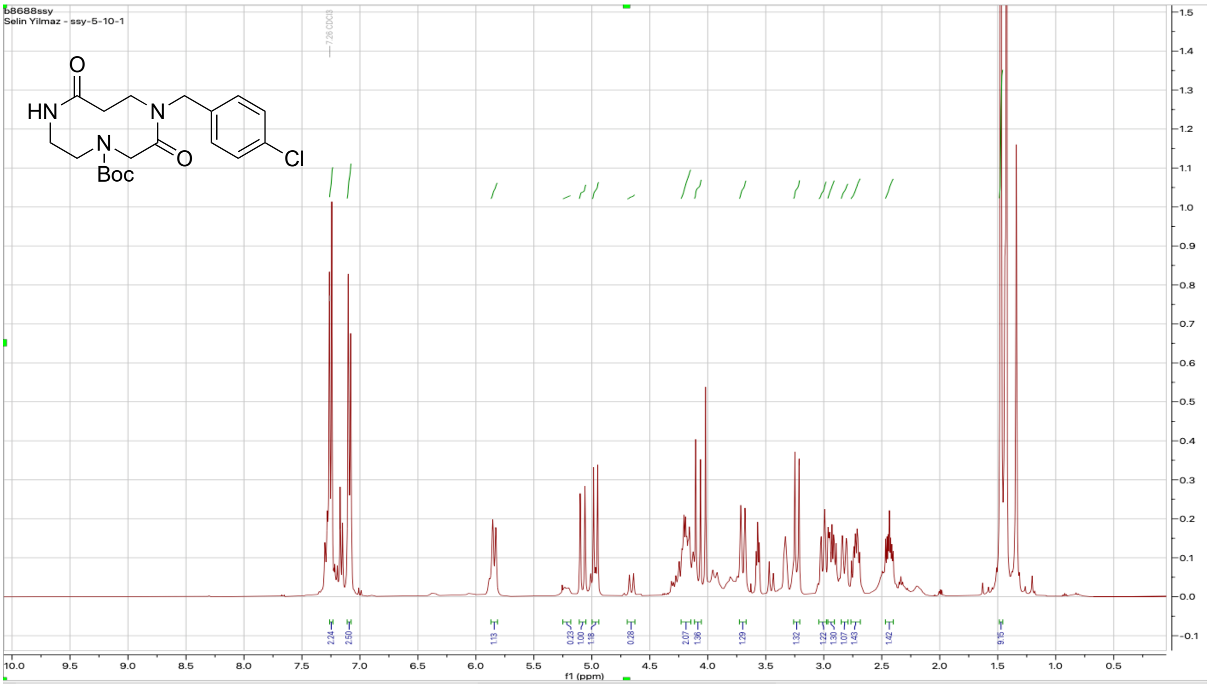


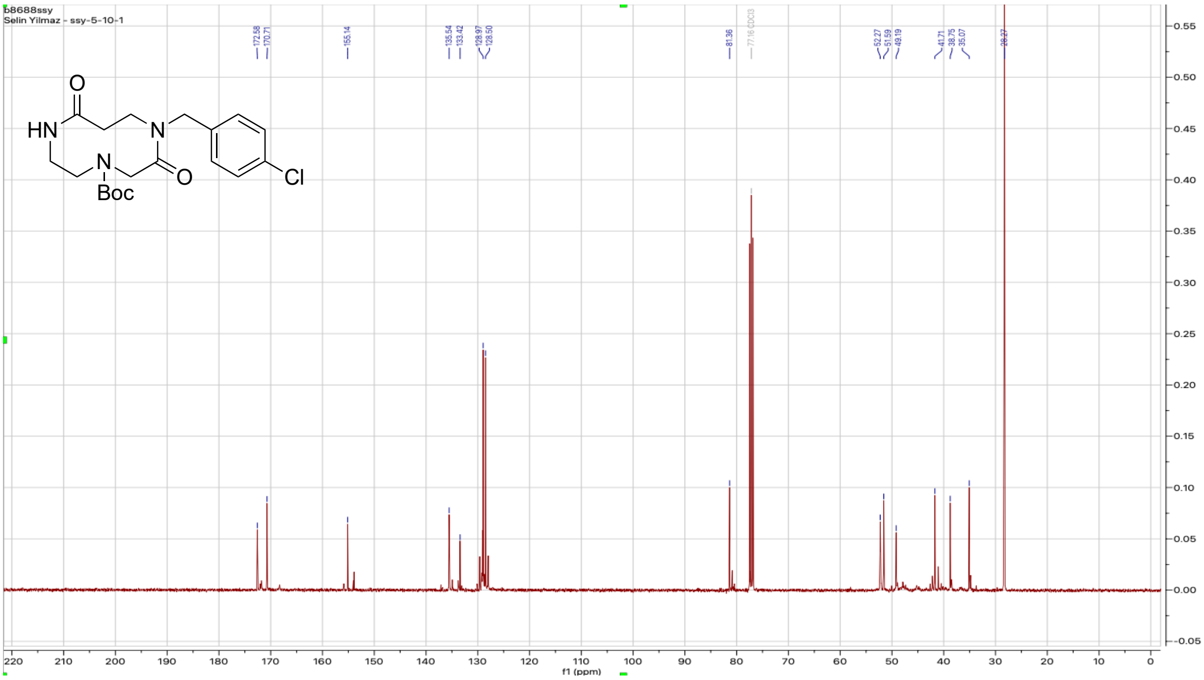




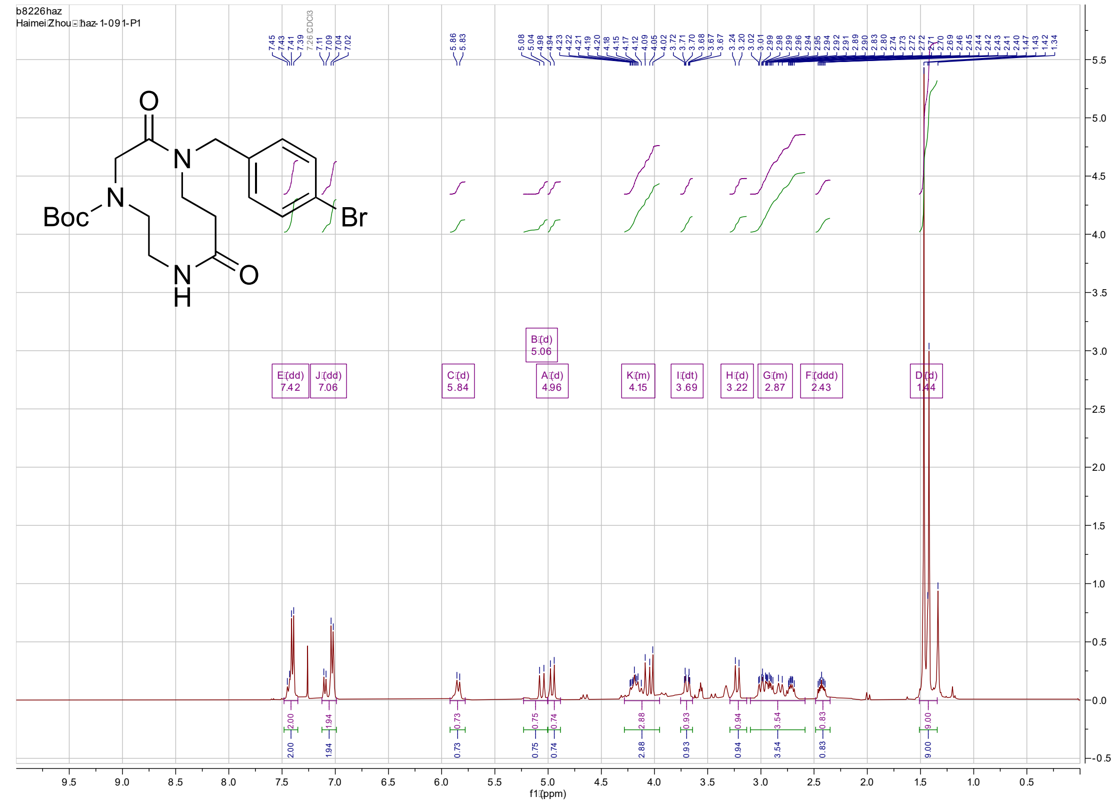
tert-Butyl 1-(4-chlorobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (11j)

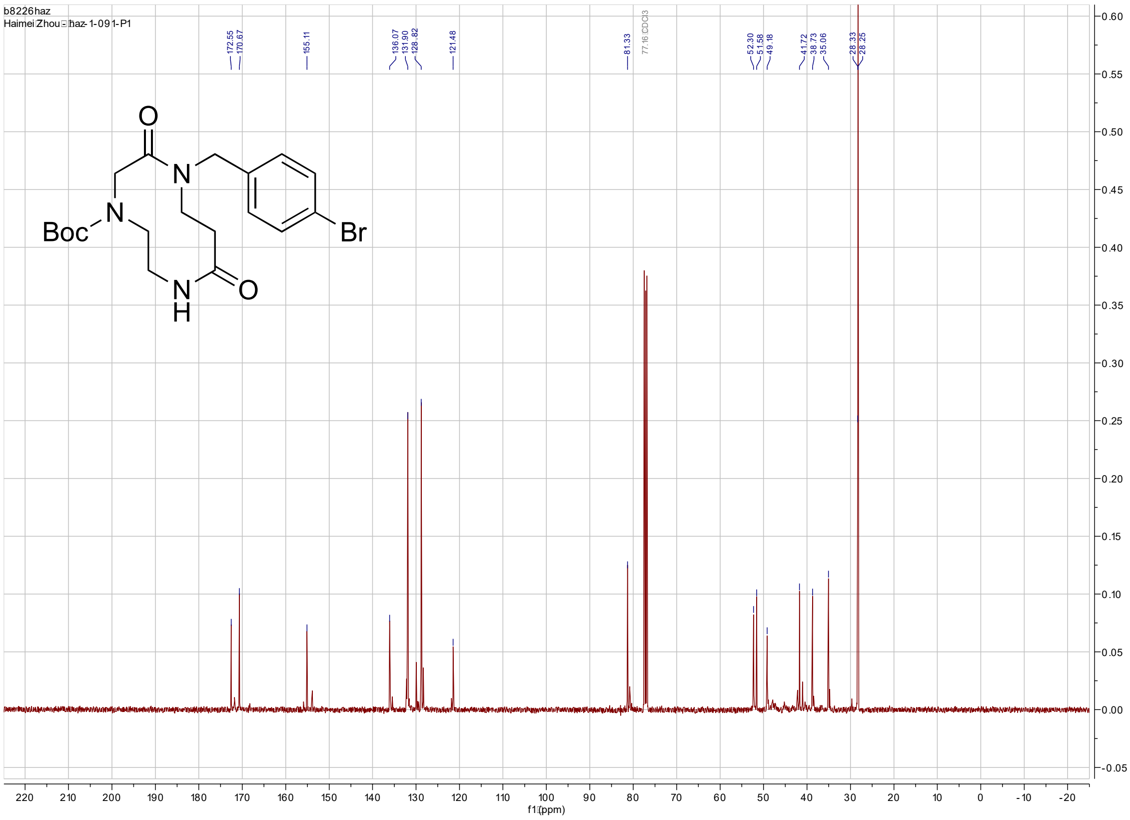




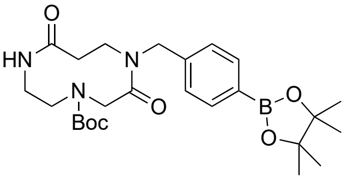


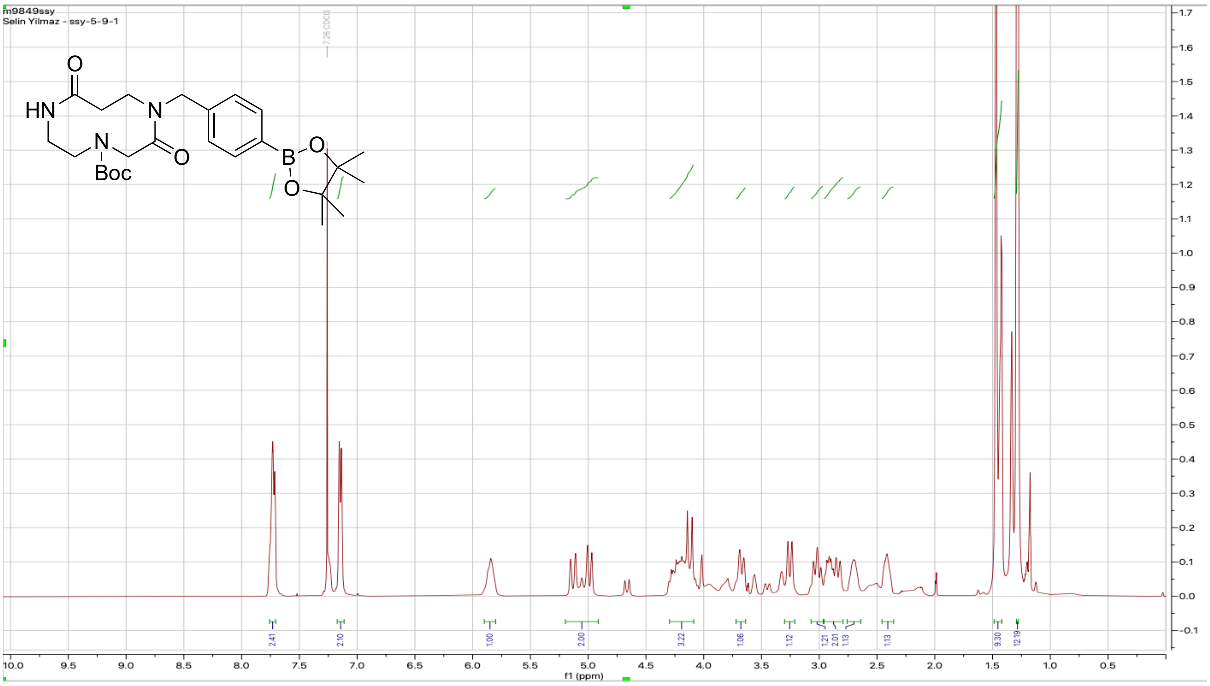
***tert*-Butyl 1-(4-bromobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (11k)** In solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with evidence of 2 minor rotamers also present (≈10:1:1)

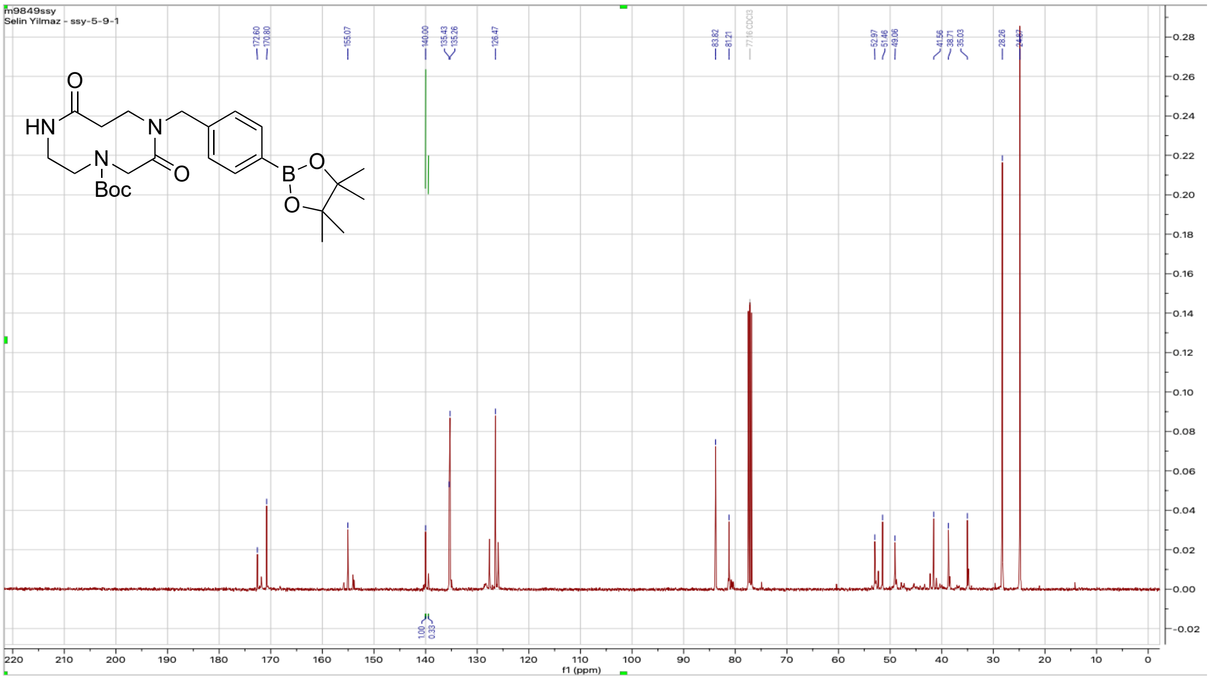




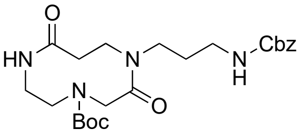
***tert*-Butyl 2,8-dioxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-7-triazecane-4-carboxylate (11l)** – 1:3 mixture of rotamers

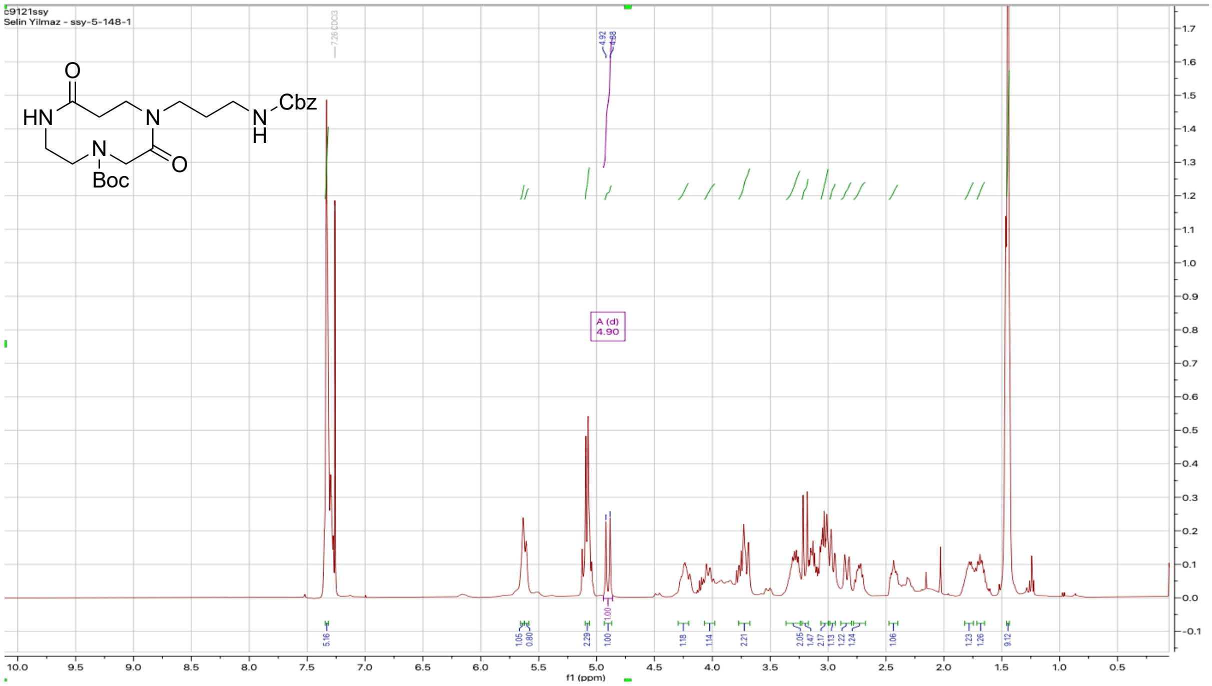


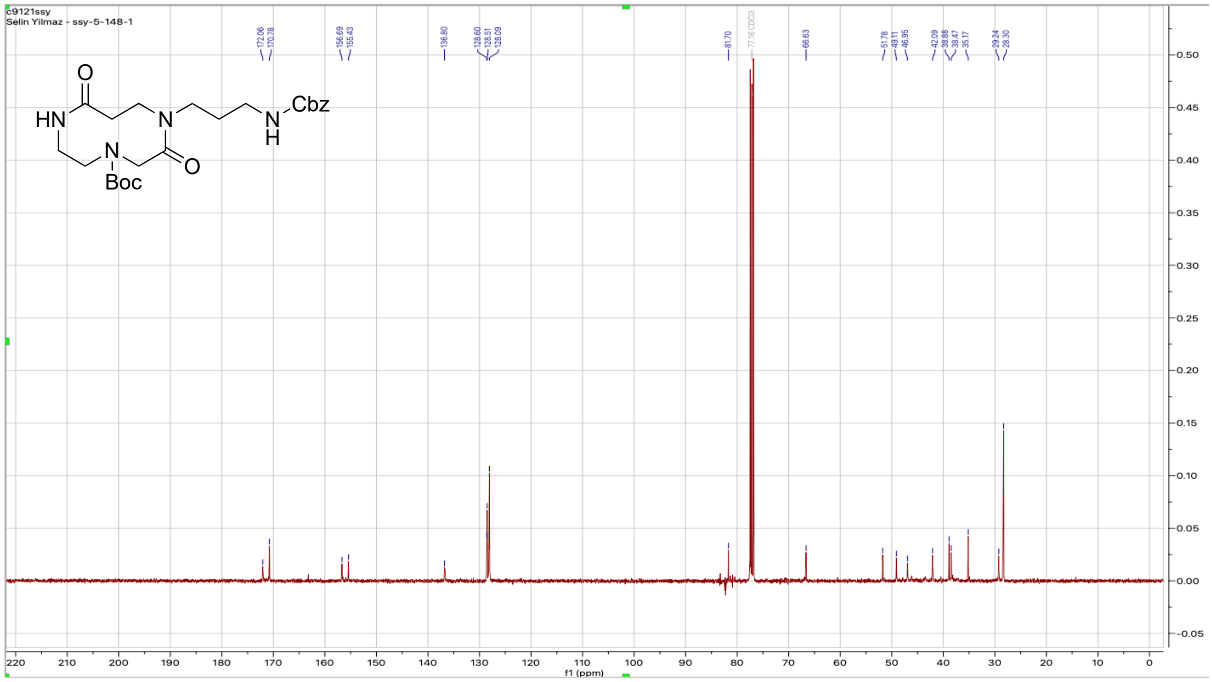




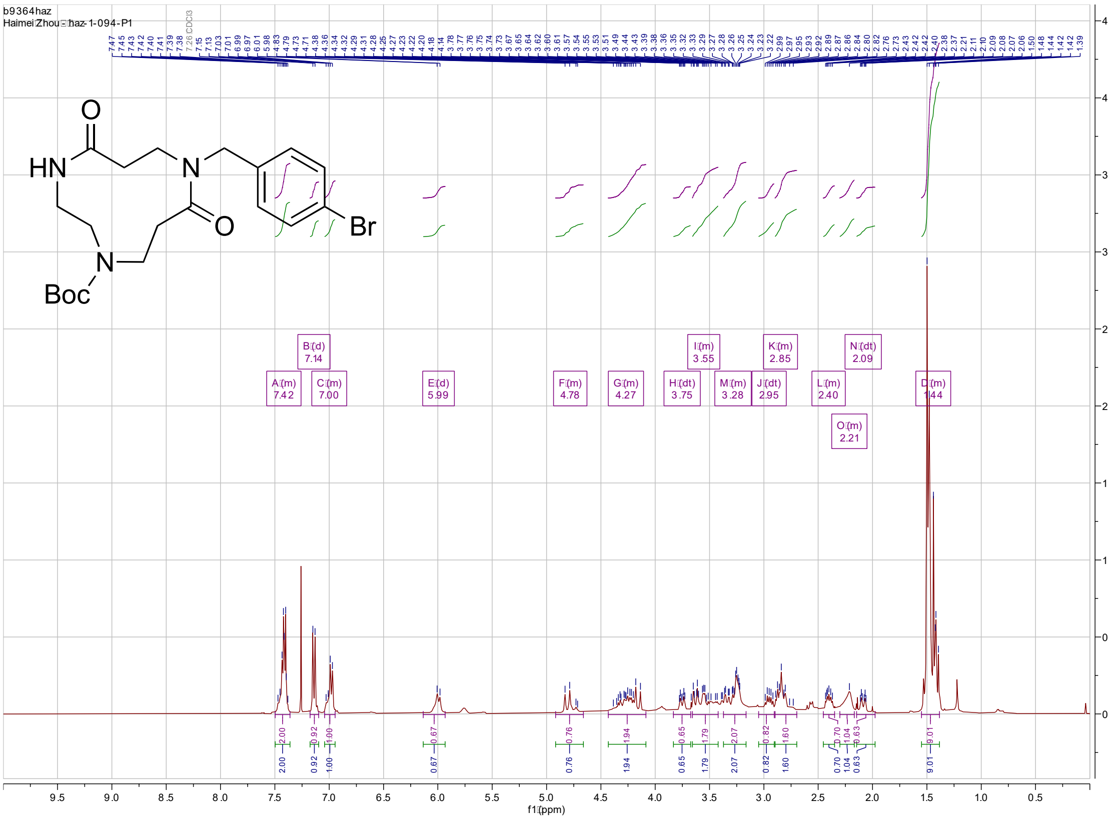
tert-Butyl1-(3-(((benzyloxy)carbonyl)aminopropyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (11n)

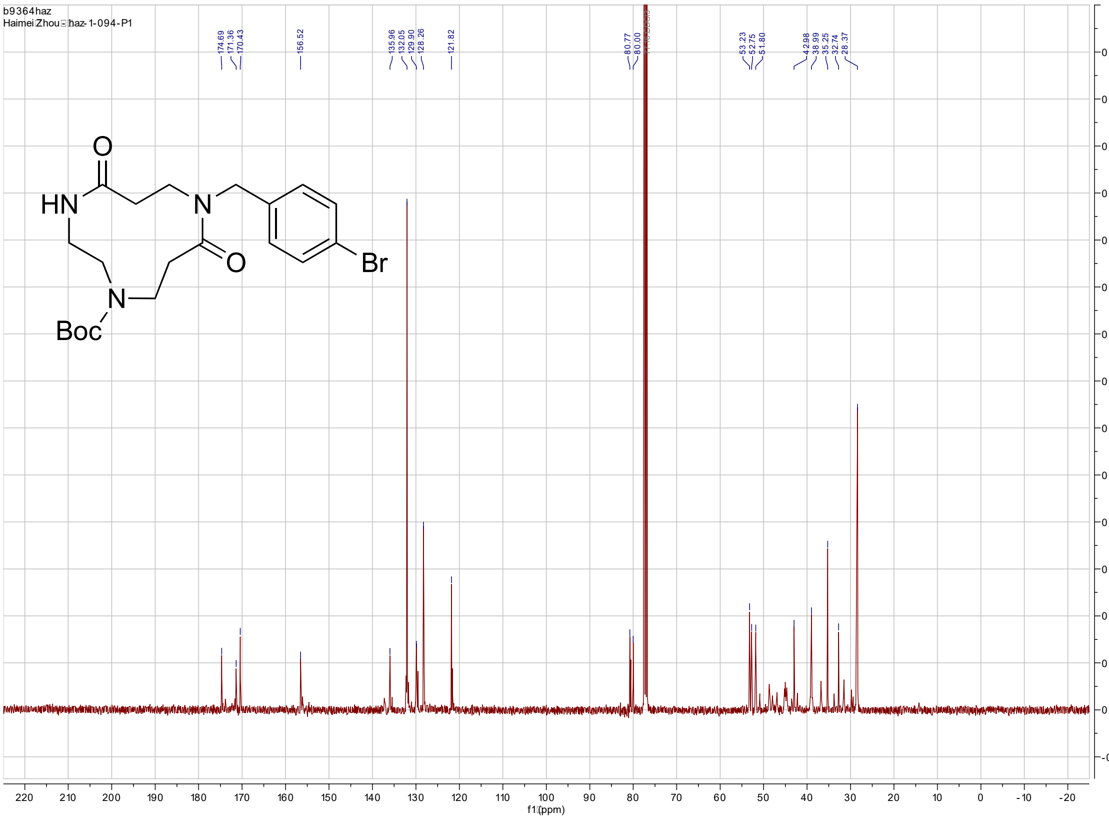




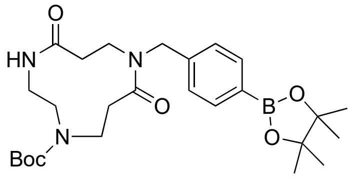


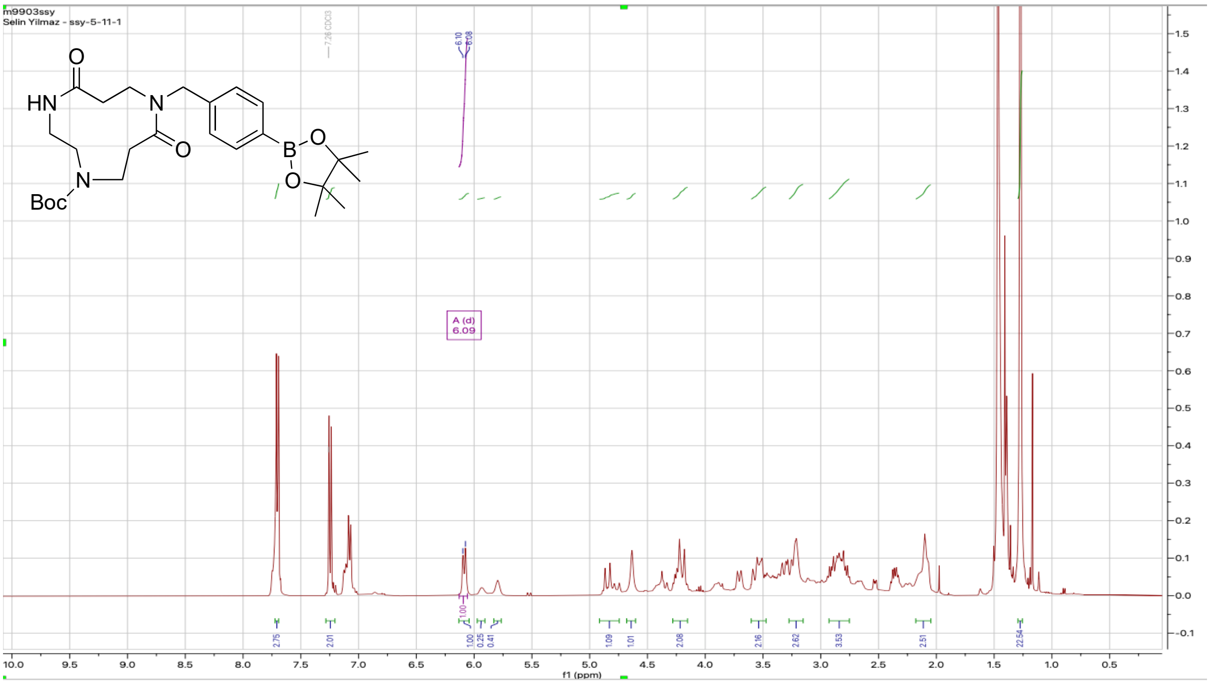
***tert*-Butyl 8-(4-bromobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (12k)** - in solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with 2 minor rotamers also evident in the NMR spectra

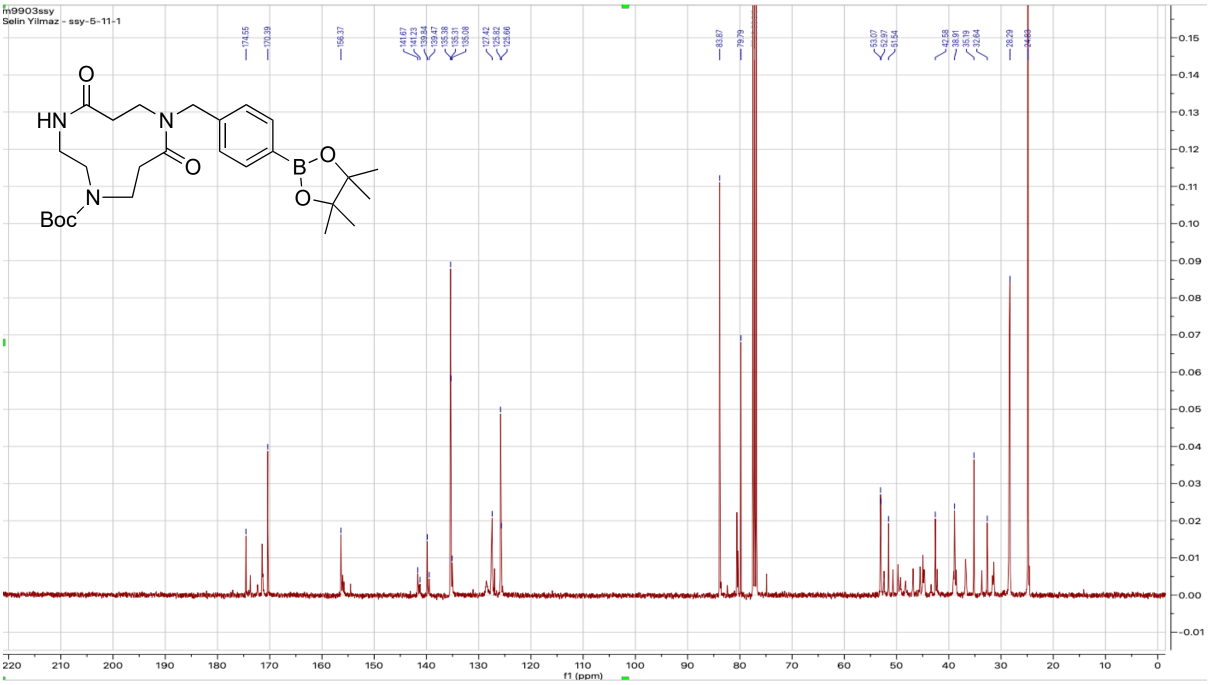




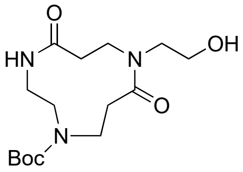
***tert*-Butyl 5,9-dioxo-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,4-8-triazacycloundecane-1-carboxylate (12l)** the ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product. 5:3:2 mixture of rotamers.

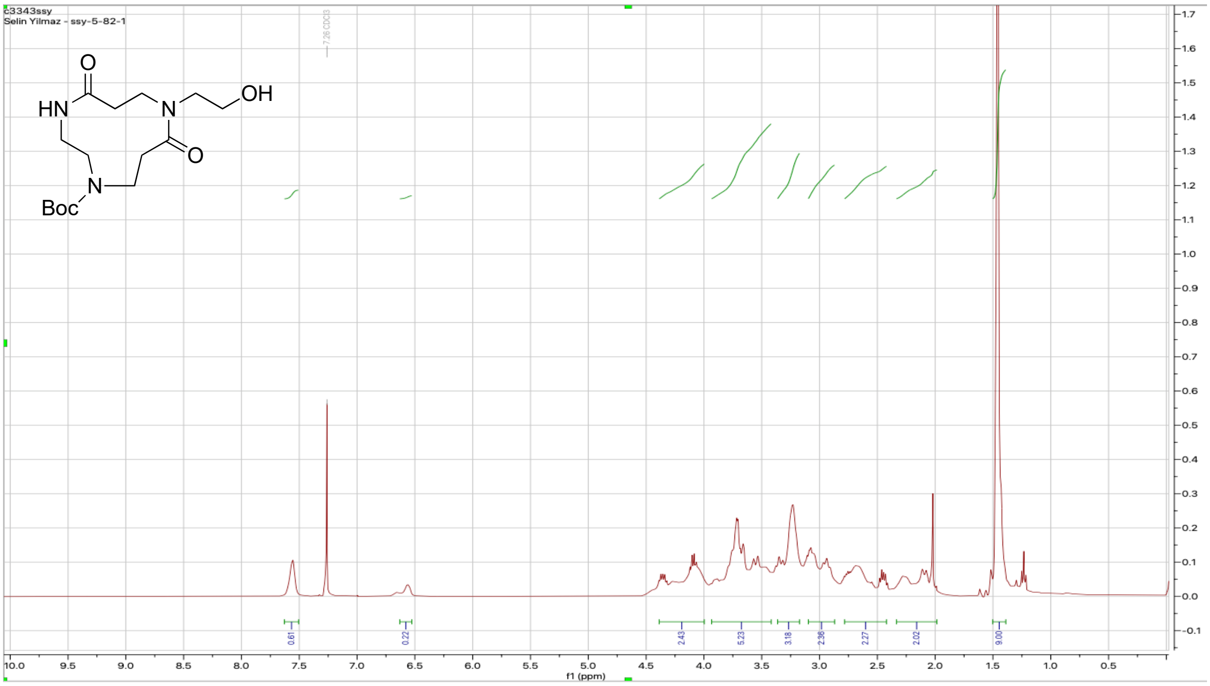


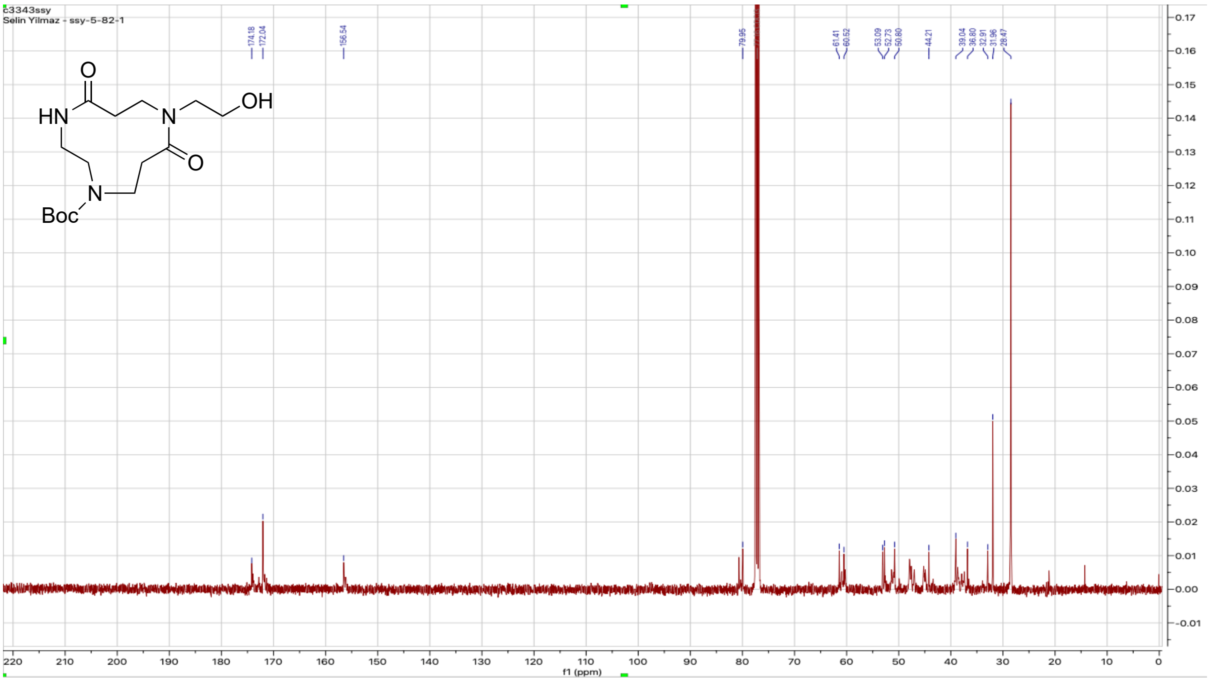




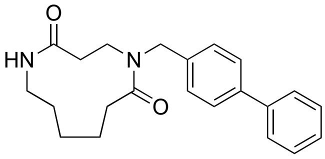
***tert*-Butyl 8-(2-hydroxyethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (12o)** The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product.

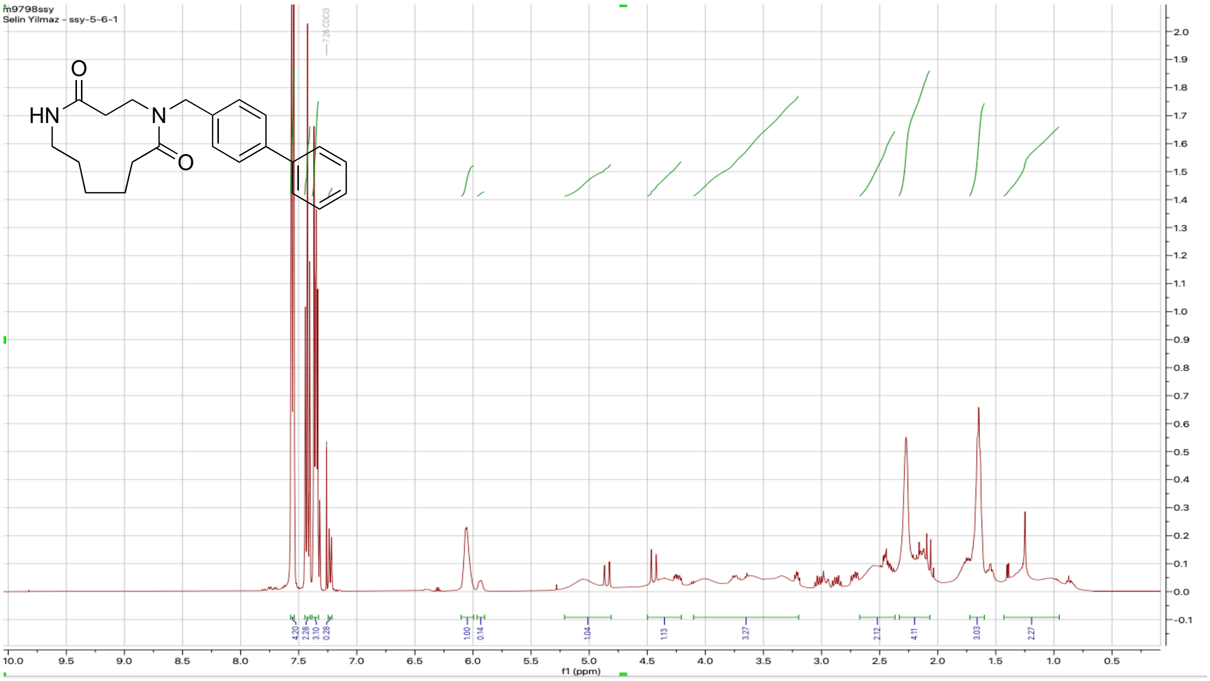


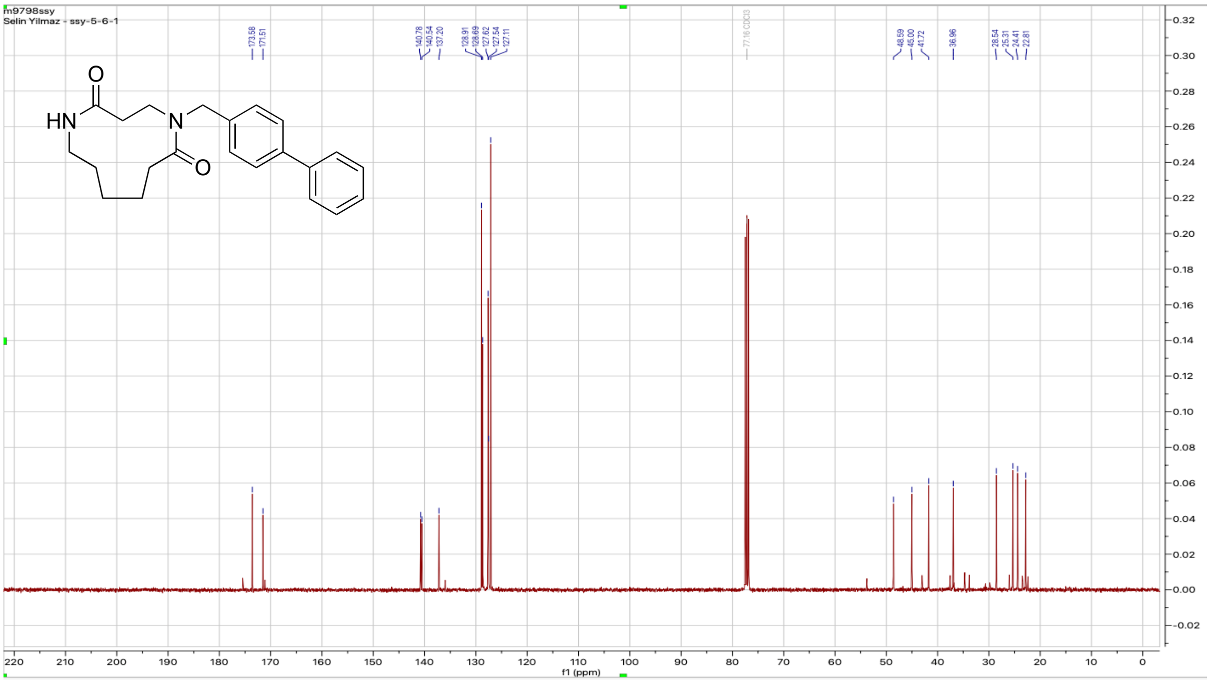




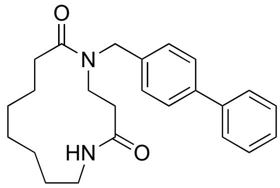
5-([1,1'-Biphenyl]-4-ylmethyl)-1,5-diazacycloundecane-2,6-dione (13a) The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (sample sample) is more useful for determining the identity and purity of the product. 7:1 mixture of rotamers

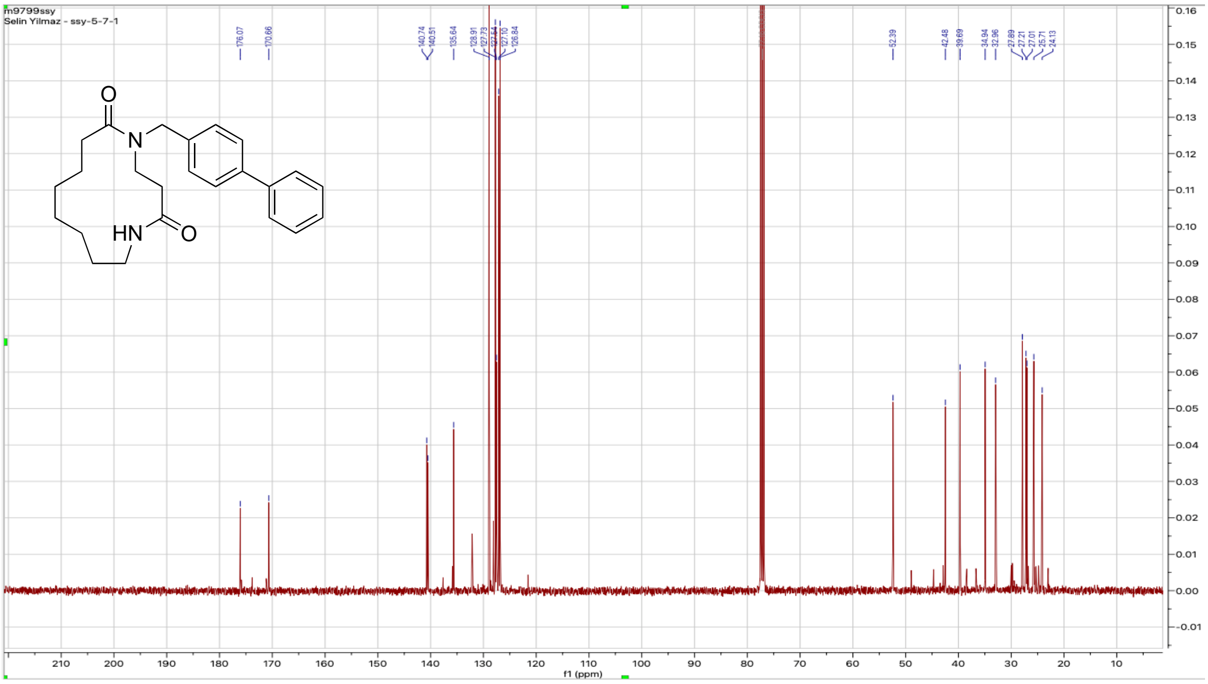


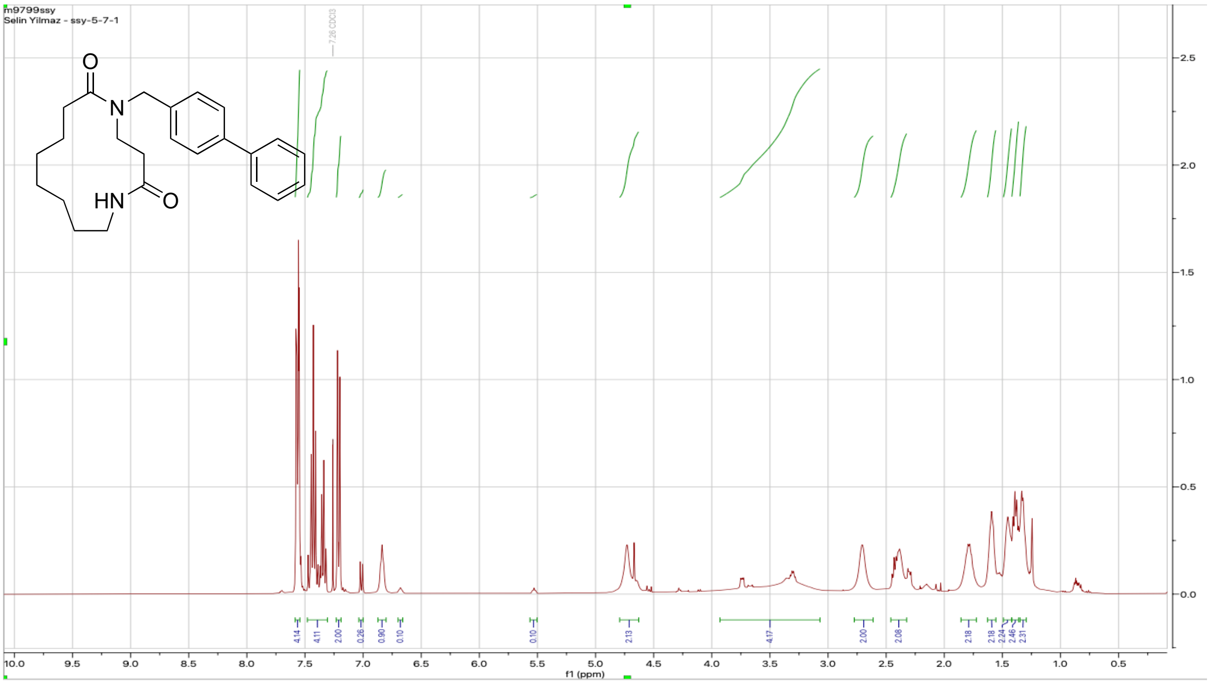




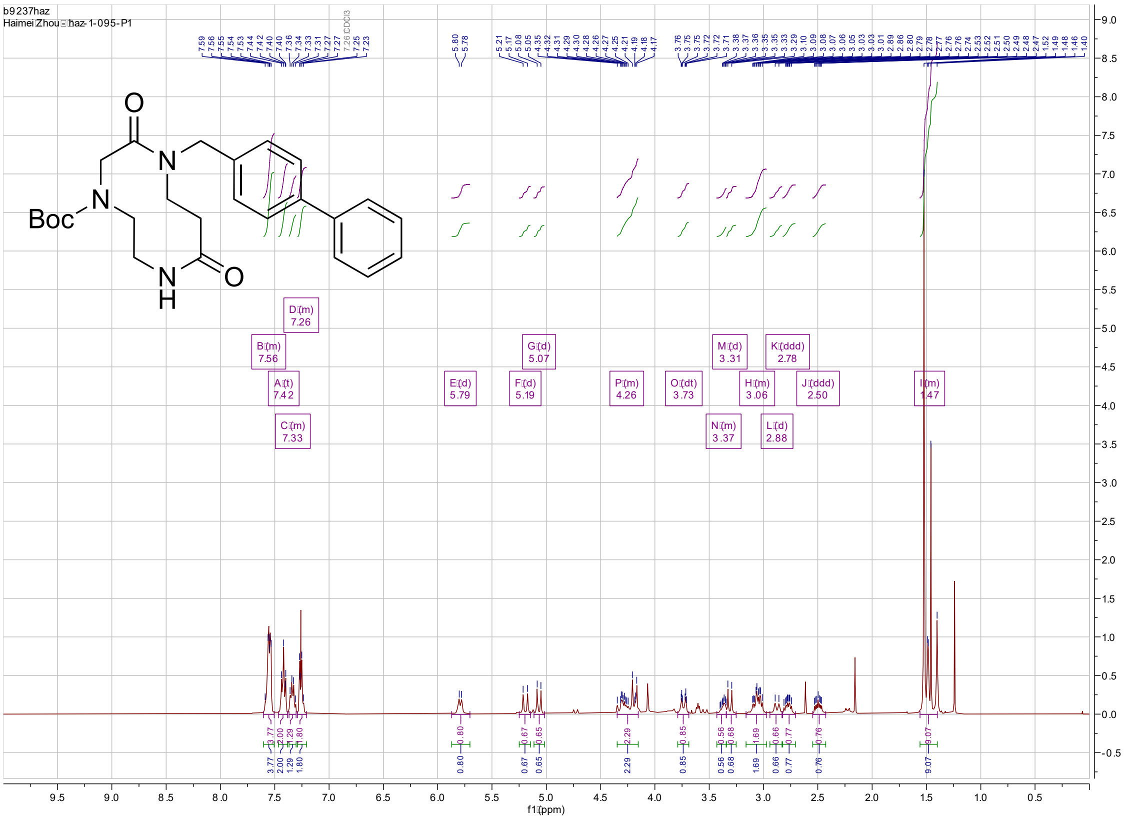
3-([1,1'-Biphenyl]-4-ylmethyl)-1,3-diazacyclotridecane-2,6-dione (13b) - The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product.

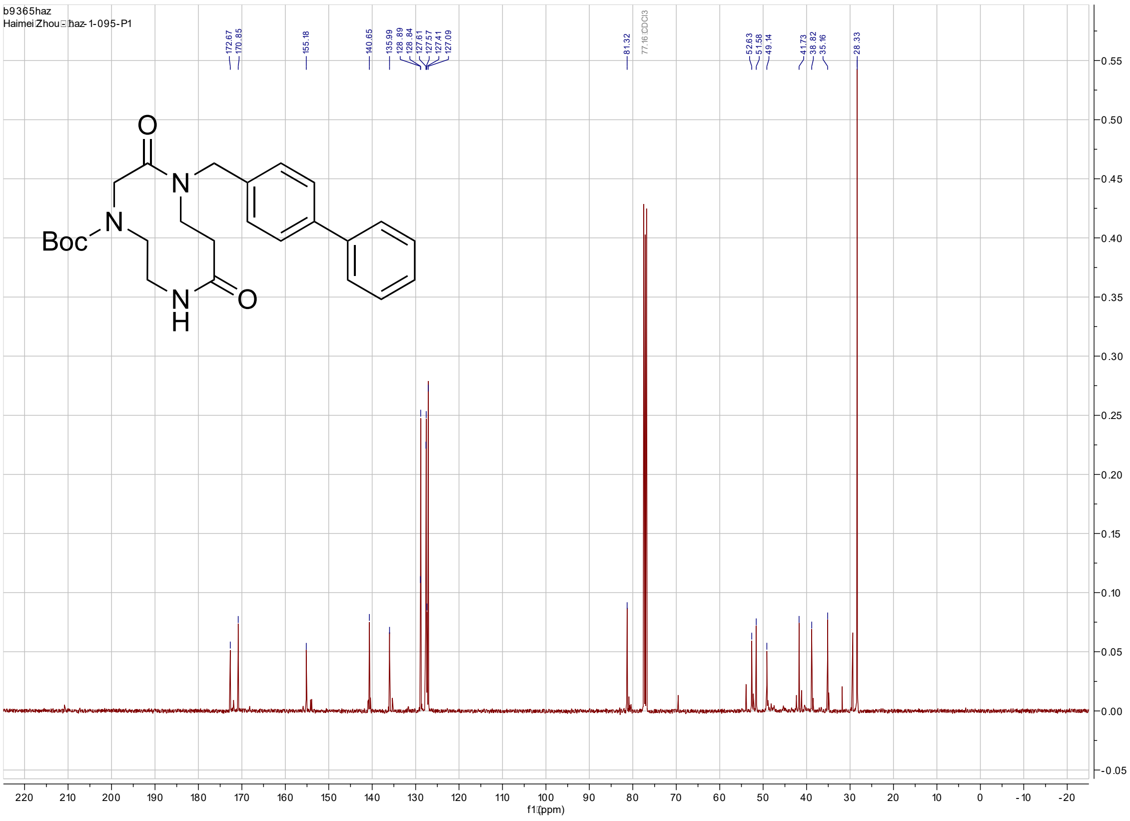




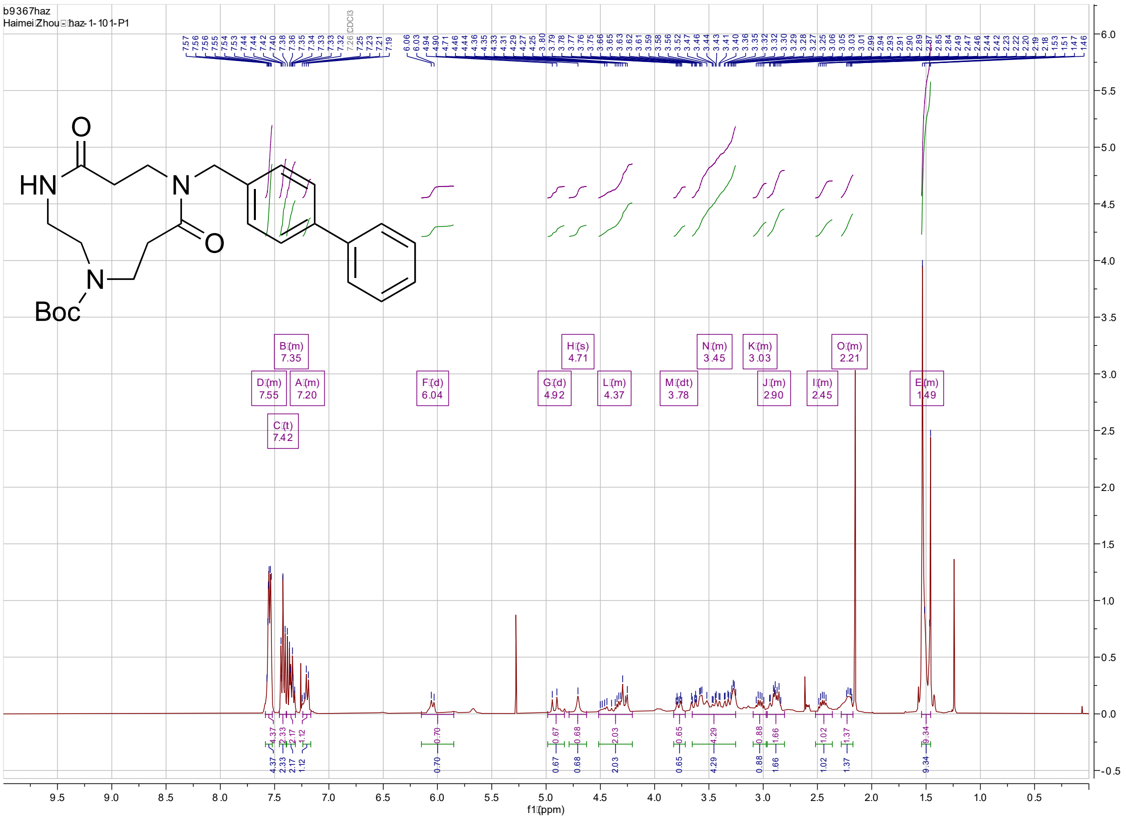


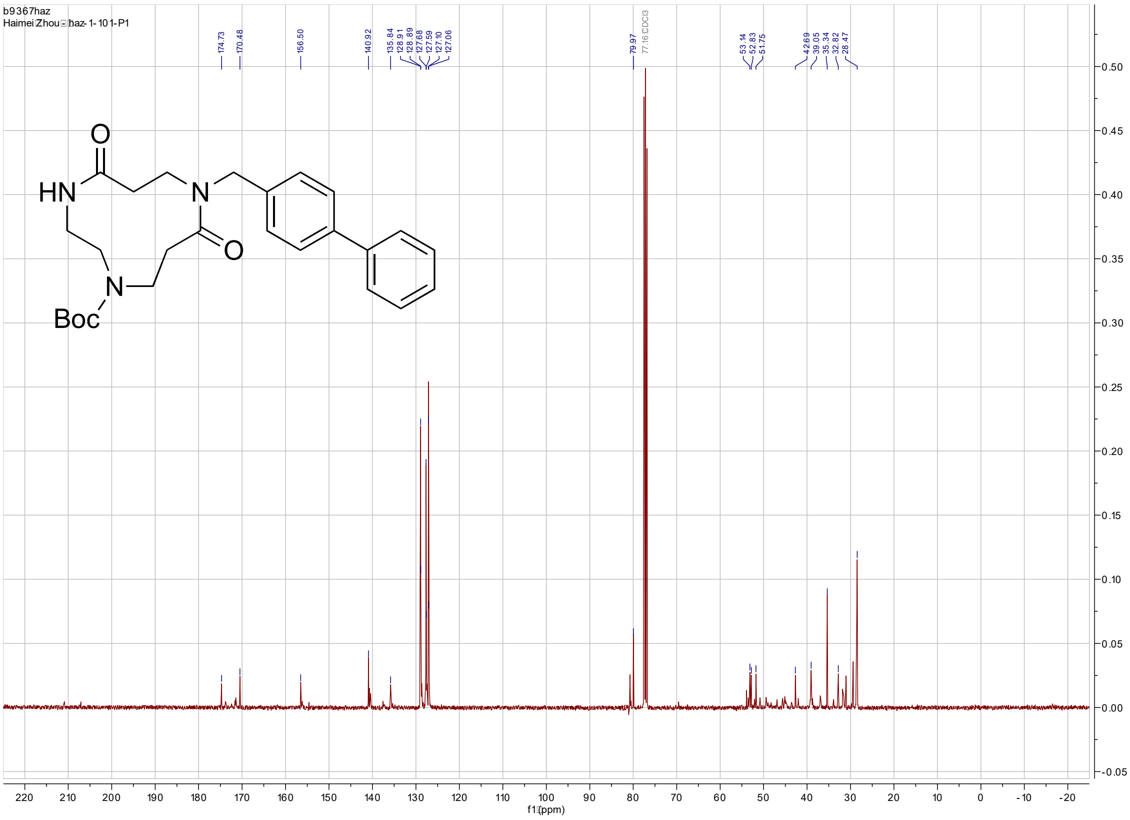
***tert*-Butyl 1-([1,1'-biphenyl]-4-ylmethyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (13c)** - in solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with 2 minor rotamers also evident in the NMR spectra.



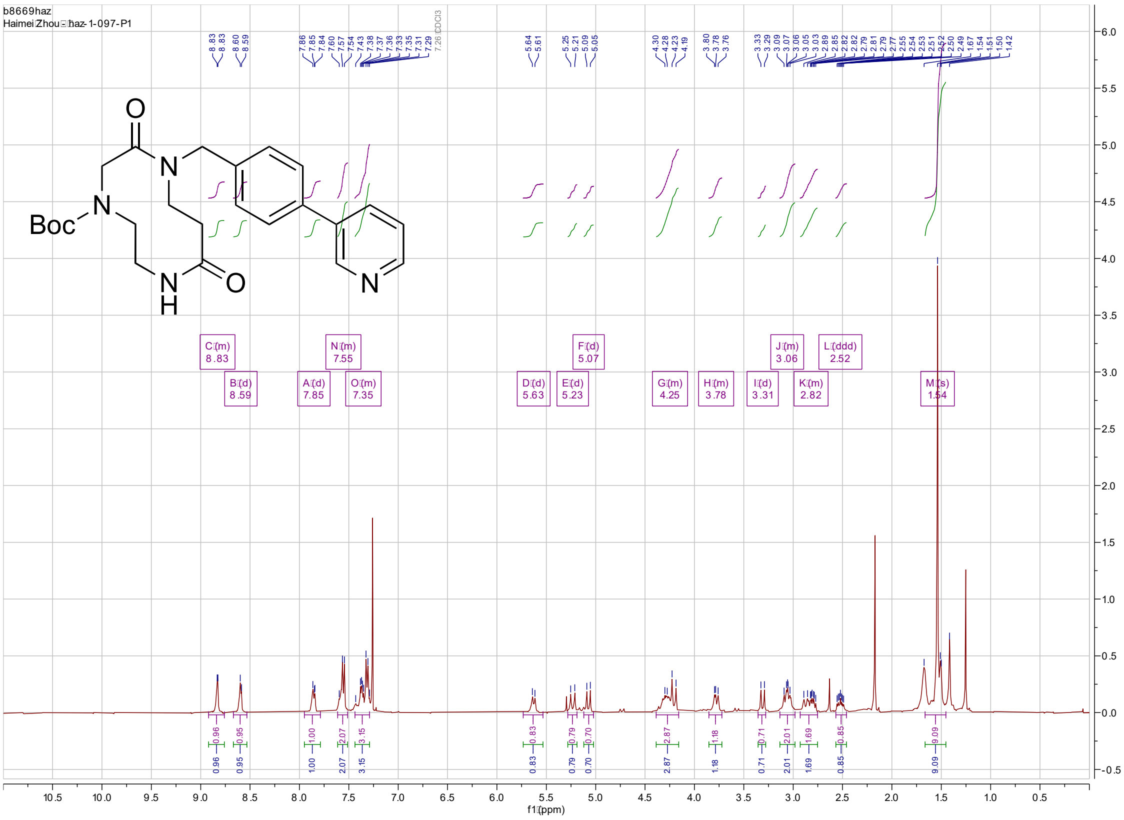


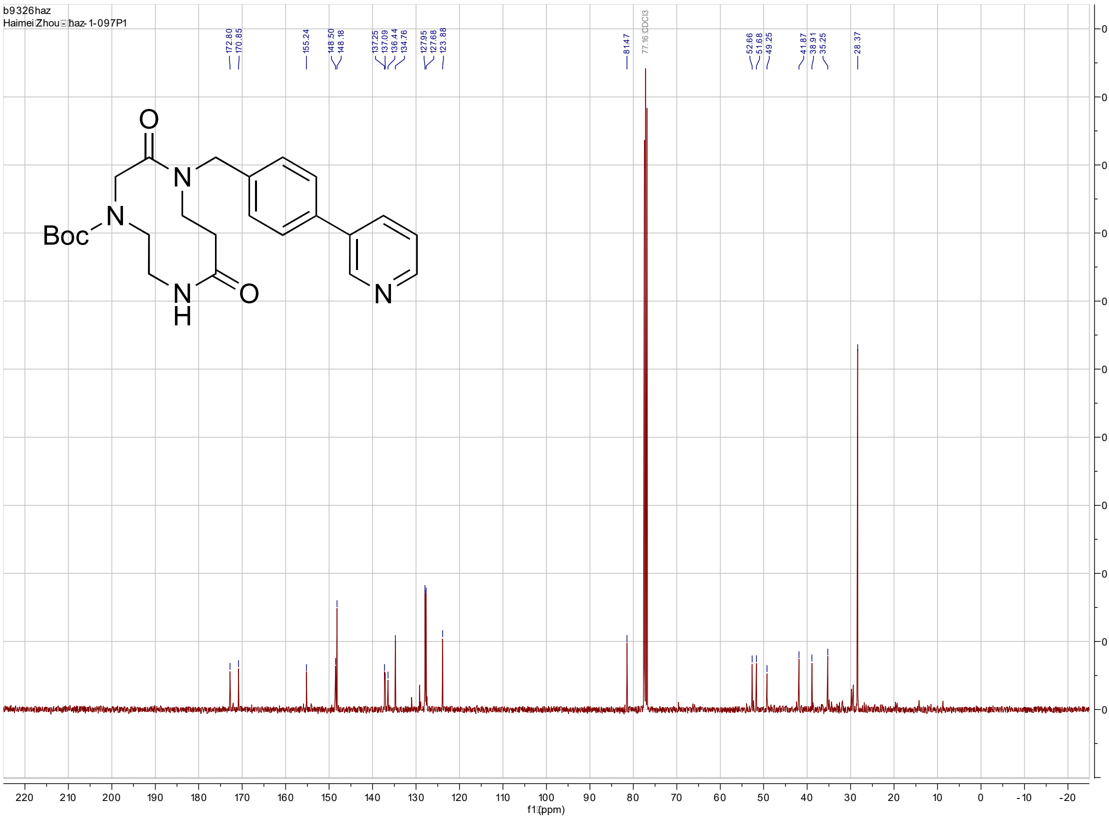
tert-Butyl 8-([1,1'-biphenyl]-4-ylmethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (13d)



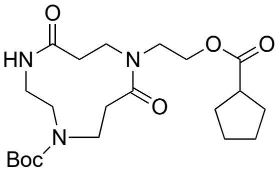


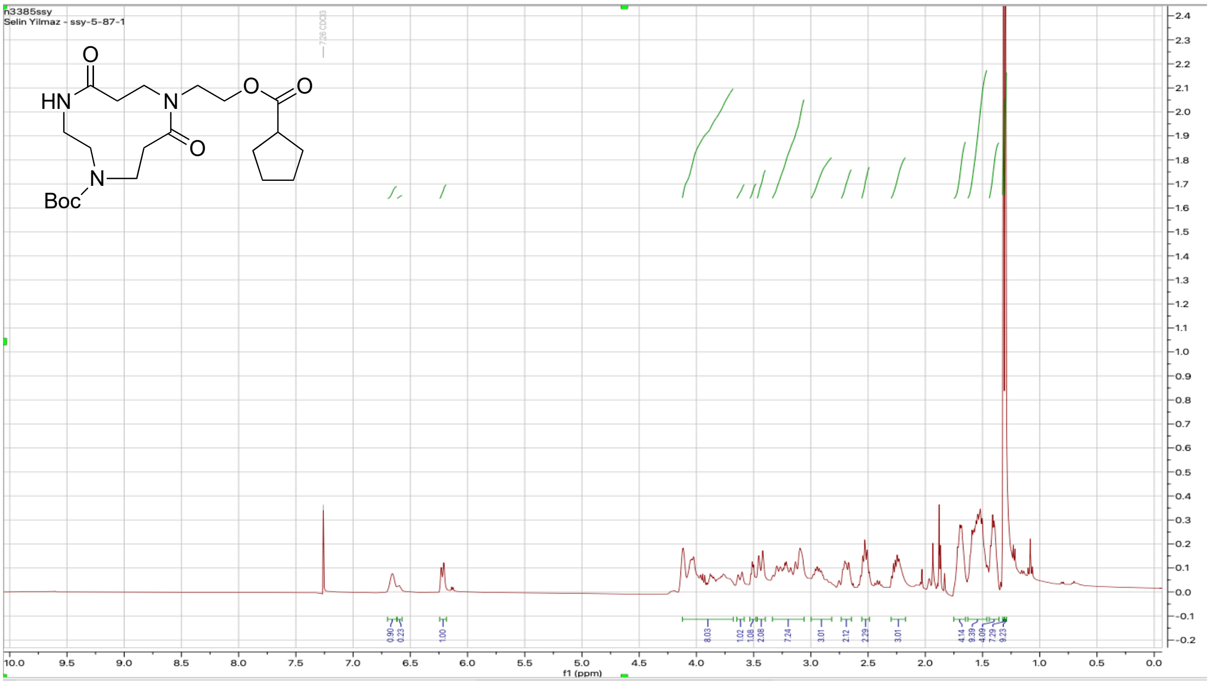
tert-Butyl 2,8-dioxo-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-4-carboxylate (13e)

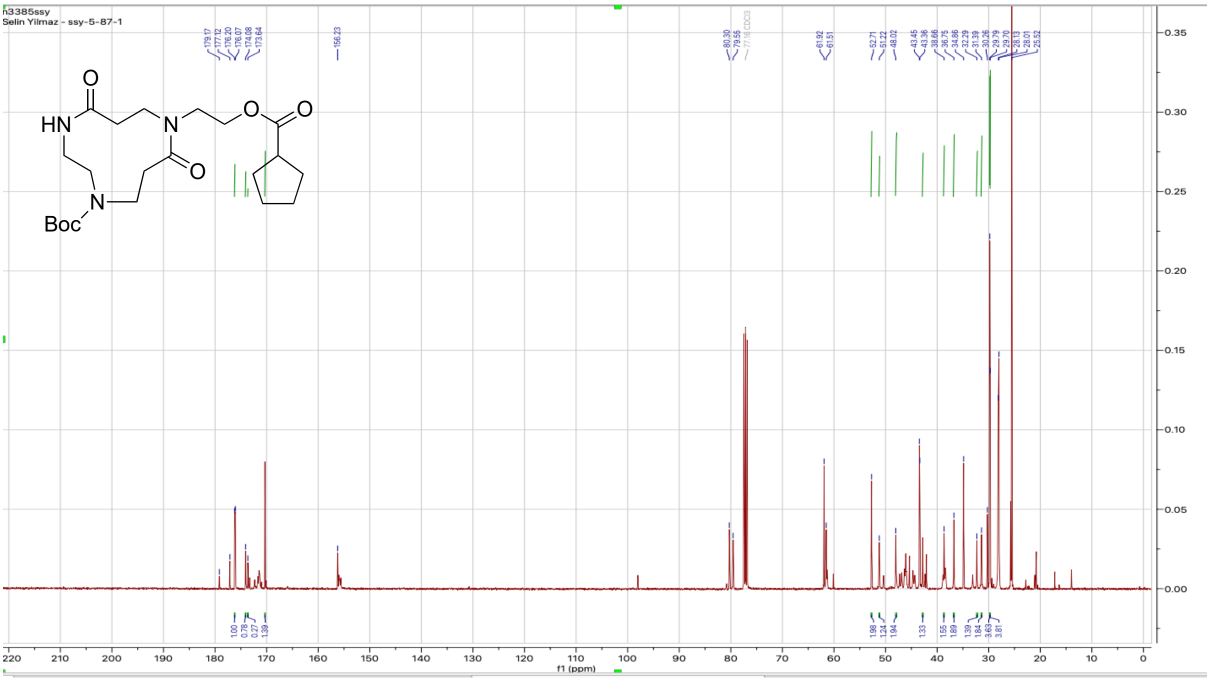




***tert*-butyl 8-(2-((Cyclopentanecarbonyl)oxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (13f) –** In solution in $CDCl_3$, the product exists as a 4:1.1:1 mixture of 3 rotamers based on NH peaks. All ^1H and ^{13}C signals are broadened due to rotamer interconversion.

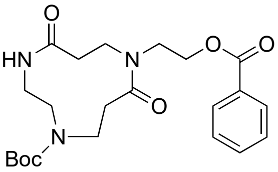


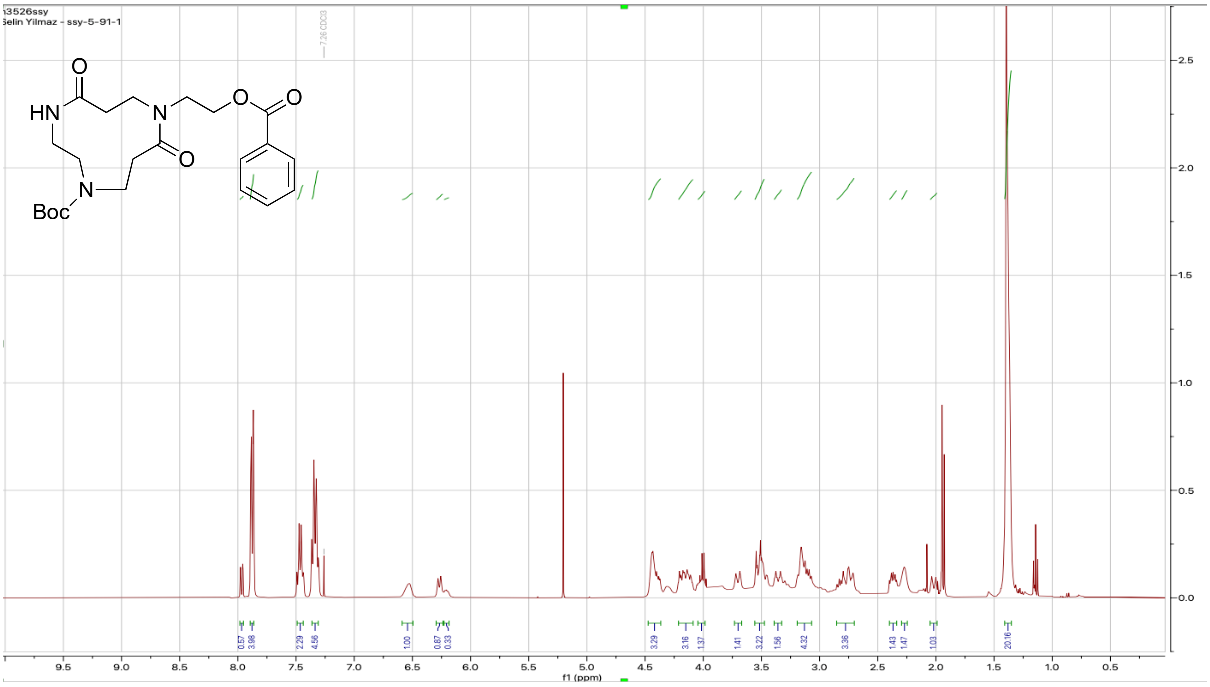


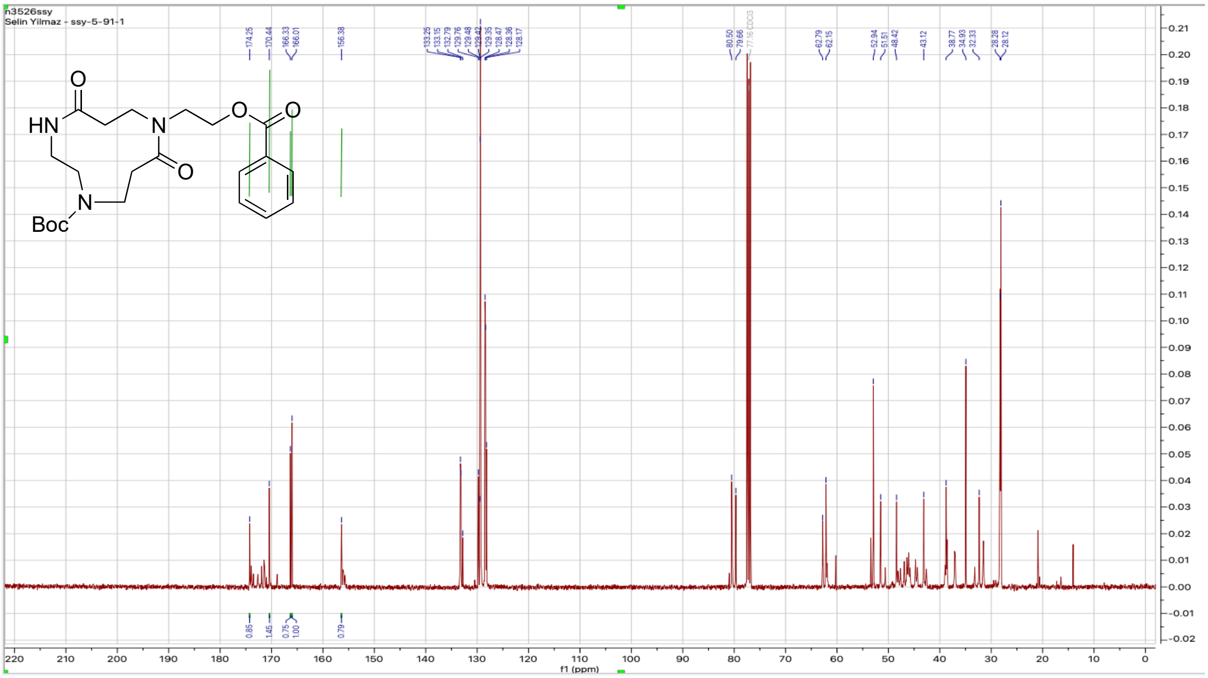


tert-Butyl 8-(2-(benzoyloxy)ethyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (13g)

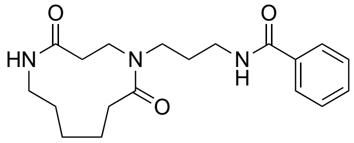
The ^{1}H NMR spectrum is complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the product exists as a 2.5:1.2:1 mixture of 3 rotamers.

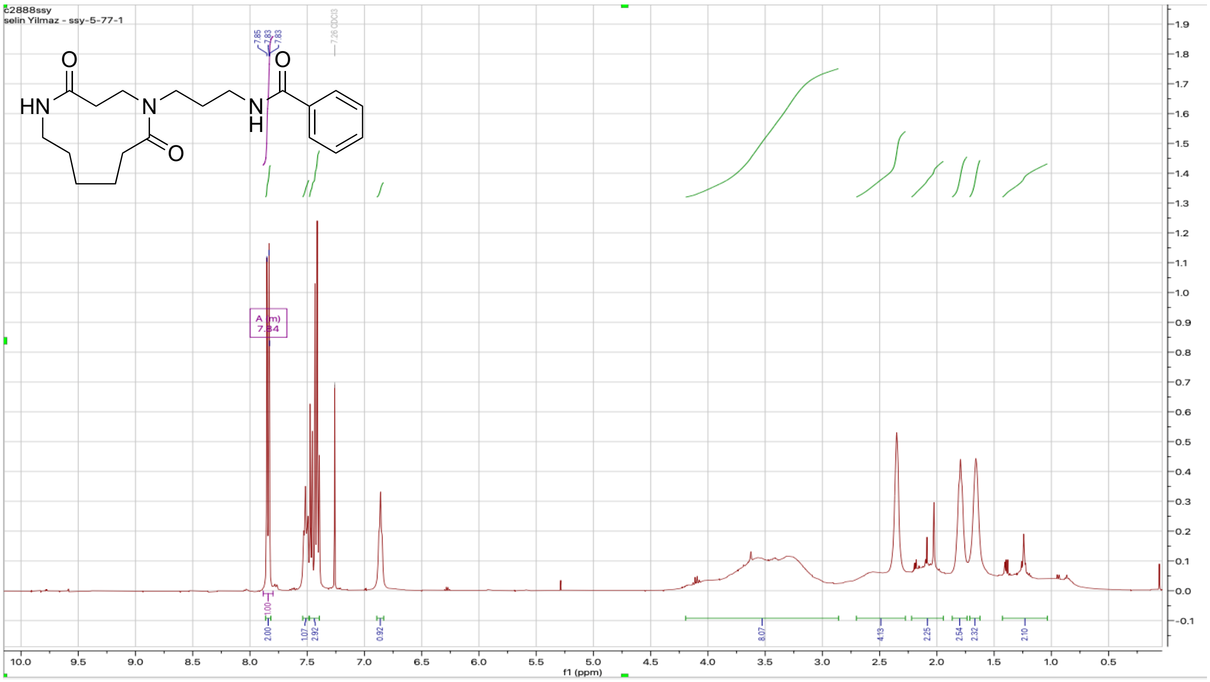


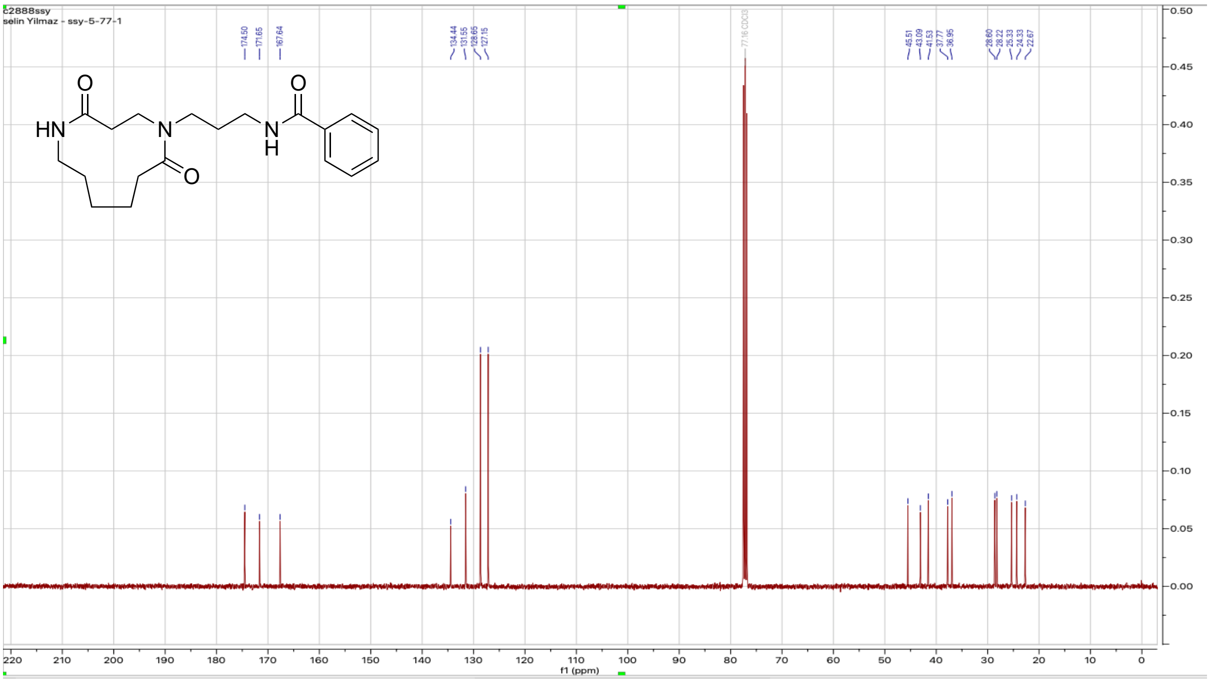




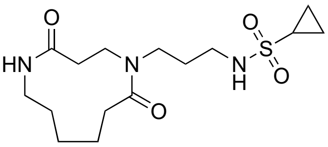
***N*-(3-(4,11-Dioxo-1,5-diazacycloundecan-1-yl)propyl)benzamide (13h)** - The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product.

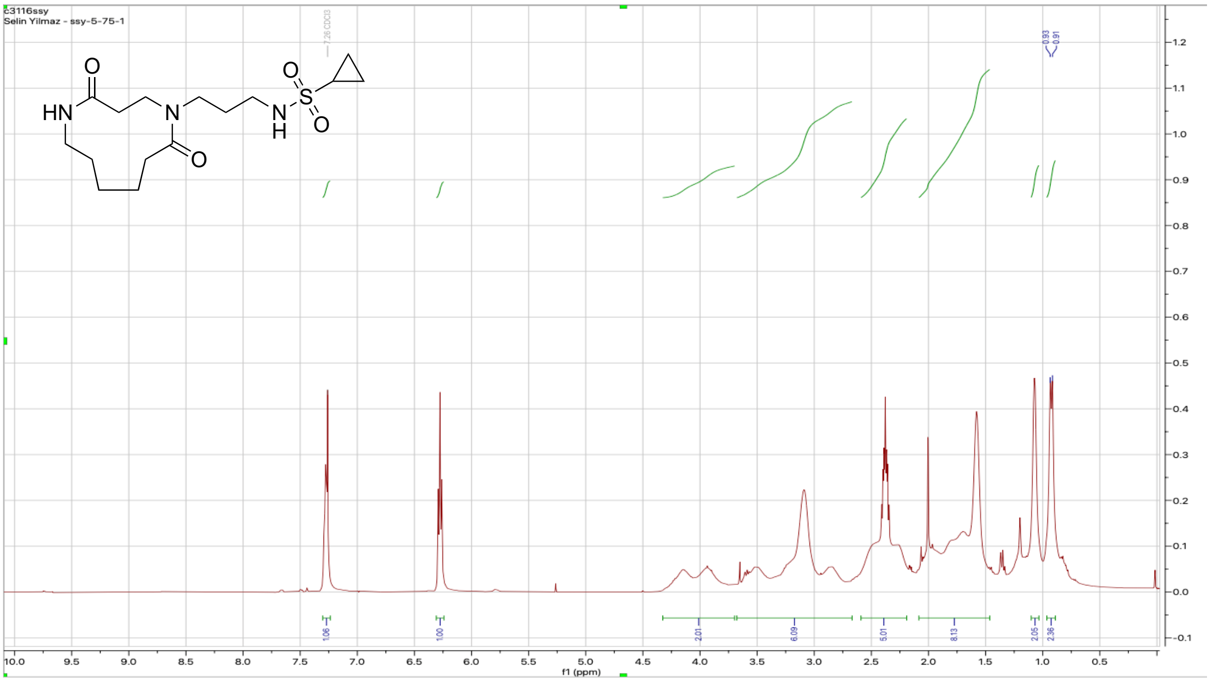


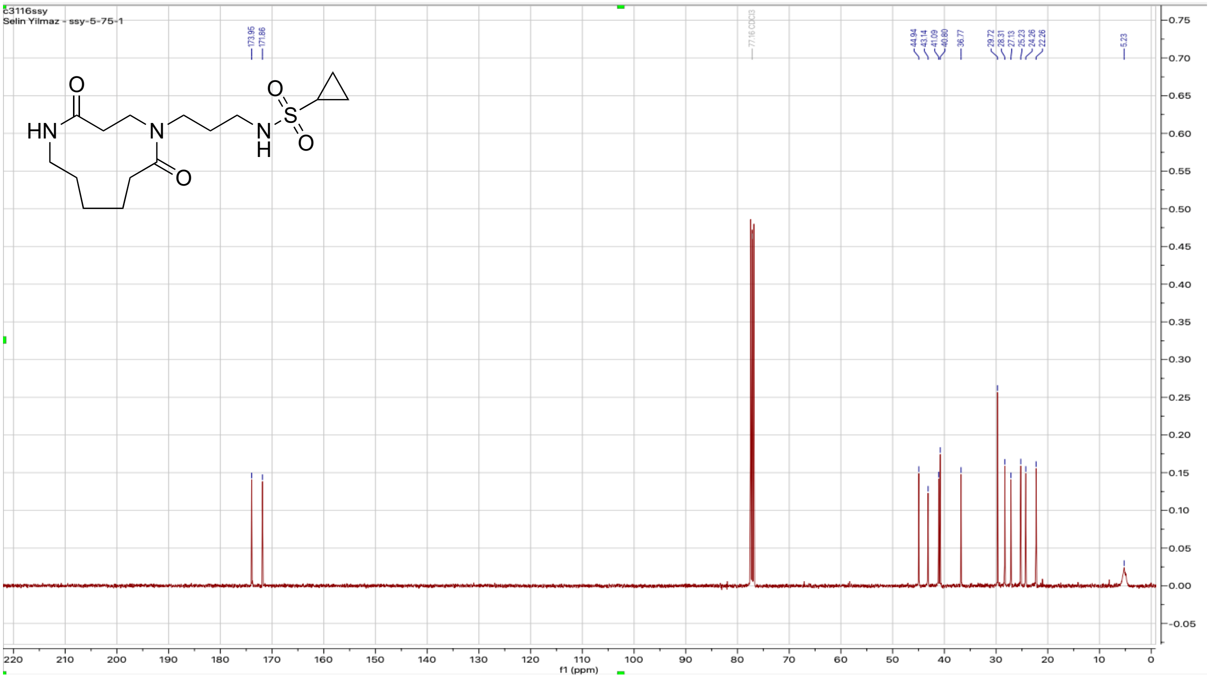




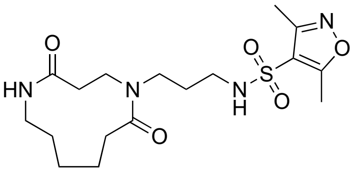
***N*-(3-(4,11-Dioxo-1,5-diazacycloundecan-1-yl)propyl)cyclopropanesulfonamide (13i)** The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product.

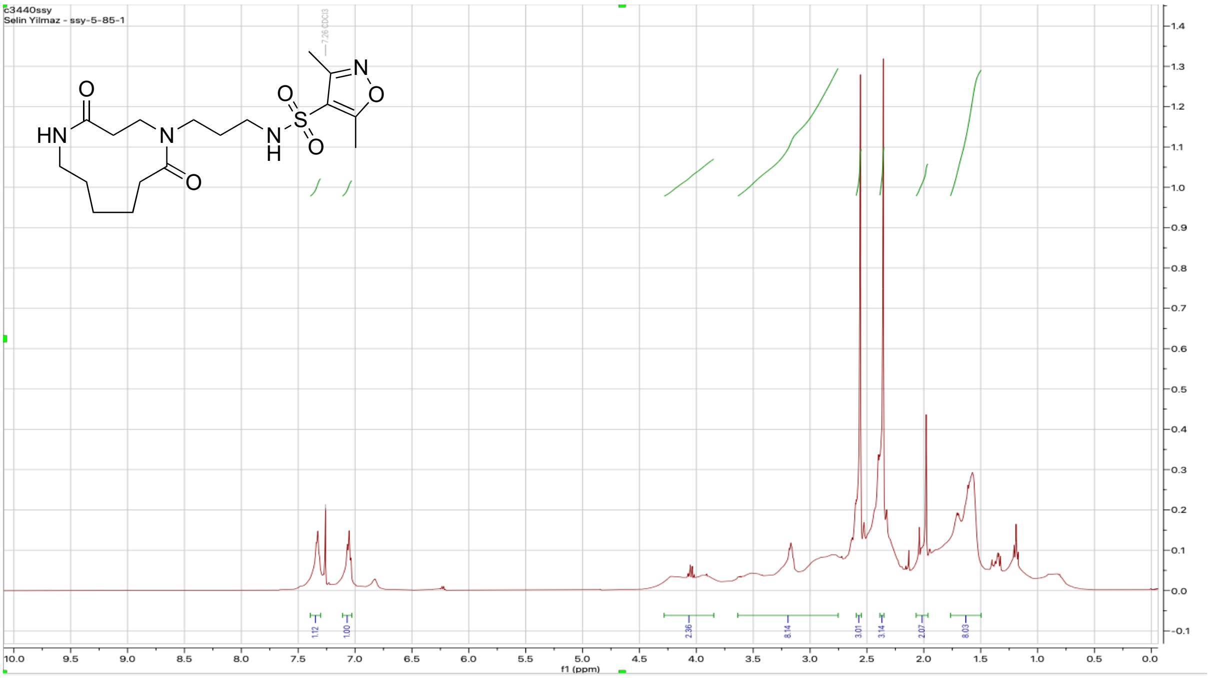


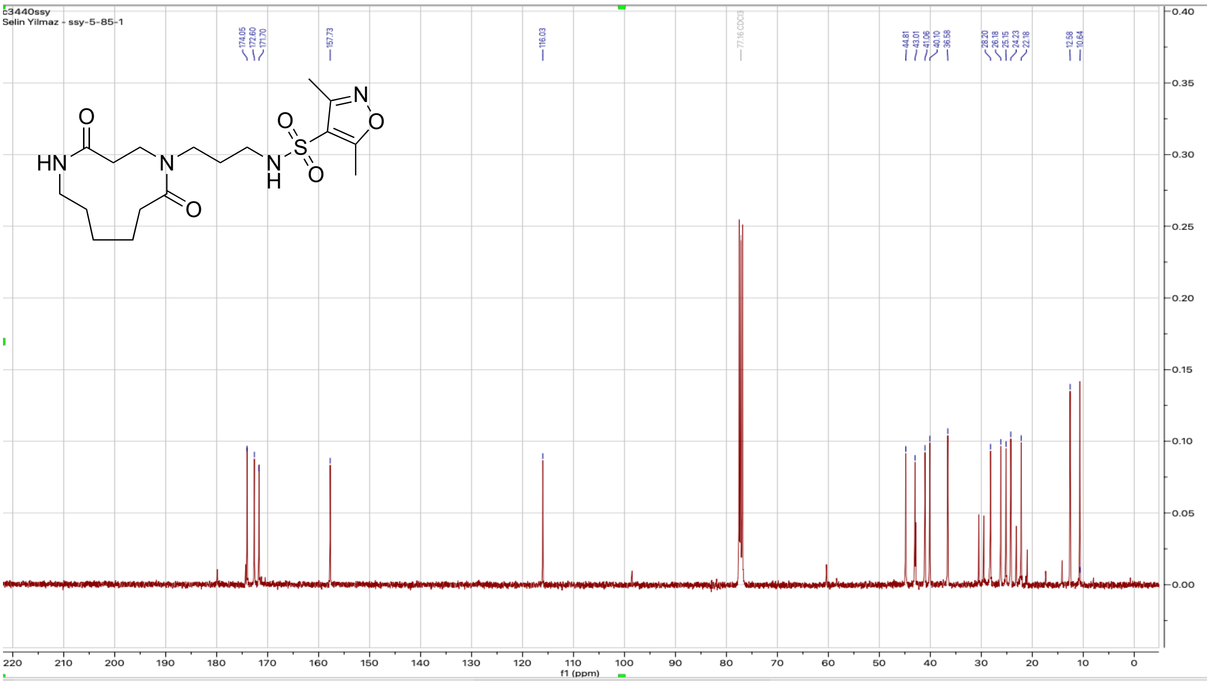




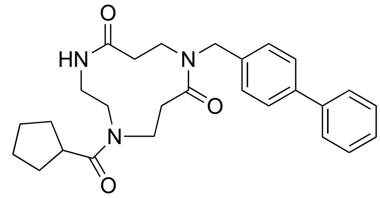
***N*-(3-(4,11-dioxo-1,5-diazacycloundecan-1-yl)propyl)-3,5-dimethylisoxazole-4-sulfonamide (13j)** The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product.

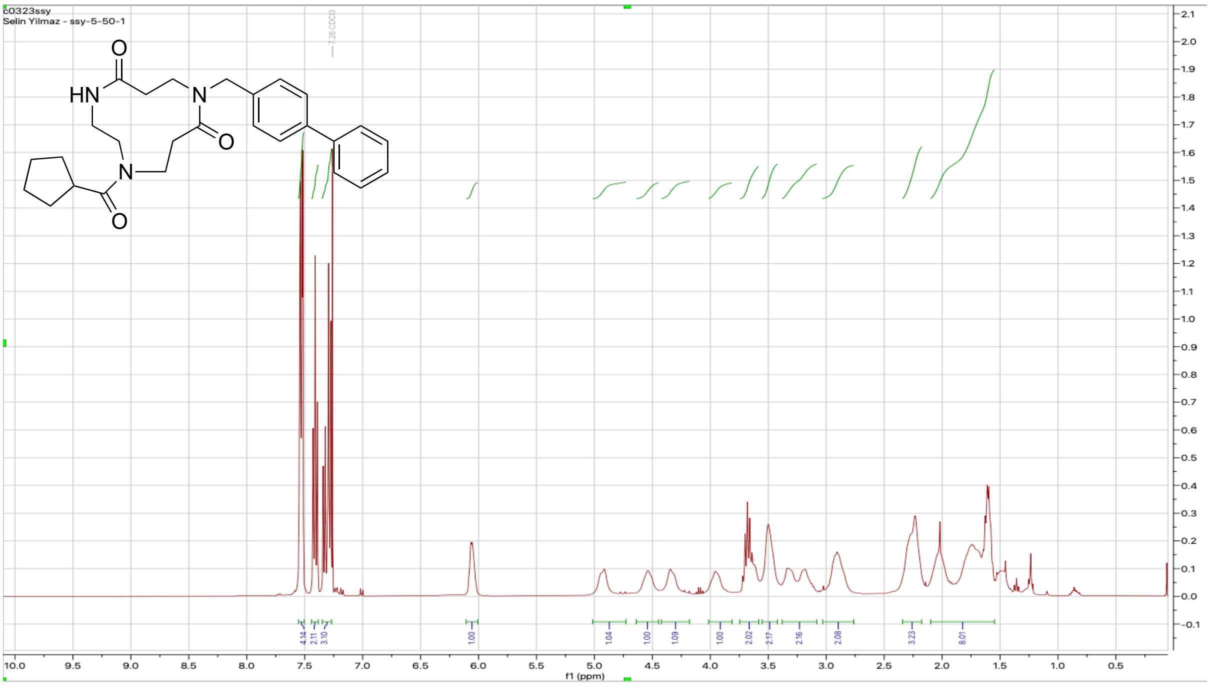


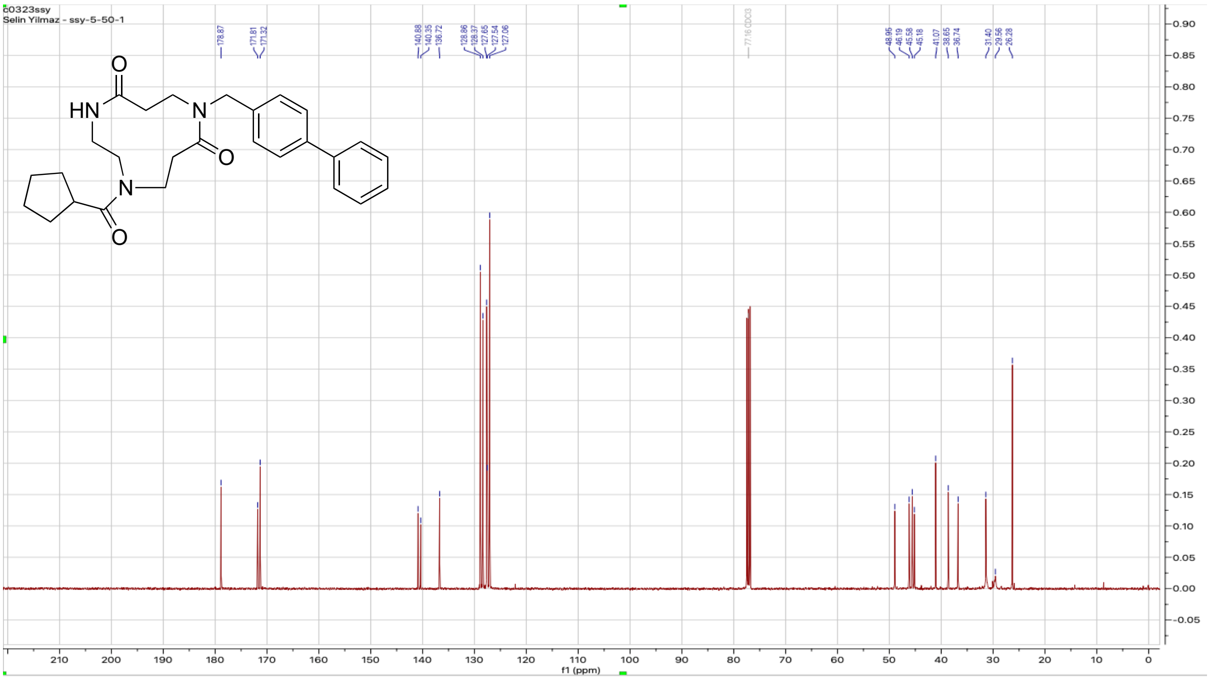




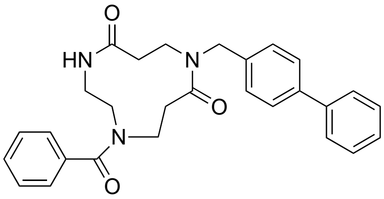
5-([1,1'-Biphenyl]-4-ylmethyl)-9-(cyclopentanecarbonyl)-1,5-diazacycloundecane-2,6-dione (14a) The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product.

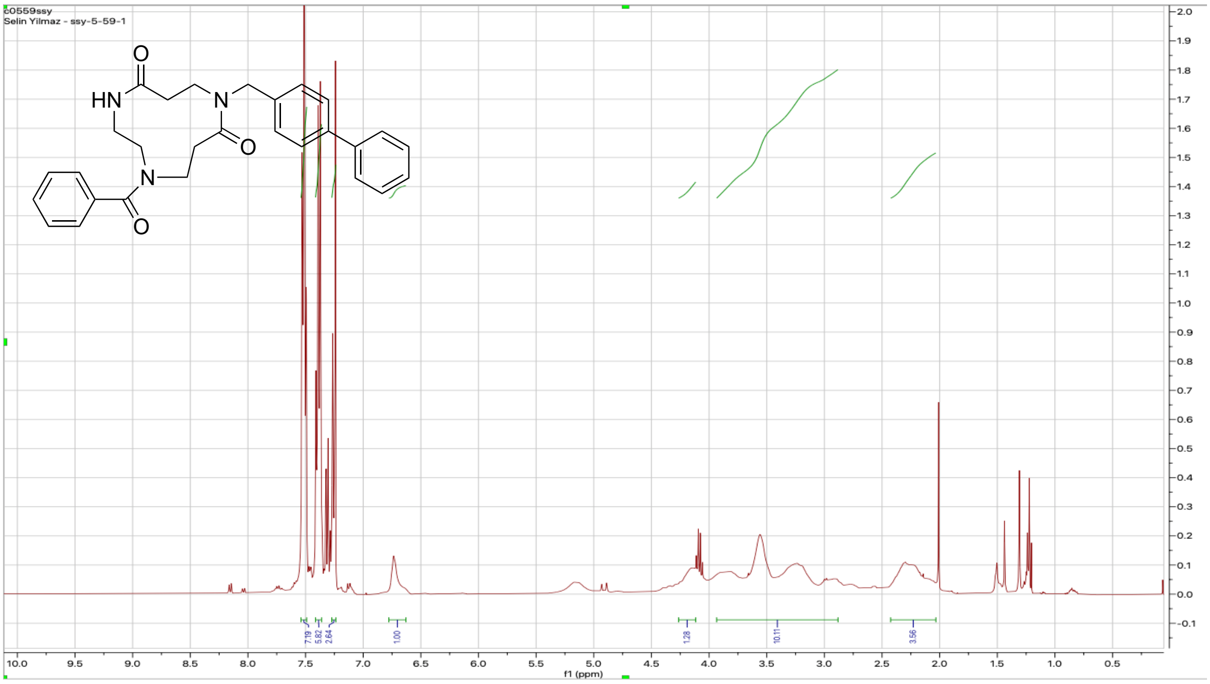


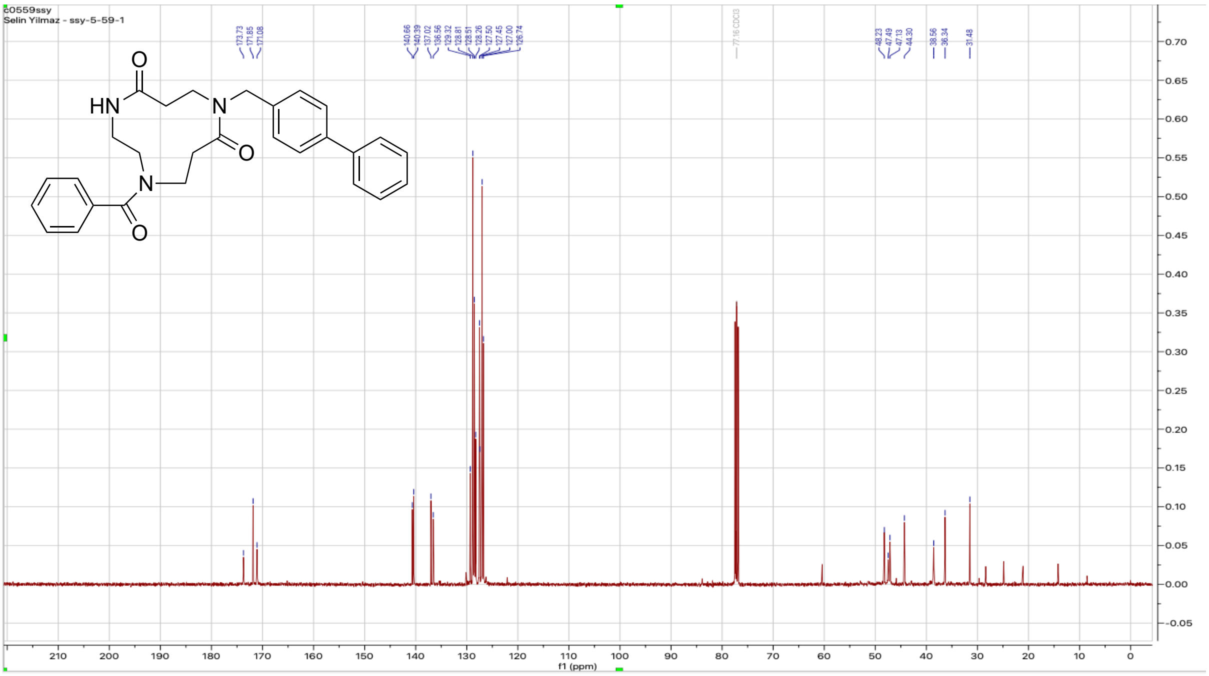




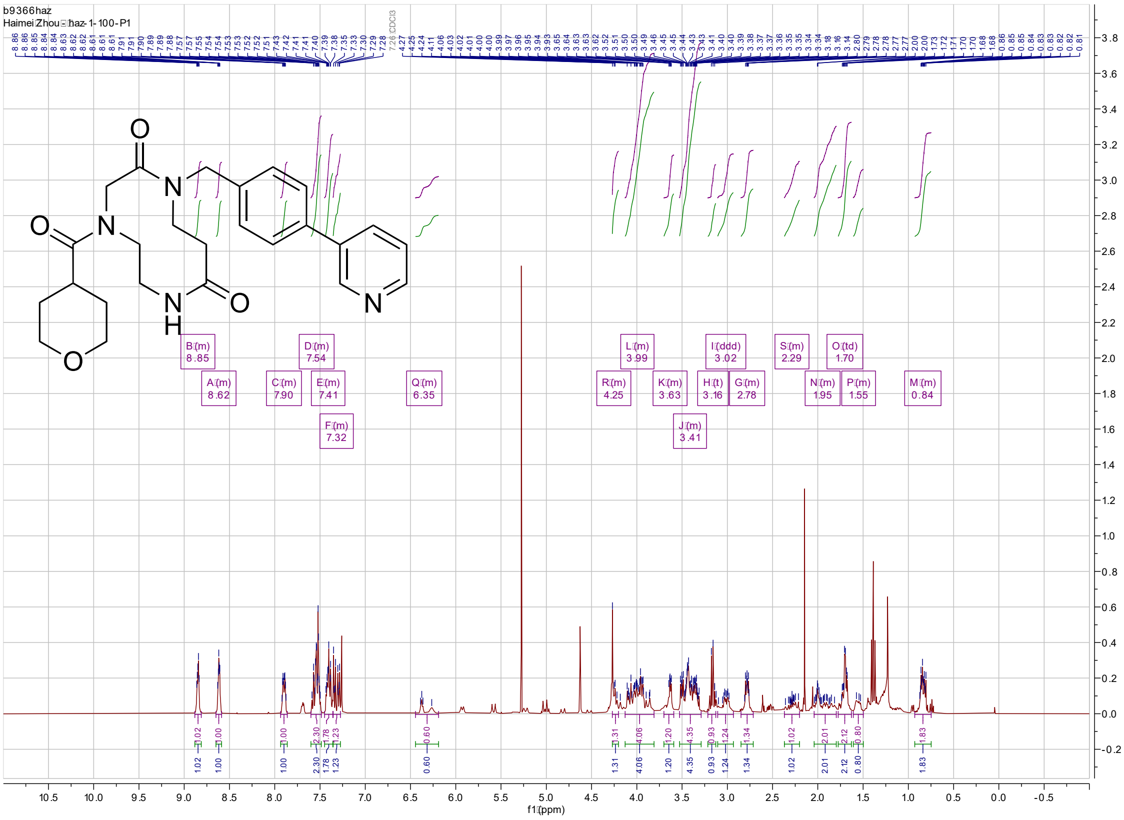
8-([1,1'-Biphenyl]-4-ylmethyl)-1-benzoyl-1,4,8-triazacycloundecane-5,9-dione (14b) The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data (the same sample) is more useful for determining the identity and purity of the product.

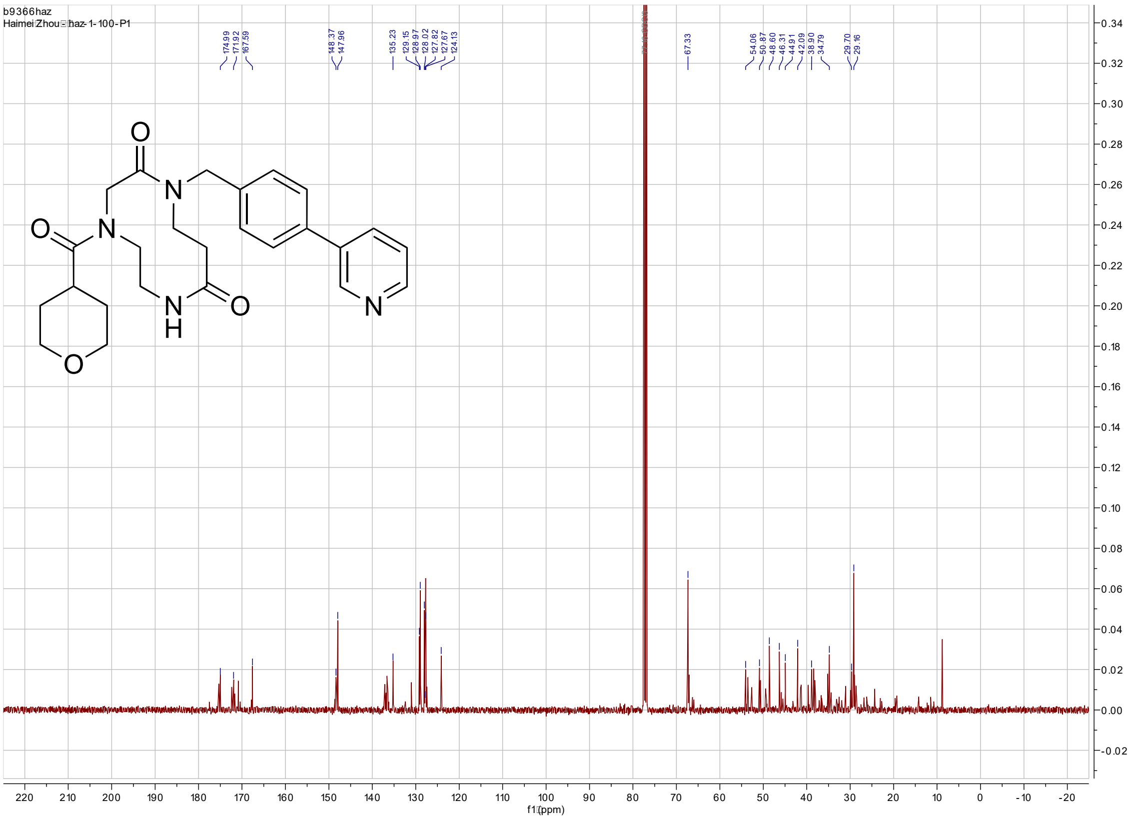




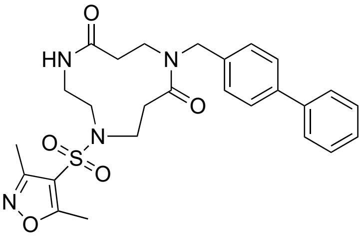


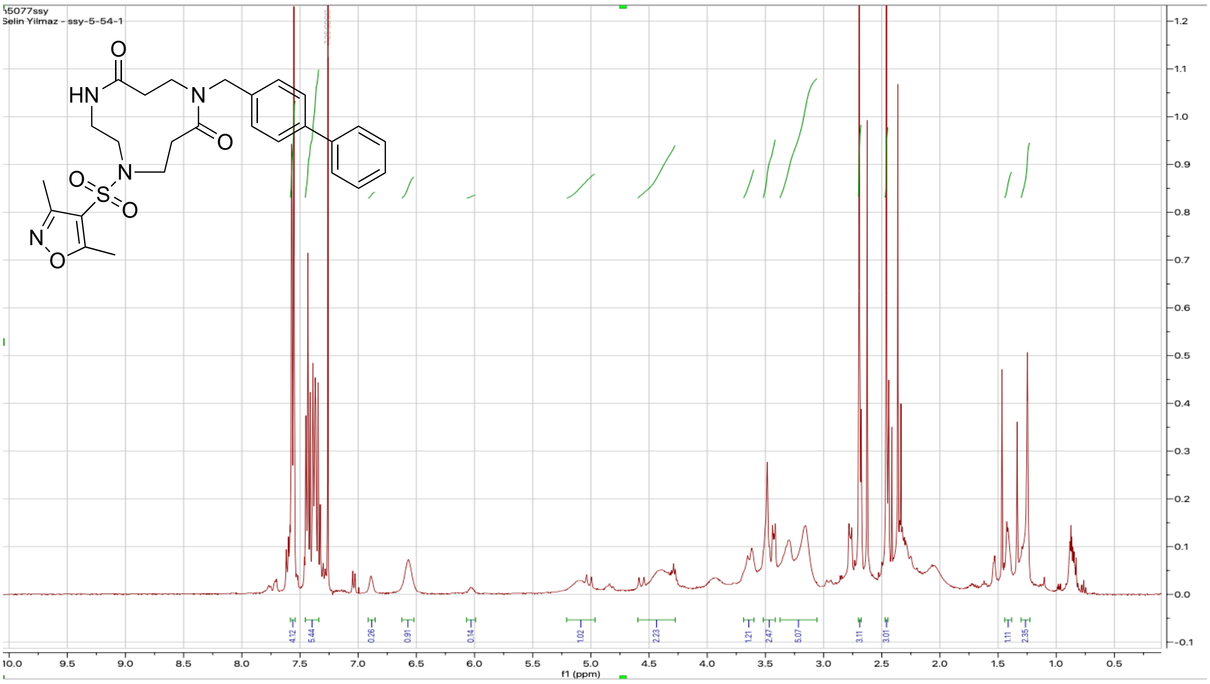
1-(4-(Pyridin-3-yl)benzyl)-4-(tetrahydro-2H-pyran-4-carbonyl)-1,4,7-triazecane-2,8-dione (14c) – mixture of rotamers

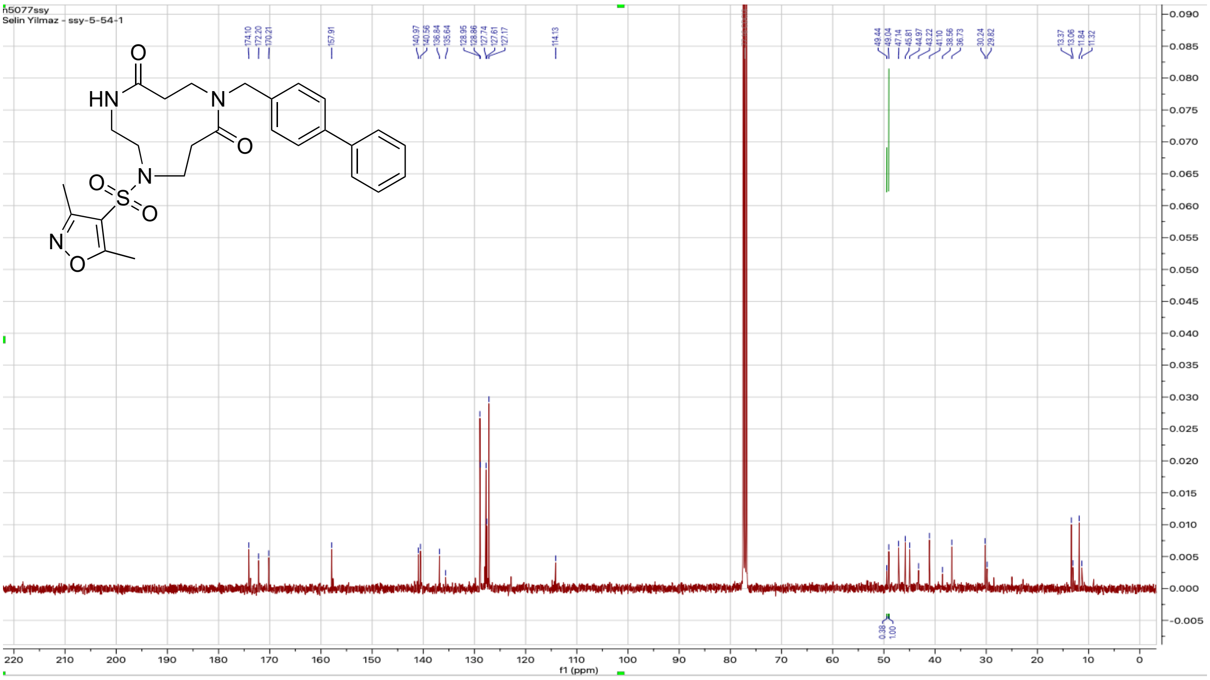




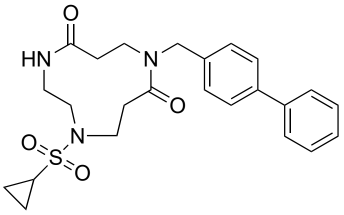
8-([1,1'-Biphenyl]-4-ylmethyl)-1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-1,4,8-triazacycloundecane-5,9-dione (14d)

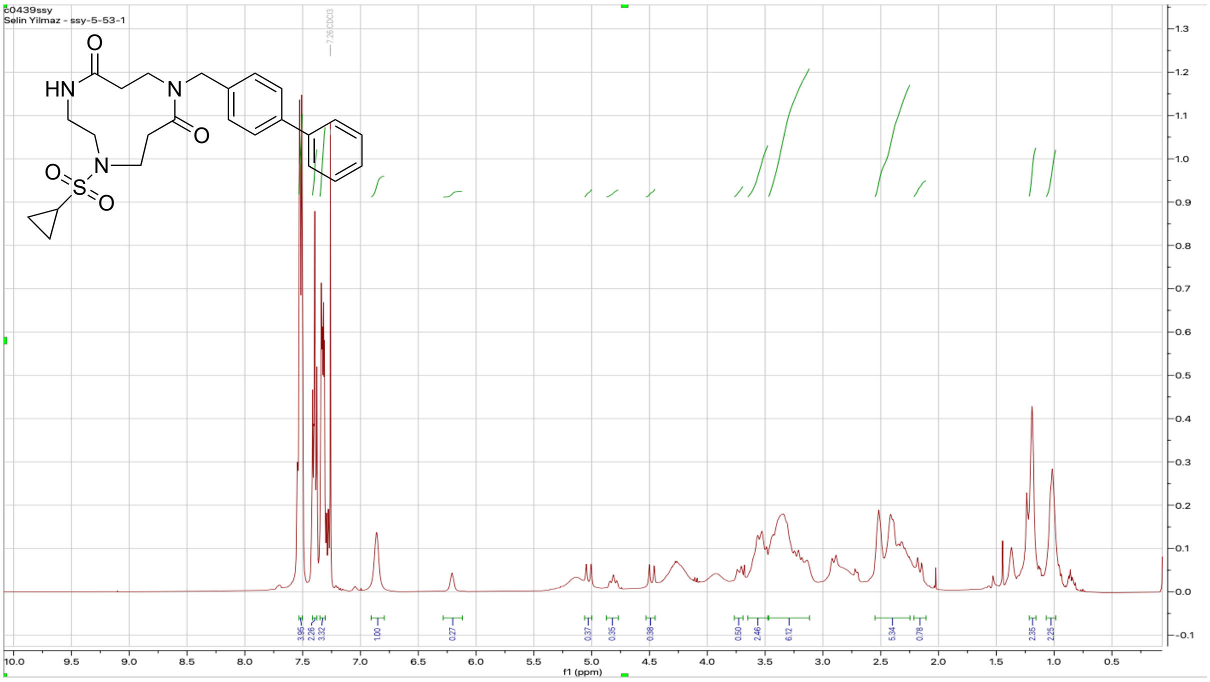


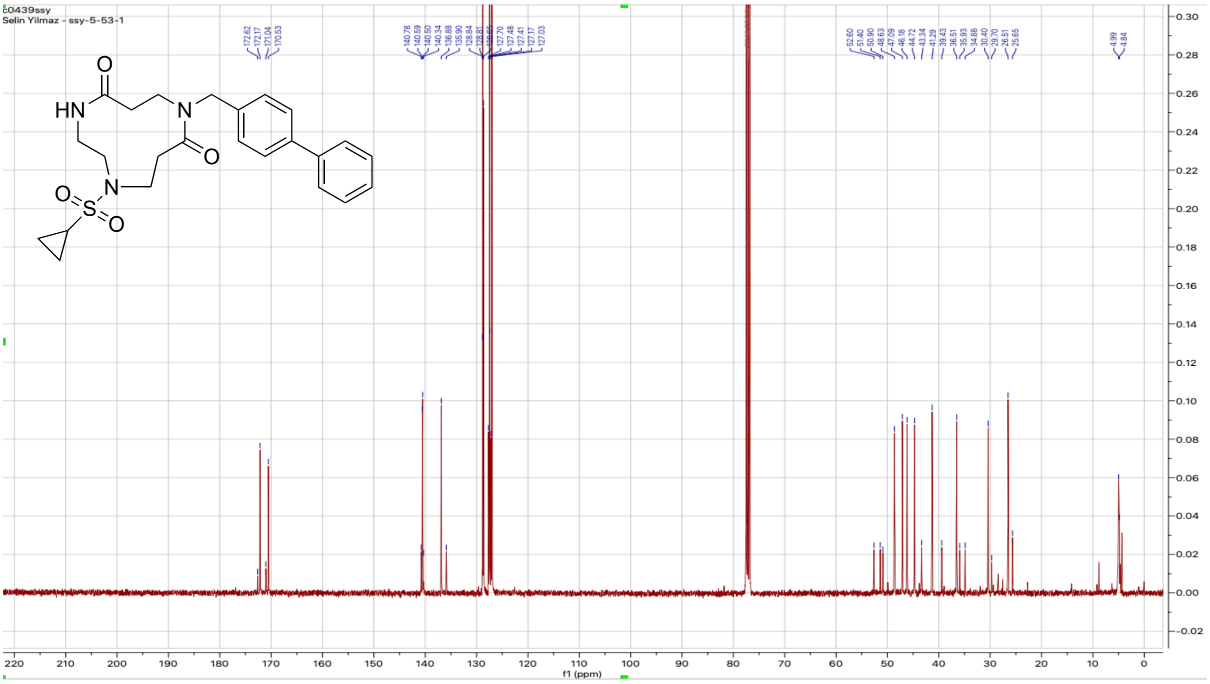




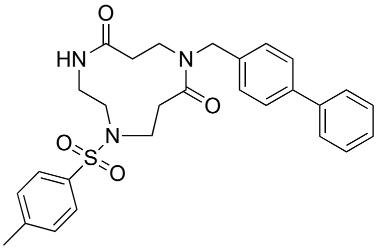
8-([1,1'-Biphenyl]-4-ylmethyl)-1-(cyclopropylsulfonyl)-1,4,8-triazacycloundecane-5,9-dione (14e) The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. 3:1 mixture of rotamers

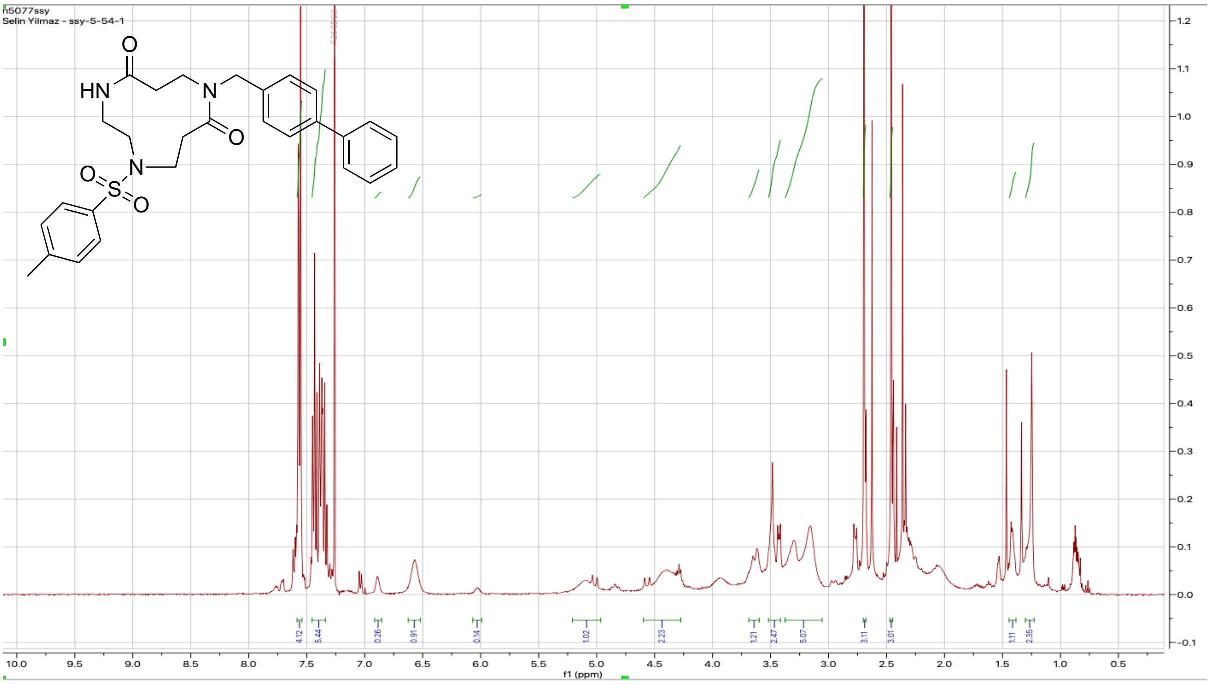


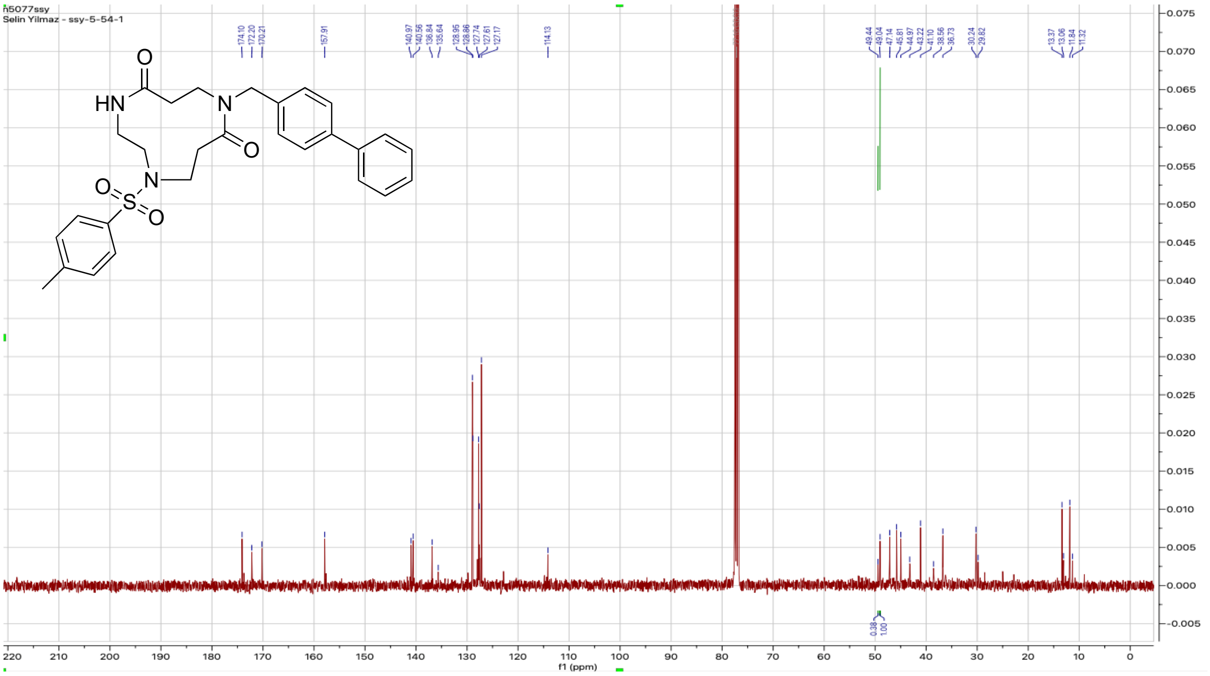




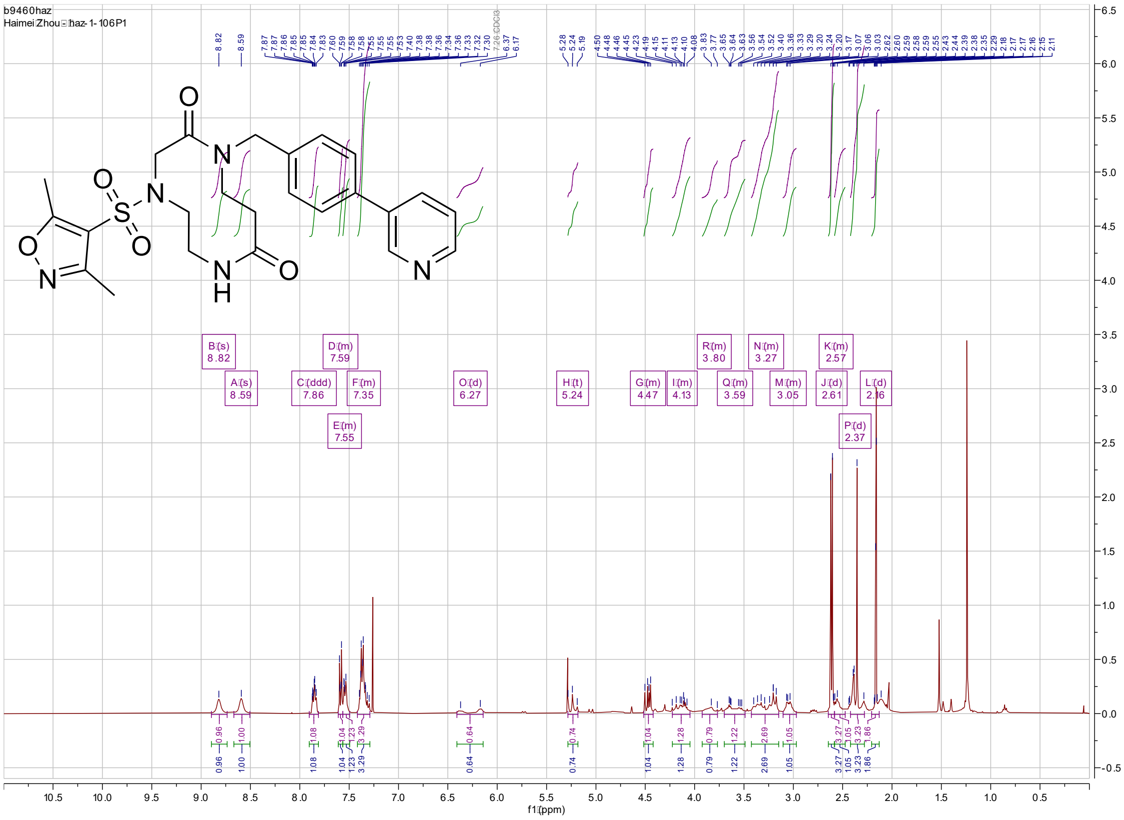
8-([1,1'-Biphenyl]-4-ylmethyl)-1-tosyl-1,4,8-triazacycloundecane-5,9-dione (14f) The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. 4:1 mixture of rotamers.

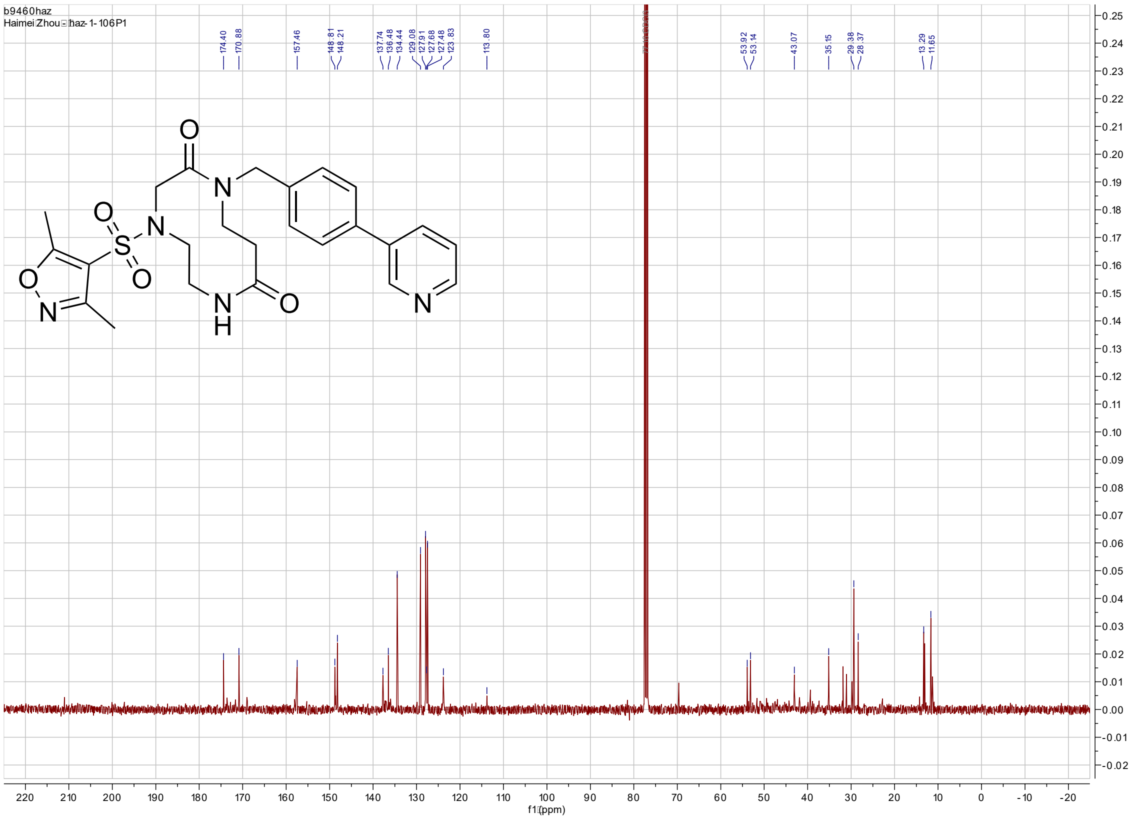




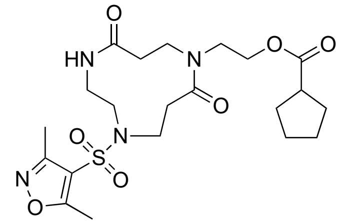


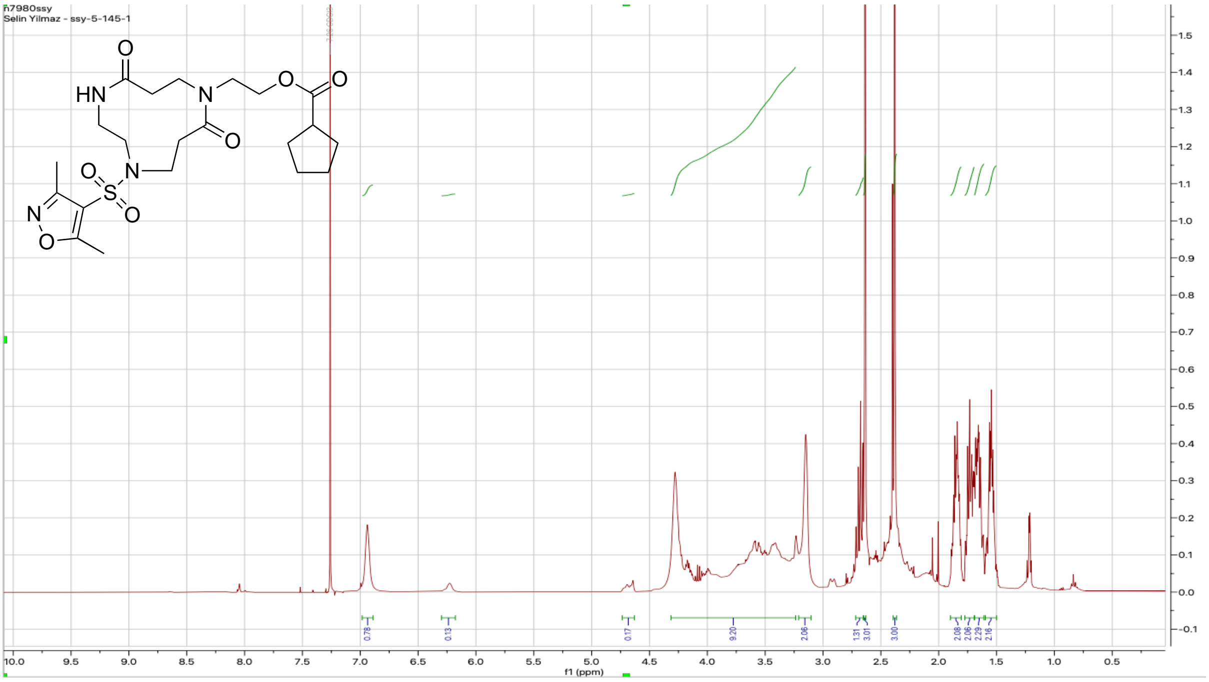
4-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-1-(4-(pyridin-3-yl)benzyl)-1,4,7-triazecane-2,8-dione (14g)

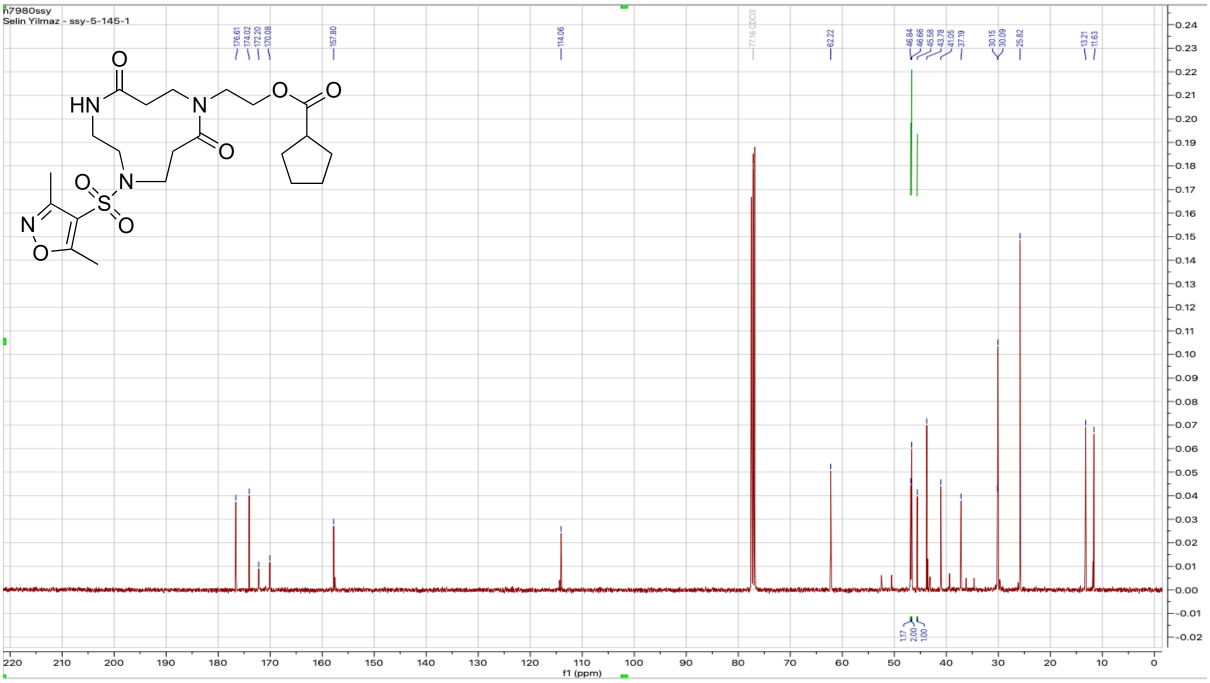




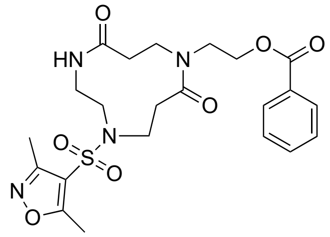
2-(1-((3,5-Dimethylisoxazol-4-yl)sulfonyl-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (14h) The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. In solution in $CDCl_3$, the compoud exists predominantly as a single rotamer, with trace amount of a minor rotamer evident in the ^{13}C NMR spectrum

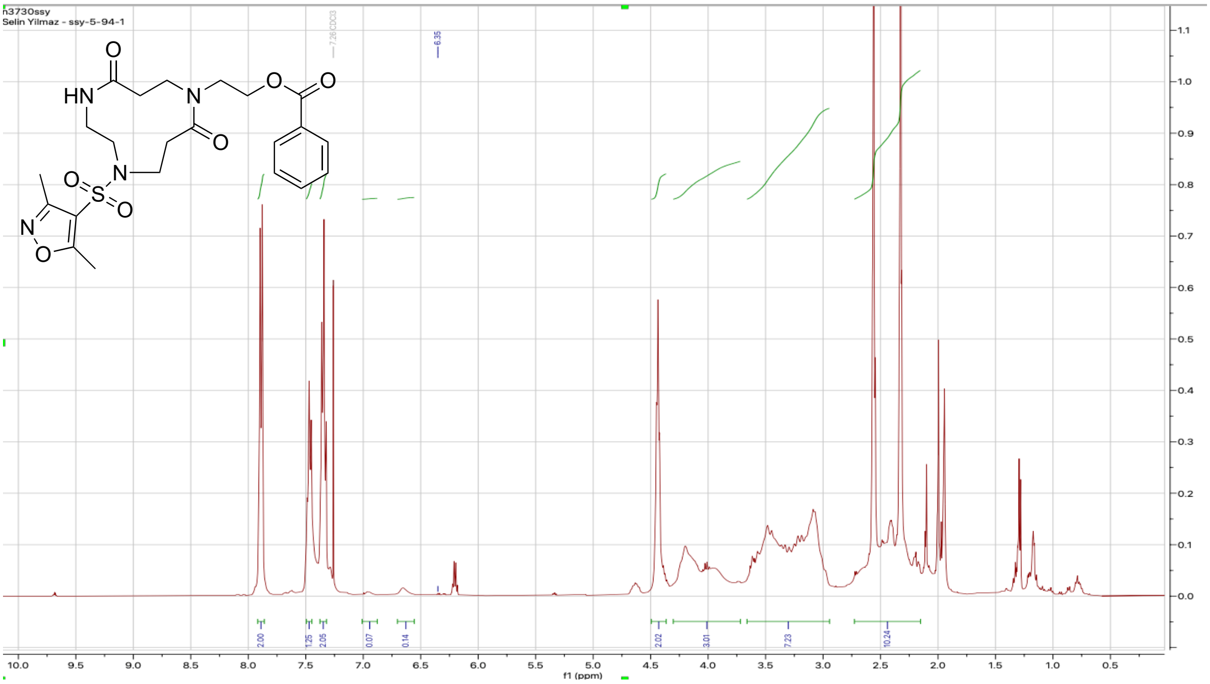


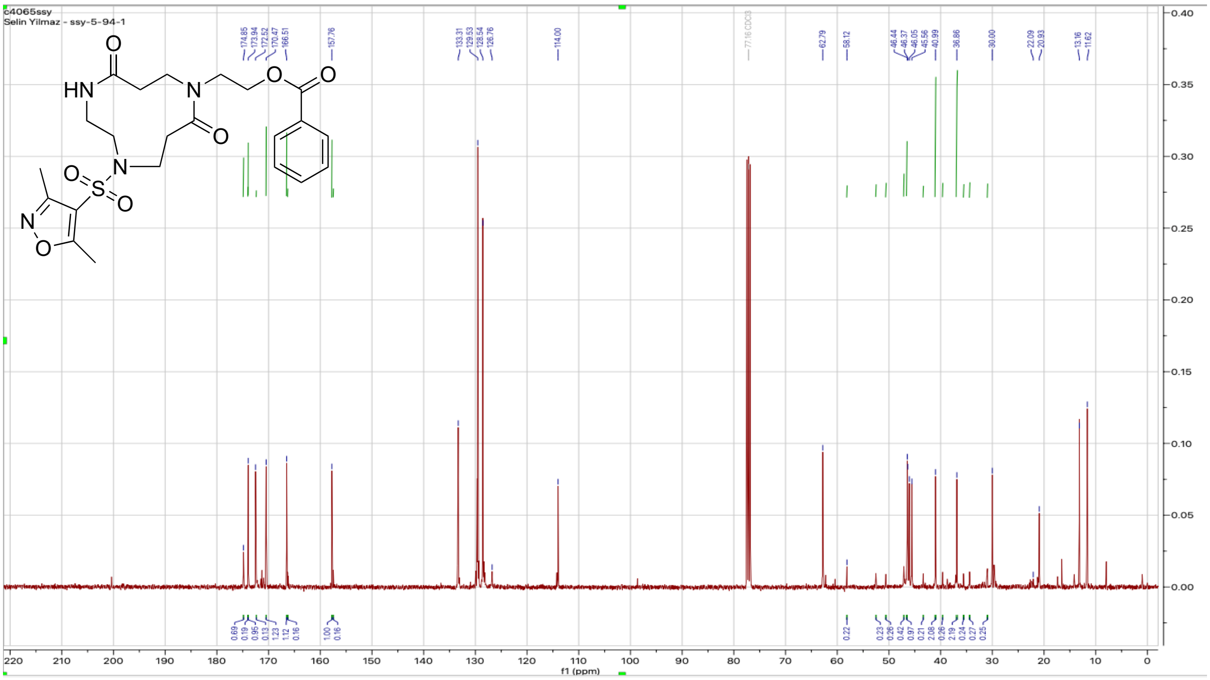




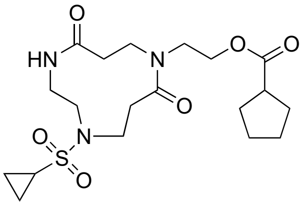
2-(1-((3,5-Dimethylisoxazol-4-yl)sulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl benzoate (14i)

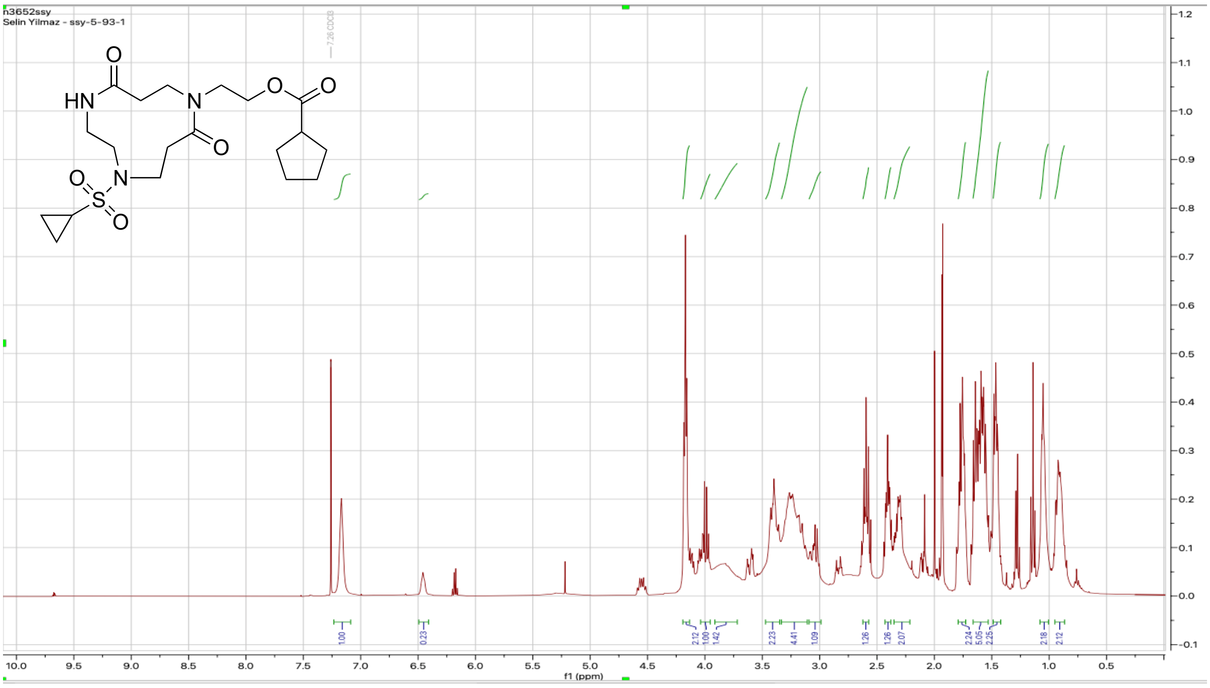


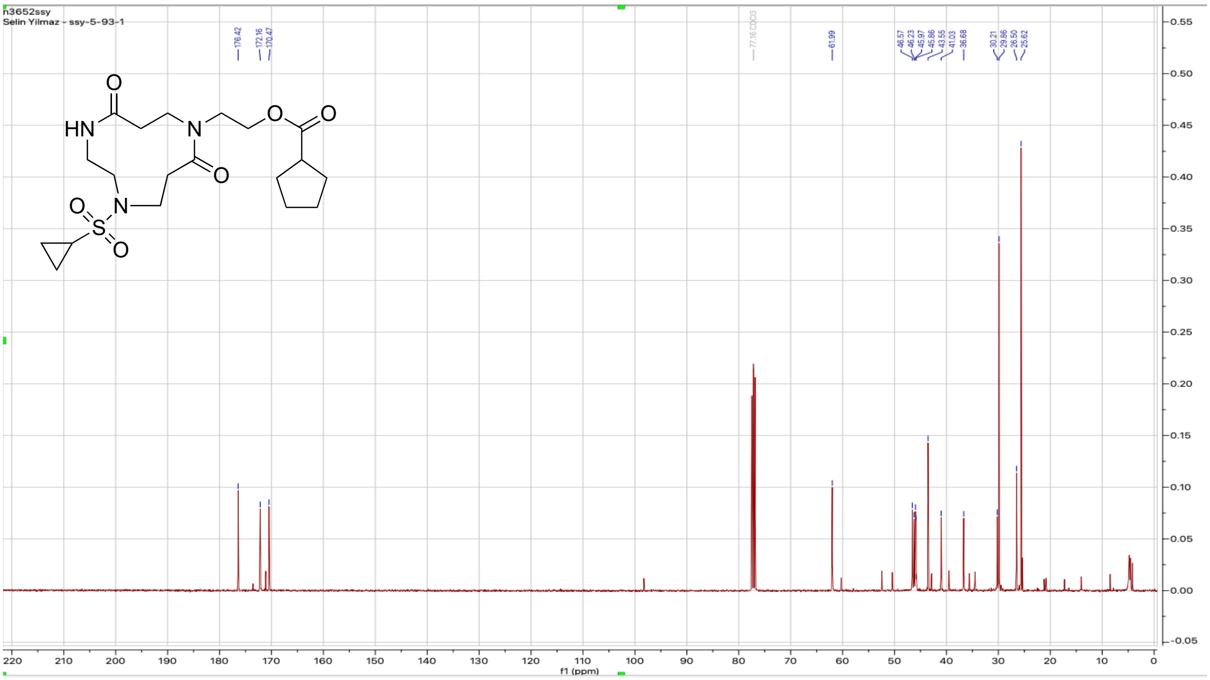




2-(1-(Cyclopropylsulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (14j) The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. 4:1 mixture of rotamers.

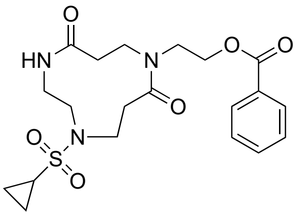


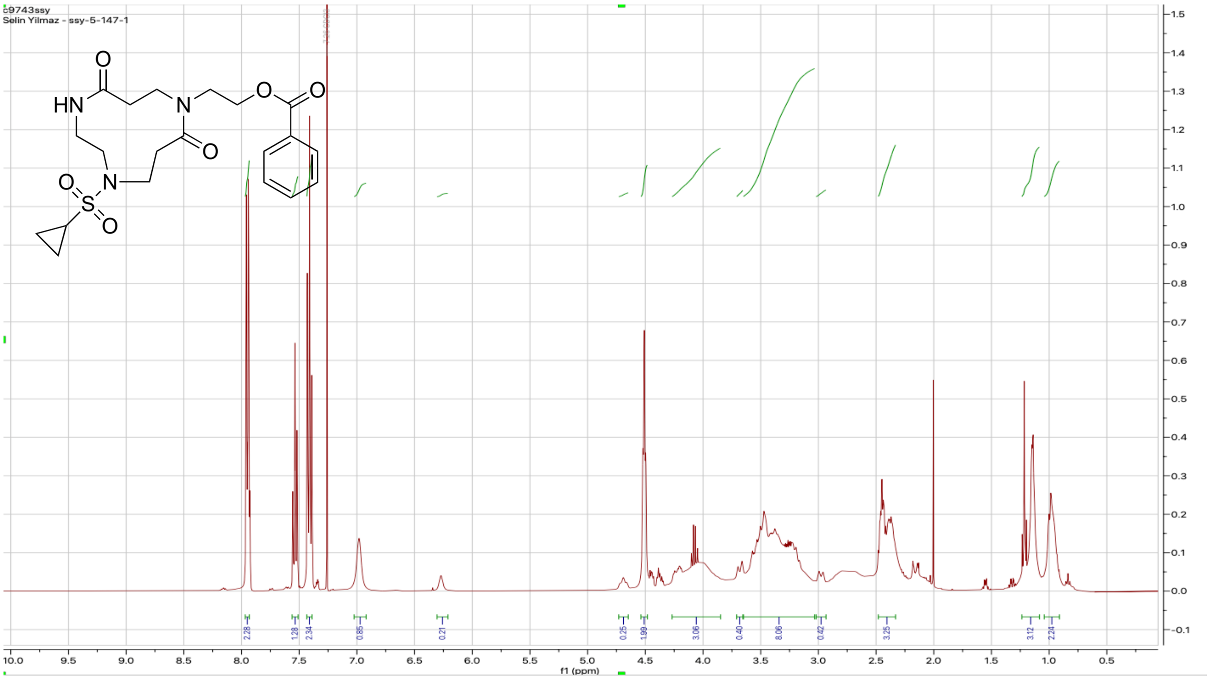


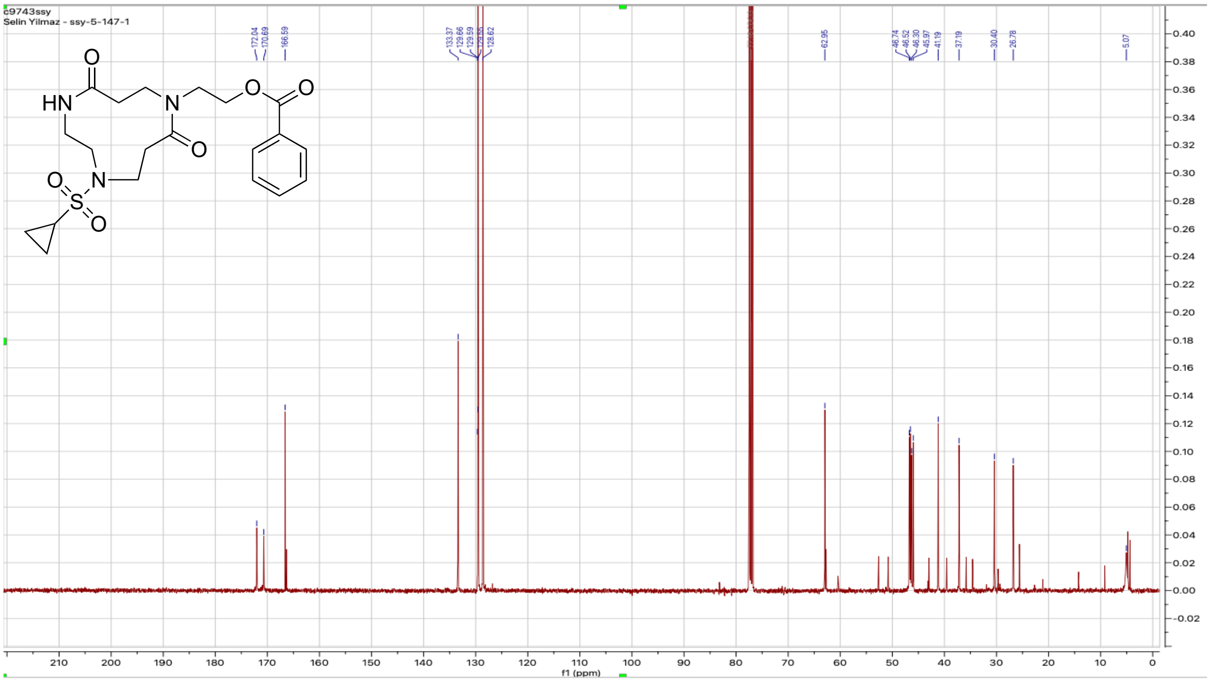


2-(1-(Cyclopropylsulfonyl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl benzoate (14k)

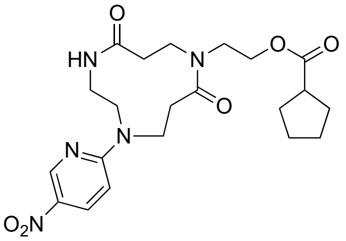
The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product. 4:1 mixture of rotamers.

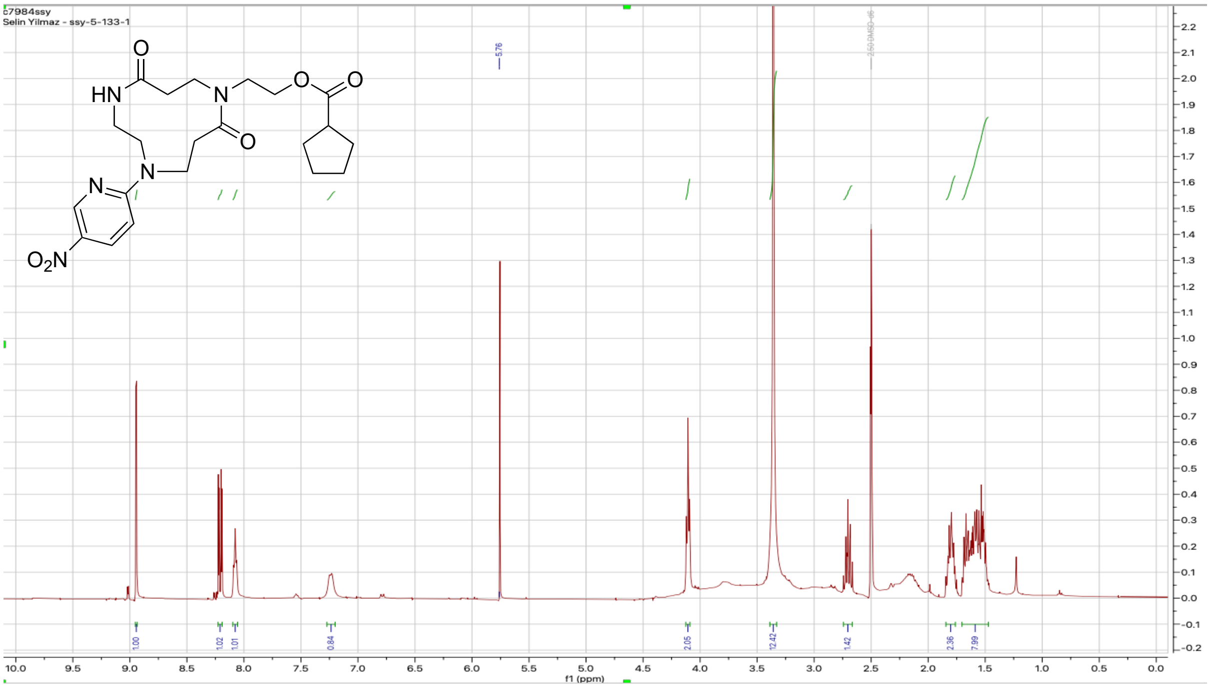


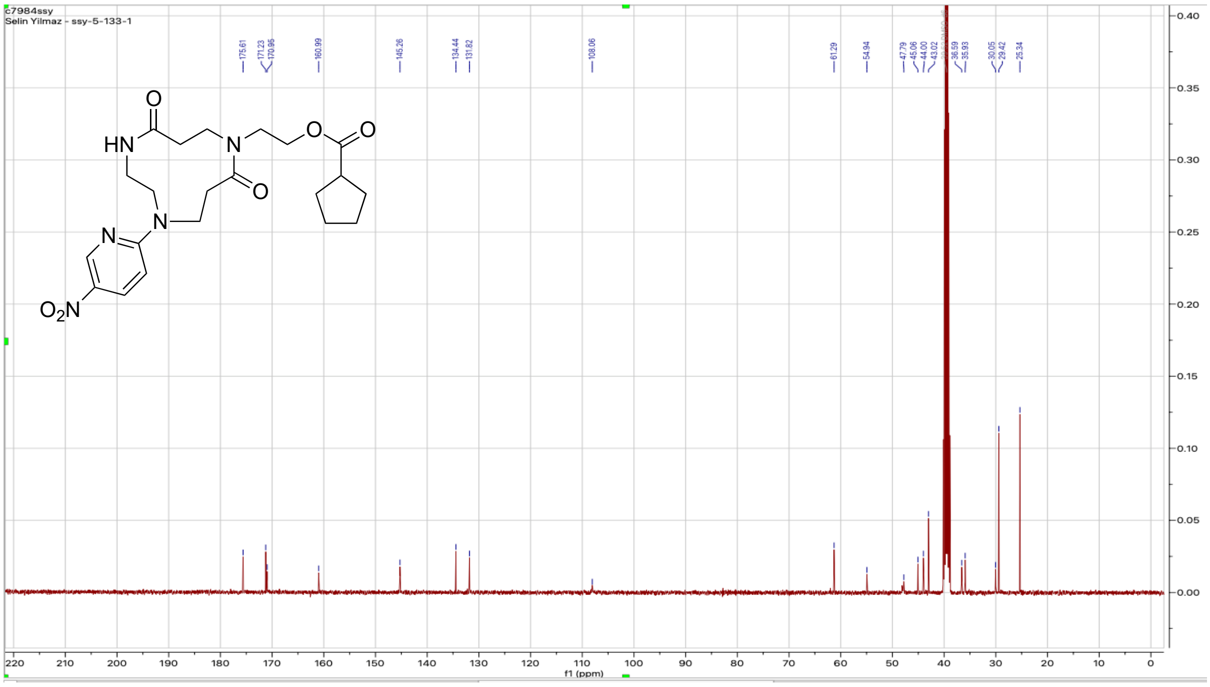




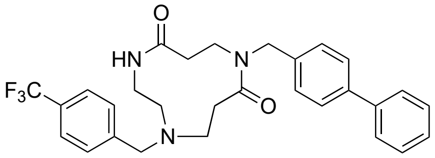
2-(1-(5-Nitropyridin-2-yl)-5,9-dioxo-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (14l) - The ^{1}H NMR spectrum is severely complicated by rotameric broadening, and the ^{13}C NMR data is more useful for determining the identity and purity of the product.

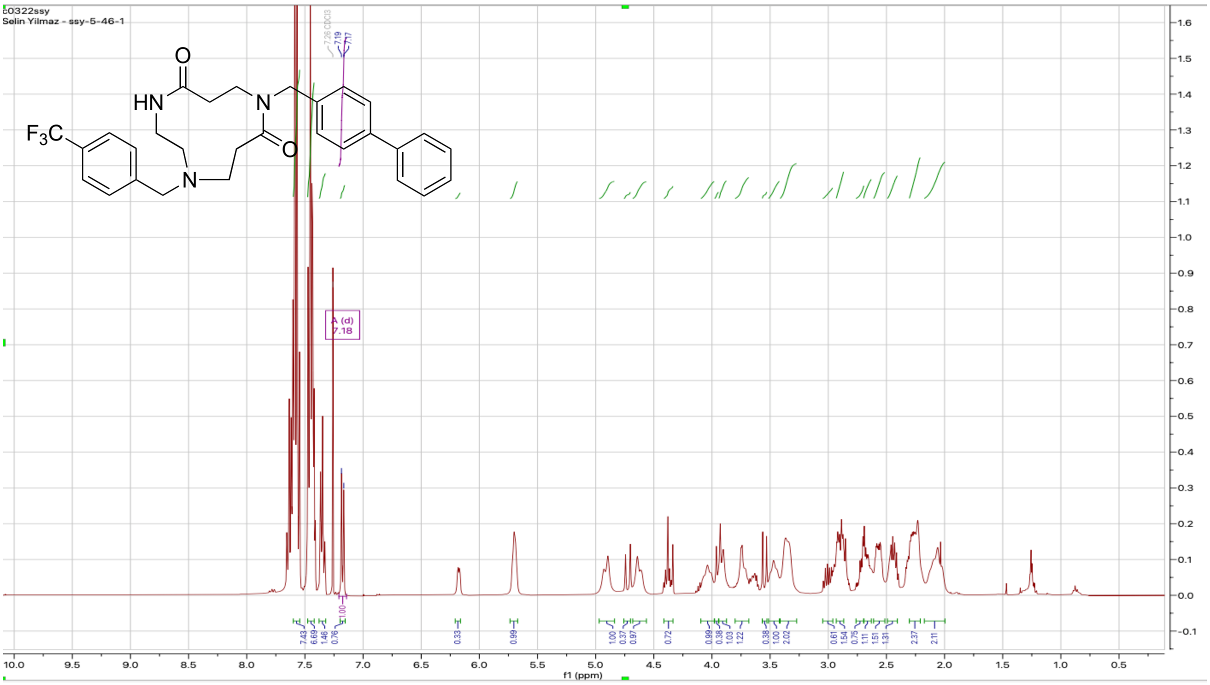


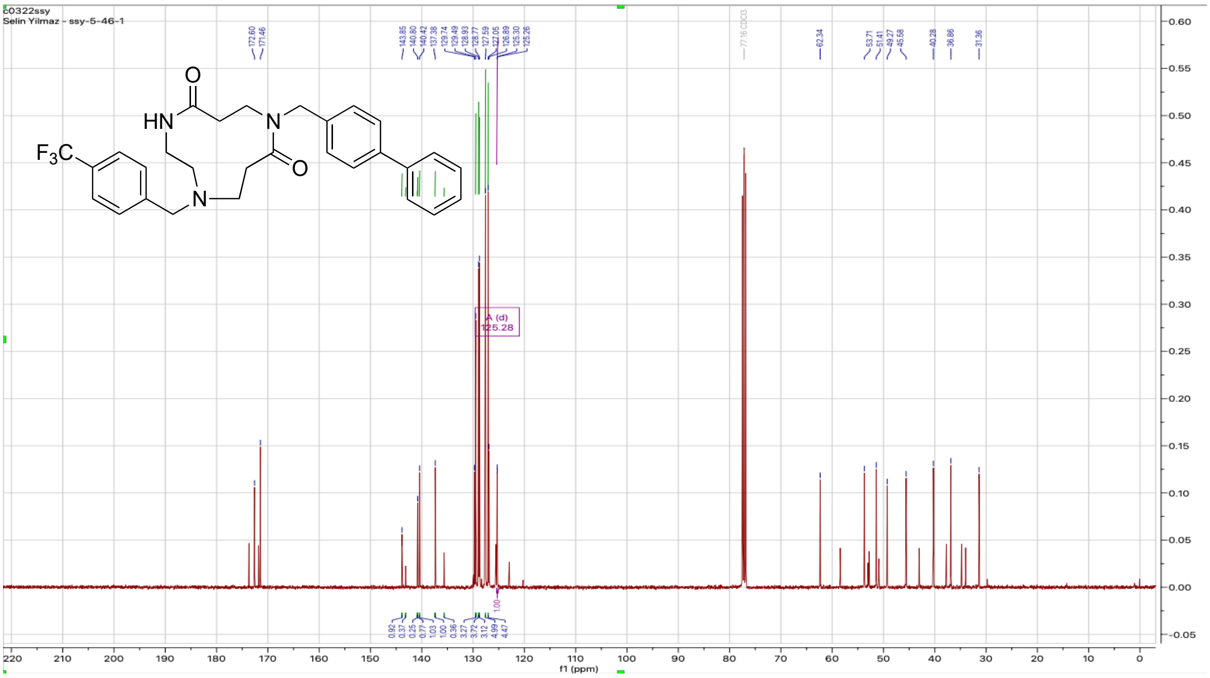




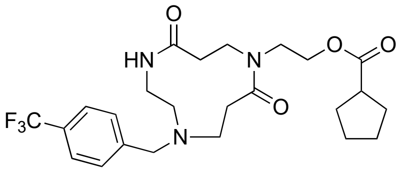
8-([1,1'-Biphenyl]-4-ylmethyl)-1-(4-(trifluoromethyl)benzyl)-1,4,8-triazacycloundecane-5,9-dione (14m) – 3:1 mixture of rotamers.

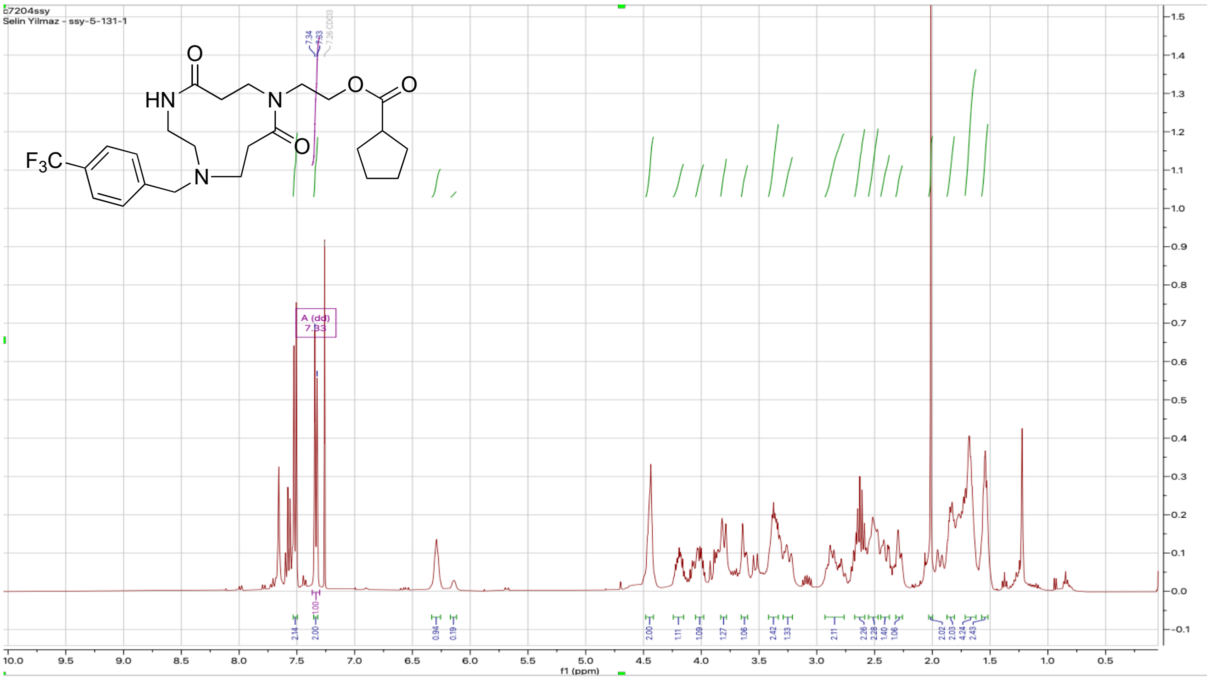


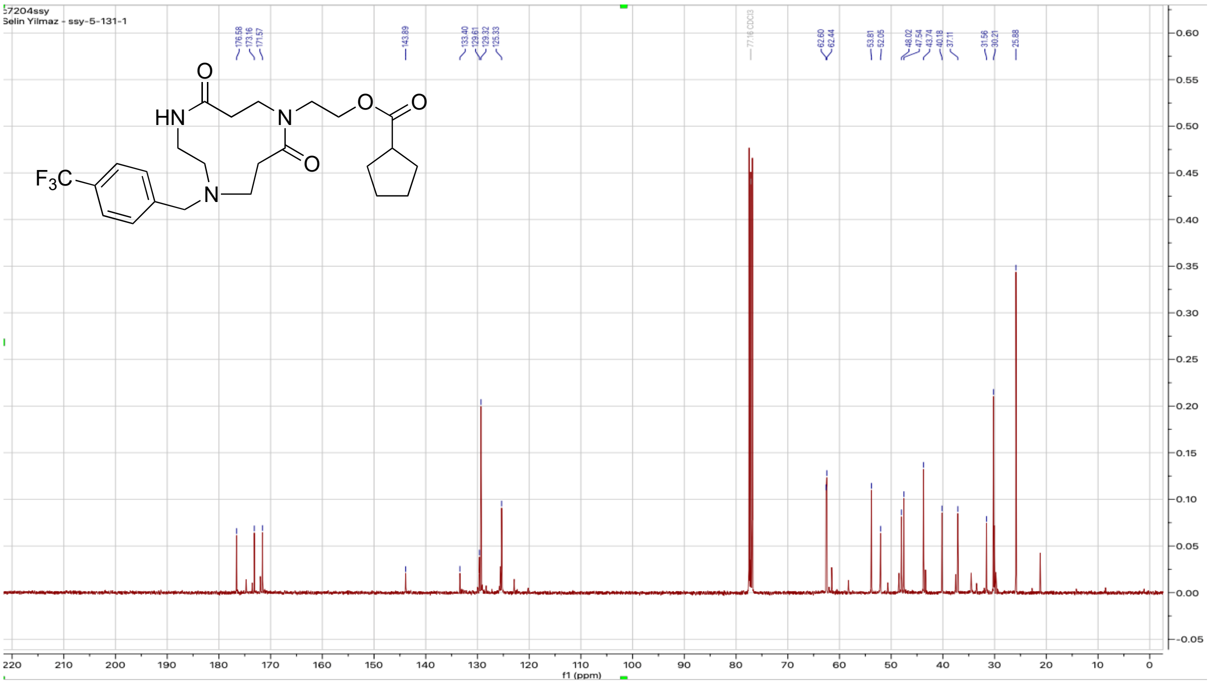




2-(5,9-Dioxo-1-(4-(trifluoromethyl)benzyl)-1,4,8-triazacycloundecan-8-yl)ethyl cyclopentanecarboxylate (14n) – 5:1 mixture of rotamers



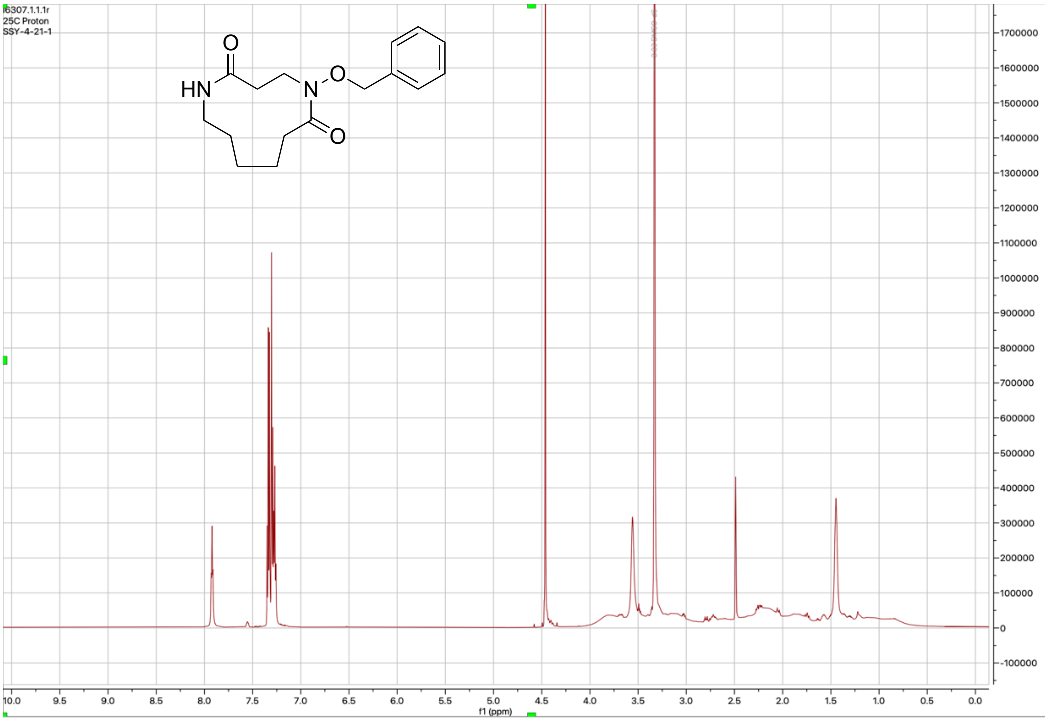




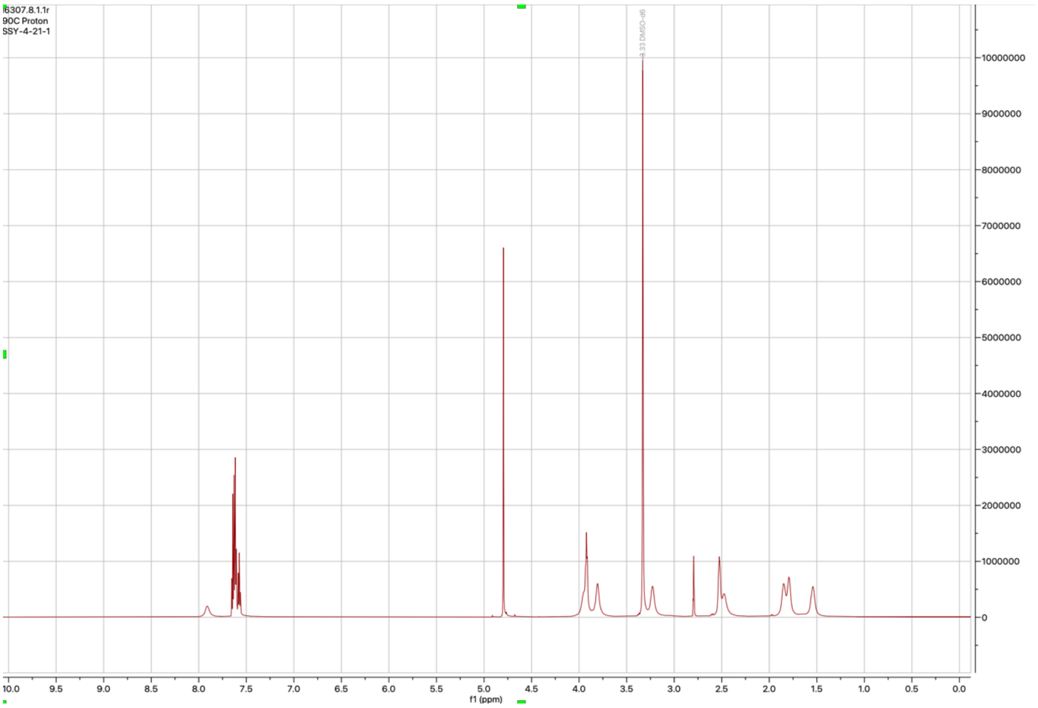
5) Elevated temperature ^{1}H NMR experiments

5-(Benzyloxyl)-1,5-diazacycloundecane-2,6-dione (8a)

^{1}H NMR in d6-DMSO at RT



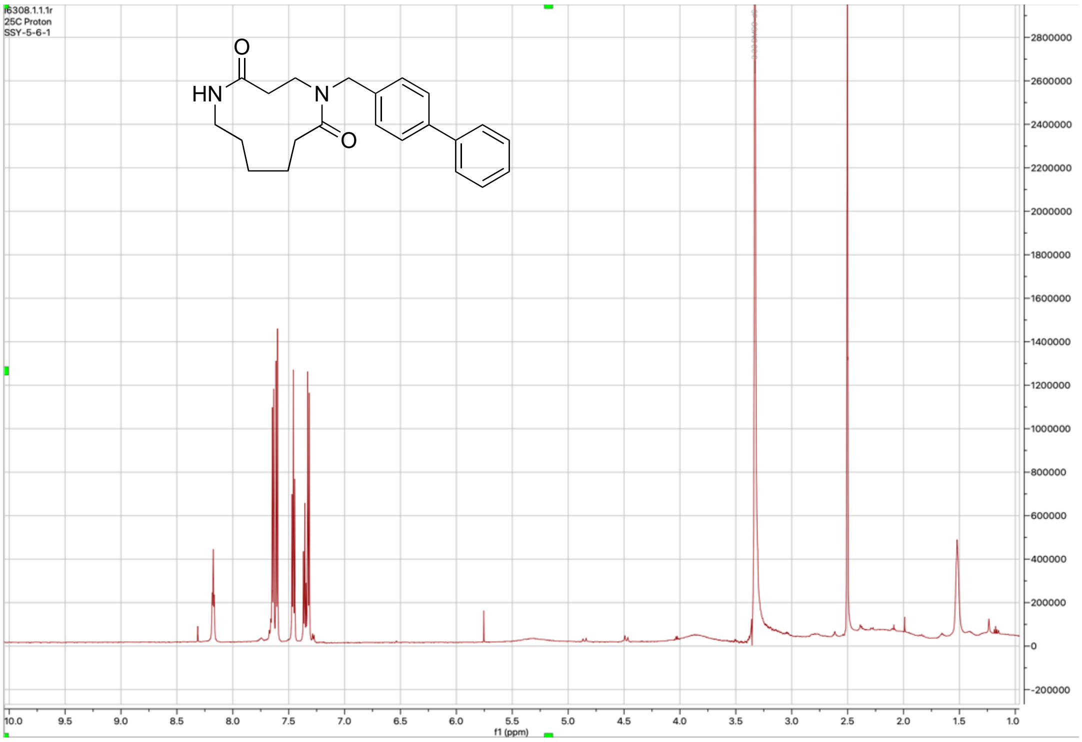
^{1}H NMR in d6-DMSO at 90 °C



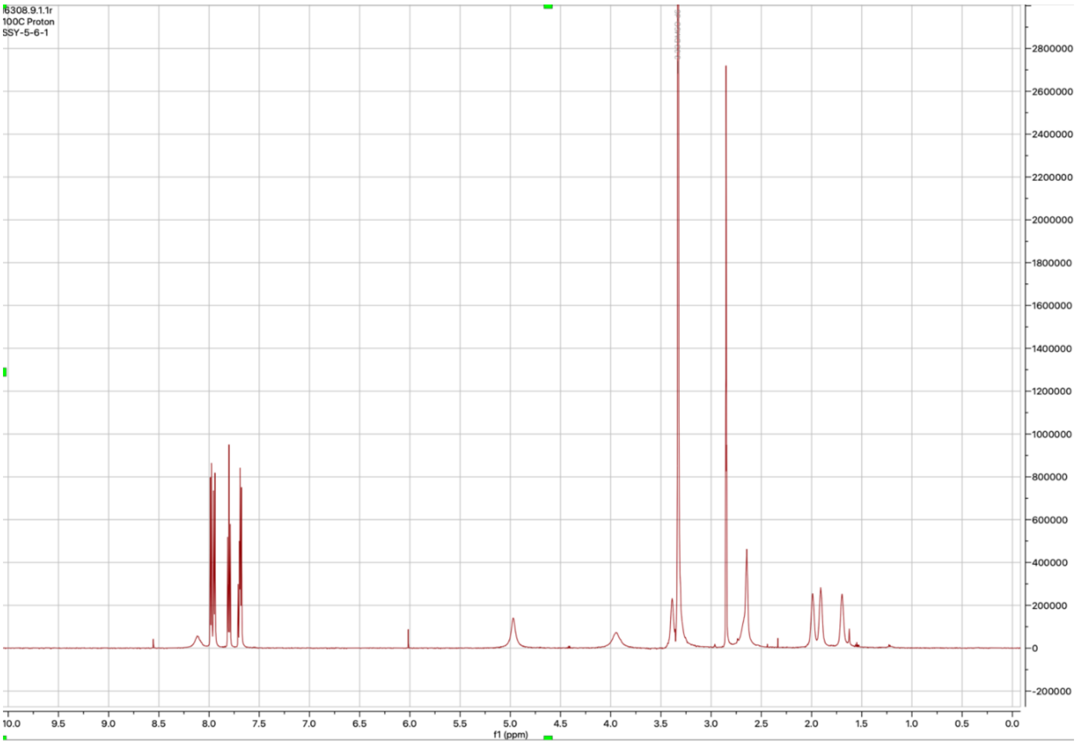
Reanalysing the heated sample gave a spectrum identical to the originally recorded RT NMR.

5-([1,1'-Biphenyl]-4-ylmethyl)-1,5-diazacycloundecane-2,6-dione (13a)

^{1}H NMR in d6-DMSO at RT



^{1}H NMR in d6-DMSO at 100 °C



Reanalysing the heated sample gave a spectrum identical to the originally recorded RT NMR.

6) LCMS data

As many of the products generated in this manuscript exist as mixture or rotamers and/or rotameric broadening is evident in their NMR spectra, assessing compound purity by inspection of their NMR spectra can be challenging. Therefore, LCMS data were obtained for representative compounds in each series, to provide additional confidence that the products isolated have >95% purity.

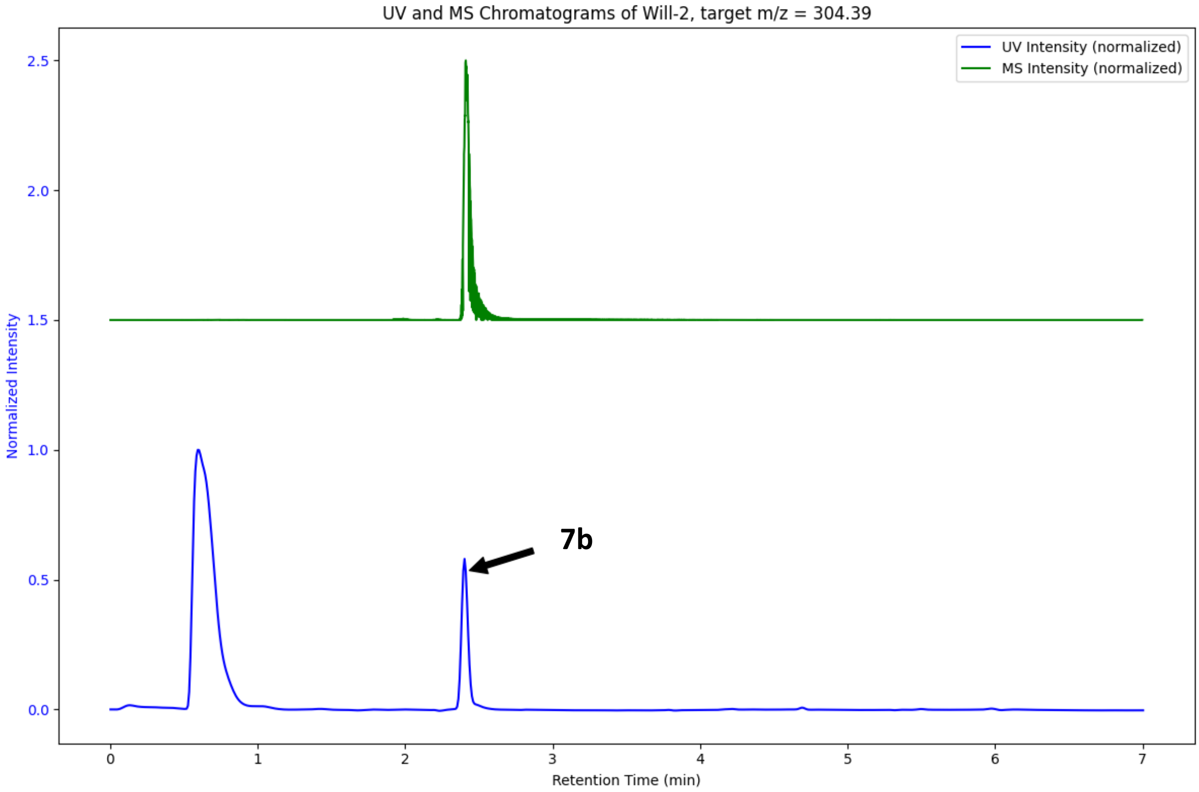
LCMS data was collected using a Dr. Maisch ReproSil-Pur 120 ODS-3, 2.4 µm, 50 mm x 3 mm column, on a ThermoScientific Vanquish instrument, coupled to a ThermoScientific HCT ultra ETD II ion trap. Mass spectrometry (ESI) was run in the positive mode. The solvent system consisted of H_2O / MeCN, both containing 0.1% formic acid. The UV trace is 200 nm.

The following flow gradient was used for all samples:

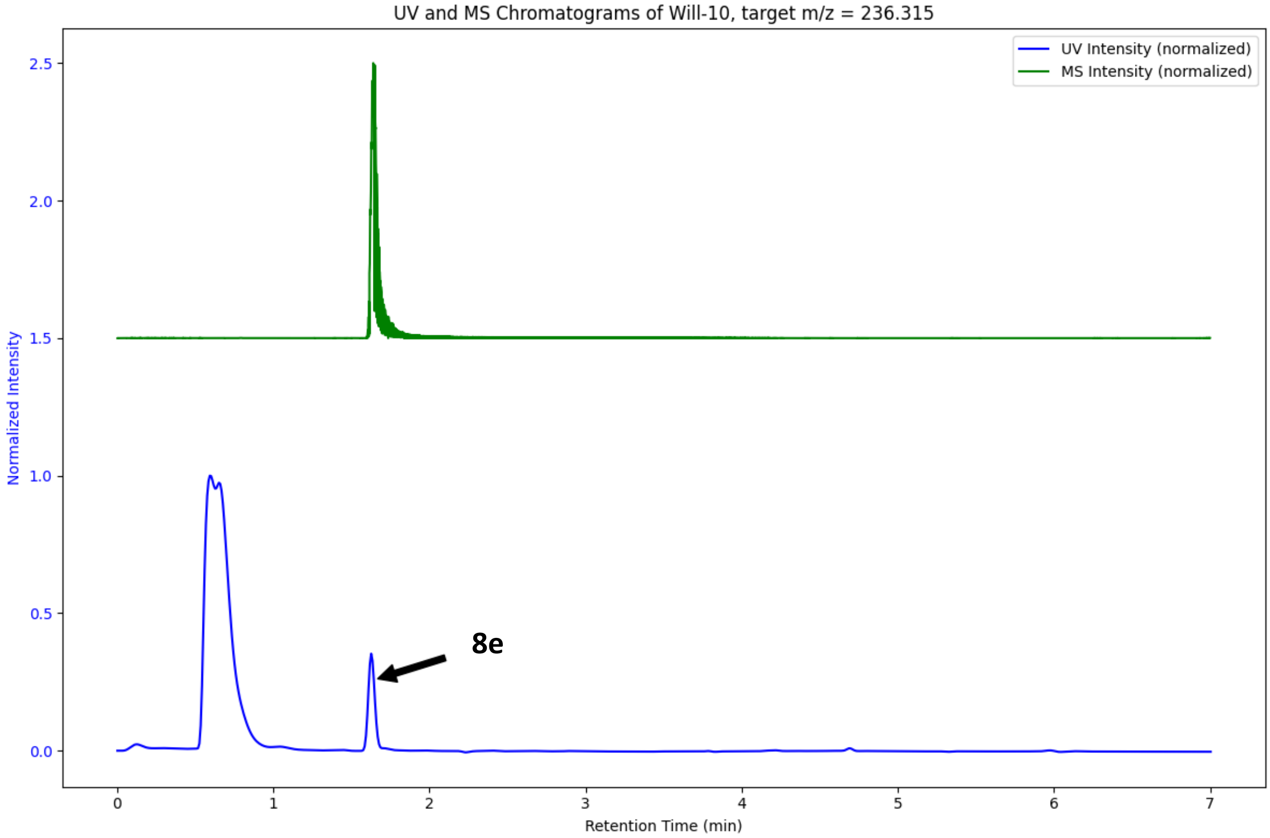
Time / min	Flow / mL min-1	% MeCN
0.0	0.500	10.0
4.0	0.500	90.0
6.3	0.500	90.0
6.4	0.500	10.0
7.0	0.500	10.0

In all chromatograms, the large peak around 0.7 min retention time is DMSO, the solvent in which the samples were dissolved for analysis (50 mM in DMSO).

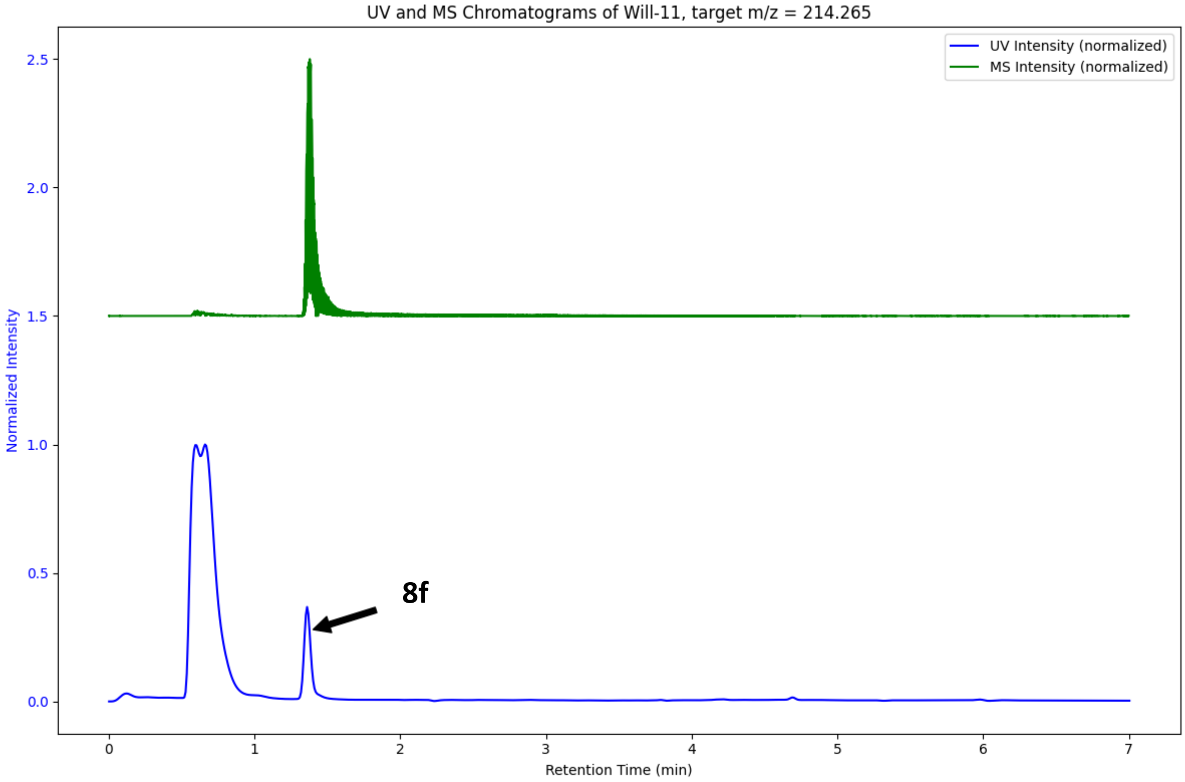
7b



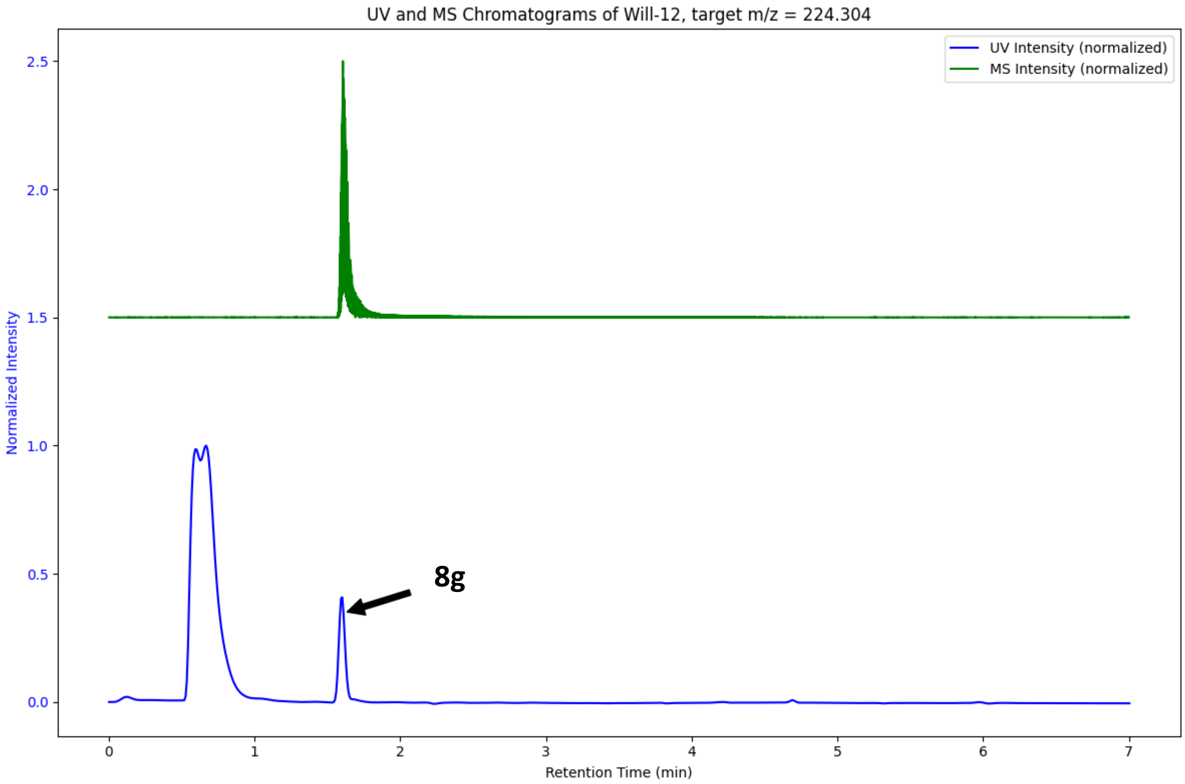
8e


UV and MS Chromatograms of Will-10, target m/z = 236.315
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
0.0
0.5
1.0
1.5
2.0
2.5
8e
0
1
2
3
4
5
6
7
Retention Time (min)

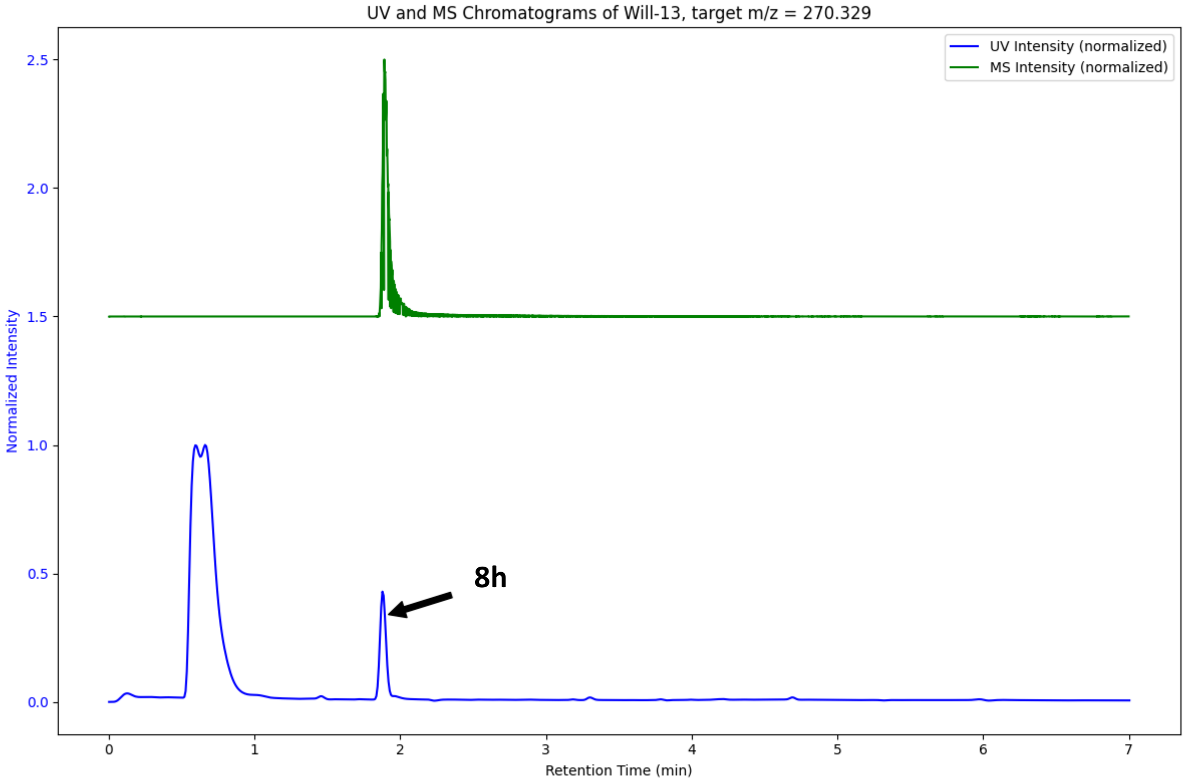
8f


UV and MS Chromatograms of Will-11, target m/z = 214.265
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
0.0
0.5
1.0
1.5
2.0
2.5
8f
0
1
2
3
4
5
6
7
Retention Time (min)

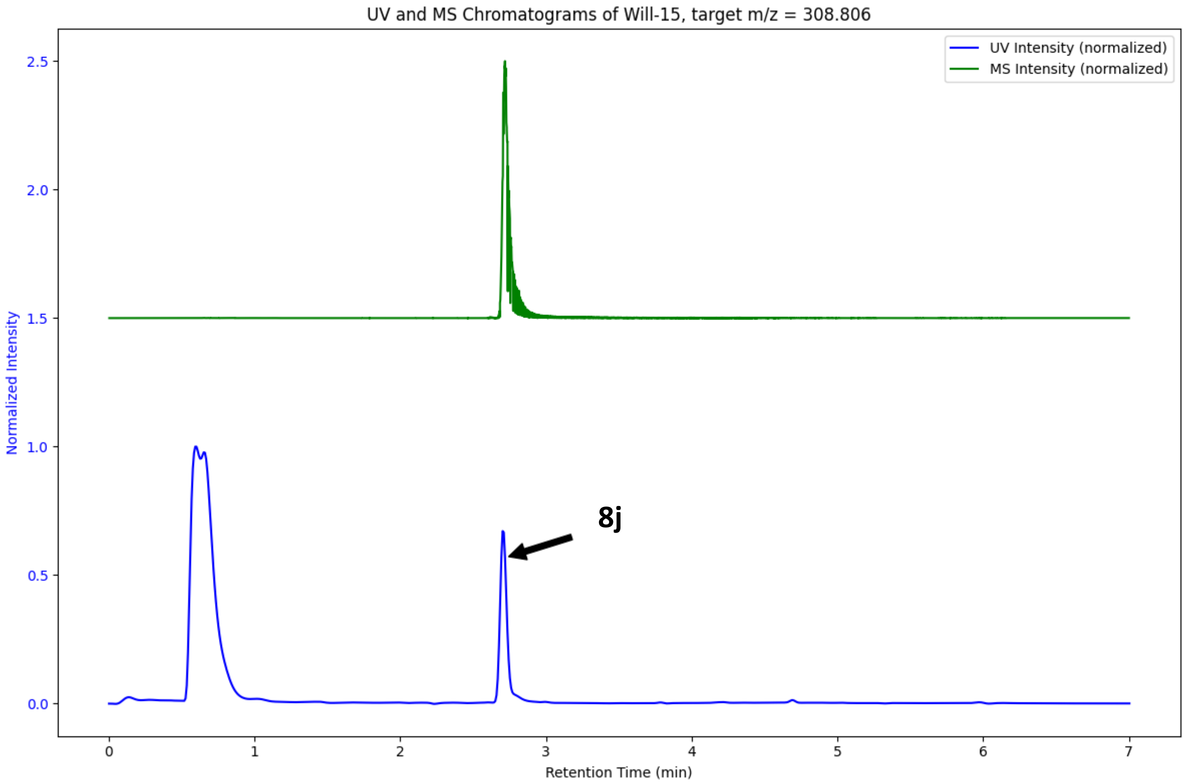
8g


UV and MS Chromatograms of Will-12, target m/z = 224.304
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
8g
0
1
2
3
4
5
6
7
Retention Time (min)

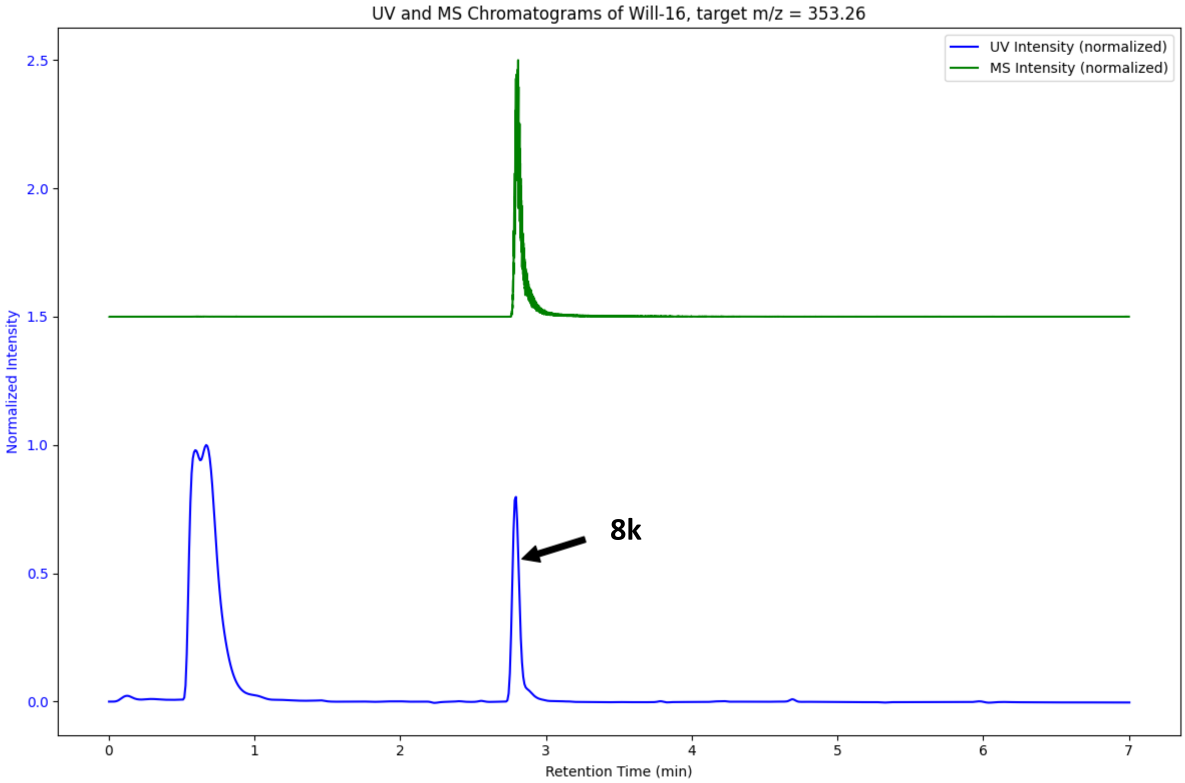
8h


UV and MS Chromatograms of Will-13, target m/z = 270.329
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
8h
0
1
2
3
4
5
6
7
Retention Time (min)

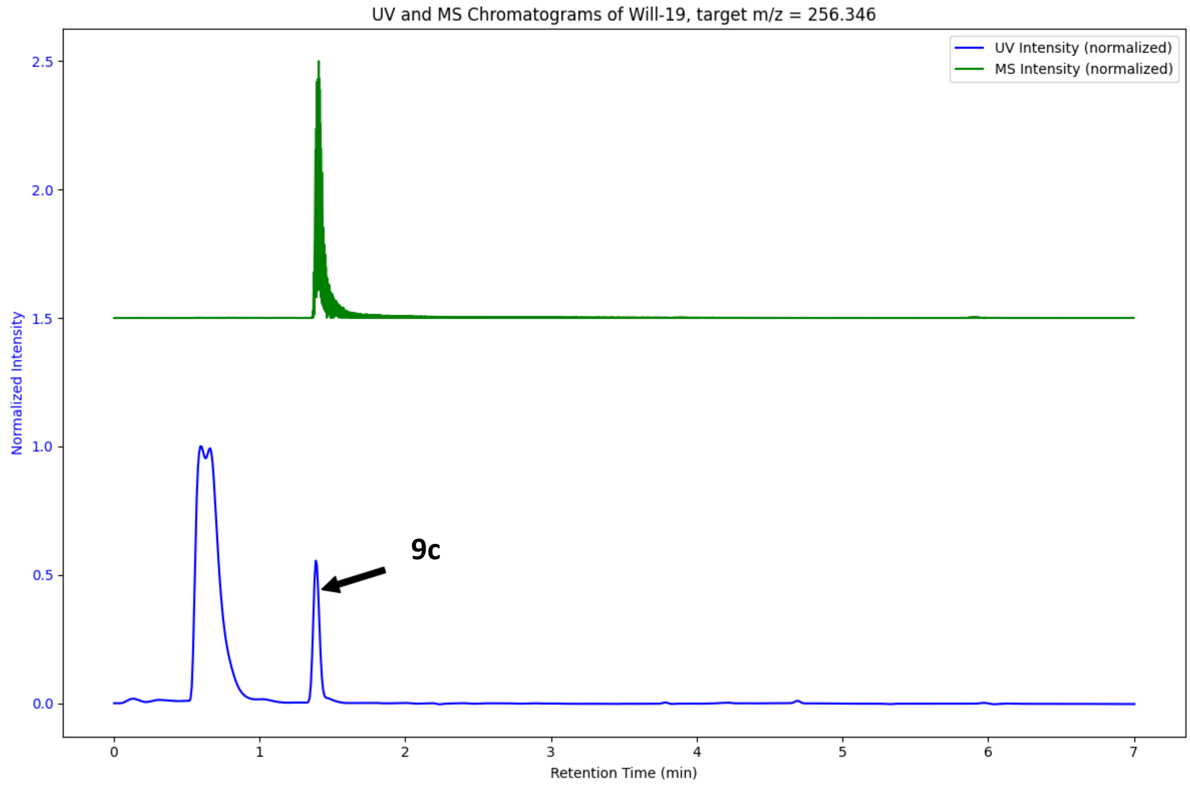
8j


UV and MS Chromatograms of Will-15, target m/z = 308.806
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
8j
0
1
2
3
4
5
6
7
Retention Time (min)

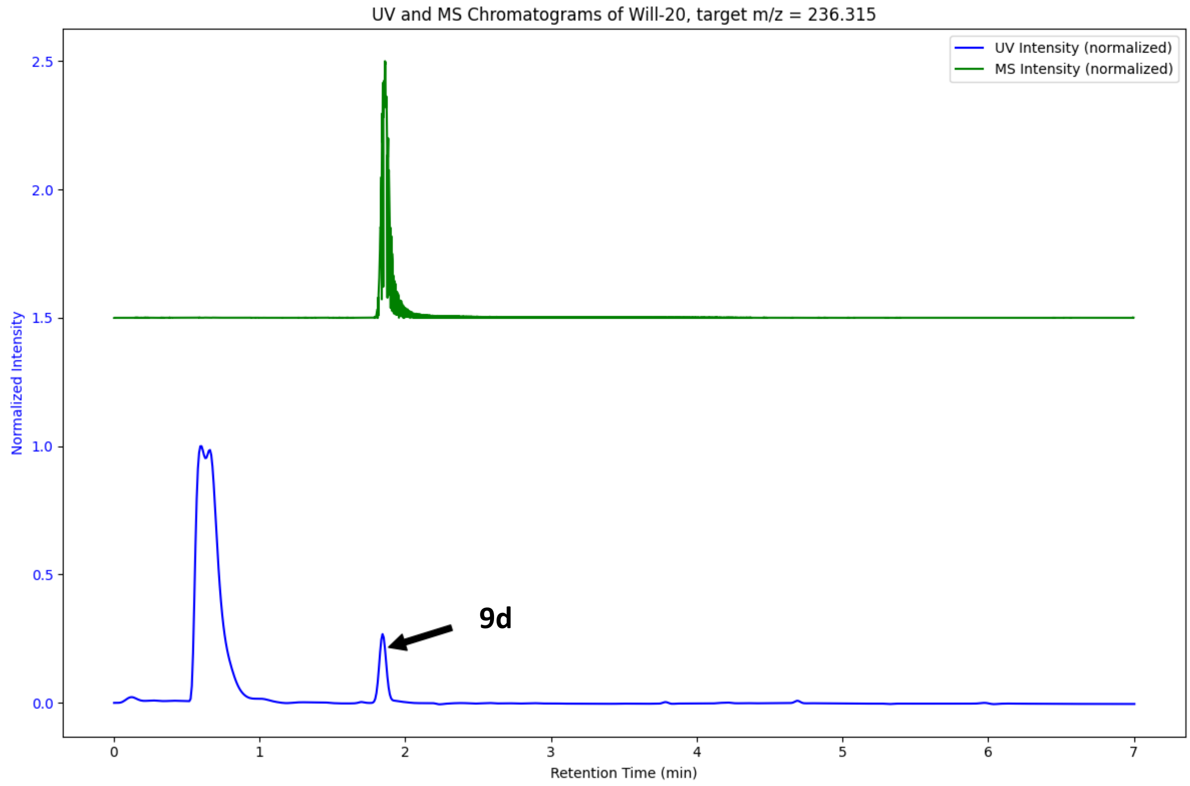
8k


UV and MS Chromatograms of Will-16, target m/z = 353.26
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
8k
0
1
2
3
4
5
6
7
Retention Time (min)

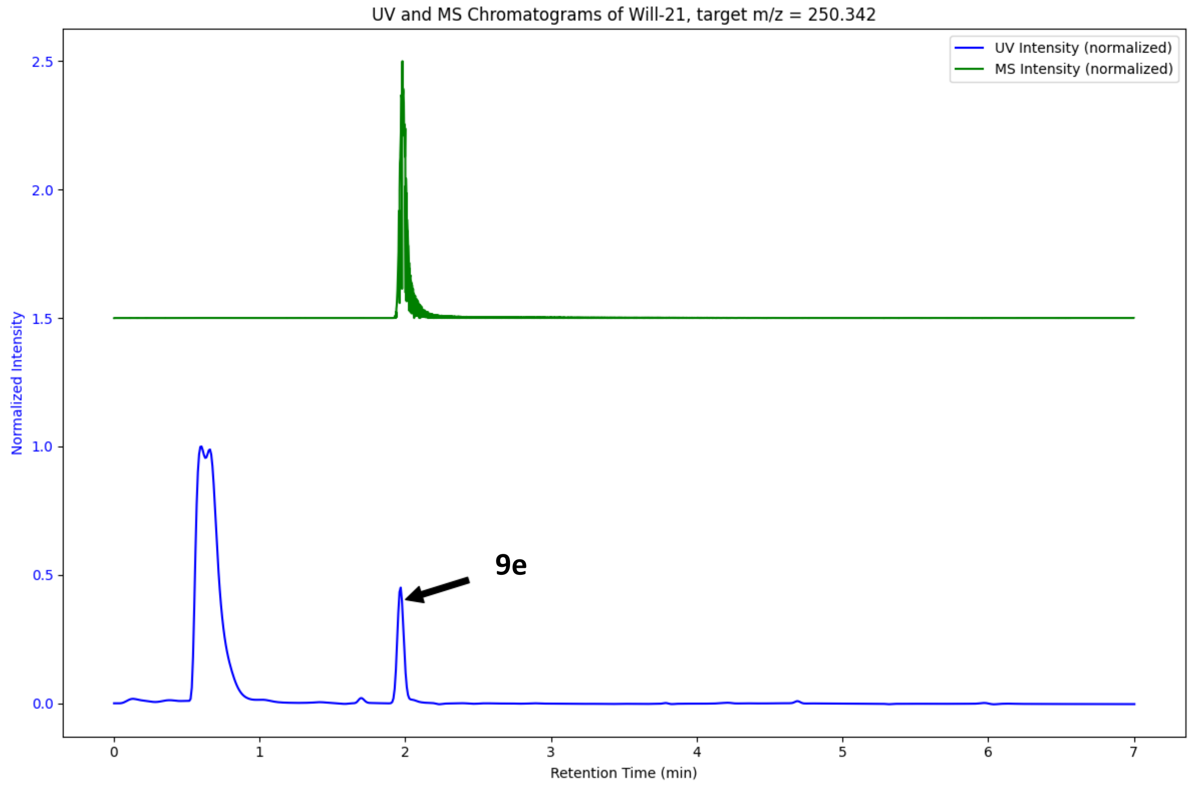
9c


UV and MS Chromatograms of Will-19, target m/z = 256.346
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
9c
0
1
2
3
4
5
6
7
Retention Time (min)

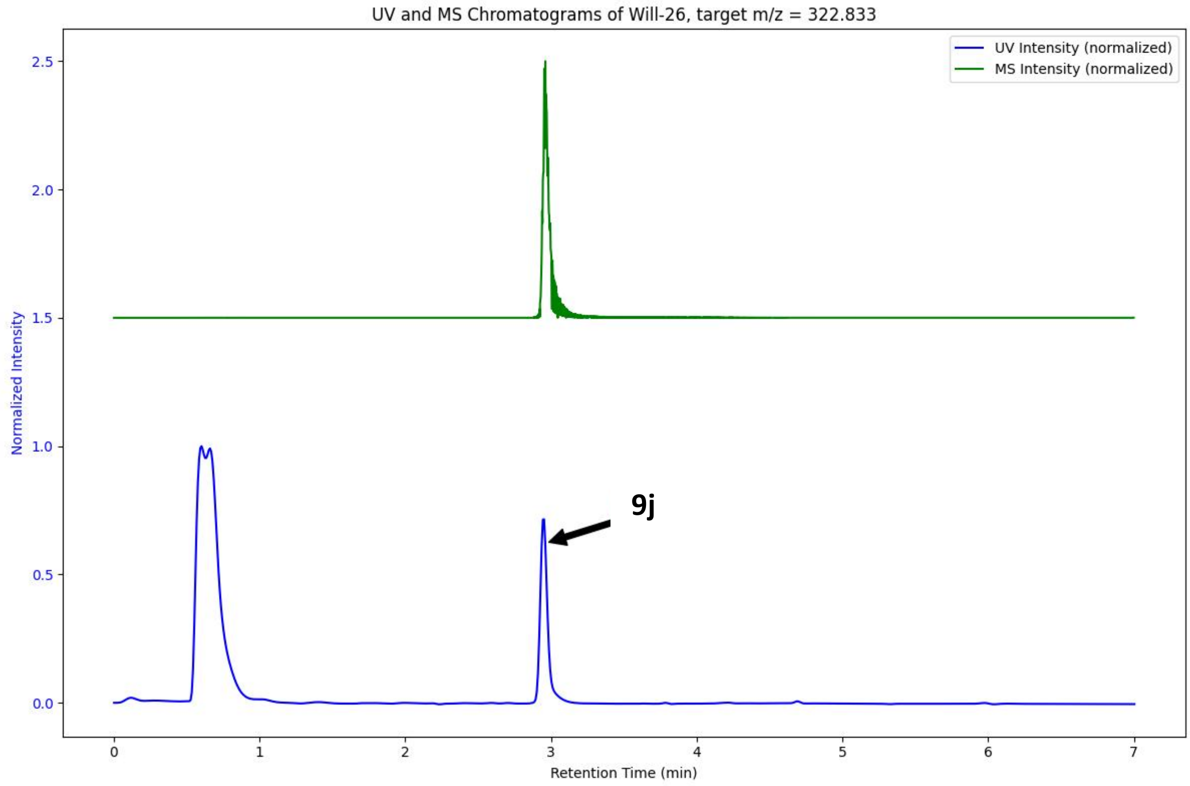
9d


UV and MS Chromatograms of Will-20, target m/z = 236.315
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
9d
0
1
2
3
4
5
6
7
Retention Time (min)

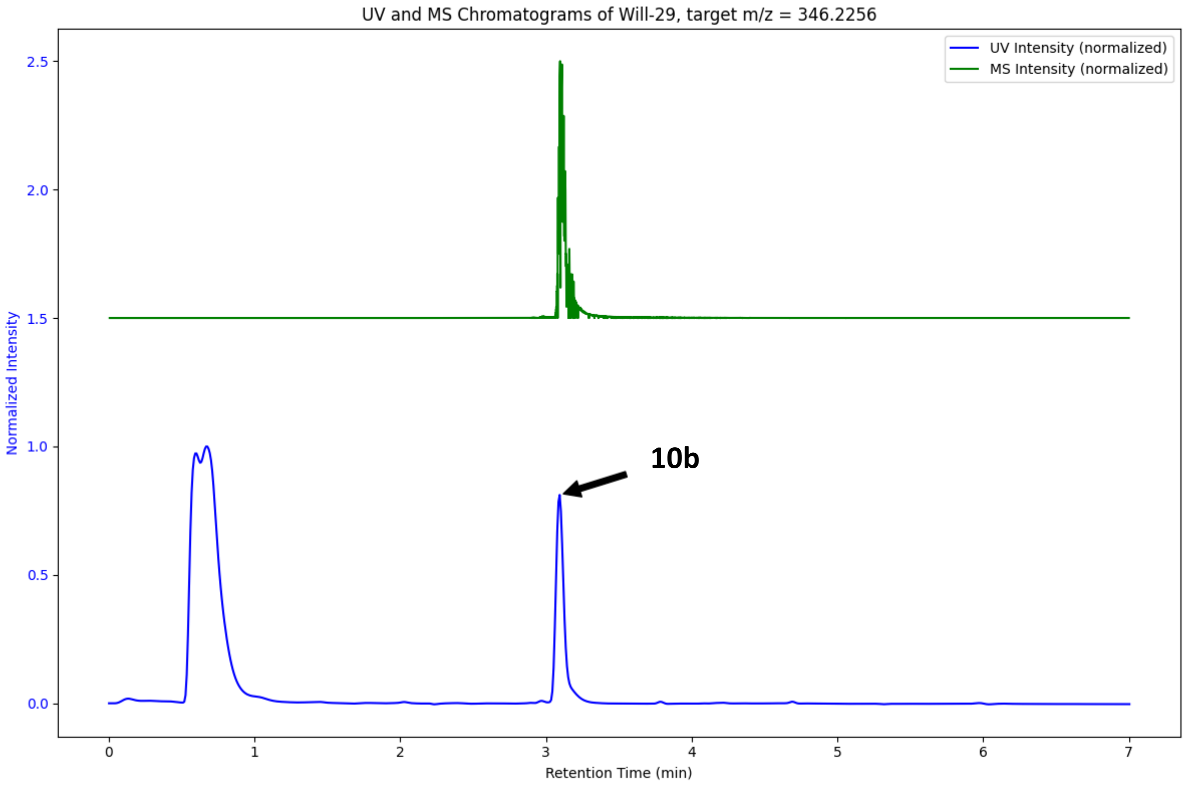
9e


UV and MS Chromatograms of Will-21, target m/z = 250.342
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
9e
0
1
2
3
4
5
6
7
Retention Time (min)

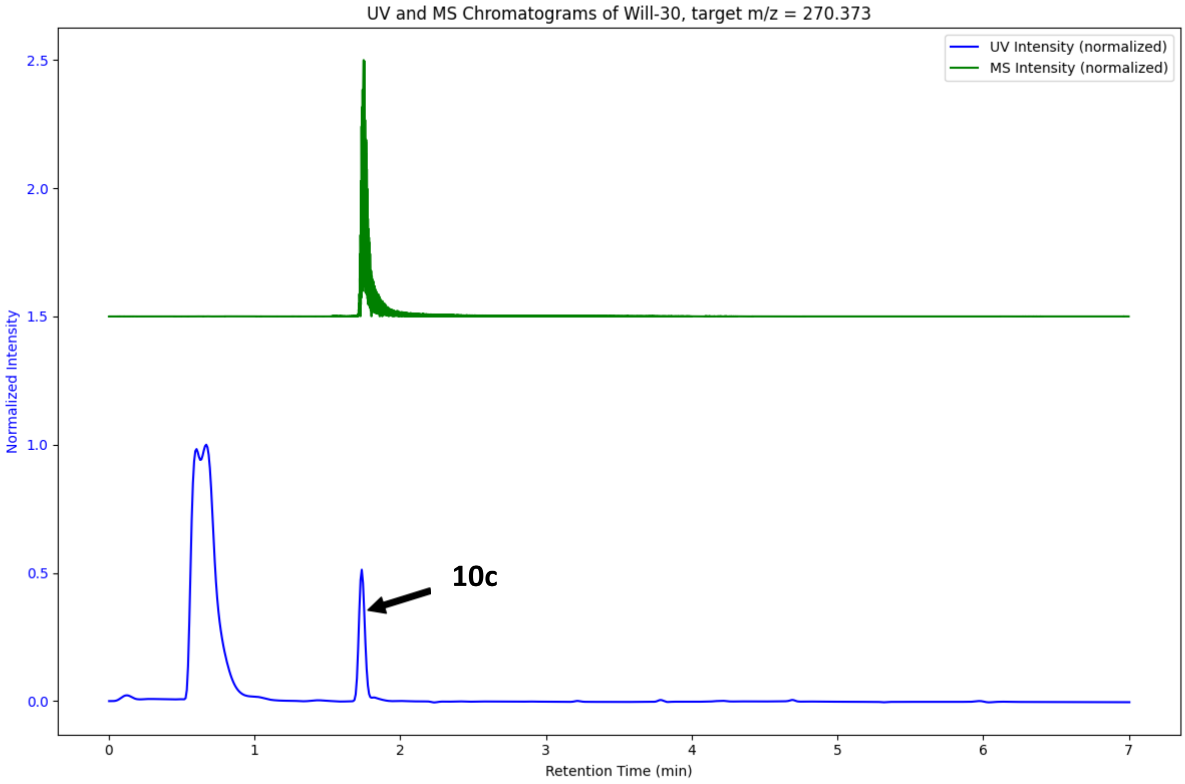
9j


UV and MS Chromatograms of Will-26, target m/z = 322.833
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
9j
0
1
2
3
4
5
6
7
Retention Time (min)

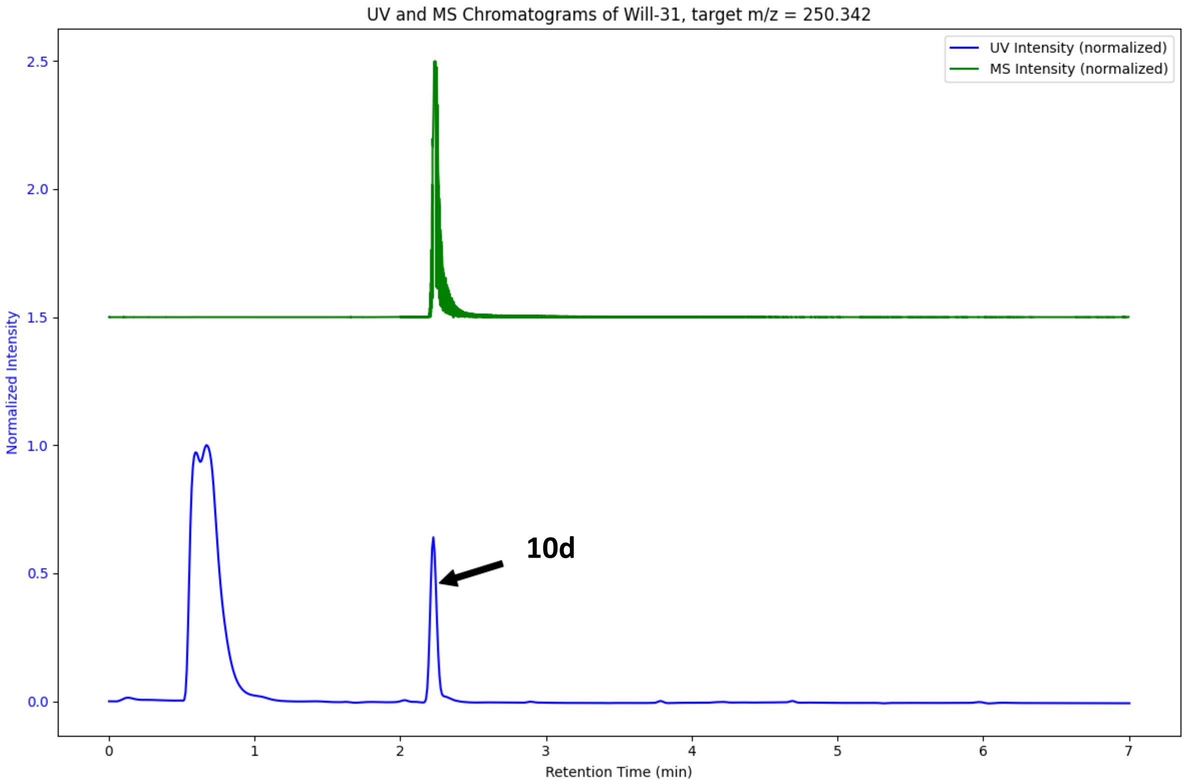
10b


UV and MS Chromatograms of Will-29, target m/z = 346.2256
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
0.0
0.5
1.0
1.5
2.0
2.5
Retention Time (min)
0
1
2
3
4
5
6
7
10b

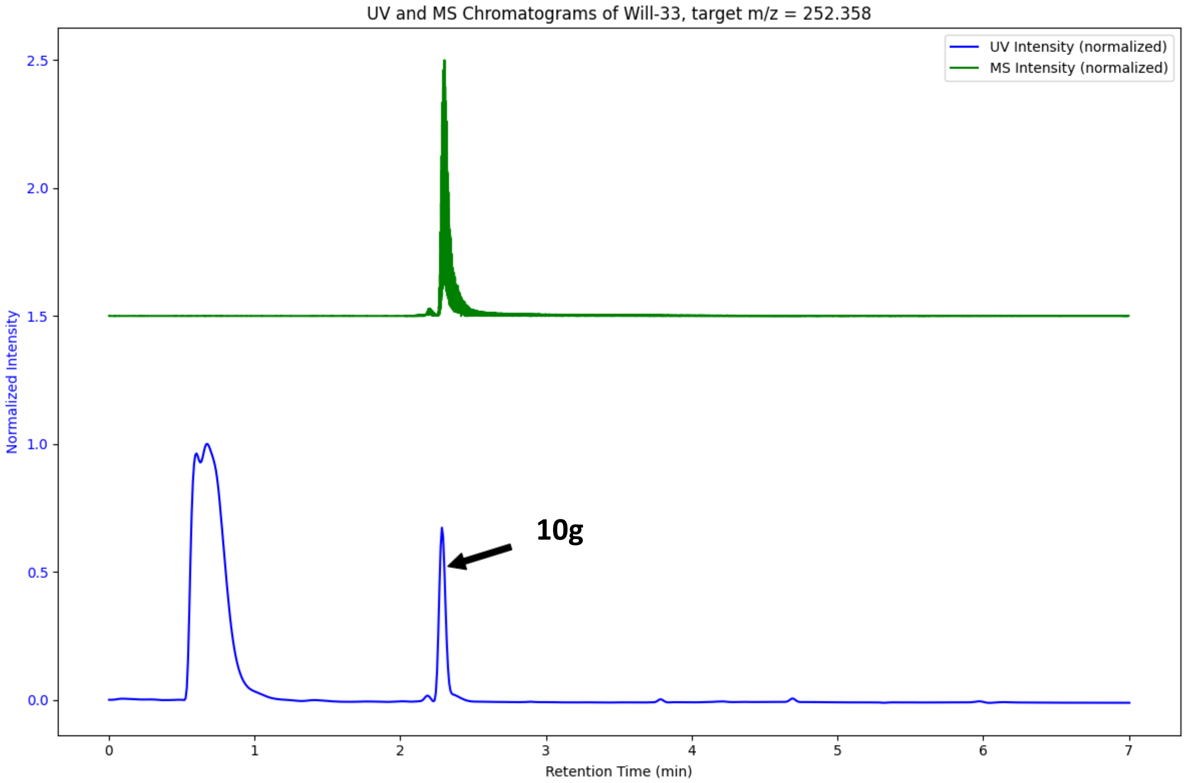
10c


UV and MS Chromatograms of Will-30, target m/z = 270.373
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
0.0
0.5
1.0
1.5
2.0
2.5
Retention Time (min)
0
1
2
3
4
5
6
7
10c

10d


UV and MS Chromatograms of Will-31, target m/z = 250.342
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
0.0
0.5
1.0
1.5
2.0
2.5
10d
Retention Time (min)
0
1
2
3
4
5
6
7

10g


UV and MS Chromatograms of Will-33, target m/z = 252.358
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
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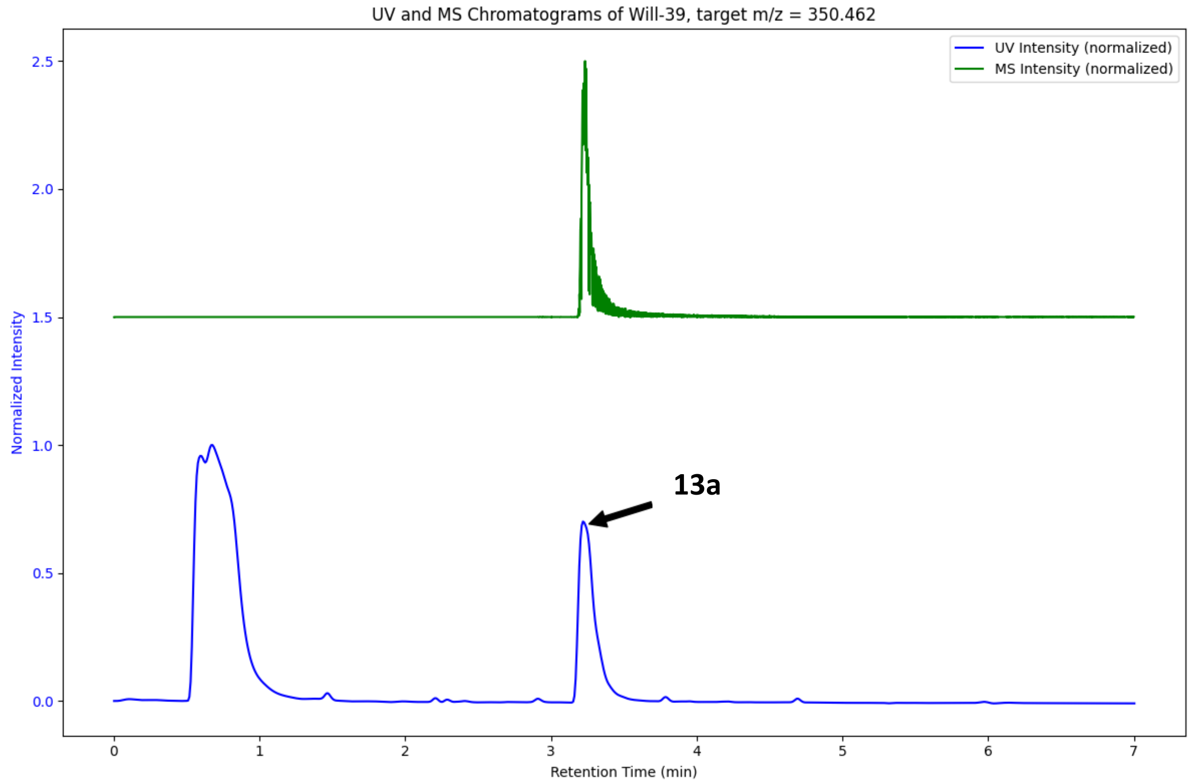
0.5
1.0
1.5
2.0
2.5
10g
Retention Time (min)
0
1
2
3
4
5
6
7

13a


UV and MS Chromatograms of Will-39, target m/z = 350.462
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
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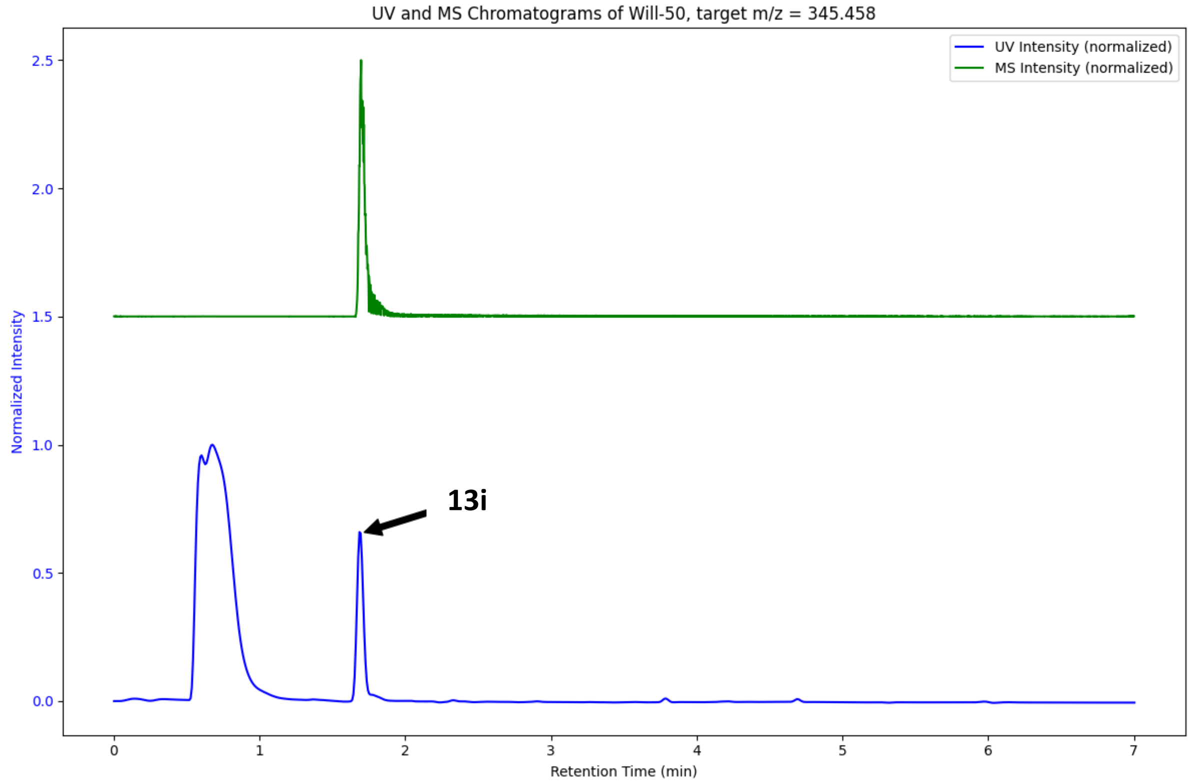
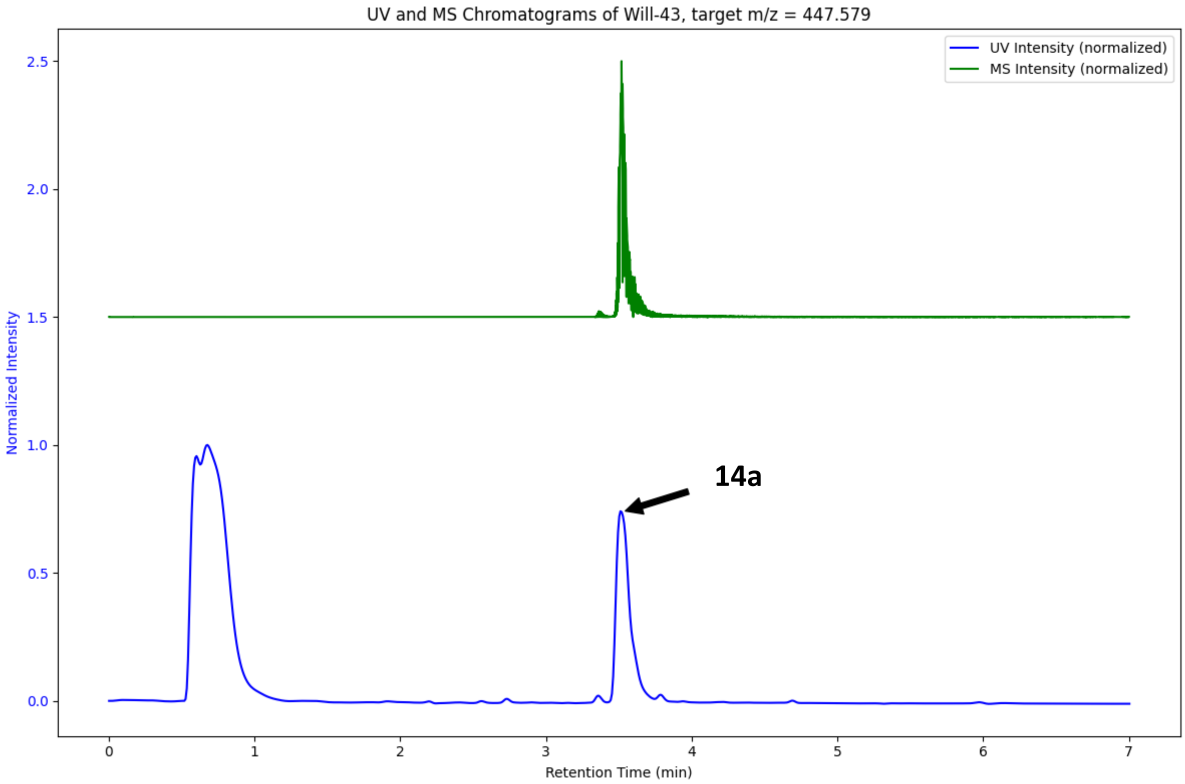
2.0
1.5
1.0
0.5
0.0
13a
0
1
2
3
4
5
6
7
Retention Time (min)

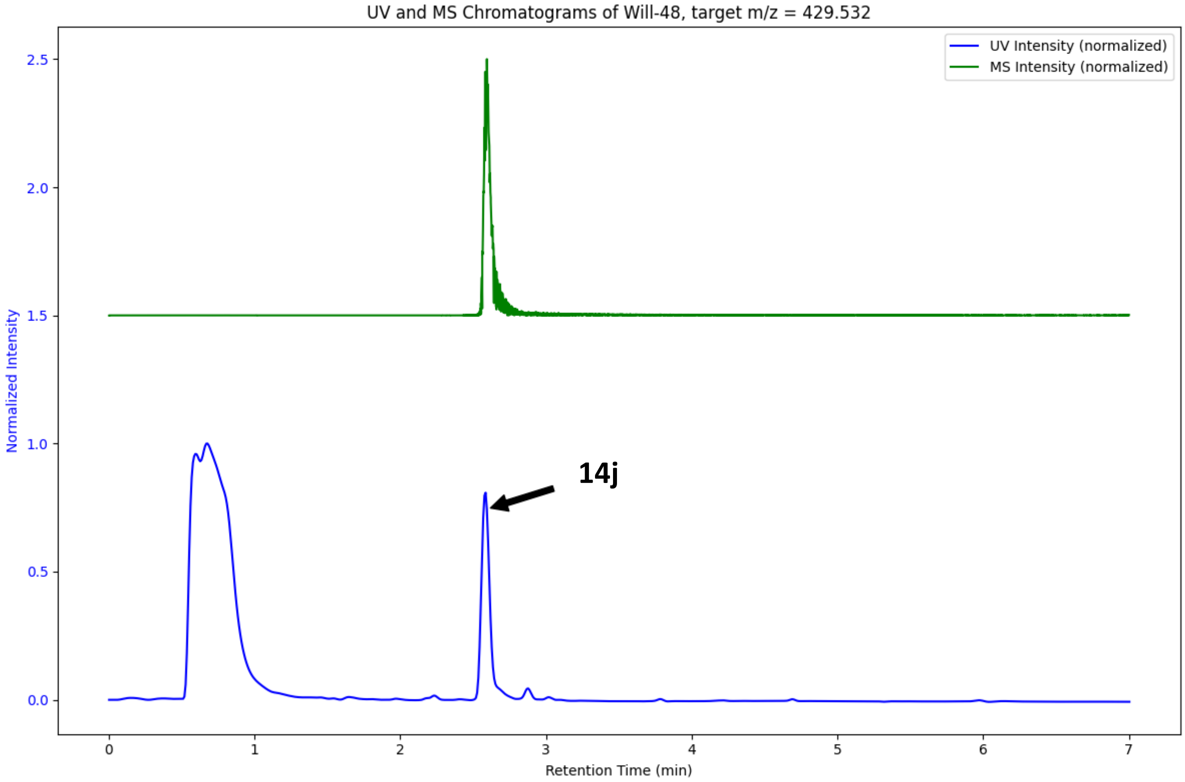
13i


UV and MS Chromatograms of Will-50, target m/z = 345.458
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
13i
0
1
2
3
4
5
6
7
Retention Time (min)

14a


UV and MS Chromatograms of Will-43, target m/z = 447.579
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
14a
0
1
2
3
4
5
6
7
Retention Time (min)

14j


UV and MS Chromatograms of Will-48, target m/z = 429.532
UV Intensity (normalized)
MS Intensity (normalized)
Normalized Intensity
2.5
2.0
1.5
1.0
0.5
0.0
14j
0
1
2
3
4
5
6
7
Retention Time (min)

7) References

1) K. Y. Palate, Z. Yang, A. C. Whitwood and W. P. Unsworth, Synthesis of medium-ring lactams and macrocyclic peptide mimetics via conjugate addition/ring expansion cascade reactions, *RSC Chem. Biol*., 2022, **3**, 334.
2) W. E. Orukotan, K. Y. Palate, B. Pogrányi, P. Bobinski, R. G. Epton, L. Duff, A. C. Whitwood, G. Grogan, J. M. Lynam and W. P. Unsworth. Divergent Cascade Ring Expansion Reactions of Acryloyl Imides. *Chem. Eur. J*. 2023, **29**, e202303270.