Electronic Supplementary Material (ESI) for RSC Chemical Biology.

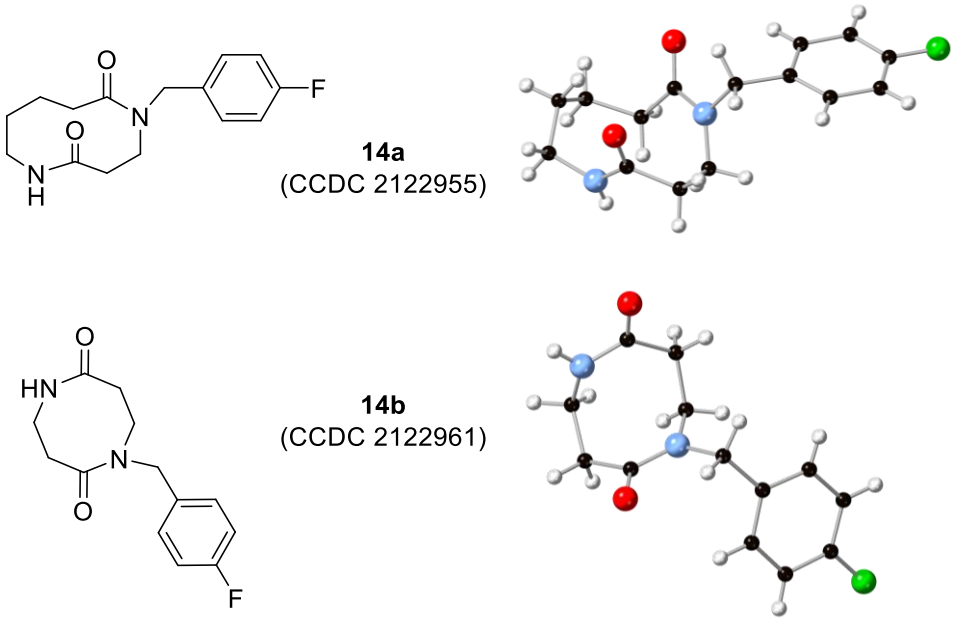
Table of Contents

General information

Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH_2Cl_2, THF, acetonitrile, hexane, Et_2O and DMF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. DME, DMSO, DMA, NMP, MeOH, and EtOH, advertised as dry solvents, were purchased from various commercial vendors and used as supplied without additional drying or purification. Standard grade *i*-PrOH, *t*-BuOH, TFE and HFIP (*i.e*. all likely to be wet) were obtained from commercially suppliers and were used as supplied. Water used in reactions was deionized. ^{1}H NMR, ^{13}C NMR, and ^{19}F spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer (operating at 400 MHz, 100 MHz, and 376 MHz), a Bruker Avance III 300 NMR spectrometer (operating at 300 MHz, 75 MHz, and 282 MHz), a Bruker Avance I 500 MHz spectrometer (operating at 500 MHz, 125 MHz, and 470 MHz), a Bruker Avance III HD 500 NMR spectrometer (operating at 500 MHz, 125 MHz, and 470 MHz), a Bruker Avance III HD 600 NMR spectrometer (operating at 600 MHz, 151 MHz, and 565 MHz), or a Bruker Avance Neo 700 NMR spectrometer (operating at 700 MHz, 176 MHz, and 659 MHz). All spectral data was acquired at 295 K unless stated otherwise. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks, δ_H 7.26 and δ_c 77.16 for $CDCl_3$ were used as a reference. Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The multiplicity abbreviations used are: br s broad singlet, s singlet, d doublet, br d broad doublet, t triplet, br t broad triplet, q quartet, p pentet, dd, doublet of doublets, ddd doublet of doublet of doublets, dddd doublet of doublet of doublet of doublets, dt doublet of triplets, ddt doublet of doublet of triplets, td triplet of doublets, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$. Mass spectra (high-resolution) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained

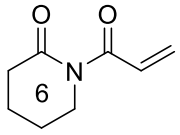
with basic aqueous potassium permanganate. In most cases, flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system. However, when noted in the procedures that products were purified using automated column chromatography (3 cases), this was done using a Teledyne ISCO NextGen 300+ automated flash column chromatography unit equipped with UV–Vis (200–800 nm) and evaporative light scattering (ELS) detectors. Crude materials were loaded onto pre-packed RediSep Rf Gold columns (SiO_2: 40–60 mesh) either by direct liquid injection or dry loading from adsorbed Celite.

X-ray crystallography



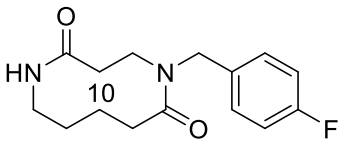
Diffraction data were collected at 110 K on an Oxford Diffraction SuperNova diffractometer with Cu-K_α radiation (λ = 1.54184 Å) using an EOS CCD camera. The crystal was cooled with an Oxford Instruments Cryojet. Diffractometer control, data collection, initial unit cell determination, frame integration and unit-cell refinement were carried out with CrysAlisPro.[1] Face-indexed absorption corrections were applied using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.[2] OLEX2[3] was used for overall structure solution, refinement and preparation of computer graphics and publication data. Within OLEX2, the algorithm used for structure solution was ShelXT dual-space[4]. Refinement by full-matrix least-squares used the SHELXL[5] algorithm within OLEX2.[3] All non-hydrogen atoms were refined anisotropically. Hydrogens were located by difference map and allowed to refine. For **14a**, there were two molecules in the asymmetric unit but the figure above and in the manuscript shows one for clarity (see CCDC 2122955 for further detail).

1-Acryloyl-piperidin-2-one (11a)



To a stirring solution of δ-valerolactam (992 mg, 10.0 mmol) in dry THF (36.4 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 3.65 mL, 11.0 mmol) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed, before acryloyl chloride (1.22 mL, 15.0 mmol) was added in a single portion and the reaction mixture was stirred for an additional 30 min at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (30 mL) and the mixture was extracted with Et_2O (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 30 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a viscous colourless liquid (1.06 g, 69%); R_f 0.59 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2953, 1679, 1404, 1384, 1289, 1211, 1156, 1004, 796; δ_H (400 MHz, $CDCl_3$), 6.97 (1H, dd, *J* = 17.0, 10.5 Hz, NCOC**H**CHH'), 6.33 (1H, dd, *J* = 17.0, 1.7 Hz, NCOCHC**H**H'), (5.69 (1H, dd, *J* = 10.5, 1.7 Hz, NCOCHCH**H'**), 3.76 – 3.71 (2H, m, NC**H₂**), 2.60 – 2.53 (2H, m, C**H₂**CON), 1.90 – 1.81 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 173.8 (**C**O), 169.7 (**C**O), 132.0 (NCO**C**HCHH'), 128.0 (NCOCH**C**HH'), 44.7 (N**C**H_2), 34.9 (**C**H_2CON), 22.6 (**C**H_2), 20.8 (**C**H_2); HRMS (ESI): calcd. for $C_8H_{11}NNaO_2$, 176.0682. Found: $[MNa]^+$, 176.0684 (–0.9 ppm error).

5-(4-Fluorobenzyl)-1,5-diazecane-2,6-dione (14a)



To a solution of 1-acryloyl-piperidin-2-one **11a** (766 mg, 5.00 mmol) in dry methanol (10.0 mL), was added 4-fluorobenzylamine (0.63 mL, 5.50 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a peach-coloured solid (1.20 g, 86%). In solution in $CDCl_3$, this compound exists as a 2:15 mixture of rotameric forms; m.p. 162 – 165 °C, R_f 0.20 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3294, 2933, 1620, 1509, 1443, 1350, 1221, 1096, 812, 501; NMR data for the major rotamer only: δ_H (400 MHz, $CDCl_3$) 7.29 – 7.22 (2H, m, Ar**H**), 7.03 – 6.96 (2H, m, Ar**H**), 5.37 – 5.19 (1H, m, N**H**), 4.96 (1H, d, *J* = 14.6 Hz, C**H₂**), 4.21 (1H, d, *J* = 14.6 Hz, C**H₂**), 3.98 – 3.73 (2H, m, C**H₂**), 4.21 (1H, dt, *J* = 15.8, 3.9 Hz, C**H₂**), 2.96 – 2.79 (1H, m, C**H₂**), 2.76 – 2.57 (1H, m, C**H₂**), 2.26 – 2.00 (4H, m, C**H₂**), 1.82 – 1.36 (3H, m, C**H₂**); δ_C (100

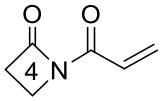
MHz, $CDCl_3$) 174.1 (**C**O), 171.0 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.4 Hz), 133.9 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 130.0 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.9 (2 × Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 48.7 (**C**H_2), 45.3 (**C**H_2), 39.3 (**C**H_2), 37.7 (**C**H_2), 28.4 (**C**H_2), 25.9 (**C**H_2), 23.9 (**C**H_2); δ_F (376 MHz, $CDCl_3$) –114.12 (1F, m, Ar**F**); HRMS (ESI): calcd. for $C_{15}H_{19}FN_2NaO_2$, 301.1323. Found: $[MNa]^+$, 301.1321 (0.5 ppm error).

Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 7.15 – 7.09 (2H, m, Ar**H**), 5.89 (1H, br d, *J* = 10.3 Hz, N**H**), 4.81 (1H, d, *J* = 16.3 Hz, C**H**$_2$), 4.28 (1H, d, *J* = 16.3 Hz, C**H**$_2$), 4.17 – 4.09 (2H, m, C**H**$_2$), 2.43 – 2.36 (2H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 171.3 (**C**O), 128.5 (2 × Ar**C**H, $^3J_{CF}$ = 8.2 Hz), 42.4 (**C**H_2), 40.2 (**C**H_2), 35.2 (**C**H_2), 27.5 (**C**H_2), 25.1 (**C**H_2); δ_F (376 MHz, $CDCl_3$) –114.43 (1F, m, Ar**F**).

The same compound **14a** was also made using the group's published SuRE chemistry[6] to provide an authentic product standard prior to optimisation, using the method below.

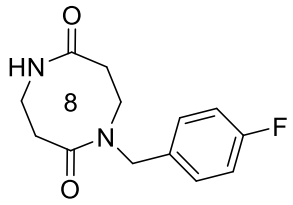
Oxalyl chloride (0.77 mL, 9.00 mmol) was added to a suspension of 3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)(4-fluorobenzyl)amino)propanoic acid (1.26 g, 3.00 mmol) in DCM (30 mL), followed by a catalytic amount of DMF (3 drops). The resulting mixture was stirred at RT for 1 h and concentrated in vacuo to remove all solvent and excess oxalyl chloride. The resulting acid chloride [(9*H*-fluoren-9-yl)methyl (3-chloro-3-oxopropyl)(4-fluorobenzyl)carbamate] was the dissolved in DCM (15 mL) and added to a pre-stirred mixture of δ-valerolactam (200 mg, 2.01 mmol), DMAP (24.2 mg, 0.200 mmol) and pyridine (0.977 mL, 12.1 mmol) in DCM (40 mL) under an argon atmosphere and heated at reflux at 50 °C for 18 h. The crude mixture was concentrated *in vacuo*. The mixture was then diluted with DCM (60 mL) and washed with 10% aq. HCl (60 mL). The aqueous layer was then extracted with DCM (3 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo* to form crude (9H-fluoren-9-yl)methyl (4-fluorobenzyl)(3-oxo-3-(2-oxopiperidin-1-yl)propyl)carbamate, which was carried forward without further purification. Thus, a solution of this crude imide was dissolved in DCM (40 mL) and DBU (2.99 mL, 20.0 mmol) was added, followed by stirring at RT for 18 h, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* **14a** as an orange solid (489 mg, 87% from δ-valerolactam).

1-Acryloyl-azetidin-2-one (11b)



A stirring solution of 2-azetidinone (357 mg, 5.02 mmol) and DIPEA (2.18 mL, 12.5 mmol) in THF (5.0 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.81 mL, 10.0 mmol) in THF (5.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2.5 hours. Afterwards it was allowed to warm to RT and stirred for a further 3.5 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (15 mL), extracted with Et_2O (20 mL), then the organic layer washed with was washed with sat. aq. $NaHCO_3$ (2 × 15 mL), and sat. aq. NaCl (2 × 15 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a fluffy white solid (237 mg, 38%); m.p. 48 – 50°C; R_f 0.16 (1:1 diethyl ether: hexane); ν_{max}/cm^{-1} (thin film) 2976, 1783, 1686, 1624, 1409, 1328, 1303, 1264, 1207, 1148, 1072, 1047, 1004, 918, 787, 602; δ_H (400 MHz, $CDCl_3$), 7.00 (1H, dd, *J* = 17.1, 10.4 Hz, NCOC**H**CHH'), 6.58 (1H, dd, *J* = 17.1, 1.6 Hz, NCOCHC**H**H'), 5.90 (1H, dd, *J* = 10.4, 1.6 Hz, NCOCHCH**H'**), 3.65 (2H, t, *J* = 5.4 Hz, C**H₂**), 3.09 (2H, t, *J* = 5.4 Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) 165.2 (**C**O), 162.7 (**C**O), 131.7 (NCOCH**C**HH'), 129.1 (NCO**C**HCHH'), 36.6 (**C**H_2), 36.2 (**C**H_2); HRMS (ESI): calcd. for $C_6H_7NNaO_2$, 148.0369. Found: $[MNa]^+$, 148.0372 (–2.1 ppm error).

1-(4-Fluorobenzyl)-1,5-diazocane-2,6-dione (14b)



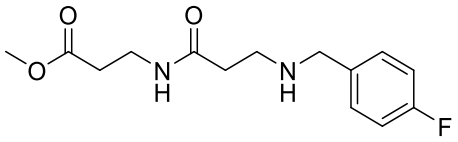
To a solution of 1-acryloyl-azetidin-2-one **11b** (71.0 mg, 0.568 mmol) in dry DCM (1.1 mL), was added 4-fluorobenzylamine (71 µL, 0.624 mmol) dropwise over the course of 1 min. The reaction mixture was allowed to stir for 3 days at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 1:32 methanol: ethyl acetate → 1:14 methanol: ethyl acetate → 1:9 methanol: ethyl acetate→ 1:6 methanol: ethyl acetate) afforded the *title compound* as a white crystalline solid (96.7 mg, 68%); m.p. 179 – 181 °C, R_f 0.38 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3266, 1627, 1509, 1476, 1414, 1320, 1220, 1157, 1099, 985, 920, 824, 730, 576, 548; δ_H (500 MHz, $CDCl_3$), 7.25 – 7.19 (2H, m, Ar**H**), 7.02 – 6.96 (2H, m, Ar**H**) 6.64 (1H, br t, *J* = 7.5 Hz, N**H**), 4.55 (2H, s, ArC**H₂**), 3.59 – 3.50 (4H, m, 2 × NC**H₂**), 2.93 (2H, t, *J* = 6.9 Hz, COC**H₂**), 2.78 (2H, t, *J* = 6.9 Hz, COC**H₂**); δ_C (125 MHz, $CDCl_3$), 173.0 (**C**O), 170.9 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.1 Hz), 132.7 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.1 (Ar**C**H, $^3J_{CF}$ = 8.2 Hz), 115.5 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 48.3 (Ar**C**H_2),

41.7 (**C**H_2), 38.0 (**C**H_2), 37.5 (**C**H_2), 35.3 (**C**H_2); δ_F (470 MHz, $CDCl_3$), –114.66 (1F, m , Ar**F**); HRMS (ESI): calcd. for $C_{13}H_{15}FN_2NaO_2$, 273.1010. Found: $[MNa]^+$, 273.1013 (–1.3 ppm error). For X-ray crystallographic data, see page 4 and CCDC 2122961.

The outcome of the reaction when the synthesis of **14b** was attempted using methanol as the reaction solvent is also described below:

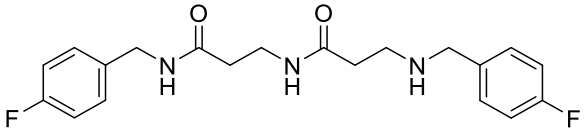
To a solution of 1-acryloyl-azetidin-2-one (58.2 mg, 0.465 mmol) in dry methanol (0.93 mL), was added 4-fluorobenzylamine (58 µL, 0.511 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:24 methanol: ethyl acetate → 1:15 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate → 1:3 methanol: ethyl acetate → 1:2 methanol: ethyl acetate → 9:19 methanol: ethyl acetate) afforded methyl 3-(3-((4-fluorobenzyl)amino)propanamido)propanoate (9.7 mg, 7%) and *N*-(4-fluorobenzyl)-3-(3-((4-fluorobenzyl)amino)propanamido)propanamide (13.6 mg, 8%). Data for each compound is included below.

Methyl 3-(3-((4-fluorobenzyl)amino)propanamido)propanoate



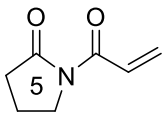
A brown paste (9.7 mg, 7%). The isolated material contained minor unidentified impurities, but the NMR data obtained were sufficient to identify this unwanted side product. R_f 0.15 (3:7 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3283, 2952, 1735, 1646, 1551, 1510, 1439, 1367, 1221, 825; ^1H and ^{13}C NMR data for the major rotamer only. δ_H (500 MHz, $CDCl_3$), 7.59 – 7.51 (1H, br m, CON**H**), 7.36 – 7.30 (2H, m, Ar**H**), 7.02 (2H, t, *J* = 8.5 Hz, Ar**H**), 3.82 (2H, s, ArC**H**$_2$), 3.66 (3H, s, C**H**$_3$), 3.50 (2H, q, *J* = 6.1 Hz, CONHC**H**$_2$), 3.72 (1H, br s, CH_2N**H**CH_2), 2.92 (2H, t, *J* = 6.0 Hz, C**H**$_2$NHCH_2Ar), 2.53 (2H, t, *J* = 6.1 Hz, C**H**$_2$CO_2CH_3), 2.44 (2H, t, *J* = 6.0 Hz, NCOC**H**$_2$CH_2NHCH_2Ar); δ_C (125 MHz, $CDCl_3$), 173.1 (**C**O), 172.1 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 133.6 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 130.4 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.6 (Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 52.6 (Ar**C**H_2), 51.9 (**C**H_3), 44.8 (NCOCH_2**C**H_2NHCH_2Ar), 35.0 (NCO**C**H_2CH_2NHCH_2Ar), 34.9 (CH_2**C**H_2NHCO), 34.1 (C**H**$_2$CO_2CH_3); δ_F (470 MHz, $CDCl_3$) –114.73 (1F, br s, Ar**F**); HRMS (ESI): calcd. for $C_{14}H_{19}FN_2NaO_3$, 305.1272. Found: $[MNa]^+$, 305.1275 (–1.0 ppm error).

***N*-(4-fluorobenzyl)-3-(3-((4-fluorobenzyl)amino)propanamido)propanamide**



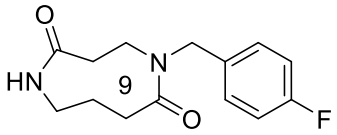
A white solid (13.6 mg, 8%); m.p. 108 – 110°C, R_f 0.15 (3:7 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3286, 1644, 1604, 1548, 1509, 1435, 1221, 1158, 1097, 1016, 824; δ_H (400 MHz, $CDCl_3$), 7.84 (1H, br t, *J* = 6.1 Hz, CON**H**), 7.32 – 7.25 (2H, m, Ar**H**), 7.24 – 7.17 (2H, m, Ar**H**), 7.05 – 6.94 (4H, m, Ar**H**), 6.47 (1H, br t, *J* = 5.8 Hz, CON**H**), 4.34 (2H, d, *J* = 5.8 Hz, ArC**H₂**), 3.74 (2H, s, ArC**H₂**), 3.51 (2H, q, *J* = 6.1 Hz, CONHC**H₂**CH_2), 3.05 (1H, br s, CH_2N**H**CH_2), 2.83 (2H, dd, *J* = 6.6, 5.4 Hz, C**H₂**$NHCH_2Ar$), 2.43 (2H, m, C**H₂**$CONCH_2Ar$), 2.34 (2H, t, *J* = 6.6, 5.4 Hz, NCOC**H₂**CH_2NHCH_2Ar); δ_C (100 MHz, $CDCl_3$), 172.7 (**C**O), 171.5 (**C**O), 162.3 (2 × Ar**C**F, $^1J_{CF}$ = 245.7 Hz), 134.4 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 134.1 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 130.2 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.6 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 115.5 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 52.6 (Ar**C**H_2), 44.9 (NCOCH_2**C**H_2NHCH_2Ar), 42.9 (Ar**C**H_2), 36.1 (C**H₂**$CONCH_2Ar$), 34.5 (2 × **C**H_2 (CH_2**C**H_2NHCO and NCO**C**$H_2CH_2NHCH_2Ar$); δ_F (282 MHz, $CDCl_3$) –114.9 (1F, m, ArF), –115.2 (1F, m, ArF); HRMS (ESI): calcd. for $C_{20}H_{24}F_2N_3O_2$, 376.1831. Found: $[MNa]^+$, 376.1832 (–0.2 ppm error)

1-Acryloyl-pyrrolidin-2-one (11c)



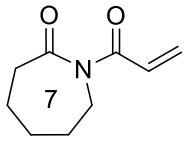
To a stirring solution of 2-pyrrolidone (426 mg, 5.01 mmol) in dry THF (18.2 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.83 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Acryloyl chloride (0.61 mL, 7.51 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (15 mL) and the mixture was extracted with Et_2O (25 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 15 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane afforded the *title compound* as a viscous colorless liquid (391 mg, 56%); R_f 0.19 (1:1 diethyl ether: hexane); ν_{max}/cm^{-1} (thin film) 2980, 1733, 1675, 1617, 1460, 1406, 1359, 1312, 1247, 1223, 1192, 1062, 1021, 980, 930, 887, 839, 799, 674, 639, 587; δ_H (400 MHz, $CDCl_3$) 7.74 (1H, dd, *J* = 17.1, 10.5 Hz, NCOC**H**CHH'), 6.49 (1H, dd, *J* = 17.1, 1.9 Hz, NCOCHC**H**H'), 5.84 (1H, dd, *J* = 10.5, 1.9 Hz, NCOCHCH**H'**), 3.89 – 3.84 (2H, m, NC**H₂**), 2.62 (2H, t, *J* = 8.1 Hz C**H₂**CON), 2.11 – 2.01 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 175.7 (**C**O), 166.2 (**C**O), 131.0 (NCOCH**C**HH'), 129.2 (NCO**C**HCHH'), 45.7 (N**C**H_2), 33.9 (**C**H_2CON), 17.4 (**C**H_2); HRMS (ESI): calcd. for $C_7H_9NNaO_2$, 162.0525. Found: $[MNa]^+$, 162.0527 (–0.6 ppm error).

5-(4-Fluorobenzyl)-1,5-diazonane-2,6-dione (14c)



To a solution of 1-acryloyl-pyrrolidin-2-one **11c** (139 mg, 0.998 mmol) in dry methanol (2.0 mL), was added 4-fluorobenzylamine (125 µL, 1.10 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (121 mg, 46%). In solution in $CDCl_3$, this compound exists as a mixture of rotameric forms (1 major rotamer and up to 3 minor rotamers, best seen in the ^{19}F NMR). The ^{1}H NMR spectrum is significantly affected by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data collected in $CDCl_3$ at 55 °C; R_f 0.06 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3280, 2941, 1622, 1508, 1461, 1413, 1359, 1219, 1157, 1098, 1053, 1015, 907, 825, 771, 730, 646, 565, 498; δ_H (400 MHz, $CDCl_3$), 7.26 – 7.14 (2H, m, Ar**H**), 7.00 – 6.90 (2H, m, Ar**H**), 6.69 (1H, br t, *J* = 7.5 Hz, N**H**, major rotamer), 6.35 – 6.27 (1H, br m, N**H**, other rotamers), 5.26 – 2.95 (6H, m, 3 × C**H₂**), 2.90 – 1.64 (6H, m, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$, 55 °C), 174.7 (**C**O), 173.8 (**C**O), 162.5 (Ar**C**F, $^{1}J_{CF}$ = 246.3 Hz), 133.2 (Ar**C**, $^{4}J_{CF}$ = 3.2 Hz), 130.1 (2 × Ar**C**H, $^{3}J_{CF}$ = 7.9 Hz), 115.7 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.4 Hz), 49.7 (**C**H_2), 44.6 (**C**H_2), 41.6 (**C**H_2), 34.7 (**C**H_2), 30.6 (**C**H_2), 29.2 (**C**H_2); δ_F (282 MHz, $CDCl_3$), –114.54 (1F, m, ArF, major rotamer), –115.12 (1F, m, ArF), –115.24 (1F, m, ArF), –115.74 (1F, m, ArF); HRMS (ESI): calcd. for $C_{14}H_{17}FN_2NaO_2$, 287.1166. Found: $[MNa]^+$, 287.1171 (–1.5 ppm error).

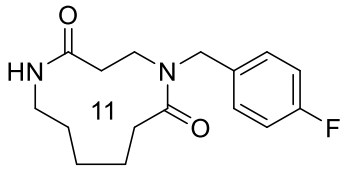
1-Acryloyl-azepan-2-one (11d)



To a stirring solution of caprolactam (226.3 mg, 2.00 mmol) in dry THF (7.3 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.73 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Acryloyl chloride (0.240 mL, 3.00 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl (8 mL) and the mixture was extracted with Et_2O (10 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title*

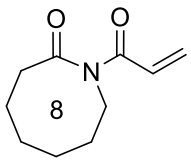
compound as viscous colorless liquid (219 mg, 72%); R_f 0.67 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2932, 1701, 1683, 1404, 1383, 1333, 1240, 1209, 1181, 1152, 1098, 980, 795; δ_H (400 MHz, $CDCl_3$), 6.91 (1H, dd, *J* = 16.8, 10.3 Hz, NCOC**H**CHH'), 6.28 (1H, dd, *J* = 16.8, 1.8 Hz, NCOCHC**H**H'), 5.66 (1H, dd, *J* = 10.3, 1.8 Hz, NCOCHCH**H'**), 3.91 – 3.86 (2H, m, NC**H₂**), 2.72 – 2.66 (2H, m, C**H₂**CON), 1.81 – 1.63 (6H, m, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 178.1 (**C**O), 168.9 (**C**O), 131.9 (NCO**C**HCHH'), 128.0 (NCOCH**C**HH'), 43.7 (N**C**H_2), 39.4 (**C**H_2CON), 29.3 (**C**H_2), 28.7 (**C**H_2), 23.7 (**C**H_2); HRMS (ESI): calcd. for $C_9H_{13}NNaO_2$, 190.0838. Found: $[MNa]^+$, 190.0841 (–1.3 ppm error).

5-(4-Fluorobenzyl)-1,5-diazacycloundecane-2,6-dione (14d)



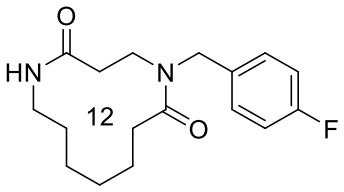
To a solution of 1-acryloyl-azepan-2-one **11d** (156 mg, 0.933 mmol) in dry methanol (2.0 mL), was added 4-fluorobenzylamine (126 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a white solid (228 mg, 84%). In solution in $CDCl_3$, this compound exists as a mixture of rotameric forms (1 major rotamer and 1 minor rotamer based on the ^{19}F NMR data). The ^1H NMR spectrum is severely complicated by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data; m.p. 180 – 183 °C, R_f 0.34 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3297, 2934, 1625, 1556, 1509, 1452, 1352, 1223, 1183, 1154, 909, 821, 731; δ_H (400 MHz, $CDCl_3$), 7.32 – 7.25 (2H, m, Ar**H**), 7.05 – 6.98 (2H, m, Ar**H**), 5.78 – 5.56 (1H, m, N**H**), 5.23 – 3.07 (5H, m, 2.5 × C**H₂**), 3.03 – 0.65 (11H, m, 5.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$), 173.6 (**C**O), 171.4 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.7 Hz), 134.1 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.1 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.9 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 48.3 (**C**H_2), 44.9 (**C**H_2), 41.9 (**C**H_2), 37.1 (**C**H_2), 28.6 (**C**H_2), 25.3 (**C**H_2), 24.4 (**C**H_2), 22.8 (**C**H_2); δ_F (282 MHz, $CDCl_3$), –114.30 (1F, m, Ar**F**, major rotamer), –114.73 (1F, m, Ar**F**, minor rotamer); HRMS (ESI): calcd. for $C_{16}H_{21}FN_2NaO_2$, 315.1479. Found: $[MNa]^+$, 315.1479 (–0.1 ppm error).

1-Acryloyl-azocan-2-one (11e)



To a stirring solution of 1-aza-2-cyclooctanone (1.28 g, 10.1 mmol) in dry THF (36 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 3.65 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Acryloyl chloride (1.22 mL, 15.0 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0°C. The reaction was then quenched with sat. aq. NH_4Cl (30 mL) and the mixture was extracted with Et_2O (50 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 30 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as an oil that turned to a white crystalline solid (1.08 g, 59%); m.p. 29–33 °C; R_f 0.67 (9:1 ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 2926, 2859, 1677, 1616, 1445, 1401, 1378, 1333, 1303, 1248, 1201, 1174, 1126, 1092, 1019, 996, 972, 867, 797, 777, 695, 585); δ_H (400 MHz, $CDCl_3$) 6.81 (1H, dd, *J* = 16.9, 10.3 Hz, NCOC**H**CHH'), 6.24 (1H, dd, *J* = 16.9, 1.7 Hz, NCOCHC**H**H'), 5.61 (1H, dd, *J* = 10.3, 1.7 Hz, NCOCHCH**H'**), 3.89 – 3.82 (2H, m, C**H₂**N), 2.63 – 2.57 (2H, m, C**H₂**CON), 1.86 – 1.77 (2H, m, C**H₂**), 1.74 – 1.65 (2H, m, C**H₂**), 1.58 – 1.50 (2H, m, C**H₂**), 1.44 – 1.36 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 178.9 (**C**ON), 169.4 (**C**OCHCH$_2$), 131.9 (CO**C**HCH$_2$), 127.6 (COCH**C**H$_2$), 43.8 (**C**H$_2$N), 36.7 (**C**H$_2$CON), 29.9 (**C**H$_2$), 29.3 (**C**H$_2$), 26.2 (**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{10}H_{16}NO_2$, 182.1176. Found: $[MH]^+$, 182.1180 (–2.3 ppm error).

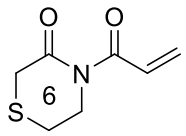
5-(4-Fluorobenzyl)-1,5-diazacyclododecane-2,6-dione (14e)



To a solution of 1-acryloyl-azocan-2-one **11e** (103 mg, 0.566 mmol) in dry methanol (1.1 mL), was added 4-fluorobenzylamine (71 µL, 0.622 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a white solid (119 mg, 69%); m.p. 149 – 155°C, R_f 0.36 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3295, 2931, 1640, 1555, 1510, 1456, 1414, 1355, 1222, 1156, 1096, 731; δ_H (400 MHz, $CDCl_3$), 7.15 – 7.09

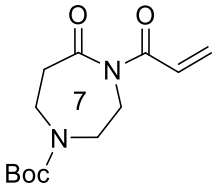
(2H, m, Ar**H**), 7.07 – 6.97 (2H, m, Ar**H**), 6.39 – 6.28 (1H, br d, *J* = 9.5 Hz, N**H**), 4.86 (1H, d, *J* = 16.7 Hz, 0.5 × ArC**H₂**), 4.54 – 4.46 (1H, m, 0.5 × C**H₂**), 4.38 (1H, d, *J* = 16.7 Hz, 0.5 × ArC**H₂**), 3.81 – 3.70 (1H, m, 0.5 × C**H₂**), 2.91 – 2.74 (3H, m, 1.5 × C**H₂**), 2.61 – 2.39 (2H, m, C**H₂**), 2.30 – 1.99 (2H, m, C**H₂**), 1.66 – 1.31 (6H, m, 3 × C**H₂**), 1.28 – 1.06 (1H, m, 0.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.9 (**C**O), 170.3 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.5 Hz), 132.3 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 128.2 (2 × Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 116.1 (2 × Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 51.3 (**C**H_2), 41.0 (**C**H_2), 39.3 (**C**H_2), 35.3 (**C**H_2), 32.5 (**C**H_2), 27.4 (**C**H_2), 25.7 (**C**H_2), 24.0 (**C**H_2), 22.3 (**C**H_2); δ_F (282 MHz, $CDCl_3$), –114.48 (1F, m, Ar**F**); HRMS (ESI): calcd. for $C_{17}H_{23}FN_2NaO_2$, 329.1636. Found: $[MNa]^+$, 329.1639 (–0.9 ppm error).

4-Acryloylthiomorpholin-3-one (16a)



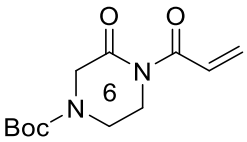
A stirring solution of thiomorpholin-3-one (56.2 mg, 0.480 mmol) and DIPEA (0.21 mL, 1.20 mmol) in THF (1.9 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.078 mL, 0.96 mmol) in THF (0.9 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 3 hours. Afterwards it was allowed to warm to RT and stirred for a further 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (5 mL), extracted with Et_2O (5 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 5 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a colorless oil (37.9 mg, 46%); R_f 0.21 (1:1 diethyl ether: hexane); ν_{max}/cm^{-1} (thin film) 1707, 1684, 1405, 1369, 1334, 1274, 1244, 1198, 1163, 1124, 1021, 977, 869, 794; δ_H (400 MHz, $CDCl_3$), 7.16 (1H, dd, *J* = 16.9, 10.4 Hz, NCOC**H**CHH'), 6.42 (1H, dd, *J* = 16.9, 1.7 Hz, NCOCHC**H**H'), 5.81 (1H, dd, *J* = 10.4, 1.7 Hz, NCOCHCH**H'**), 4.22 – 4.16 (2H, m, SCH_2C**H₂**N), 3.40 (2H, s, C**H₂**CON), 2.99 – 2.94 (2H, m, SC**H₂**CH_2N); δ_C (100 MHz, $CDCl_3$) 170.3 (**C**O), 167.9 (**C**O), 131.2 (NCO**C**HCHH'), 130.2 (NCOCH**C**HH'), 41.5 (SCH_2**C**H_2N), 31.5 (**C**H_2CON), 26.0 (S**C**H_2CH_2N); HRMS (ESI): calcd. for $C_7H_9NNaO_2S$, 194.0246. Found: $[MNa]^+$, 194.0248 (–1.1 ppm error).

***tert*-Butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate (16b)**



To a stirring solution of *tert*-butyl 5-oxo-1,4-diazepane-1-carboxylate (642.8 mg, 3.0 mmol) in dry THF (11 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.1 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Acryloyl chloride (0.360 mL, 4.5 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0°C. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 diethyl ether: hexane) afforded the *title compound* as colourless liquid (676 mg, 84%); R_f 0.65 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 2979, 1685, 1366, 1329, 1245, 1165, 1116, 1042, 957, 795; δ_H (400 MHz, $CDCl_3$-*d*): δ 6.84 (dd, *J* = 16.8, 10.3 Hz, 1H, NCOC**H**CHH'), 6.25 (dt, *J* = 2.0, 16.9 Hz, 1H, NCOCHC**H**H'), 5.64 (dt, *J* = 2.0, 10.4 Hz, 1H, NCOCHCH**H'**), 3.95 – 3.87 (m, 2H, C**H₂**), 3.60 – 3.55 (m, 2H, C**H₂**), 3.54 – 3.49 (m, 2H, C**H₂**), 2.79 – 2.70 (m, 2H, C**H₂**), 1.36 (s, 9H, 3 × OCC**H₃**); δ_C (100 MHz, $CDCl_3$-*d*, 50 °C): 175.7 (**C**O), 168.4 (**C**O), 154.6 (**C**O), 131.4 (NCOCH**C**HH'), 128.8 (NCO**C**HCHH'), 80.7 (COO**C**), 47.2 **(C**H_2), 44.0 **(C**H_2), 41.3 (2 × **C**H_2), 28.4 (3 × OC**C**H_3); HRMS (ESI): calcd. for $C_{13}H_{20}N_2NaO_4$, 291.1315. Found: $[MNa]^+$, 291.1319 (–1.3 ppm error).

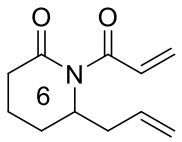
***tert*-Butyl 4-acryloyl-3-oxopiperazine-1-carboxylate (16c)**



To a stirring solution of *tert*-butyl 3-oxopiperazine-1-carboxylate (401 mg, 2.00 mmol) in dry THF (7.3 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.73 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Acryloyl chloride (0.243 mL, 3.00 mmol) was then added in a single portion and the reaction was stirred for an additional 30 min at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (15 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 15 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title*

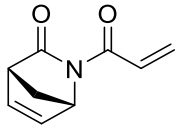
compound as a colourless oil (361 mg, 71%); R_f 0.16 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2977, 1685, 1616, 1406, 1389, 1365, 1303, 1243, 1160, 1131, 1097, 1021, 974, 919, 864, 795, 769, 608, 527; δ_H (400 MHz, $CDCl_3$) 7.13 (1H, dd, *J* = 16.9, 10.4 Hz, NCOC**H**CHH'), 6.40 (1H, dd, *J* = 16.9, 1.7 Hz, NCOCHC**H**H'), 5.79 (1H, dd, *J* = 10.4, 1.7 Hz, NCOCHCH**H**'), 4.21 (2H, s, N(Boc)C$\mathbf{H}_2$CON), 3.89 – 3.84 (2H, m, C$\mathbf{H}_2$), 3.65 – 3.58 (2H, m, C$\mathbf{H}_2$), 1.45 (9H, s, 3 × C$\mathbf{H}_3$); δ_C (100 MHz, $CDCl_3$) 168.8 (**C**O), 168.0 (**C**O), 153.7 (*t*-BuO-**C**O), 131.1 (NCO**C**HCHH'), 130.2 (NCOCH**C**HH'), 81.3 (**C**), 49.3 (**C**H_2), 42.3 (**C**H_2), 41.7 (**C**H_2), 28.4 (3 × **C**H_3); HRMS (ESI): calcd. for $C_{12}H_{18}N_2NaO_4$, 277.1159. Found: $[MNa]^+$, 277.1156 (1.0 ppm error).

1-Acryloyl-6-allylpiperidin-2-one (16d)



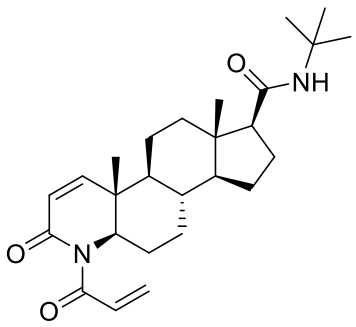
To a stirring solution of 6-allylpiperidin-2-one (126 mg, 0.903 mmol) in dry THF (3.6 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.37 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0°C after addition was completed. Acryloyl chloride (1.22 mL, 1.36 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl (15 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 15 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a colourless oil (73.3 mg, 42%); R_f 0.25 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 3211, 3077, 2944, 1664, 1448, 1406, 1347, 1309, 1209, 1167, 996, 916, 796; δ_H (400 MHz, $CDCl_3$) 6.79 (1H, dd, *J* = 16.8, 10.3 Hz, NCOC**H=**CHH'), 6.28 (1H, dd, J = 16.8, 1.8 Hz, NCOCH=C**H**H'), 5.71 (1H, dddd, *J* = 17.1, 10.2, 8.2, 6.1 Hz, NCHCH_2C**H=**CH_2), 5.64 (1H, dd, J = 10.3, 1.8 Hz, NCOCH=CH**H'**), 5.11 – 5.01 (2H, m, NCHCH_2CHC$\mathbf{H}_2$), 4.54 – 4.46 (1H, m, NC**H**CH_2CHCH_2), 2.61 – 2.42 (3H, m, 1.5 × C$\mathbf{H_2}$), 2.19 (1H, dddt, *J* = 13.7, 10.1, 8.2, 0.9 Hz, 0.5 × C$\mathbf{H_2}$), 2.00 – 1.87 (2H, m, C$\mathbf{H_2}$), 1.83 – 1.68 (2H, m, C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 174.3 (**C**O), 169.1 (**C**O), 134.0 (NCHCH_2**C**HCH_2), 131.9 (NCO**C**HCHH'), 127.7 (NCOCH**C**HH'), 118.1 (NCHCH_2CH**C**H_2), 53.2 (N**C**HCH_2CHCH_2), 37.8 (**C**H_2), 34.3 (**C**H_2), 24.8 (**C**H_2), 16.9 (**C**H_2); HRMS (ESI): calcd. for $C_{11}H_{15}NNaO_2$, 216.0995. Found: $[MNa]^+$, 216.0996 (–0.3 ppm error).

(1*SR*,4*RS*)-2-acryloyl-2-azabicyclo[2.2.1]hept-5-en-3-one (16e)



Acryloyl chloride (0.300 mL, 3.45 mmol), Et_3N (0.480 mL, 3.40 mmol) and DMAP (30 mg, 0.230 mmol) were added to a solution of (1*SR*,4S*R*)-2-azabicyclo[2.2.1]hept-5-en-3-one (249 mg, 2.30 mmol) in DCM (11 mL) under argon at 0 °C. The reaction mixture was stirred at RT for 18 h. After this time, 0.5 M aq. HCl was added (15 mL). The crude reaction mixture was washed with sat. aq. $NaHCO_3$ (15 mL) and sat. aq. NaCl (15 mL) and the organic layer dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a colourless oil (63.8 mg, 17%); R_f 0.28 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 1734, 1672, 1619, 1405, 1327, 1236, 1174, 1146, 1066, 968, 914, 838, 795, 758, 694, 598; δ_H (400 MHz, $CDCl_3$) 7.28 (1H, dd, *J* = 17.1, 10.4 Hz, NCOC**H**CHH'), 6.89 (1H, ddd, *J* = 5.3, 2.4, 0.8 Hz), 6.62 (1H, ddd, *J* = 5.1, 3.2, 1.5 Hz), 6.44 (1H, dd, *J* = 17.1, 1.9 Hz, NCOCHC**H**H'), 5.77 (1H, dd, *J* = 10.4, 1.9 Hz, NCOCHCH**H'**), 5.29 (1H, ddt, *J* = 4.1, 2.5, 1.6 Hz), 3.42 (1H, ddtd, *J* = 3.2, 2.3, 1.5, 0.7 Hz), 2.30 (1H, dt, *J* = 8.7, 1.8 Hz, 0.5 × C**H**$_2$), 2.19 (1H, dt, *J* = 8.7, 1.5 Hz, 0.5 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 177.5 (**C**O), 164.7 (**C**O), 140.5 (**C**H), 138.1 (**C**H), 130.7 (NCOCH**C**H$_2$), 128.7 (NCO**C**HCH$_2$), 60.5 (**C**H), 54.7 (**C**H), 54.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_9H_9NNaO_2$, 186.0525. Found: $[MNa]^+$, 186.0527 (–0.7 ppm error).

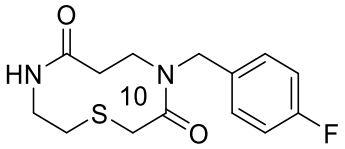
4a*R*,4b*S*,6a*S*,7*S*,9a*S*,9b*S*,11a*R*)-1-Acryloyl-*N*-(*tert*-butyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5, 6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-1*H*-indeno[5,4-*f*]quinoline-7-carboxamide (16f)



To a stirring solution of finasteride (125 mg, 0.335 mmol) and DIPEA (0.14 mL, 0.84 mmol) in THF (1.3 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.053 mL, 0.67 mmol) in THF (0.3 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 3 hours. Afterwards it was allowed to warm to RT and stirred for a further 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (1.5 mL), extracted with Et_2O (2.0 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 1.5 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl

acetate → 1:1 hexane: ethyl acetate) afforded the *title compound* as a colourless oil (89.3 mg, 62%); R_f 0.63 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3365, 2966, 2940, 2243, 1665, 1619, 1517, 1451, 1391, 1363, 1334, 1302, 1287, 1254, 1196, 1170, 1155, 1125, 1088, 1051, 1027, 975, 914, 867, 821, 729, 646, 600; δ_H (400 MHz, $CDCl_3$) 6.94 (1H, d, *J* = 10.0 Hz, C**H**CHCONCOCHCHH'), 6.52 (1H, dd, *J* = 17.0, 10.2 Hz, CHCHCONCOC**H**CHH'), 6.27 (1H, dd, *J* = 17.0, 1.5 Hz, CHCHCONCOCHC**H**H'), 5.81 (1H, d, *J* = 10.0 Hz, CH**C**HCONCOCHCHH'), 5.67 (1H, dd, *J* = 10.2, 1.5 Hz, CHCHCONCOCHCH**H'**), 5.12 (1H, s, N**H**), 3.62 (1H, ddd, *J* = 12.2, 3.5, 1.5 Hz), 2.41 (1H, dd, *J* = 13.3, 3.6 Hz), 2.16 – 2.03 (1H, m), 2.03 – 1.89 (2H, m), 1.78 – 1.57 (4H, m), 1.50 – 1.33 (3H, m), 1.30 (9H, s, CONC(C**H₃**)$_3$), 1.27 – 1.15 (2H, m, C**H₂**), 1.09 – 0.87 (6H, m), 0.66 (3H, s, C**H₃**); δ_C (100 MHz, $CDCl_3$) 171.68 (**C**O), 171.66 (**C**O), 166.5 (**C**O), 153.4 (**C**HCHCONCOCHCH$_2$), 133.6 (CHCHCONCO**C**HCH$_2$), 128.1 (CHCHCONCOCH**C**H$_2$), 122.6 (CH**C**HCONCOCHCH$_2$), 65.1 (**C**H), 57.4 (**C**H), 55.6 (**C**H), 51.1 (NH**C**(CH$_3$)$_3$), 47.9 (**C**H), 43.8 (**C**), 40.0 (**C**), 38.4 (**C**H$_2$), 35.0 (**C**H), 29.9 (**C**H$_2$), 29.1 (NHC(**C**H$_3$)$_3$), 24.2 (**C**H$_2$), 23.6 (**C**H$_2$), 23.4 (**C**H$_2$), 21.4 (**C**H$_2$), 13.4 (**C**H$_3$), 13.3 (**C**H$_3$); HRMS (ESI): calcd. for $C_{26}H_{38}N_2NaO_3$, 449.2775. Found: $[MNa]^+$, 449.2779 (–1.0 ppm error).

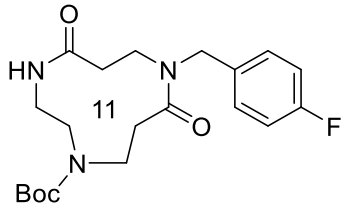
4-(4-Fluorobenzyl)-1,4,8-thiadiazecane-3,7-dione (17a)



To a solution of 4-acryloylthiomorpholin-3-one **16a** (37.9 mg, 0.222 mmol) in dry methanol (0.44 mL), was added 4-fluorobenzylamine (28 µL, 0.244 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 → ethyl acetate → 1:49 methanol: ethyl acetate → 1:24 methanol: ethyl acetate → 1:16 methanol: ethyl acetate → 1:12 methanol: ethyl acetate) afforded the *title compound* as a colorless oil (48.2 mg, 73%). In solution in $CDCl_3$, this compound exists as a mixture of 2 rotameric forms (5:2 ratio, best seen in the ^{19}F NMR). The ^1H NMR spectrum is difficult to interpret due rotameric broadening, even when recorded at 80 °C in d_6-DMSO, with product identity and purity best determined using ^{13}C NMR data; R_f 0.11 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2928, 1628, 1553, 1509, 1413, 1359, 1222, 1156, 1098, 826, 731, 500; δ_H (400 MHz, d_6-DMSO, 80 °C), 8.00 (1H, br s, N**H**), 7.36 – 7.22 (2H, m, Ar**H**), 7.20 – 6.99 (2H, m, Ar**H**), 5.09 – 4.17 (2H, m, C**H₂**), 3.80 – 2.61 (8H, m, C**H₂**), 2.44 – 2.07 (2H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$), 172.3 (**C**O, major rotamer), 172.0 (**C**O, minor rotamer), 171.4 (**C**O, minor), 170.7 (**C**O, major), 162.5 (Ar**C**F, $^1J_{CF}$ = 246.5 Hz, minor, [overlapping]), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.5 Hz, major [overlapping]), 133.0 (Ar**C**, $^4J_{CF}$ = 3.1 Hz, minor), 132.1 (Ar**C**, $^4J_{CF}$ = 3.1 Hz, major), 130.1 (2 × Ar**C**H, $^3J_{CF}$

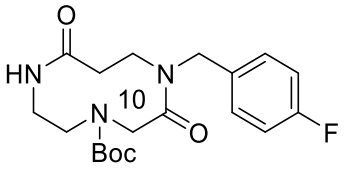
= 8.0 Hz, minor), 128.2 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.2 Hz, major), 116.1 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.7 Hz, major, [overlapping]), 115.9 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.7 Hz, minor [overlapping]), 52.4 (**C**H_2, major), 48.6 (**C**H_2, minor), 45.3 (**C**H_2, minor), 43.2 (**C**H_2, minor), 42.4 (**C**H_2, major), 39.5 (**C**H_2, major), 36.9 (**C**H_2, minor), 35.4 (**C**H_2, major), 34.8 (**C**H_2, major), 34.5 (**C**H_2, minor), 32.4 (**C**H_2, major), 30.8 (**C**H_2, minor); δ_F (282 MHz, $CDCl_3$) –114.11 (1F, m, ArF, minor rotamer), –114.13 (1F, m, ArF, major rotamer); HRMS (ESI): calcd. for $C_{14}H_{17}FN_2NaO_2S$, 319.0887. Found: $[MNa]^+$, 319.0891 (–1.4 ppm error).

***tert*-Butyl 8-(4-fluorobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (17b)**



To a solution of *tert*-butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate **16b** (268 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-flurobenzylamine (126 µL, 1.10 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, ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (370 mg, 94%). In solution in $CDCl_3$, this compound exists as a mixture of 3 rotameric forms (28:5:1 ratio, based on the ^{19}F NMR data). The ^{1}H NMR and ^{13}C NMR spectra are both affected by rotameric broadening, even when recorded at elevated temperatures; R_f 0.22 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3304, 2975, 2932, 1644, 1509, 1409, 1365, 1222, 1165, 919, 731, 592; δ_H (400 MHz, DMSO-*d*$_6$ at 50 °C): δ 7.99 (s, 1H, N**H**), 7.35 – 7.05 (m, 4H, Ph-C**H**), 4.89 – 4.12 (m, 2H, NC**H$_2$**Ph), 3.70 – 3.36 (m, 4H, 2 × C**H$_2$**), 3.25 (d, *J* = 9.9 Hz, 2H, C**H$_2$**), 3.19 – 3.07 (m, 2H, C**H$_2$**), 2.66 – 2.03 (m, 4H, 2 × C**H$_2$**), 1.42 (s, 9H, 3 × C**H$_3$**); δ_C (125 MHz, DMSO-*d*$_6$ at 90 °C): 175.4 (**C**O), 171.8 (**C**O), 161.9 (Ph-**C**F, $^{1}J_{CF}$ = 243.0 Hz), 155.6 (**C**O), 134.8 (Ph-**C**), 130.1 (Ph-**C**H, $^{3}J_{CF}$ = 7.5 Hz), 115.5 (Ph-**C**H, $^{2}J_{CF}$ = 23.0 Hz), 79.1 (COO**C**CH3), 48.6 (N**C**H_2Ph), 47.1 (**C**H_2), 45.2 (**C**H_2), 44.1 (**C**H_2), 38.5 (**C**H_2), 36.1 (**C**H_2), 31.7 (**C**H_2), 28.7 (3 × **C**H_3); Diagnostic ^{13}C NMR resonances for the minor rotamer: 171.3 (**C**O), 79.6 (COO**C**CH_3), 28.6 (3 × **C**H_3); δ_F (376 MHz, DMSO-*d*$_6$ at 50 °C), 3 rotamers in a 28:5:1 ratio: –115.46 (1F, m, Ar**F**), –115.89 (1F, m, Ar**F**, major rotamer), –16.26 (1F, m, Ar**F**); HRMS (ESI): calcd. for $C_{20}H_{28}FN_3NaO_4$, 416.1956. Found: $[MNa]^+$, 416.1959 (–0.6 ppm error).

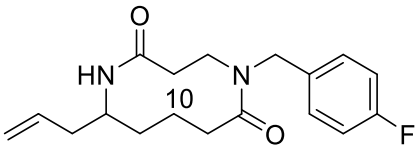
***tert*-Butyl 1-(4-fluorobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (17c)**



To a solution of *tert*-butyl 4-acryloyl-3-oxopiperazine-1-carboxylate **16c** (128 mg, 0.503 mmol) in dry methanol (1.0 mL), was added 4-fluorobenzylamine (63 µL, 0.553 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 → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:13 methanol: ethyl acetate) afforded the *title compound* as a white solid (158 mg, 83%). In solution in $CDCl_3$, this compound exists as a mixture of 3 rotameric forms (20:5:4 ratio, best seen in the ^{19}F NMR); m.p. 169–172 °C; R_f 0.18 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2977, 1652, 1510, 1405, 1366, 1222, 1159, 910, 832, 728, 646, 499; ^1H and ^{13}C NMR data for the major rotamer. δ_H (400 MHz, $CDCl_3$) 7.19 – 7.10 (2H, m, Ar**H**), 7.07 – 6.96 (2H, m, Ar**H**), 5.74 – 5.64 (1H, m, N**H**), 5.11 (1H, d, *J* = 16.3 Hz, C**H**$_2$), 5.03 (1H, d, *J* = 14.2 Hz, C**H**$_2$), 4.28 – 4.04 (3H, m, C**H**$_2$), 3.79 – 3.70 (1H, m, C**H**$_2$), 3.27 (1H, d, *J* = 14.2 Hz, C**H**$_2$), 3.11 – 2.69 (4H, m, C**H**$_2$), 2.52 – 2.39 (1H, m, C**H**$_2$), 1.51 (9H, s, 3 × C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.7 (**C**O), 170.8 (**C**O), 155.2 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.3 Hz), 132.7 (Ar**C**, $^4J_{CF}$ = 3.5 Hz), 128.9 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 115.8 (2 × Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 81.5 (quat **C**), 52.3 (**C**H$_2$), 51.7 (**C**H$_2$), 49.3 (**C**H$_2$), 41.6 (**C**H$_2$), 38.9 (**C**H$_2$), 35.2 (**C**H$_2$), 28.35 (3 × **C**H$_3$); δ_F (470 MHz, $CDCl_3$), –113.85 (1F, m, ArF, minor rotamer), –114.36 (1F, m, ArF, minor rotamer), –114.87 (1F, m, ArF, major rotamer); HRMS (ESI): calcd. for $C_{19}H_{26}FN_3NaO_4$, 402.1800. Found: $[MNa]^+$, 402.1808 (–2.1 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 4.69 (1H, d, *J* = 14.3 Hz, C**H**$_2$), 3.52 (1H, d, *J* = 14.3 Hz, C**H**$_2$), 1.46 (9H, s, 3 × C**H**$_3$), 1.37 (9H, s, 3 × C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 130.2 (2 × Ar**C**H, $^3J_{CF}$ = 8.3 Hz), 128.4 (2 × Ar**C**H, $^3J_{CF}$ = 8.3 Hz), 116.1 (2 × Ar**C**H, $^2J_{CF}$ = 22.9 Hz), 42.3 (**C**H$_2$), 41.3 (**C**H$_2$), 38.7 (**C**H$_2$), 34.9 (**C**H$_2$), 28.42 (3 × **C**H$_3$).

10-Allyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (17d)

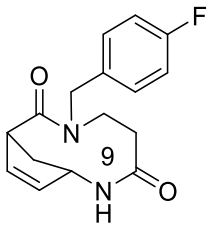


To a solution of 1-acryloyl-6-allylpiperidin-2-one **16d** (73.2 mg, 0.379 mmol) in dry methanol (0.76 mL), was added 4-fluorobenzylamine (48 µL, 0.417 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column

chromatography (SiO_2, 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:24 methanol: ethyl acetate → 1:16 methanol: ethyl acetate) afforded the *title compound* as a white solid (88.3 mg, 73%). In solution in $CDCl_3$, this compound exists as a mixture of 2 rotameric forms (12:1 ratio, best seen in the ^{19}F NMR); m.p. 195–198 °C; R_f 0.46 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3287, 2933, 1621, 1552, 1509, 1414, 1361, 1221, 1157, 1096, 994, 915, 810, 729, 645, 600, 483; ^1H and ^{13}C NMR data for the major rotamer. δ_H (400 MHz, $CDCl_3$) 7.34 – 7.23 (2H, m, Ar**H**), 6.99 (2H, t, *J* = 8.5 Hz, Ar**H**), 5.68 (1H, ddt, *J* = 17.3, 10.4, 7.1 Hz, C**H**CH_2), 5.10 – 4.90 (3H, m, CHC**H₂** and N**H**), 4.82 (1H, d, *J* = 14.5 Hz, C**H₂**), 4.34 (1H, d, *J* = 14.5 Hz, C**H₂**), 4.05 – 3.84 (2H, m, C**H₂**), 3.26 (1H, dt, *J* = 15.6, 3.8 Hz, C**H₂**), 2.69 – 2.56 (1H, m, C**H₂**), 2.24 – 1.92 (6H, m, C**H₂**), 1.71 – 1.53 (2H, m, C**H₂**), 1.42 – 1.28 (1H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 170.3 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.7 Hz), 134.1 (Ar**C**, $^4J_{CF}$ = 3.5 Hz), 134.0 (**C**HCH_2), 130.1 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 118.1 (CH**C**H_2), 115.9 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 49.2 (CONH**C**HCH$_2$CHCH_2), 49.0 (**C**H_2), 45.5 (**C**H_2), 41.0 (**C**H_2), 37.8 (**C**H_2), 31.0 (**C**H_2), 28.0 (**C**H_2), 23.3 (**C**H_2); δ_F (282 MHz, $CDCl_3$), –114.15 (1F, m, ArF, major rotamer), –114.15 (1F, m, ArF, minor rotamer); HRMS (ESI): calcd. for $C_{18}H_{23}FN_2NaO_2$, 341.1636. Found: $[MNa]^+$, 341.1643 (–2.0 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 7.14 – 7.09 (2H, m, Ar**H**), 4.75 (1H, d, *J* = 16.3 Hz, C**H₂**), 4.26 (1H, d, *J* = 16.3 Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) 176.4 (**C**O), 134.5 (**C**HCH_2), 128.5 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 117.7 (CH**C**H_2), 115.87 (2 × Ar**C**H, $^2J_{CF}$ = 21.4 Hz), 50.2 (**C**H_2), 41.7 (**C**H_2), 40.2 (**C**H_2), 36.0 (**C**H_2), 35.2 (**C**H_2), 32.5 (**C**H_2).

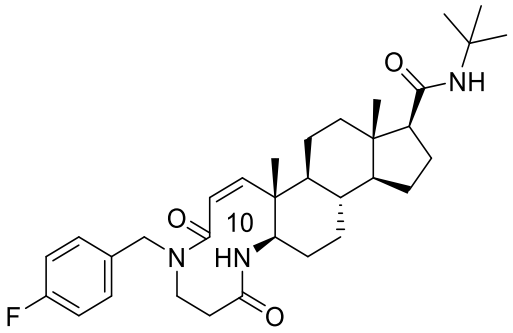
(1*SR*,8*SR*)-6-(4-fluorobenzyl)-2,6-diazabicyclo[6.2.1]undec-9-ene-3,7-dione (17e)



To a solution of (1*SR*,4*SR*)-2-acryloyl-2-azabicyclo[2.2.1]hept-5-en-3-one **16e** (63.8 mg, 0.391 mmol) in dry methanol (0.78 mL), was added 4-fluorobenzylamine (49 µL, 0.430 mmol) in a single portion. The reaction mixture was allowed to stir for 5 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 3:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as an off-white solid (98.7 mg, 88%); m.p. 125–131 °C; R_f 0.19 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3277, 1627, 1605, 1509, 1413, 1348, 1320, 1220, 1157, 1097, 1049, 992, 965, 910, 841, 727, 645, 550, 494; δ_H (400 MHz, $CDCl_3$) 7.21 – 7.14 (2H, m, Ar**H**), 7.00 (1H, d, *J* = 6.9 Hz, N**H**), 6.98 – 6.91 (2H, m, Ar**H**), 6.15 (1H, ddd, *J* = 5.5, 2.9, 1.4 Hz, CHC**H**=CHCH), 5.84 (1H, dt, *J* = 5.3, 2.5

Hz, CHCH=C**H**CH), 4.61 (1H, d, *J* = 14.4 Hz, 0.5 × C**H₂**), 4.48 – 4.39 (1H, m, C**H**CH=CHCH), 4.36 (1H, d, *J* = 14.4 Hz, 0.5 × C**H₂**), 4.04 – 3.89 (2H, m, 0.5 × C**H₂**, and C**H**CH=CHCH), 3.36 (1H, dt, *J* = 16.6, 7.3 Hz, 0.5 × C**H₂**), 2.75 – 2.50 (3H, m, 1.5 × C**H₂**), 2.31 (1H, ddd, *J* = 14.7, 7.4, 5.6 Hz, 0.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.7 (**C**O), 171.9 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 246.3 Hz), 134.9 (CH**C**H=CHCH), 133.8 (CHCH=**C**HCH, **C**H), 133.0 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 130.1 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 58.8 (**C**HCH=CHCH), 54.7 (CHCH=CH**C**H), 51.7 (**C**H_2), 40.4 (**C**H_2), 38.6 (**C**H_2), 30.1 (**C**H_2); δ_F (282 MHz, $CDCl_3$), –114.48 (1F, m, ArF); HRMS (ESI): calcd. for $C_{16}H_{17}FN_2NaO_2$, 311.1166. Found: $[MNa]^+$, 311.1169 (–0.7 ppm error).

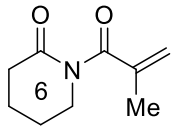
(8a*R*,8b*S*,10a*S*,11*S*,13a*S*,13b*S*,15a*R*,Z)-*N*-(*tert*-Butyl)-5-(4-fluorobenzyl)-8a,10a-dimethyl-2,6-dioxo-2,3,4,5,6,8a,8b,9,10,10a,11,12,13,13a,13b,14,15,15a-octadecahydro-1*H*-cyclopenta[5,6]naphtho[2,1-*f*][1,5]diazecine-11-carboxamide trione (17f)



To a solution of 4a*R*,4b*S*,6a*S*,7*S*,9a*S*,9b*S*,11a*R*)-1-acryloyl-*N*-(*tert*-butyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-1*H*-indeno[5,4-*f*]quinoline-7-carboxamide **16f** (89.3 mg, 0.209 mmol) in dry methanol (0.42 mL), was added 4-fluorobenzylamine (26 µL, 0.23 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 → ethyl acetate) afforded the *title compound* as a white crystalline solid (83.5 mg, 77%); m.p. 226–229 °C; R_f 0.12 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3319, 2934, 1632, 1542, 1509, 1452, 1414, 1365, 1222, 1157, 910, 821, 729, 645, 537; δ_H (400 MHz, $CDCl_3$) 7.29 (2H, dd, *J* = 8.6, 5.5 Hz, Ar**H**), 7.02 (2H, t, *J* = 8.6 Hz, Ar**H**), 6.03 (1H, d, *J* = 13.4 Hz, =C**H**), 5.48 – 5.42 (1H, m, N**H**), 5.39 (1H, d, *J* = 13.4 Hz, =C**H**), 5.07 (1H, s, N**H**), 4.97 (1H, d, *J* = 14.1 Hz, ArC**H₂**), 4.15 (1H, d, *J* = 14.1 Hz, ArC**H₂**), 3.84 – 3.67 (2H, m, C**H₂**), 3.32 – 3.22 (1H, m, C**H₂**), 2.28 – 1.96 (4H, m), 1.90 – 1.60 (7H, m), 1.53 – 1.36 (3H, m), 1.33 (9H, s, CONC(C**H₃**)₃), 1.27 – 1.16 (2H, m), 1.12 – 0.95 (2H, m, [overlapping] C**H**), 1.06 (3H, s, C**H₃**,[overlapping]), 0.66 (3H, s, C**H₃**); δ_C (100 MHz, $CDCl_3$) 172.3 (**C**O), 171.8 (**C**O), 169.9 (**C**O), 162.5 (Ar**C**F, $^1J_{CF}$ = 246.6 Hz), 143.3 (**C**H), 133.1 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.4 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 125.4 (**C**H), 115.9 (2 × Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 57.6 (**C**H), 55.8 (**C**H), 53.8 (**C**H), 53.6 (**C**H), 51.2 (quat **C**), 48.4 (**C**H_2), 47.2 (**C**), 47.0 (**C**H_2), 44.1 (**C**), 38.8 (**C**H_2), 37.8 (**C**H_2), 33.9 (**C**H), 30.2 (**C**H_2), 29.2 (NHC(**C**H_3)$_3$), 26.6 (**C**H_2), 24.3 (**C**H_2), 24.0 (**C**H_2),

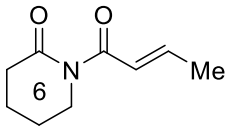
23.2 (**C**H_2), 13.3 (**C**H_3), 12.5 (**C**H_3); δ_F (376 MHz, $CDCl_3$), –113.99 (1F, m, ArF); HRMS (ESI): calcd. for $C_{33}H_{46}FN_3NaO_3$, 574.3415. Found: $[MNa]^+$, 574.3431 (–2.8 ppm error).

1-Methacryloylpiperidin-2-one (18a)



To a stirring solution of δ-valerolactam (300 mg, 3.03 mmol) in dry THF (11.0 mL) cooled to 0°C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.10 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0°C after addition was completed. Methacryloyl chloride (0.436 mL, 4.50 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0°C. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a white solid (237 mg, 47%); m.p. 33–39 °C; R_f 0.21 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2953, 1677, 1455, 1387, 1324, 1288, 1268, 1196, 1173, 1148, 1111, 1093, 994, 918, 822, 787, 558; δ_H (400 MHz, $CDCl_3$) 5.20 (1H, app h, *J* = 1.0, NCOC(CH_3)C**H**H'), 5.15 – 5.13 (1H, m, NCOC(CH_3)CH**H'**), 3.65 – 3.57 (2H, m, NC**H₂**), 2.51 – 2.43 (2H, m, C**H₂**CON), 1.93 – 1.92 (3H, m, NCOC(C**H₃**)CHH'), 1.88 – 1.81 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.8 (**C**O), 173.3 (**C**O), 142.8 (NCO**C**(CH_3)CHH'), 117.0 (NCOC(CH_3)**C**HH'), 45.3 (N**C**H_2), 34.6 (**C**H_2CON), 22.6 (**C**H_2), 21.3 (**C**H_2), 18.9 (**C**H_3); HRMS (ESI): calcd. for $C_9H_{13}NNaO_2$, 190.0838. Found: $[MNa]^+$, 190.0841 (–1.3 ppm error).

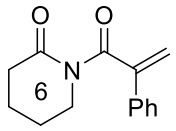
(*E*)-1-(But-2-enoyl)piperidin-2-one (18b)



To a stirring solution of δ-valerolactam (300 mg, 3.03 mmol) in dry THF (11.0 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 1.13 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Crotonoyl chloride (0.431 mL, 4.50 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 10 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded an

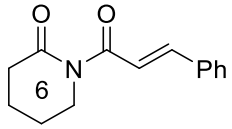
impure batch of product (contaminated with crotonic acid), that was further purified by diluting with Et_2O (5 mL) and washing with sat. aq. $NaHCO_3$ (3 × 5 mL). The organic extract dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* as a colourless oil (96.4 mg, 19%). Trace impurities were evident in the ^1H NMR data for this compound, but the purity was deemed sufficient to test the subsequent CARE reaction; R_f 0.19 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2951, 1679, 1637, 1445, 1385, 1328, 1290, 1202, 1154, 1086, 966, 924, 828, 614; δ_H (400 MHz, $CDCl_3$) 6.98 (1H, dq, *J* = 15.2, 6.9 Hz, $CH_3C\mathbf{H}CHCON$), 6.77 (1H, dd, *J* = 15.2, 1.6 Hz, $CH_3CHC\mathbf{H}CON$), 3.75 – 3.68 (2H, m, $C\mathbf{H_2}N$), 2.59 – 2.51 (2H, m, $C\mathbf{H_2}CON$), 1.90 (3H, dd, *J* = 6.9, 1.6 Hz, $C\mathbf{H_3}$), 1.87 – 1.81 (4H, m, $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**ON), 169.7 (**C**OCHCH(CH_3)), 143.3 (COCH**C**H(CH_3)), 126.6 (CO**C**HCH(CH_3)), 44.6 (**C**H_2N), 35.0 (**C**H_2CON), 22.7 (**C**H_2), 20.8 (**C**H_2), 18.4 (**C**H_3); HRMS (ESI): calcd. for $C_9H_{14}NO_2$, 168.1019. Found: $[MNa]^+$, 168.1021 (–1.0 ppm error).

1-(2-Phenylacryloyl)piperidin-2-one (18c)



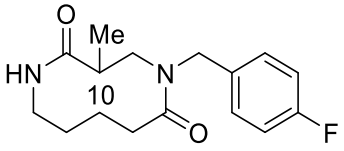
A mixture of δ-valerolactam (991 mg, 10.0 mmol), DMAP (122 mg, 1.00 mmol), and pyridine (4.86 mL, 60.0 mmol) in dry CH_2Cl_2 (20 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of atropic acid chloride (15 mmol, freshly prepared using a published method)[6] in dry CH_2Cl_2 (20 mL) was added and resulting mixture was refluxed at 50 °C for 18 h. The mixture was then diluted with DCM (50 mL) and washed with 10% aq. HCl (50 mL), the aqueous layer was then extracted with DCM (2 × 30 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 4: 1 hexane: ethyl acetate → 3:1 hexane: ethyl acetate) afforded the *title compound* as a yellow oil (1.55 g, 68%); R_f 0.55 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2951, 1704, 1674, 1382, 1327, 1288, 1210, 1146, 1090, 996, 904, 775, 697, 595, 555, 459; δ_H (400 MHz, $CDCl_3$-*d*): δ 7.33 – 7.20 (m, 5H, Ph-C**H**), 5.55 (s, 1H, PhC=C**H**H'), 5.48 (s, 1H, PhC=CH**H**'), 3.77 – 3.72 (m, 2H, $C\mathbf{H_2}$), 2.35 – 2.13 (m, 2H, $C\mathbf{H_2}$), 1.89 – 1.62 (m, 4H, 2 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$-*d*): 173.2 (**C**O), 172.2 (**C**O), 147.3 (Ph**C**=CH_2), 136.5 (Ph-**C**), 128.1 (2 × Ph-**C**H), 127.8 (Ph-**C**H), 126.2 (2 × Ph-**C**H), 116.2 (PhC=**C**H_2), 44.8 (**C**H_2), 34.1 (**C**H_2), 22.3 (**C**H_2), 20.7 (**C**H_2); HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_2$, 225.0995. Found: $[MNa]^+$, 252.0994 (0.5 ppm error).

1-Cinnamoylpiperidin-2-one (18d)



To a solution of cinnamoyl chloride (1.66 g, 10 mmol) in CH_2Cl_2 (20 mL) were added triethylamine (4.18 mL, 30.0 mmol) and δ-valerolactam (1.19 g, 12.0 mmol). The reaction mixture was stirred at room temperature overnight before it was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phases were washed with brine and dried over $MgSO_4$ then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 hexane: ethyl acetate → 5:1 hexane: ethyl acetate) afforded the *title compound* as a white solid (740 mg, 33%); m.p: 40– 42 °C; R_f 0.55 (1:1 hexane: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2951, 1690, 1672, 1617, 1449, 1386, 1332, 1289, 1203, 1154, 1018, 973, 766, 565; δ_H (400 MHz, $CDCl_3$-*d*): δ 7.67 (d, *J* = 15.6 Hz, 1H, COC**H**=CHPh), 7.55 – 7.50 (m, 2H, Ph-C**H**), 7.42 (d, *J* = 15.6 Hz, 1H, COCH=C**H**Ph), 7.35 – 7.28 (m, 3H, Ph-C**H**), 3.85 – 3.64 (m, 2H, C**H₂**), 2.58 – 2.45 (m, 2H, C**H₂**), 1.94 – 1.67 (m, 4H, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$-*d*): 173.8 (**C**O), 169.6 (**C**O), 142.9 (Ph-**C**H), 135.0 (Ph-**C**), 129.9 (CO**C**H=CHPh), 128.7 (2 × Ph-**C**H), 128.2 (2 × Ph-**C**H), 122.1 (COCH=**C**HPh), 44.5 (**C**H_2), 34.8 (**C**H_2), 22.4 (**C**H_2), 20.5 (**C**H_2); HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_2$, 225.0995. Found: $[MNa]^+$, 252.0991 (1.7 ppm error).

5-(4-Fluorobenzyl)-3-methyl-1,5-diazecane-2,6-dione (19a)

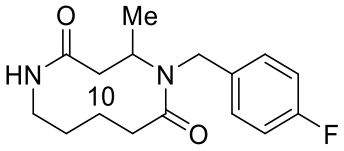


To a solution of 1-methacryloylpiperidin-2-one **18a** (168 mg, 1.01 mmol) in dry methanol (2.0 mL), was added 4-fluorobenzylamine (126 µL, 1.11 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a colourless oil (78.0 mg, 37%). In solution in $CDCl_3$, this compound exists largely as a single rotamer, along with 3 minor rotamers (most clearly seen in the ^{19}F NMR data); R_f 0.36 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3303, 2932, 1621, 1553, 1509, 1442, 1414, 1350, 1219, 1181, 1157, 1097, 1072, 909, 815, 727, 645, 585, 48j1; NMR data for the major rotamer only. δ_H (400 MHz, $CDCl_3$) 7.25 – 7.19 (2H, m, Ar**H**), 7.01 – 6.94 (2H, m, Ar**H**), 5.46 (1H, d, *J* = 10.0 Hz, N**H**), 5.00 (1H, d, *J* = 14.6 Hz, C**H₂**), 4.16 (1H, d, *J* = 14.6 Hz, C**H₂**), 3.90 – 3.76 (1H, m, C**H₂**), 3.65 – 3.53 (1H, m, C**H₂**), 2.95 – 2.77 (2H, m, C**H₂**), 2.64 – 2.52 (1H, m, C**H₂**), 2.20 – 2.02 (2H, m, C**H₂**, [overlapping]), 2.20 – 2.10 (1H, m, C**H**, [overlapping]), 1.70 – 1.38 (3H, m, C**H₂**), 1.00 (3H,

d, J = 6.8 Hz, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 173.3 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 246.4 Hz), 133.8 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 129.9 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.8 (2 × Ar**C**H, $^2J_{CF}$ = 21.2 Hz), 52.2 (**C**H$_2$), 48.9 (**C**H$_2$), 40.5 (**C**H), 38.9 (**C**H$_2$), 28.1 (**C**H$_2$), 25.8 (**C**H$_2$), 23.9 (**C**H$_2$), 13.6 (**C**H$_3$); δ_F (376 MHz, $CDCl_3$), –114.25 (1F, m, ArF); HRMS (ESI): calcd. for $C_{16}H_{21}FN_2NaO_2$, 315.1479. Found: $[MNa]^+$, 315.1480 (–0.2 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.88 (1H, d, J = 10.4 Hz, N**H**), 4.80 (1H, d, J = 16.4 Hz, C**H**$_2$), 4.21 (1H, d, J = 16.4 Hz, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**O), 174.2 (**C**O), 132.5 (Ar**C**, $^4J_{CF}$ = 3.3 Hz), 128.4 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 54.9 (**C**H$_2$), 39.95 (**C**H$_2$), 38.8 (**C**H), 35.4 (**C**H$_2$), 27.6 (**C**H$_2$), 25.4 (**C**H$_2$), 15.1 (**C**H$_3$); δ_F (376 MHz, $CDCl_3$) –114.55 (1F, m, ArF), –115.23 (1F, m, ArF), –116.05 (1F, m, ArF).

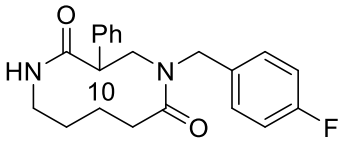
5-(4-Fluorobenzyl)-4-methyl-1,5-diazecane-2,6-dione (19b)



To a solution of (*E*)-1-(but-2-enoyl)piperidin-2-one **18b** (92.6 mg, 0.554 mmol) in dry methanol (1.10 mL), was added 4-fluorobenzylamine (70 µL, 0.609 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (84.3 mg, 72%). In solution in $CDCl_3$, this compound exists as a roughly 3:2:1 mixture of rotamers, based on the CH_3 signals in the ^{1}H NMR spectrum; R_f 0.23 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2934, 1607, 1555, 1510, 1463, 1412, 1337, 1221, 1156, 1097, 812, 731, 501; δ_H (400 MHz, $CDCl_3$) 7.28 – 6.91 (4H, m, Ar**H**, all rotamers), 6.12 (1H, d, J = 10.5 Hz, N**H**, rotamer), 5.93 (1H, d, J = 9.3 Hz, N**H**, rotamer), 5.82 (1H, d, J = 15.4 Hz, N**H**, rotamer), 5.46 (1H, dp, J = 10.7, 6.8 Hz, C**H**, rotamer), 4.83 – 3.99 (2H, m, C**H$_2$** overlapping]), 4.51 – 4.41 (1H, m, C**H**, rotamer [overlapping]), 3.90 – 3.56 (1H, m, C**H$_2$**), 3.50 (1H, dp, J = 10.7, 6.8 Hz, C**H**, rotamer), 3.22 – 2.66 (3H, m, C**H$_2$**), 2.41– 2.29 (1H, m, C**H$_2$**), 2.21– 1.48 (5H, m, C**H$_2$**), 1.22 (3H, d, J = 6.8 Hz, C**H**$_3$, major rotamer), 1.16 (3H, d, J = 6.8 Hz, C**H**$_3$, minor rotamer), 1.06 (3H, d, J = 6.8 Hz, C**H**$_3$, minor rotamer); δ_C (100 MHz, $CDCl_3$) where possible, equivalent signals from the 3 rotamers are grouped in square brackets – [177.7, 176.4, 174.6, 171.8, 170.8 and 170.7 (2 × **C**O from the 3 rotamers)], [162.4 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.0 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.9 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz)], [135.4 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 134.2 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 132.6 (Ar**C**, $^4J_{CF}$ = 3.2 Hz)], [129.4 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.15 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.19 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz)], [115.76 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.73 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.57 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz)], 57.1 (**C**H), 56.5 (**C**H$_2$), 51.8 (**C**H), 46.0 (**C**H), 45.4 (**C**H$_2$), 44.3 (**C**H$_2$), 44.1 (**C**H$_2$), 43.3 (**C**H$_2$), 42.5

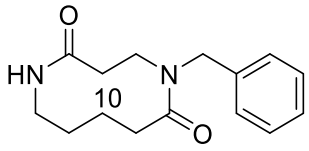
(**C**H_2), 40.2 (**C**H_2), 40.1 (**C**H_2), 39.6 (**C**H_2), 37.1 (**C**H_2), 35.6 (**C**H_2), 28.6 (**C**H_2), 28.0 (**C**H_2), 26.4 (**C**H_2), 25.3 (**C**H_2), 25.1 (**C**H_2), 24.2 (**C**H_2), 24.0 (**C**H_2), [21.4 (**C**H_3), 19.1 (**C**H_3), 18.7 (**C**H_3)]; δ_F (376 MHz, $CDCl_3$), –114.14 (1F, m, ArF, major rotamer), –115.24 (1F, m, ArF, minor rotamer), –115.32 (1F, m, ArF, minor rotamer); HRMS (ESI): calcd. for $C_{16}H_{21}FN_2NaO_2$, 315.1479. Found: $[MNa]^+$, 315.1471 (2.7 ppm error).

5-(4-Fluorobenzyl)-3-phenyl-1,5-diazecane-2,6-dione (19c)



To a solution of 1-(2-phenylacryloyl)piperidin-2-one (229 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-flurobenzylamine (126 µL, 1.10 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 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (196 mg, 55%). In solution in $CDCl_3$, this compound exists as a roughly 10:1 mixture of rotamers; R_f 0.30 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2931, 1620, 1508, 1442, 1218, 1155, 1095, 816, 700, 590, 502; δ_H (400 MHz, $CDCl_3$-*d*) δ 7.32–7.23 (m, 5H, Ph-C**H**, both rotamers), 7.22–7.12 (m, 2H, both rotamers), 7.03–6.91 (m, 2H, both rotamers), 6.64–6.49 (m, 1H, N**H**, major rotamer), 6.26 (d, *J* = 9.9 Hz, 1H, N**H**, minor rotamer), 5.17 (d, *J* = 14.6 Hz, 1H, C**H**Ph, major rotamer), 4.95 (d, *J* = 16.2 Hz, 1H, C**H**Ph, minor rotamer), 4.25–4.01 (m, 2H, C**H₂**, both rotamers), 3.91–3.35 (m, 2H, C**H₂**, both rotamers), 3.28–3.10 (m, 1H, C**H₂**, both rotamers), 2.99–2.74 (m, 2H, C**H₂**, both rotamers), 2.30–2.12 (m, 2H, C**H₂**, both rotamers), 1.77 – 1.46 (m, 3H, C**H₂**, both rotamers); δ_C (100 MHz, $CDCl_3$-*d*) data for major rotamer: 173.8 (**C**O), 171.2 (**C**O), 162.2 (Ph-**C**F, $^1J_{CF}$ = 246.4 Hz), 136.5 (Ph-**C**), 133.5 (Ph-**C,** $^4J_{CF}$ = 2.7 Hz), 129.7 (Ph-CH, $^3J_{CF}$ = 8.0 Hz), 128.4 (Ph-**C**H), 128.2 (Ph-**C**H), 127.5 (Ph-**C**H), 115.6 (Ph-**C**H, $^2J_{CF}$ = 21.4 Hz), 51.5 (**C**HPh), 51.3 (N**C**H_2Ph), 48.5 (**C**H_2), 39.0 (**C**H_2), 28.0 (**C**H_2), 25.8 (**C**H_2), 23.9 (**C**H_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 175.9 (**C**O), 171.9 (**C**O), 137.1 (Ph-**C**), 132.3(Ph-**C**), 128.5 (Ph-**C**H), 128.5 (Ph-**C**H), 128.3 (Ph-**C**H), 127.3 (Ph-**C**H), 115.8 (Ph-**C**H), 115.6 (Ph-**C**H), 55.0 (**C**HPh), 52.7 (N**C**H_2Ph), 50.1 (**C**H_2), 40.1 (**C**H_2), 35.4 (**C**H_2), 27.5 (**C**H_2), 25.2 (**C**H_2); δ_F (376 MHz, $CDCl_3$-*d*): –114.15 (s, 1F, Ph-**F**, major rotamer), –114.28 (s, 1F, Ph-**F**, minor rotamer); HRMS (ESI): calcd. for $C_{21}H_{23}FN_2NaO_2$, 377.1636. Found: $[MNa]^+$, 377.1635 (0.1 ppm error).

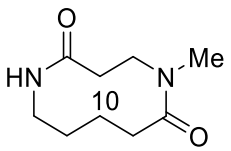
5-Benzyl-1,5-diazecane-2,6-dione (20a)



To a solution of 1-acryloyl-piperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added benzylamine (120 µL, 1.10 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as an off-white solid (217 mg, 83%). In solution in $CDCl_3$, this compound exists as a roughly 10:1 mixture of rotamers; m.p. 165–167 °C; R_f 0.21 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3293, 2931, 1617, 1559, 1449, 1349, 1204, 1110, 919, 728, 699, 618; δ_H (400 MHz, $CDCl_3$) 7.36 – 7.25 (5H, m, Ar**H**), 5.88 (1H, br d, *J* = 9.9 Hz, N**H**), 4.91 (1H, d, *J* = 14.4 Hz, C**H**H'), 4.39 (1H, d, *J* = 14.4 Hz, CH**H'**), 4.01 – 3.69 (2H, m, C**H₂**), 4.21 (1H, dt, *J* = 15.6, 3.8 Hz, C**H₂**), 2.92 – 2.80 (1H, m, C**H₂**), 2.78 – 2.59 (1H, m, C**H₂**), 2.25 – 1.99 (4H, m, C**H₂**), 1.84 – 1.43 (3H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 171.1 (**C**O), 138.2 (Ar**C**), 129.1 (2 × Ar**C**H), 128.3 (2 × Ar**C**H), 128.0 (Ar**C**H), 49.5 (Ar**C**H_2), 45.4 (**C**H_2), 39.3 (**C**H_2), 37.7 (**C**H_2), 28.3 (**C**H_2), 25.9 (**C**H_2), 23.9 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_2$, 283.1417. Found: $[MNa]^+$, 283.1421 (–1.3 ppm error).

Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 5.94 (1H, br d, *J* = 10.4 Hz, N**H**), 4.32 (1H, d, *J* = 16.5 Hz, C**H₂**), 4.22 – 4.13 (1H, m, C**H₂**), 3.00 – 2.92 (1H, m, C**H₂**), 2.42 (1H, ddd, *J* = 12.4, 8.7, 3.5 Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) 176.4 (**C**O), 171.4 (**C**O), 136.7 (Ar**C**), 129.0 (2 × Ar**C**H), 127.8 (Ar**C**H), 126.8 (2 × Ar**C**H), 54.4 (**C**H_2), 42.5 (**C**H_2), 40.2 (**C**H_2), 35.2 (**C**H_2), 27.4 (**C**H_2), 25.1 (**C**H_2).

5-Methyl-1,5-diazecane-2,6-dione (20b)

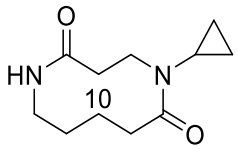


To a solution of 1-acryloyl-piperidin-2-one **11a** (154 mg, 1.00 mmol) in dry methanol (2.0 mL), was added methylamine solution (33 wt% in EtOH, 136 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:13 methanol: ethyl acetate → 1:9 methanol: ethyl acetate

→ 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate) afforded the *title compound* as a sticky white paste (118 mg, 64%); In solution in $CDCl_3$, this compound exists as a roughly 7:1 mixture of rotamers. R_f 0.19 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3287, 2933, 1609, 1443, 1401, 1332, 1259, 1198, 1168, 1081, 1033, 729; δ_H (400 MHz, $CDCl_3$) 6.00 – 5.88 (1H, br m, N**H**, minor rotamer), 5.80 – 5.64 (1H, br m, N**H**, major rotamer), 4.11 – 3.94 (2H, m, C**H₂**), 3.81 – 3.65 (2H, m, C**H₂**), 3.33 – 3.13 (2H, m, C**H₂**), 3.06 (3H, s, C**H₃**, minor rotamer), 2.98 (3H, s, C**H₃**, major rotamer), 2.95 – 2.83 (2H, m, C**H₂**), 2.74 – 2.53 (2H, m, C**H₂**), 2.36 – 2.22 (4H, m, 2 × C**H₂**), 2.14 – 1.98 (4H, m, 2 × C**H₂**), 1.75–1.38 (6H, m, 3 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 171.1 (**C**O), 47.9 (**C**H_2), 39.5 (**C**H_2), 37.3 (**C**H_2), 34.0 (**C**H_3), 28.3 (**C**H_2), 25.7 (**C**H_2), 23.8 (**C**H_2); HRMS (ESI): calcd. for $C_9H_{16}N_2NaO_2$, 207.1104. Found: $[MNa]^+$, 207.1101 (1.3 ppm error).

Characteristic ^{13}C NMR data for the minor rotamers can be found at: δ_C (100 MHz, $CDCl_3$) 176.2 (**C**O), 171.2 (**C**O), 44.8 (**C**H_2), 40.1 (**C**H_2), 38.8 (**C**H_2), 35.3 (**C**H_2), 35.1 (**C**H_2), 27.4 (**C**H_2), 24.3 (**C**H_2).

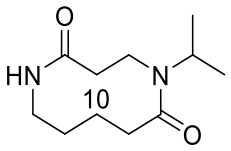
5-Cyclopropyl-1,5-diazecane-2,6-dione (20c)



To a solution of 1-acryloylpiperidin-2-one **11a** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added cyclopropylamine (62.8 mg, 76.2 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane →1:50 methanol: ethyl acetate→ 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (189 mg, 90%). In solution in $CDCl_3$, this compound exists as a roughly 20:1 mixture of rotamers. R_f 0.21 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3300, 3087, 2929, 1649, 1550, 1442, 1324, 1270, 1195, 1065; δ_H (400 MHz, $CDCl_3$-*d*) 6.66 (s, 1H, N**H**, minor rotamer), 6.01 (d, *J* = 4.0 Hz, 1H, N**H**, major rotamer), 4.30 (dt, *J* = 14.1, 7.2 Hz, 1H, NC**H₂**, major rotamer), 4.19 – 4.09 (m, 1H, NC**H₂**, minor rotamer), 3.94 – 3.85 (m, 1H, NC**H**, minor rotamer), 3.79 – 3.65 (m, 1H, NC**H**, major rotamer), 3.38 – 3.30 (m, 1H, NC**H₂**, minor rotamer), 3.12 (dt, *J* = 13.5, 7.8 Hz, 1H, NC**H₂**, major rotamer), 3.07 – 2.94 (m, 1H, NC**H₂**, both rotamers), 2.84 – 2.73 (m, 1H, COC**H₂**, both rotamers), 2.76 – 2.63 (m, 2H, COC**H₂**, both rotamers), 2.52 – 2.41 (m, 1H, NC**H₂**, both rotamers), 2.11 – 1.95 (m, 1H, COC**H₂**, both rotamers), 1.86 – 1.75 (m, 2H, C**H₂**, both rotamers), 1.73 – 1.56 (m, 2H, C**H₂**, both rotamers), 1.00 – 0.72 (m, 2H, C**H₂**, both rotamers), 0.71 – 0.53 (m, 2H, C**H₂**, both rotamers); δ_C (100 MHz, $CDCl_3$-*d*) for the major rotamer: 179.0 (**C**O), 171.5 (**C**O), 43.8 (N**C**H_2), 40.0 (N**C**H_2), 36.0 (CO**C**H_2), 35.5 (CO**C**H_2), 30.9 (N**C**H), 27.5 (**C**H_2), 24.2 (**C**H_2), 12.1 (**C**H_2), 7.5 (**C**H_2); ^{13}C NMR resonances for the minor rotamer: 176.0 (**C**O), 171.3 (**C**O), 46.6 (N**C**H_2), 39.2 (N**C**H_2), 38.0

(CO**C**H_2), 29.6 (CO**C**H_2), 29.1 (N**C**H), 25.0 (**C**H_2), 23.2 (**C**H_2), 9.2 (**C**H_2), 6.6 (**C**H_2); HRMS (ESI): calcd. for $C_{11}H_{18}N_2NaO_2$, 233.1260. Found: $[MNa]^+$, 233.1259 (0.6 ppm error).

5-Isopropyl-1,5-diazecane-2,6-dione (20d)



To a solution of 1-acryloyl-piperidin-2-one **11a** (154 mg, 1.00 mmol) in dry DMF (2.0 mL), was added isopropylamine (95 µL, 1.10 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*, with dry loading onto Celite using DCM to aid the removal of most of the DMF. Purification of the crude material loaded onto Celite by flash column chromatography (SiO_2, ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate) afforded the *title compound* as a colorless oil (106 mg, 50%). In solution in $CDCl_3$, this compound exists as a roughly 11:1 mixture of rotamers. R_f 0.24 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3297, 2932, 1608, 1422, 1368, 1314, 1241, 1212, 1160, 1062, 1043, 922, 727, 644, 581; NMR data for the major rotamer: δ_H (400 MHz, $CDCl_3$) 5.75 – 5.63 (1H, br m, N**H**), 4.77 (1H, hept, *J* = 6.9 Hz, C**H**), 3.81 – 3.56 (2H, m, C$\mathbf{H}_2$), 3.34 – 3.20 (1H, m, C$\mathbf{H}_2$), 2.92 – 2.77 (1H, m, C$\mathbf{H}_2$), 2.61 – 2.46 (1H, m, C$\mathbf{H}_2$), 2.34 – 1.88 (4H, m, C$\mathbf{H}_2$), 1.63 – 1.31 (3H, m, C$\mathbf{H}_2$), 1.17 (3H, d, *J* = 7.0 Hz, C$\mathbf{H}_3$), 1.10 – 0.99 (3H, m, C$\mathbf{H}_3$); δ_C (100 MHz, $CDCl_3$) 174.0 (**C**O), 171.2 (**C**O), 45.6 (**C**H), 40.3 (**C**H_2), 39.6 (**C**H_2), 39.2 (**C**H_2), 29.2 (**C**H_2), 25.7 (**C**H_2), 23.8 (**C**H_2), 20.8 (**C**H_3), 20.2 (**C**H_3); HRMS (ESI): calcd. for $C_{11}H_{20}N_2NaO_2$, 235.1417. Found: $[MNa]^+$, 235.1414 (1.2 ppm error).

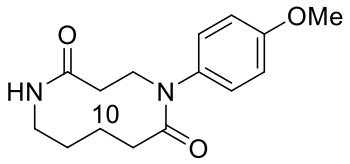
Characteristic NMR data for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.97 – 5.86 (1H, br m, N**H**), 3.95 (1H, hept, *J* = 6.7 Hz, C**H**); δ_C (100 MHz, $CDCl_3$) 49.9 (**C**H), 22.5 (**C**H_3), 20.5 (**C**H_3).

The same reaction was also performed using methanol as solvent, as detailed below:

To a solution of 1-acryloyl-piperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added isopropylamine (95 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 5 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:6 methanol: DCM → 1:4 methanol: DCM → 1:3 methanol: DCM → 1:2 methanol: DCM) afforded 5-isopropyl-1,5-diazecane-2,6-dione **20d** as a colourless oil (100 mg, 47%), a trace amount of δ-valerolactam (not quantified) and methyl 5-acrylamidopentanoate **26** as a pale-yellow oil (57.9 mg, 31%). Data for **20d** is included above. Data for methyl 5-acrylamidopentanoate **26**: R_f 0.56 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film)

3285, 2939, 1735, 1658, 1625, 1547, 1437, 1409, 1366, 1242, 1167, 1100, 986, 959, 806, 702; δ_H (400 MHz, $CDCl_3$) 6.30 (1H, dd, *J* = 17.0, 1.5 Hz, NCOC**H**CHH'), 6.11 (1H, dd, *J* = 17.0, 10.2 Hz, NCOCHC**H**H'), 5.81 (1H, br s, N**H**), 5.65 (1H, dd, *J* = 10.2, 1.5 Hz, NCOCHCH**H'**), 3.69 (3H, s, C$\mathbf{H}_3$), 3.37 (2H, td, *J* = 6.8, 5.8 Hz, NC$\mathbf{H}_2$), 2.37 (2H, t, *J* = 7.1 Hz, C$\mathbf{H}_2CO_2CH_3$), 1.75 – 1.54 (4H, m, 2 × C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 165.7 (**C**O), 131.0 (NCO**C**HCHH'), 126.5 (NCOCH**C**HH'), 51.8 (**C**H_3), 39.2 (N**C**H_2), 33.6 (**C**$H_2CO_2CH_3$), 29.0 (**C**H_2), 22.1 (**C**H_2); HRMS (ESI): calcd. for $C_9H_{15}NNaO_3$, 208.0944. Found: $[MNa]^+$, 208.0940 (1.8 ppm error).

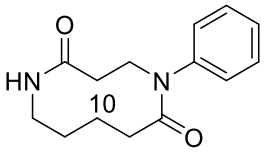
5-(4-Methoxyphenyl)-1,5-diazecane-2,6-dione (20f)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-methoxybenzenamine (136 mg, 1.10 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, 1:50 methanol: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a white solid (240 mg, 88%). In solution in $CDCl_3$, this compound largely as a single rotamer, with a trace amount of a minor rotamer visible in the ^1H and ^{13}C NMR spectra; R_f 0.30 (1:9 methanol: ethyl acetate); m.p. 52 –55°C, ν_{max}/cm^{-1} (thin film) 3301, 2934, 1622, 1510, 1444, 1244, 1174, 1030, 835, 729; NMR data for the major rotamer only. δ_H (400 MHz, $CDCl_3$-*d*) δ 7.30 – 7.07 (m, 2H, Ph-C**H**), 6.90 – 6.80 (m, 2H, Ph-C**H**), 6.21 (d, *J* = 9.3 Hz, 1H, NH), 4.34 (dd, *J* = 13.6, 7.9 Hz, 1H, NC$\mathbf{H}_2$), 3.82 (dt, *J* = 13.7, 4.4 Hz, 1H, NC$\mathbf{H}_2$), 3.76 (s, 3H, OC$\mathbf{H_3}$), 3.38 (dt, *J* = 14.2, 8.7 Hz, 1H, NC$\mathbf{H}_2$), 3.09 (dt, *J* = 11.6, 8.6 Hz, 1H, NC$\mathbf{H}_2$), 2.65 – 2.51 (m, 1H, COC$\mathbf{H_2}$), 2.46 – 2.24 (m, 2H, COC$\mathbf{H_2}$), 2.08 – 1.90 (m, 1H, COC$\mathbf{H_2}$), 1.72 – 1.34 (m, 4H, C$\mathbf{H_2}$); δ_C (400 MHz, $CDCl_3$-*d*) 177.1 (**C**O), 172.6 (**C**O), 158.7 (Ph-**C**), 137.4 (Ph-**C**), 128.4 (2 × Ph-**C**H), 114.7 (2 × Ph-**C**H), 55.5 (O**C**H_3), 49.1 (N**C**H_2), 40.1 (N**C**H_2), 36.3 (CO**C**H_2), 35.6 (CO**C**H_2), 27.8 (**C**H_2), 25.2 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_3$, 299.1366. Found: $[MNa]^+$, 299.1358 (2.8 ppm error).

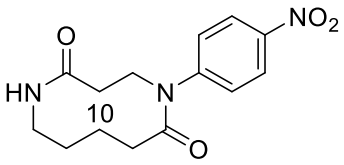
Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 7.13 (2H, m, Ph-C**H**), 6.87 (2H, m, Ph-C**H**), 5.97 (1H, m, N**H**), 3.60 (1H, m, C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 171.0 (**C**O), 158.3 (Ph-**C**), 128.6 (Ph-**C**H), 49.4 (**C**H_2), 39.6 (**C**H_2), 38.2 (**C**H_2), 28.8 (**C**H_2), 26.0 (**C**H_2), 24.0 (**C**H_2).

5-Phenyl-1,5-diazecane-2,6-dione (20g)



To a solution of 1-acryloyl-piperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added aniline (100 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 3 days at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* as a fluffy white solid (118 mg, 48%); m.p. 70–75 °C; R_f 0.25 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3312, 2933, 1623, 1593, 1548, 1493, 1444, 1416, 1321, 1244, 1165, 1105, 911, 764, 726, 698, 645, 588, 503; δ_H (400 MHz, $CDCl_3$) 7.41 – 7.16 (5H, m, Ar**H**), 6.12 (1H, br d, *J* = 10.2 Hz, N**H**), 4.35 (1H, ddd, *J* = 13.7, 8.5, 1.9 Hz, 0.5 × C**H₂**), 3.81 (1H, ddt, *J* = 14.1, 9.5, 4.5 Hz, 0.5 × C**H₂**), 3.45 (1H, dt, *J* = 13.5, 8.6 Hz, 0.5 × C**H₂**), 3.11 (1H, dt, *J* = 12.4, 8.9 Hz, 0.5 × C**H₂**), 2.57 (1H, ddt, *J* = 13.3, 9.8, 3.2 Hz, 0.5 × C**H₂**), 2.40 (1H, ddd, *J* = 12.4, 8.0, 1.8 Hz, 0.5 × C**H₂**), 2.33 (1H, ddd, *J* = 13.6, 10.3, 3.6 Hz, 0.5 × C**H₂**), 2.00 (1H, ddd, *J* = 13.0, 7.1, 3.1 Hz, 0.5 × C**H₂**), 1.74 – 1.52 (3H, m, 1.5 × C**H₂**), 1.47 – 1.34 (1H, m, 0.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 177.0 (**C**O), 172.5 (**C**O), 144.5 (Ar**C**), 129.8 (2 × Ar**C**H), 127.6 (Ar**C**H), 127.3 (2 × Ar**C**H), 49.2 (**C**H_2), 40.1 (**C**H_2), 36.5 (**C**H_2), 35.6 (**C**H_2), 27.8 (**C**H_2), 25.2 (**C**H_2); HRMS (ESI): calcd. for $C_{14}H_{18}N_2NaO_2$, 269.1260. Found: $[MNa]^+$, 269.1260 (0.2 ppm error).

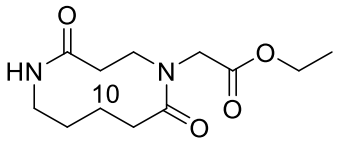
5-(4-Nitrophenyl)-1,5-diazecane-2,6-dione (20h)



To a solution of 1-acryloylpiperidin-2-one **11a** (60 mg, 0.39 mmol) in dry methanol (2.0 mL), was added 4-nitroaniline (59.2 mg, 0.43 mmol) in a single portion. The reaction mixture was allowed to stir for 3 days at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate) afforded the *title compound* as a yellow solid (24 mg, 21%); R_f 0.25 (1:1 hexane: ethyl acetate); m.p. 118 – 120 °C, ν_{max}/cm^{-1} (thin film) 3374, 2958, 1686,1600, 1503, 1474, 1307, 1193, 1110, 835, 754; δ_H (400 MHz, $CDCl_3$-*d*) δ 8.05 (dd, *J* = 9.2, 0.6 Hz, 2H, Ph-C**H**), 6.55 – 6.50 (dd, *J* = 9.2, 0.6 Hz, 2H, Ph-C**H**), 3.75 – 3.70 (m, 2H, NC**H₂**), 3.58 (t, *J* = 6.0 Hz, 2H, NC**H₂**), 3.21 (t, *J* = 6.0 Hz, 2H, COC**H₂**), 2.60 – 2.50 (m, 2H, COC**H₂**), 1.88 – 1.80 (m, 4H, 2 × C**H₂**); δ_C (400 MHz, $CDCl_3$-*d*) 175.2 (**C**O), 173.9 (**C**O), 153.2 (Ph-**C**), 138.0 (Ph-**C**), 126.6 (2 × Ph-**C**H), 111.1 (2 × Ph-**C**H), 44.3 (N**C**H_2), 39.2

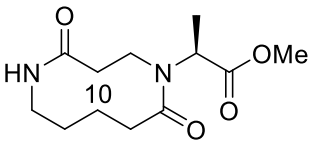
(N**C**H_2), 38.9 (CO**C**H_2), 34.9 (CO**C**H_2), 22.4 (**C**H_2), 20.3 (**C**H_2); HRMS (ESI): calcd. for $C_{14}H_{17}N_3NaO_4$, 314.1111. Found: $[MNa]^+$, 314.1110 (0.5 ppm error).

Ethyl 2-(4,10-dioxo-1,5-diazecan-1-yl)acetate (20i)



To a solution of 1-acryloyl-piperidin-2-one **11a** (159 mg, 1.04 mmol) in dry methanol (2.0 mL), was added glycine ethyl ester (115 µL, 1.14 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 → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl) afforded the *title compound* as a white solid (204 mg, 77%); m.p. 143–145 °C; R_f 0.18 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3316, 2932, 1721, 1640, 1555, 1477, 1441, 1380, 1212, 1153, 1112, 1071, 1022, 861, 715, 658, 566, 524, 499; δ_H (400 MHz, $CDCl_3$) 7.58 (1H, br d, *J* = 10.0 Hz, N**H**), 4.74 (1H, d, *J* = 17.2 Hz, C**H₂**$CO_2CH_2CH_3$), 4.23 – 4.14 (2H, m, CH_2CO_2C**H₂**CH_3), 4.09 (1H, ddd, *J* = 15.2, 13.0, 1.6 Hz, C**H₂**), 3.81 (1H, dddd, *J* = 13.5, 11.6, 10.0, 1.6 Hz, C**H₂**), 3.32 (1H, d, *J* = 17.2 Hz, C**H₂**$CO_2CH_2CH_3$), 3.24 (1H, dd, *J* = 15.6, 3.6 Hz, C**H₂**), 2.95 – 2.86 (1H, m, C**H₂**), 2.62 (1H, ddd, *J* = 16.8, 14.0, 4.0 Hz, C**H₂**), 2.41 (1H, td, *J* = 12.8, 3.2 Hz, C**H₂**), 2.21 (1H, ddd, *J* = 12.6, 4.0, 1.6 Hz, C**H₂**), 2.12 – 2.00 (2H, m, C**H₂**), 1.67 – 1.53 (2H, m, C**H₂**), 1.52 – 1.38 (1H, m, C**H₂**), 1.29 (3H, t, *J* = 7.2 Hz, $CH_2CO_2CH_2C$**H₃**); δ_C (100 MHz, $CDCl_3$) 174.4 (**C**O), 172.3 (**C**O), 170.7 (**C**O), 62.1 (CH_2CO_2**C**H_2CH_3), 51.5 (**C**$H_2CO_2CH_2CH_3$), 48.9 (**C**H_2), 39.0 (**C**H_2), 37.5 (**C**H_2), 27.9 (**C**H_2), 25.2 (**C**H_2), 24.1 (**C**H_2), 14.1 (**C**H_3); HRMS (ESI): calcd. for $C_{12}H_{20}N_2NaO_4$, 279.1315. Found: $[MNa]^+$, 279.1316 (–0.2 ppm error).

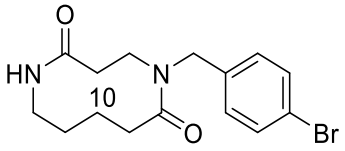
Methyl (*S*)-2-(4,10-dioxo-1,5-diazecan-1-yl)propanoate (20j)



To a solution of 1-acryloylpiperidin-2-one **11a** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added *L*-alanine methyl ester (113.4 mg, 1.10 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, 1:9 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (154 mg, 60%). In solution in $CDCl_3$, this compound as a roughly 2:1 mixture of rotamers; R_f 0.23 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3320, 2937, 1717, 1633, 1557, 1443, 1316, 1260, 1213, 1159, 1103, 1061, 1030, 719; δ_H (400 MHz, $CDCl_3$-*d*) δ 7.39 (d, *J* = 9.7 Hz, 1H, N**H**, minor rotamer), 7.29

(d, *J* = 9.1 Hz, 1H, N**H**, major rotamer), 4.81 (q, *J* = 7.8 Hz, 1H, NC**H**, minor rotamer), 3.89 – 3.68 (m, 2H, NC**H₂**, major rotamer), 3.67 (s, 3H, OC**H₃**, major rotamer), 3.65 (s, 3H, OC**H₃**, minor rotamer), 3.60 – 3.58 (m, 1H, NC**H₂**, minor rotamer), 3.44 (q, *J* = 6.9 Hz, 1H, NC**H**, major rotamer), 3.43 – 3.31 (m, 1H, NC**H**, minor rotamer), 3.17 (dt, *J* = 15.4, 3.6 Hz, 1H, NC$\mathbf{H}_2$, both rotamers), 2.78 (dd, *J* =13.7, 3.9 Hz, 1H, NC$\mathbf{H}_2$, both rotamers), 2.45 – 1.83 (m, 6H, 3 × C**H₂**, both rotamers), 1.52 – 1.42 (m, 2H, C**H₂**, both rotamers), 1.40 (d, *J* = 6.9 Hz, 3H, C**H₃**, major rotamer), 1.35 (d, *J* = 7.9 Hz, 3H, C**H₃**, minor rotamer); δ_C (100 MHz, $CDCl_3$-*d*) for major rotamer: 173.3 (**C**O), 173.0 (**C**O), 170.5 (**C**O), 58.5 (O**C**H_3), 52.7 (N**C**H), 47.2 (N**C**H_2), 38.8 (N**C**H_2), 36.7 (CO**C**H_2), 27.8 (CO**C**H_2), 24.6 (**C**H_2), 23.6 (**C**H_2), 14.1 (**C**H_3); Diagnostic ^{13}C NMR resonances for minor rotamer: 176.0 (**C**O), 174.6 (**C**O), 170.8 (**C**O), 53.1 (N**C**H), 40.4 (N**C**H_2), 38.7 (N**C**H_2), 38.0 (CO**C**H_2), 28.4 (CO**C**H_2), 24.9 (**C**H_2), 23.8 (**C**H_2), 14.6 (**C**H_3); HRMS (ESI): calcd. for $C_{12}H_{20}N_2NaO_4$, 279.1315. Found: $[MNa]^+$, 279.1316 (–0.2 ppm error).

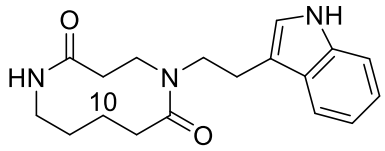
5-(4-Bromobenzyl)-1,5-diazecane-2,6-dione (20k)



To a solution of 1-acryloylpiperidin-2-one **11a** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-bromobenzylamine (204.6 mg, 1.11 mmol) in a single portion. The reaction mixture was allowed to stir for 2 h at RT until a white solid precipitated out of solution and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 1:50 methanol: ethyl acetate) afforded the *title compound* as a white solid (330 mg, 97%). In solution in $CDCl_3$, this compound as a roughly 10:1 mixture of rotamers; m.p. 167 – 170 °C, R_f 0.23 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3291, 3092, 2931, 1618, 1560, 1487, 1264, 1010, 731; δ_H (400 MHz, $CDCl_3$-*d*) 7.43 (d, *J* = 8.2 Hz, 2H, Ar**H**, both rotamers), 7.14 (d, *J* = 8.3 Hz, 2H, Ph-C**H**, major rotamer), 7.03 (d, *J* = 8.2 Hz, 2H, Ph-C**H**, minor rotamer), 5.94 (d, *J* = 10.0 Hz, 1H, N**H**, minor rotamer), 5.53 (d, *J* = 9.3 Hz, 1H, N**H**, major rotamer), 5.02 (d, *J* = 14.7 Hz, 1H, NC**H₂**Ph, major rotamer), 4.79 (d, *J* = 16.6 Hz, 1H, NC**H₂**Ph, minor rotamer), 4.28 (d, *J* = 16.6 Hz, 1H, NC**H₂**Ph, minor rotamer), 4.10 (d, *J* = 14.7 Hz, 1H, NC**H₂**Ph, major rotamer), 3.97 – 3.73 (m, 2H, NC**H₂**, both rotamers), 3.28 – 3.19 (d, 1H, NC**H₂**, both rotamers), 2.95 – 2.82 (m, 1H, NC**H₂**, both rotamers), 2.73 – 2.61 (m, 1H, COC**H₂**, both rotamers), 2.27 – 2.07 (m, 4H, 2 × C**H₂**, both rotamers), 1.64 (m, 2H, COC**H₂**, both rotamers), 1.56 – 1.40 (m, 1H, COC**H₂**, both rotamers); δ_C (100 MHz, $CDCl_3$-*d*) for major rotamer: 174.2 (**C**O), 171.0 (**C**O), 137.0 (Ph-**C**Br), 132.1 (2 × Ph-**C**H), 129.9 (2 × Ph-**C**H), 121.8 (Ph-**C**), 48.7 (**C**H_2), 45.2 (**C**H_2), 39.3 (**C**H_2), 37.6 (**C**H_2), 28.3 (**C**H_2), 25.9 (**C**H_2), 23.8 (**C**H_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 176.4 (**C**O), 171.3 (**C**O), 135.8 (Ph-**C**Br), 128.5 (Ph-**C**H), 53.9 (**C**H_2), 42.5 (**C**H_2), 40.2

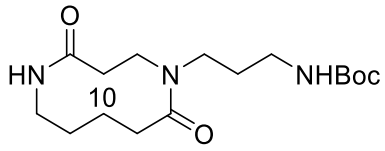
(**C**H_2), 35.1 (**C**H_2), 27.4 (**C**H_2), 25.0 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{19}BrN_2NaO_2$, 361.0519. Found: $[MNa]^+$, 361.0522 (1.0 ppm error).

5-(2-(1*H*-Indol-3-yl)ethyl)-1,5-diazecane-2,6-dione (20l)



To a solution of 1-acryloyl-piperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (1.0 mL), was added a solution of tryptamine (176 mg, 1.10 mmol) in dry methanol (1.0 mL). The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by automated flash column chromatography (using a 24 g pre-packed SiO_2 column, 0% → 100% ethyl acetate in hexanes, then 0% → 10% methanol in ethyl acetate) afforded the *title compound* as a white solid (220 mg, 70%).; m.p. 189–196 °C; R_f 0.11 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3263, 2933, 2404, 1612, 1457, 1351, 1199, 1107, 744; δ_H (400 MHz, d_4-MeOD) 7.59 (1H, dt, *J* = 8.0, 1.1 Hz, Ar**H**), 7.30 (1H, dt, *J* = 8.0, 1.1 Hz, Ar**H**), 7.09 – 7.03 (2H, m, Ar**H**), 7.01 – 6.95 (1H, m, Ar**H**), 4.28 – 4.13 (1H, m, C**H₂**), 3.81 – 3.64 (1H, m, C**H₂**), 3.30 – 3.36 (1H, m, C**H₂**), 3.23 – 3.15 (1H, m, C**H₂**), 3.07 – 2.85 (4H, m, 2 × C**H₂**), 2.76 – 2.55 (1H, m, C**H₂**), 2.34 – 2.19 (1H, m, C**H₂**), 2.14 – 1.93 (3H, m, 1.5 × C**H₂**), 1.61 – 1.38 (3H, m, 1.5 × C**H₂**); δ_C (100 MHz, d_4-MeOD) 175.9 (**C**O), 173.6 (**C**O), 138.1 (Ar**C**), 128.8 (Ar**C**), 123.5 (Ar**C**H), 122.4 (Ar**C**H), 119.7 (Ar**C**H), 119.3 (Ar**C**H), 113.2 (Ar**C**), 112.3 (Ar**C**H), 48.8 (**C**H_2), 46.9 (**C**H_2), 40.5 (**C**H_2), 37.6 (**C**H_2), 29.6 (**C**H_2), 26.2 (**C**H_2), 25.1 (**C**H_2), 24.3 (**C**H_2);; HRMS (ESI): calcd. for $C_{18}H_{23}N_3NaO_2$, 336.1682. Found: $[MNa]^+$, 336.1685 (–0.6 ppm error).

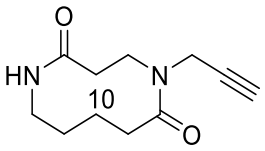
***tert*-Butyl (3-(4,10-dioxo-1,5-diazecan-1-yl)propyl)carbamate (20m)**



To a solution of 1-acryloyl-piperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added *N*-Boc-1,3-diaminopropane (192 µL, 1.10 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, ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate) afforded the *title compound* as an off-white solid (225 mg, 69%); m.p. 151–153 °C; R_f 0.11 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3302, 2934, 1692, 1617, 1513, 1428, 1366, 1250, 1165, 914, 727, 645; δ_H (400 MHz, $CDCl_3$) 6.63 – 6.53 (1H, m, N**H**), 5.42 (1H, t, *J* = 6.3

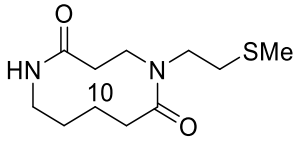
Hz, N**H**), 4.19 – 3.46 (3H, m, C**H**$_2$), 3.27 – 3.05 (2H, m, C**H**$_2$), 2.99 – 2.72 (3H, m, C**H**$_2$), 2.67 – 2.49 (1H, m, C**H**$_2$), 2.35 – 2.11 (2H, m, C**H**$_2$), 2.07 – 1.87 (2H, m, C**H**$_2$), 1.76 – 1.42 (5H, m, C**H**$_2$), 1.32 (9H, s, 3 × **C**H$_3$); δ_C (100 MHz, $CDCl_3$) 174.5 (**C**O), 171.0 (**C**O), 156.2 (N**C**O$_2$), 79.0 (**C**), 45.4 (**C**H$_2$), 43.1 (**C**H$_2$), 39.1 (**C**H$_2$), 37.8 (**C**H$_2$), 37.5 (**C**H$_2$), 28.4 (3 × **C**H$_3$, and 1 × **C**H$_2$ [overlapping]), 28.2 (**C**H$_2$), 25.7 (**C**H$_2$), 23.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{16}H_{29}N_3NaO_4$, 350.2050. Found: $[MNa]^+$, 350.2051 (–0.3 ppm error).

5-(Prop-2-yn-1-yl)-1,5-diazecane-2,6-dione (20n)



To a solution of 1-acryloyl-piperidin-2-one **11a** (123 mg, 0.806 mmol) in dry methanol (1.61 mL), was added propargylamine (57 µL, 0.886 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 → ethyl acetate → 1:49 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (128 mg, 77%); R_f 0.25 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2933, 1625, 1560, 1447, 1351, 1205, 1149, 701; δ_H (400 MHz, $CDCl_3$) 6.05 (1H, br s, N**H**), 4.45 – 4.30 (1H, m, C**H**$_2$), 4.07 – 3.86 (2H, m, C**H**$_2$), 3.81 – 3.65 (1H, m, C**H**$_2$), 3.53 – 3.42 (1H, m, C**H**$_2$), 2.92 – 2.79 (1H, m, C**H**$_2$), 2.71 – 2.49 (2H, m, C**H**$_2$), 2.31 – 2.28 (1H, m, C≡C**H**), 2.26 – 2.17 (1H, m, C**H**$_2$), 2.10 – 1.94 (2H, m, C**H**$_2$), 1.66 – 1.34 (3H, m, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 173.6 (**C**O), 171.0 (**C**O), 80.5 (**C**CH), 72.3 (C**C**H), 46.6 (**C**H$_2$), 39.2 (**C**H$_2$), 37.4 (**C**H$_2$), 36.0 (**C**H$_2$), 28.2 (**C**H$_2$), 25.5 (**C**H$_2$), 23.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{11}H_{16}N_2NaO_2$, 231.1104. Found: $[MNa]^+$, 231.1106 (–0.8 ppm error).

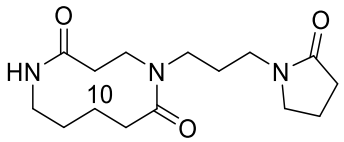
5-(2-(Methylthio)ethyl)-1,5-diazecane-2,6-dione (20o)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 2-(methylthio)ethylamine (102 µL, 1.10 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, 1:10 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (178 mg, 72%); R_f 0.35 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3291, 2928, 1617, 1432, 1350, 1199, 1173, 1107, 700; δ_H (400 MHz, $CDCl_3$-*d*) δ 6.67 (d, *J* = 9.2 Hz, 1H, N**H**), 3.92 (t, *J* = 13.7 Hz, 1H, NC**H**$_2$), 3.79 – 3.58 (m, 2H, NC**H**$_2$), 3.41 (dt, *J* = 13.0, 5.6 Hz, 1H, NC**H**$_2$), 3.23 – 3.14 (m, 1H, NC**H**$_2$), 2.85 – 2.70 (m, 2H), 2.64 – 2.47 (m, 2H, C**H**$_2$), 2.32 – 2.14 (m, 2H, C**H**$_2$), 2.07

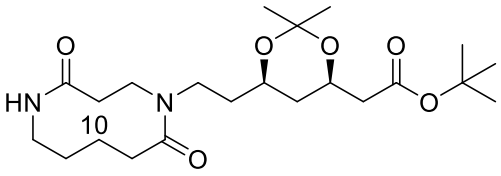
(s, 3H, SC**H₃**), 2.04 – 1.90 (m, 2H, C**H₂**), 1.63 – 1.44 (m, 2H, C**H₂**), 1.42 – 1.30 (m, 1H, C**H₂**); δ_C (400 MHz, $CDCl_3$-*d*) 174.2 (N**C**O), 170.8 (N**C**O), 46.5 (N**C**H_2), 46.0 (N**C**H_2), 39.0 (N**C**H_2), 38.2 (CO**C**H_2), 32.2 (CO**C**H_2), 28.4 (**C**H_2), 25.7 (**C**H_2), 23.9 (**C**H_2), 15.1 (S**C**H_3); HRMS (ESI): calcd. for $C_{11}H_{21}N_2O_2S$, 245.1318. Found: $[MH]^+$, 245.1315 (1.4 ppm error).

5-(3-(2-Oxopyrrolidin-1-yl)propyl)-1,5-diazecane-2,6-dione (20p)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 1-(3-aminopropyl)-2-pyrrolidinone (154 µL, 1.10 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 hexane: ethyl acetate → 1:2 methanol: ethyl acetate → 1:1 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (263 mg, 89%); R_f 0.22 (1:1 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2933, 1651, 1614, 1562, 1427, 1295, 1008, 815; δ_H (400 MHz, $CDCl_3$-*d*) δ 7.00 (m, 1H, N**H**), 4.02 – 3.62 (m, 2H, NC**H₂**), 3.43 – 3.17 (m, 6H, 3 × NC**H₂**), 3.16 – 2.78 (m, 2H, NC**H₂**), 2.72 – 2.57 (m, 1H, C**H₂**), 2.34 – 2.16 (m, 4H, 2 × C**H₂**), 2.07 – 1.88 (m, 4H, 2× C**H₂**), 1.85 – 1.73 (m, 1H, C**H₂**), 1.66 – 1.28 (m, 4H, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$-*d*) 175.2 (**C**O), 174.3 (**C**O), 171.1 (**C**O), 47.1 (N**C**H_2), 46.8 (N**C**H_2), 45.3 (N**C**H_2), 40.5 (N**C**H_2), 39.0 (N**C**H_2), 38.9 (CO**C**H_2), 30.9 (CO**C**H_2), 28.2 (CO**C**H_2), 26.7 (**C**H_2), 26.1 (**C**H_2), 23.9 (**C**H_2), 17.9 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{25}N_3NaO_3$, 318.1788. Found: $[MNa]^+$, 318.1783 (1.6 ppm error).

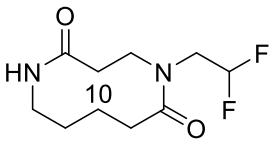
***tert*-Butyl 2-((4*R*,6*R*)-6-(2-(4,10-dioxo-1,5-diazecan-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (20q)**



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added tert-butyl [(4R,6R)-6-aminoethyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (301 mg, 1.10 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, 1:20 methanol: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* (as a 1:1 mixture of rotamers) as a colourless oil (292 mg, 68%); R_f 0.35 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2979, 2936, 1726, 1614, 1427, 1367, 1267, 1201, 1155, 951, 842, 732; δ_H (400 MHz, Methanol-d_4): δ 4.40 –

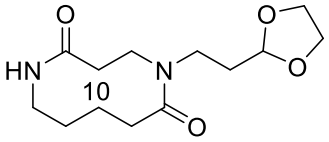
4.28 (m, 1H, O**C**H), 4.13 – 3.93 (m, 3H, OC**H** + C**H₂**), 3.65 – 3.44 (m, 2H, C**H₂**), 3.22 – 2.72 (m, 3H, C**H₂** + C**H₂**), 2.49 – 2.20 (m, 4H, 2 × C**H₂**), 2.17 – 1.98 (m, 2H, C**H₂**), 1.88 – 1.54 (m, 6H, 3 × C**H₂**), 1.49 (s, 12H, 3 ×COOCC**H₃** + OCC**H₃**), 1.36 (s, 3H, OCC**H₃**), 1.27 – 1.16 (m, 1H, C**H**$_2$); δ_C (100 MHz, Methanol-*d*$_4$): 174.4 and 174.3 (**C**O), 172.1 (**C**O, both rotamers), 170.6 (**C**O, both rotamers), 98.7 and 98.6 (O**C**O), 80.4 (COO**C**, both rotamers), 67.3 and 66.7 (O**C**H), 66.3 (O**C**H, both rotamers), 45.6 (N**C**H$_2$, both rotamers), 44.8 (N**C**H$_2$, both rotamers), 42.4 (N**C**H$_2$, both rotamers), 39.2 (**C**H$_2$, both rotamers), 36.3 (**C**H$_2$, both rotamers), 36.2 (**C**H$_2$, both rotamers), 33.9 and 33.8 (**C**H$_2$), 29.3 (OC**C**H$_3$, both rotamers), 28.2 (**C**H$_2$, both rotamers), 27.2 (3 × COOC**C**H$_3$, both rotamers), 25.0 (**C**H$_2$, both rotamers), 23.8 (**C**H$_2$, both rotamers), 18.9 (OC**C**H$_3$, both rotamers); HRMS (ESI): calcd. for $C_{22}H_{38}N_2NaO_6$, 449.2622. Found: [MNa]$^+$, 449.2628 (−1.3 ppm error).

5-(2,2-Difluoroethyl)-1,5-diazecane-2,6-dione (20r)



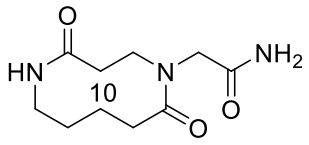
To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 2,2-difluoroethylamine (76.0 µL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1: 1 hexane: ethyl acetate → 1:20 methanol: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (220 mg, 94%); R_f 0.40 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3285, 2940, 1624, 1438, 1163, 1115, 1056, 860; δ_H (400 MHz, $CDCl_3$-*d*) δ 6.17 (ttd, *J* = 57.0, 4.4, 0.9 Hz, 1 H, C**H**F$_2$), 5.61 (d, *J* = 6.6 Hz, 1H, N**H**), 4.07 (t, *J* = 13.8 Hz, 1H, NC**H**$_2$), 3.95 – 3.68 (m, 2H, NC**H₂**), 3.68 – 3.49 (m, 1H, NC**H**$_2$), 3.39 – 3.29 (m, 1H, NC**H**$_2$), 2.95 – 2.86 (m, 1H, NC**H**$_2$), 2.65 (t, *J* = 15.1 Hz, 1H, C**H**$_2$), 2.41 – 2.26 (m, 2H, C**H₂**), 2.15 – 2.01 (m, 3H, C**H₂**), 1.78 – 1.50 (m, 1H, C**H₂**), 1.44 – 1.31 (m, 1H, C**H₂**); δ_C (400 MHz, $CDCl_3$-*d*) 175.2 (**C**O), 170.8 (**C**O), 113.7 (**C**HF$_2$, $^1J_{CF}$ = 241.8 Hz), 50.8 (**C**H$_2$CHF$_2$, $^2J_{CF}$ = 26.8 Hz), 48.2 (N**C**H$_2$), 39.2 (N**C**H$_2$), 37.9 (CO**C**H$_2$), 28.3 (CO**C**H$_2$), 26.0 (**C**H$_2$), 23.9 (**C**H$_2$); δ_F (376 MHz, $CDCl_3$-*d*) −120.0 (1F, dddd, *J* = 290, 57, 16, 13 Hz, CH**F**$_2$), −121.4 (1F, dddd, *J* = 290, 57, 16, 13, CH**F**$_2$); HRMS (ESI): calcd. for $C_{10}H_{16}F_2N_2NaO_2$, 257.1072. Found: [MNa]$^+$, 257.1067 (1.8 ppm error).

5-(2-(1,3-Dioxolan-2-yl)ethyl)-1,5-diazecane-2,6-dione (20s)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 1,3-dioxolane-2-ethanamine (120 µL, 1.10 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 hexane: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (216 mg, 80%). In solution in $CDCl_3$, this compound exists as a 10:1 mixture of rotamers; R_f 0.20 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2933, 1615, 1427, 1137, 1025, 942; δ_H (400 MHz, $CDCl_3$-*d*) δ 6.48 (d, *J* = 9.7 Hz, 1H, N**H**, major rotamer), 5.90 (d, *J* = 9.6 Hz, 1H, N**H**, minor rotamer), 4.98 – 4.91 (m, 1H, OC**H**, major rotamer), 4.80 – 4.77 (m, 1H, OC**H**, minor rotamer), 4.02 – 3.65 (m, 7H, OC**H₂** + NC**H₂**, both rotamers), 3.46 – 3.33 (m, 1H, NC**H**$_2$, both rotamers), 3.30 – 3.19 (m, 1H, NC**H**$_2$, both rotamers), 2.92 – 2.79 (m, 1H, NC**H**$_2$, both rotamers), 2.64 – 2.48 (m, 1H, C**H₂**, both rotamers), 2.40 – 2.20 (m, 2H, C**H₂**, both rotamers), 2.13 – 1.80 (m, 4H, C**H₂**, both rotamers), 1.68 – 1.36 (m, 3H, C**H₂**, both rotamers); δ_C (400 MHz, $CDCl_3$-*d*) for the major rotamer: 174.2 (**C**O), 171.2 (**C**O), 103.6 (O**C**H), 64.8 (O**C**H$_2$), 64.5 (O**C**H$_2$), 46.8 (N**C**H$_2$), 43.9 (N**C**H$_2$), 39.2 (N**C**H$_2$), 38.8 (CO**C**H$_2$), 32.8 (CO**C**H$_2$), 28.5 (**C**H$_2$), 25.6 (**C**H$_2$), 23.9 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 176.2 (**C**O), 172.3 (**C**O), 101.9 (O**C**H), 65.1 (O**C**H$_2$), 64.9 (O**C**H$_2$), 45.8 (N**C**H$_2$), 42.3 (N**C**H$_2$), 40.1(N**C**H$_2$), 35.1 (CO**C**H$_2$), 31.5 (CO**C**H$_2$), 25.1 (**C**H$_2$), 22.3 (**C**H$_2$), 20.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{22}N_2NaO_4$, 293.1472. Found: $[MNa]^+$, 293.1471 (0.4 ppm error).

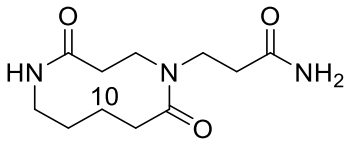
2-(4,10-Dioxo-1,5-diazecan-1-yl)acetamide (20t)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added glycinamide (81.5 mg, 1.10 mmol, made from glycinamide hydrochloride using reported method)[1] 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, 1:9 methanol: ethyl acetate → 1:3 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (203 mg, 89%); R_f 0.13 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3268, 2933, 1618, 1457, 1308, 1210, 1154, 1110, 1072, 736; δ_H (400 MHz, Methanol-*d*$_4$) δ 4.56 – 3.98 (m, 2H, NC**H₂**CO), 3.72 (m, 2H, NC**H**$_2$), 3.43 (m, 1H, NC**H**$_2$), 2.94 (m, 1H, NC**H**$_2$), 2.68 – 2.47 (m, 2H, COC**H₂**), 2.22 – 1.47 (m, 6H, 3 × C**H₂**); δ_C (100 MHz,

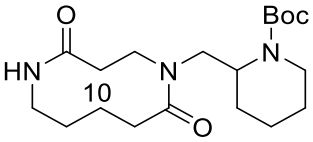
Methanol-d_4) 176.5 (**C**O), 175.0 (**C**O), 173.6 (**C**O), 52.4 (N**C**H_2CO), 49.3 (N**C**H_2), 40.0 (N**C**H_2), 37.5 (CO**C**H_2), 29.1 (CO**C**H_2), 26.0 (**C**H_2), 25.2 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{17}N_3NaO_3$, 250.1162. Found: $[MNa]^+$, 250.1165 (−1.3 ppm error).

3-(4,10-Dioxo-1,5-diazecan-1-yl)propanamide (20u)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 3-aminopropanamide (97 mg, 1.10 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, 1:3 methanol: ethyl acetate → 1:2 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (173 mg, 72%); R_f 0.17 (1:3 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3299, 2934, 1612, 1434, 1349, 1201, 1151, 1108, 1070, 608; δ_H (400 MHz, Methanol-d_4) δ 4.07 – 3.91 (m, 2H, NC**H₂**), 3.66 – 3.43 (m, 2H, NC**H₂**), 3.34 – 3.23 (m, 1H, C**H**$_2$), 3.16 – 2.67 (m, 2H, C**H₂**), 2.59 – 2.48 (m, 2H, C**H₂**), 2.51 – 2.40 (m, 1H, C**H**$_2$), 2.33 – 2.20 (m, 1H, C**H**$_2$), 2.13 – 1.96 (m, 2H, C**H₂**), 1.68 – 1.39 (m, 3H, C**H**$_2$ + C**H₂**); δ_C (100 MHz, Methanol-d_4) 176.7 (**C**O), 175.9 (**C**O), 173.4 (**C**O), 47.0 (N**C**H_2), 44.6 (N**C**H_2), 40.3 (N**C**H_2), 37.8 (CO**C**H_2), 34.7 (CO**C**H_2), 29.4 (CO**C**H_2), 26.2 (**C**H_2), 25.0 (**C**H_2); HRMS (ESI): calcd. for $C_{11}H_{19}N_3NaO_3$, 264.1319. Found: $[MNa]^+$, 264.1315 (1.5 ppm error).

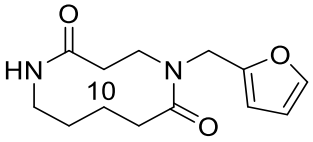
***tert*-Butyl 2-((4,10-dioxo-1,5-diazecan-1-yl)methyl)piperidine-1-carboxylate (20v)**



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 2-(aminomethyl)-1-*N*-Boc-piperidine (233 µL, 1.10 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, 1:20 methanol: ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (265 mg, 72%). In methanol-d_4 at 50 °C the 1H NMR spectra is severely broadened due to rotamer interconversion, while the ^{13}C NMR spectrum shows it exists as a roughly 1:1 mixture of rotamers under the same conditions; R_f 0.33 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2933, 1640, 1415, 1364, 1272, 1154, 1089, 927, 767, 729; δ_H (400 MHz, Methanol-d_4 at 50 °C): δ 4.82 – 4.68 (m, 1H, NC**H**), 4.39 – 4.11 (m, 2H, NC**H₂**), 3.92 – 3.62 (m, 3H, C**H**$_2$ + C**H₂**), 3.53 – 3.16 (m, 2H, C**H₂**), 3.17 – 2.87 (m, 1H, C**H**$_2$), 2.84 – 2.18 (m, 4H, 2 × C**H₂**), 2.11 – 1.78

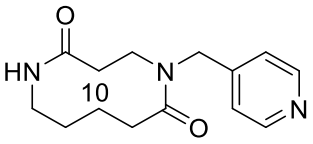
(m, 8H, 4 × C**H₂**), 1.72 (s, 9H, 3 × CC**H₃**), 1.69 – 1.53 (m, 2H, C**H₂**); δ_C (100 MHz, Methanol-*d₄* at 50 °C): 175.9 and 175.7 (**C**O), 173.4 and 173.3 (**C**O), 156.7 (**C**O, both rotamers), 80.9 and 80.6 (COO**C**), 50.7 (NC**H**, both rotamers), 46.7 and 46.1 (N**C**H₂), 40.4 (N**C**H₂, both rotamers), 37.6 (N**C**H₂, both rotamers), 29.5 (N**C**H₂, both rotamers), 28.8 (3 × C**C**H₃, both rotamers), 28.4 (**C**H₂, both rotamers), 27.6 (**C**H₂, both rotamers), 26.5 (**C**H₂, both rotamers), 26.1 (**C**H₂, both rotamers), 24.8 (**C**H₂, both rotamers), 20.6 (**C**H₂, both rotamers), 20.2 (**C**H₂, both rotamers); HRMS (ESI): calcd. for $C_{19}H_{33}N_3NaO_4$, 390.2363. Found: $[MNa]^+$, 390.2358 (1.4 ppm error).

5-(Furan-2-ylmethyl)-1,5-diazecane-2,6-dione (20w)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 2-furanylmethyl amine (97 µL, 1.10 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 hexane: ethyl acetate → ethyl acetate → 1:10 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (150 mg, 60%); R_f 0.35 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3288, 2931, 1615, 1442, 1349, 1174, 1011, 813, 730; δ_H (400 MHz, $CDCl_3$-*d*) δ 7.39 – 7.34 (m, 1H, OC**H**), 6.36 – 6.29 (m, 2H, C**H**C**H**), 5.56 (d, *J* = 8.9 Hz, 1H, N**H**), 5.10 (d, *J* = 15.2 Hz, 1H, NC**H₂**), 4.16 (d, *J* = 15.2 Hz, 1H, NC**H₂**), 4.04 – 3.68 (m, 2H, NC**H₂**), 3.41 – 2.78 (m, 2H, NC**H₂**), 2.66 – 2.02 (m, 4H, 2 × C**H₂**), 1.90 – 1.32 (m, 4H, 2 × C**H₂**); δ_C (400 MHz, $CDCl_3$-*d*) 173.9 (**C**O), 171.1 (**C**O), 151.3 (O**C**CH), 142.1 (O**C**HCH), 111.3 (**C**HCH), 109.0 (CH**C**H), 46.4 (N**C**H₂), 43.3 (N**C**H₂), 39.2 (N**C**H₂), 37.6 (CO**C**H₂), 28.3 (CO**C**H₂), 25.8 (**C**H₂), 24.0 (**C**H₂); HRMS (ESI): calcd. for $C_{13}H_{18}N_2NaO_3$, 273.1210. Found: $[MNa]^+$, 273.1204 (2.0 ppm error).

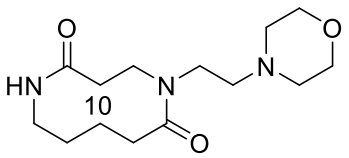
5-(Pyridin-4-ylmethyl)-1,5-diazecane-2,6-dione (20x)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-(aminomethyl)pyridine (112 µL, 1.10 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, 1:9 methanol: ethyl acetate → 1:3 methanol: ethyl acetate) afforded the *title compound* as a pale-yellow oil (240 mg, 92%). In solution in $CDCl_3$, this compound exists as a 10:1

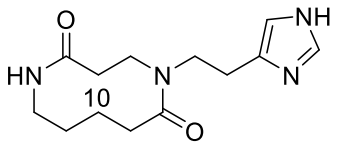
mixture of rotamers; R_f 0.36 (1:1 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3285, 2932, 1620, 1561, 1416, 1349, 1205, 1001,794; δ_H (400 MHz, $CDCl_3$-*d*) δ 8.55 – 8.47 (m, 2H, Ar**H**, both rotamers), 7.15 – 7.05 (m, 2H, Ar**H**, both rotamers), 6.21 (d, *J* = 9.1 Hz, 1H, N**H**, major rotamer), 5.96 (d, *J* = 10.1 Hz, 1H, N**H**, minor rotamer), 5.29 (d, *J* = 15.5 Hz, 1H, NC**H**$_2$Py, major rotamer), 4.82 (d, *J* = 17.4 Hz, 1H, NC**H**$_2$Py, minor rotamer), 4.35 (d, *J* = 17.5 Hz, 1H, NC**H**$_2$Py, minor rotamer), 4.03 – 3.91 (m, 1H, NC**H**$_2$, both rotamers), 3.84 (d, *J* = 15.6 Hz, 1H, NC**H**$_2$Py, major rotamer), 3.80 – 3.67 (m, 1H, NC**H**$_2$, both rotamers), 3.18 (m, 1H, NC**H**$_2$, both rotamers), 2.90 (m, 1H, NC**H**$_2$, both rotamers), 2.80 – 2.66 (m, 1H, NC**H**$_2$, both rotamers), 2.31 – 2.21 (m, 2H, C**H**$_2$, both rotamers), 2.21 – 2.05 (m, 2H, C**H**$_2$, both rotamers), 3.68 – 1.44 (m, 2H, C**H**$_2$, both rotamers); δ_C (400 MHz, $CDCl_3$-*d*) for the major rotamer: 174.3 (**C**O), 170.8 (**C**O), 150.1 (2 × Ar**C**H), 146.9 (Ar**C**), 122.7 (2 × Ar**C**H), 48.0 (N**C**H$_2$Py), 45.4 (N**C**H$_2$), 39.3 (N**C**H$_2$), 37.4 (CO**C**H$_2$), 28.2 (CO**C**H$_2$), 25.7 (**C**H$_2$), 23.0 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 176.3 (**C**O), 171.1 (**C**O), 150.2 (Ar**C**H), 146.3 (Ar**C**), 121.6 (Ar**C**H), 53.5 (N**C**H$_2$Py), 43.0 (N**C**H$_2$), 40.1 (N**C**H$_2$), 35.1 (CO**C**H$_2$), 35.0 (CO**C**H$_2$), 27.3 (**C**H$_2$), 24.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{20}N_3O_2$, 262.1550. Found: $[MH]^+$, 262.1555 (−2.0 ppm error).

5-(2-Morpholinoethyl)-1,5-diazecane-2,6-dione (20y)



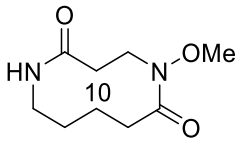
To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-(2-aminoethyl)morpholine (143 mg, 144 μL, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 methanol: ethyl acetate → 1:2 methanol: ethyl acetate → 1:1 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (252 mg, 89%); R_f 0.23 (1:1 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3436, 2927, 2855, 1615, 1443, 1356, 1213, 1171, 1115, 921, 765; δ_H (400 MHz, $CDCl_3$-*d*) δ 7.89 (d, *J* = 10.1 Hz, 1H, N**H**), 4.76 – 4.66 (m, 1H, NC**H$_2$**CH$_2$N), 4.01 (m, 1H, NC**H$_2$**CH$_2$N), 3.96 – 3.80 (m, 1H, NCH$_2$C**H$_2$**N), 3.71 – 3.56 (m, 4H, 2 × OCH2), 3.16 (dt, *J* = 15.5, 3.8 Hz, 1H, NCH$_2$C**H$_2$**N), 2.88 – 2.52 (m, 7H, C**H$_2$**), 2.44 – 2.34 (m, 2H, C**H$_2$**), 2.28 – 2.20 (m, 2H, C**H$_2$**), 2.10 – 1.96 (m, 2H, C**H$_2$**), 1.70 – 1.51 (m, 2H, C**H$_2$**), 1.45 – 1.32 (m, 1H, C**H$_2$**); δ_C (400 MHz, $CDCl_3$-*d*) 174.6 (**C**O), 170.8 (**C**O), 66.6 (2 × O**C**H$_2$), 57.0 (N**C**H$_2$), 53.7 (2 × N**C**H$_2$), 46.6 (N**C**H$_2$), 44.0 (CO**C**H$_2$), 38.5 (2 × N**C**H$_2$), 28.6 (CO**C**H$_2$), 26.0 (**C**H$_2$), 24.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{14}H_{25}N_3NaO_3$, 306.1788. Found: $[MNa]^+$, 306.1787 (0.4 ppm error).

5-(2-(1*H*-Imidazol-4-yl)ethyl)-1,5-diazecane-2,6-dione (20z)



To a solution of 1-acryloylpiperidin-2-one **11a** (153 mg, 1.00 mmol) in dry methanol (2.0 mL), was added histamine (122 mg, 1.10 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, 1:3 methanol: ethyl acetate → 1:1 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (135 mg, 51%). In solution in methanol-d_4, this compound experiences rotameric broadening; R_f 0.22 (1:1 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3261, 2934, 1612, 1436, 1199, 1174, 1106, 822, 664, 623; δ_H (400 MHz, Methanol-d_4) δ 7.34 (d, *J* = 1.2 Hz, 1H, Ar-C**H**), 6.58 (d, *J* = 1.2 Hz, 1H, Ar-C**H**), 3.88 – 3.51 (m, 2H, NC**H₂**), 3.45 – 2.77 (m, 4H, 2 × NC**H₂**), 2.66 – 2.41 (m, 3H, C**H**$_2$ + C**H₂**), 2.19 – 2.06 (m, 1H, C**H**$_2$), 1.98 – 1.87 (m, 1H, C**H**$_2$), 1.85 – 1.70 (m, 2H, C**H₂**), 1.39 – 1.16 (m, 3H, C**H**$_2$ + C**H₂**); δ_C (100 MHz, Methanol-d_4) 175.8 (**C**O), 173.4 (**C**O), 136.1 (2 × Ar-**C**H), 117.8 (Ar-**C**), 47.7 (N**C**H$_2$), 46.7 (N**C**H$_2$), 40.4 (N**C**H$_2$), 37.7 (CO**C**H$_2$), 29.4 (CO**C**H$_2$), 26.3 (**C**H$_2$), 25.9 (**C**H$_2$Ar), 25.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{21}N_4O_2$, 265.1659. Found: $[MH]^+$, 265.1657 (0.7 ppm error).

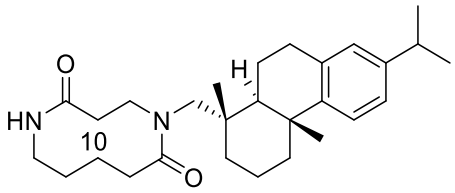
5-Methoxy-1,5-diazecane-2,6-dione (20za)



To a solution of 1-acryloylpiperidin-2-one **11a** (100 mg, 0.65 mmol) in dry methanol (2.0 mL), was added methoxyamine (51.8 mg, 0.95 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, 1:9 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (110 mg, 85%). In solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with rotameric broadening seen in the ^{1}H NMR spectrum and traces of a minor rotamer evident in the ^{13}C NMR spectrum; R_f 0.18 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3317, 3087, 2935, 1652, 1545, 4443, 1318, 1178, 1013, 946, 572; δ_H (400 MHz, $CDCl_3$-*d*) δ 5.60 (d, *J* = 3.0 Hz, 1H, N**H**), 4.61 – 4.49 (m, 1H, NC**H**$_2$), 3.63 (s, 3H, OC**H₃**), 3.48 – 3.31 (m, 1H, NC**H**$_2$), 3.32 – 3.16 (m, 1H, NC**H**$_2$), 2.90 (m, 1H, NC**H**$_2$), 2.86 – 2.75 (m, 1H, C**H**$_2$), 2.57 – 2.40 (m, 1H, C**H**$_2$), 2.15 – 2.02 (m, 2H, C**H₂**), 1.89 – 1.79 (m, 1H, C**H**$_2$), 1.78 – 1.64 (m, 2H, C**H₂**), 1.44 – 1.30 (m, 1H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$-*d*) 178.0 (**C**O), 170.0 (**C**O), 62.1 (O**C**H$_3$), 43.9 (N**C**H$_2$), 39.7 (N**C**H$_2$), 34.1 (CO**C**H$_2$), 31.1 (CO**C**H$_2$), 27.4 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_9H_{16}N_2NaO_3$, 223.1053. Found: $[MNa]^+$, 223.1053 (0.0 ppm error).

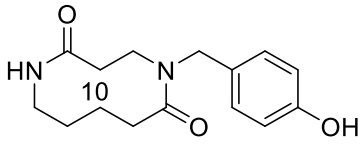
Characteristic ^{13}C NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$-*d*) 6.30 (1H, m, N**H**), 4.00 (1H, m, NC**H**$_2$); δ_C (100 MHz, $CDCl_3$) 171.0 (**C**O), 61.0 (O**C**H$_3$), 47.3 (**C**H$_2$), 36.5 (**C**H$_2$), 28.9 (**C**H$_2$), 24.6 (**C**H$_2$), 22.7 (**C**H$_2$).

5-(((1*S*,4a*R*,10a*S*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10aoctahydrophenanthren-1-yl)methyl)-1,5-diazecane-2,6-dione (20zb)



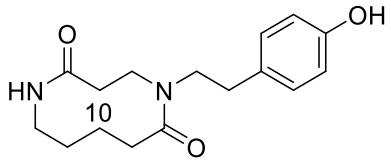
To a solution of 1-acryloylpiperidin-2-one **11a** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added leelamine (314 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (215 mg, 49%). In solution in methanol-d_4, this compound exists as a roughly 3:2 mixture of rotamers; R_f 0.30 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3291, 3085, 2928, 2867, 1768, 1643, 1556, 1448, 1417, 1375, 1304, 1167, 1105, 1046, 820, 733; δ_H (400 MHz, Methanol-d_4): δ 7.13 – 7.03 (m, 1H, Ph-C**H**, both rotamers), 6.96 – 6.84 (m, 1H, Ph-C**H**, both rotamers), 6.88 – 6.79 (m, 1H, Ph-C**H**, both rotamers), 4.34 – 4.14 (m, 1H, PhC**H**CH$_3$, both rotamers), 4.13 – 3.87 (m, 1H, CC**H**C, both rotamers), 3.77 – 3.40 (m, 2H, NC**H$_2$**C, both rotamers), 2.97 – 2.67 (m, 4H, C**H$_2$**, both rotamers), 2.59 – 2.38 (m, 2H, C**H$_2$**, both rotamers), 2.32 – 2.20 (m, 1H, C**H**$_2$, C**H$_2$**, both rotamers), 2.10 – 1.96 (m, 3H, C**H$_3$**, both rotamers), 1.84 – 1.38 (m, 9H, C**H$_2$**, both rotamers), 1.35 – 1.24 (m, 2H C**H$_2$**, both rotamers), 1.20 – 1.14 (m, 9H, C**H$_3$**, both rotamers), 1.02 – 0.78 (m, 4H, C**H$_2$**, both rotamers); δ_C (100 MHz, Methanol-d_4): 176.9 and 176.7 (**C**O), 173.5 (**C**O, both rotamers), 148.6 and 148.5 (Ph-**C**), 146.6 and 146.5 (Ph-**C**), 135.8 and 135.3 (Ph-**C**), 127.7 (Ph-**C**H, both rotamers), 124.9 and 124.8 (Ph-**C**H), 124.7 and 124.6 (Ph-**C**H), 49.9 (Ph**C**HCH$_3$, both rotamers), 48.0 (N**C**H$_2$C, both rotamers), 47.6 (C**C**HC, both rotamers), 41.3 and 41.0 (**C**CHC), 39.7 and 39.5 (**C**H$_2$), 38.7 and 38.6 (**C**CHC), 38.2 (**C**H$_2$, both rotamers), 37.3 (**C**H$_2$, both rotamers), 34.7 (C**C**H$_3$, both rotamers), 31.2 and 31.1 (**C**H$_2$), 29.1 (**C**H$_2$, both rotamers), 26.5 and 26.4 (**C**H$_3$), 25.6 (**C**H$_2$, both rotamers), 24.6 (**C**H$_3$, both rotamers), 24.4 (**C**H$_2$, both rotamers), 20.7 (**C**H$_2$, both rotamers), 20.5 and 20.4 (**C**H$_2$, both rotamers), 19.7 and 19.6 (**C**H$_2$, both rotamers), 18.9 (**C**H$_3$, both rotamers); HRMS (ESI): calcd. for $C_{28}H_{42}N_2NaO_2$, 461.3138. Found: $[MNa]^+$, 461.3152 (−2.8 ppm error).

(4-Hydroxylbenzyl)-1,5-diazecane-2,6-dione (20zc)



To a solution of 1-acryloylpiperidin-2-one **11a** (153.2 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-aminomethylphenol (135.5 mg, 1.10 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, 1:50 methanol: ethyl acetate → 1:20 methanol: ethyl acetate→ 1:10 methanol: ethyl acetate) afforded the *title compound* as a white solid (205 mg, 74%). Rotameric broadening is evident in both the ^1H and ^{13}C NMR spectra; m.p. 70–72°C, R_f 0.32 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3275, 2934, 1609, 1514, 1349, 1229, 1101, 813, 776; δ_H (400 MHz, Methanol-d_4) δ 7.05 (d, *J* = 8.5 Hz, 2H, Ar**H**), 6.70 (d, *J* = 8.5 Hz, 2H, Ar**H**), 5.33 (d, *J* = 14.7 Hz, 1H, NC**H**$_2$Ar), 3.90 – 3.74 (m, 1H, NC**H**$_2$), 3.66 (d, *J* = 14.7 Hz, 1H, NC**H**$_2$Ar), 3.30 – 3.22 (m, 1H, NC**H**$_2$), 3.10 – 2.91 (m, 1H, C**H$_2$**), 2.84 – 2.62 (m, 1H, C**H$_2$**), 2.49 – 2.36 (m, 1H, C**H$_2$**), 2.24 – 2.13 (m, 1H, C**H$_2$**), 2.13 – 1.93 (m, 2H, C**H$_2$**), 1.65 – 1.41 (m, 3H, C**H$_2$**); δ_C (100 MHz, Methanol-d_4) 175.9 (**C**O), 173.6 (**C**O), 157.9 (Ar-**C**OH), 130.4 (2 × Ar-**C**H), 129.4 (Ar-**C**), 116.4 (2 × Ar-**C**H), 49.9 (N**C**H$_2$Ar), 44.9 (N**C**H$_2$), 40.4 (N**C**H$_2$), 37.1 (CO**C**H$_2$), 29.4 (CO**C**H$_2$), 26.2 (**C**H$_2$), 25.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_2$, 299.1366. Found: $[MNa]^+$, 299.1362 (1.4 ppm error).

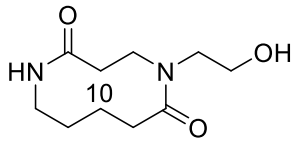
5-(4-Hydroxyphenethyl)-1,5-diazecane-2,6-dione (20zd)



To a mixture of 1-acryloyl-piperidin-2-one **11a** (154 mg, 1.00 mmol) and tyramine (151 mg, 1.10 mmol) was added dry methanol (2.0 mL). The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by automated flash column chromatography (using a 24 g pre-packed SiO_2 column, 0% → 100% ethyl acetate in hexanes, then 0% → 15% methanol in ethyl acetate) afforded the *title compound* as a white solid (164 mg, 56%). Rotameric broadening is evident in both the ^1H and ^{13}C NMR spectra; m.p. 102–108 °C; R_f 0.21 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3271, 2940, 1636, 1613, 1516, 1495, 1447, 1353, 1329, 1232, 1200, 1173, 1111, 940, 830, 526, 460; δ_H (400 MHz, d_4-MeOD) 7.03 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.70 (2H, d, *J* = 8.4 Hz, Ar**H**), 4.10 (1H, dt, *J* = 13.5, 7.6 Hz, 0.5 × **C**H$_2$), 3.88 – 3.71 (1H, m, 0.5 × C**H$_2$**), 3.27 – 3.17 (2H, m, C**H$_2$**), 2.90 (1H, dt, *J* = 13.5, 7.6 Hz, 0.5 × **C**H$_2$), 2.74 (2H, t, *J* = 7.6 Hz, **C**H$_2$), 2.38 – 2.24 (2H, m, C**H$_2$**), 2.21 – 1.97 (2H, m, C**H$_2$**),

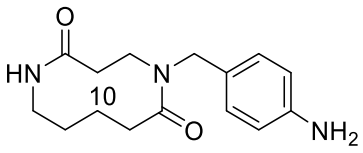
1.81 – 1.68 (3H, m, 1.5 × C**H₂**), 1.61 – 1.46 (2H, m, C**H₂**); δ_C (100 MHz, d_4-MeOD) data for major rotamer: 175.7 (**C**O), 173.5 (**C**O), 157.0 (Ar**C**OH), 131.1 (Ar**C**),130.8 (2 × Ar**C**H), 116.3 (2 × Ar**C**H), 46.8 (**C**H_2), 42.9 (**C**H_2), 37.7 (**C**H_2), 33.7 (**C**H_2), 32.0 (**C**H_2), 25.0 (**C**H_2), 23.0 (**C**H_2), 21.7 (**C**H_2), Characteristic NMR signal for minor rotamer: 174.9 (**C**O); HRMS (ESI): calcd. for $C_{16}H_{22}N_2NaO_3$, 313.1523. Found: $[MNa]^+$, 313.1527 (–1.3 ppm error).

5-(2-Hydroxyethyl)-1,5-diazecane-2,6-dione (20ze)



To a solution of 1-acryloyl-piperidin-2-one **11a** (154 mg, 1.00 mmol) in dry methanol (2.0 mL), was added ethanolamine (66 µL, 1.10 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, ethyl acetate → 1:39 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate) afforded the *title compound* as a white solid (149 mg, 69%). Rotameric broadening is evident in both the ^{1}H and ^{13}C NMR spectra; m.p. 164–166 °C; R_f 0.11 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3351, 2937, 2412, 1604, 1487, 1460, 1442, 1351, 1238, 1203, 1069, 1038, 549, 462; δ_H (400 MHz, d_4-MeOD) 4.13 – 3.19 (7H, m, C**H₂**), 3.14 – 2.42 (3H, m, C**H₂**), 2.37 – 1.83 (3H, m, C**H₂**), 1.78 – 1.24 (3H, m, C**H₂**); δ_C (100 MHz, d_4-MeOD) 176.4 (**C**O), 173.7 (**C**O), 60.1 (**C**H_2), 51.0 (**C**H_2), 48.3 (**C**H_2), 40.2 (**C**H_2), 37.6 (**C**H_2), 29.6 (**C**H_2), 26.5 (**C**H_2), 25.3 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{18}N_2NaO_3$, 237.1210. Found: $[MNa]^+$, 237.1208 (0.7 ppm error).

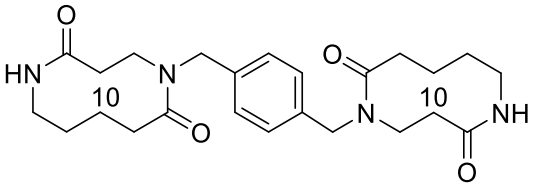
5-(4-Aminobenzyl)-1,5-diazecane-2,6-dione (20zf)



To a solution of 1-acryloyl-piperidin-2-one **11a** (154 mg, 1.00 mmol) in dry methanol (2.0 mL), was added 4-aminobenzylamine (125 µL, 1.10 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, DCM → 1:19 methanol: DCM → 1:9 methanol: DCM) afforded the *title compound* as a white solid (140 mg, 51%). Rotameric broadening is evident in the ^{1}H NMR spectrum. Product identity and purity is best seen in the ^{13}C NMR data; m.p. 165–176 °C; R_f 0.21 (1:9 methanol: DCM); ν_{max}/cm^{-1} (thin film) 3314, 2931, 1613, 1517, 1424, 1282, 1201, 1177, 1140, 910, 729, 506; δ_H (400 MHz, $CDCl_3$) 7.14 – 7.10 (2H, m, Ar**H**), 6.66 – 6.61 (2H, m, Ar**H**), 5.28 (1H, s, ArN**H₂**), 5.25 – 5.17

(1H, m, N**H**), 4.53 (2H, s, ArC**H₂**), 3.96 – 3.66 (3H, m, 1.5 × C**H₂** and 1H, s, ArN**H₂** [overlapping]), 3.30 (1H, dt, *J* = 15.6, 3.8 Hz, 0.5 × C**H₂**), 2.90 – 2.79 (1H, m, 0.5 × C**H₂**), 2.68 – 2.56 (1H, m, 0.5 × C**H₂**), 2.22 – 1.95 (3H, m, 1.5 × C**H₂**), 1.73 – 1.42 (3H, m, 1.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 171.2 (**C**O), 146.3 (Ar**C**NH_2), 129.7 (2 × Ar**C**H), 128.2 (Ar**C**), 115.5 (2 × Ar**C**H), 49.5 (**C**H_2), 45.5 (**C**H_2), 39.3 (**C**H_2), 37.8 (**C**H_2), 28.4 (**C**H_2), 25.9 (**C**H_2), 24.0 (**C**H_2); HRMS (ESI): calcd. for $C_{15}H_{21}N_3NaO_2$, 298.1526. Found: $[MNa]^+$, 298.1515 (3.6 ppm error).

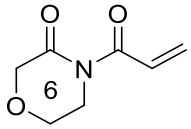
5,5'-(1,4-Phenylenebis(methylene))bis(1,5-diazecane-2,6-dione) (20zg)



To a solution of 1,4-phenylenedimethanamine (103 mg, 0.75 mmol) in dry DMF (1.5 mL), was added a solution of 1-acryloyl-piperidin-2-one **11a** (230 mg, 1.50 mmol) in dry DMF (1.5 mL) dropwise. 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate → 1:24 methanol: ethyl acetate → 1:16 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate) afforded the *title compound* as a white solid (98.3 mg, 30%). Severe rotameric broadening is evident in the ^{1}H NMR spectrum. Product identity and purity is best seen in the ^{13}C NMR data. The product exists primarily as a single rotamer, with traces of a minor rotamer also evident; m.p. 163–170 °C; R_f 0.37 (1:4 methanol: DCM); ν_{max}/cm^{-1} (thin film) 3290, 2931, 1615, 1557, 1416, 1349, 1202, 1177, 1145, 1109, 1054, 910, 726, 645, 497; δ_H (400 MHz, $CDCl_3$) 7.21 – 7.05 (4H, m, Ar**H**), 6.19 – 5.80 (2H, m, 2 × N**H**), 5.20 – 4.98 (2H, m, C**H₂**), 4.17 – 3.55 (6H, m, C**H₂**), 3.28 – 3.10 (2H, m, C**H₂**), 2.98 – 2.43 (5H, m, C**H₂**), 2.23 – 2.03 (7H, m, C**H₂**), 1.81 – 1.38 (6H, m, C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.1 (2 × **C**O) 171.1 (2 × **C**O), 137.4 (2 × Ar**C**), 128.5 (4 × Ar**C**H), 48.5 (2 × **C**H_2), 45.0 (2 × **C**H_2), 39.3 (2 × **C**H_2), 37.3 (2 × **C**H_2), 28.3 (2 × **C**H_2), 25.7 (2 × **C**H_2), 23.9 (2 × **C**H_2); HRMS (ESI): calcd. for $C_{24}H_{34}N_4NaO_4$, 465.2472. Found: $[MNa]^+$, 465.2481 (–1.8 ppm error).

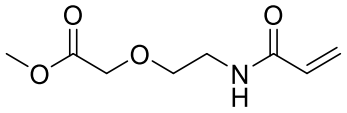
Characteristic NMR data for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 4.81 (2H, d, *J* = 16.3 Hz, C**H₂**), 4.27 (2H, d, *J* = 16.3 Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) 176.3 (2 × **C**O), 171.3 (2 × **C**O), 127.3 (4 × Ar**C**H), 35.1 (2 × **C**H_2), 27.3 (2 × **C**H_2), 24.9 (2 × **C**H_2).

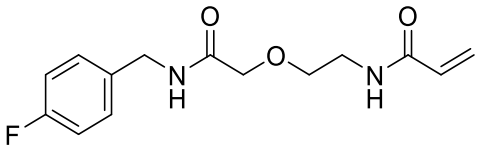
4-Acryloylmorpholin-3-one (21)



To a stirring solution of morpholin-3-one (202 mg, 1.99 mmol) in dry THF (7.3 mL) cooled to 0 °C was added a solution of MeMgBr (3.0 M in diethyl ether, 0.73 mL) *via* dropwise addition using a syringe pump over 30 min. The reaction mixture was allowed to stir for 10 min at 0 °C after addition was completed. Acryloyl chloride (0.240 mL, 3.00 mmol) was then added in a single portion and the reaction mixture was stirred for an additional 30 min at 0 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and the mixture was extracted with Et_2O (10 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 × 8 mL), and organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a fluffy white powder (106 mg, 34%); m.p. 44 – 47°C; R_f 0.16 (1:1 diethyl ether: hexane); ν_{max}/cm^{-1} (thin film) 1686, 1396, 1345, 1312, 1204, 1148, 1114, 940; δ_H (400 MHz, $CDCl_3$), 7.22 (1H, dd, *J* = 16.9, 10.5 Hz, NCOC**H**CHH'), 6.43 (1H, dd, *J* = 16.9, 1.7 Hz, NCOCHC**H**H'), 5.81 (1H, dd, *J* = 10.5, 1.7 Hz, NCOCHCH**H'**), 4.28 (2H, s, OC**H₂**CON), 3.96 – 3.92 (2H, m, OC**H₂**CH_2N), 3.85 – 3.80 (2H, m, OCH_2C**H₂**N); δ_C (100 MHz, $CDCl_3$) 169.8 (**C**O), 168.3 (**C**O), 131.3 (NCO**C**HCHH'), 130.3 (NCOCH**C**HH'), 69.0 (O**C**H_2CON), 64.1 (O**C**H_2CH_2N), 43.8 (OCH_2**C**H_2N); HRMS (ESI): calcd. for $C_7H_9NNaO_3$, 178.0475. Found: $[MNa]^+$, 178.0475 (–0.3 ppm error).

Methyl 2-(2-acrylamidoethoxy)acetate (23) and *N*-(2-(2-((4-fluorobenzyl)amino)-2-oxoethoxy)ethyl)acrylamide (24)





To a solution of 4-acryloylmorpholin-3-one **21** (77.8 mg, 0.501 mmol) in dry methanol (1.0 mL), was added 4-fluorobenzylamine (63 µL, 0.551 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, 1:4 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → ethyl acetate → 1:49 methanol: ethyl acetate) afforded methyl 2-(2-acrylamidoethoxy)acetate (**23**) as a colorless oil (61.4 mg, 65%), *N*-(2-(2-((4-fluorobenzyl)amino)-2-oxoethoxy)ethyl)acrylamide (**24**), contaminated with morpholin-3-one, as an orange oil (25.3 mg, 18%).

Data for **23**: R_f 0.45 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3292, 2954, 1742, 1659, 1626, 1543, 1437, 1216, 1139, 985, 888, 806, 705, 580; δ_H (400 MHz, $CDCl_3$) 6.73 (1H, br s, N**H**), 6.27 (1H, dd, *J* = 17.0, 1.6 Hz, NCOC**H**CHH'), 6.14 (1H, dd, *J* = 17.0, 10.2 Hz, NCOCHC**H**H'), 5.62 (1H, dd, *J* = 10.2, 1.6 Hz, NCOCHCH**H'**), 4.10 (2H, s, OC$\mathbf{H_2}CO_2CH_3$), 3.74 (3H, s, $CO_2C\mathbf{H_3}$), 3.66 – 3.62 (2H, m, C$\mathbf{H_2}$), 3.55 – 3.48 (2H, m, C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 171.5 (**C**O), 165.8 (**C**O), 131.0 (NCO**C**HCHH'), 126.3 (NCOCH**C**HH'), 70.5 (**C**H_2), 68.0 (**C**H_2), 52.1 (**C**H_3), 39.5 (**C**H_2); HRMS (ESI): calcd. for $C_8H_{13}NNaO_4$, 210.0737. Found: $[MNa]^+$, 210.0737 (–0.2 ppm error).

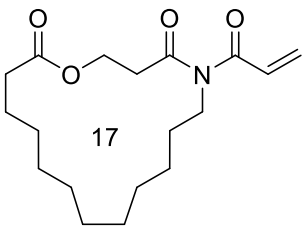
Data for **24** (isolated as a roughly 2:1 mixture of **24** and morpholin-3-one): R_f 0.23 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3296, 2927, 1660, 1544, 1511, 1414, 1347, 1222, 1124, 983, 822; δ_H (400 MHz, $CDCl_3$) 7.27 – 7.20 (2H, m, Ar**H**), 7.03 – 6.96 (2H, m, Ar**H**), 6.51 (1H, br s, N**H**), 6.30 (1H, br s, N**H**), 6.24 (1H, dd, *J* = 16.9, 1.5 Hz, NCOCHC**H**H'), 6.05 (1H, dd, *J* = 16.9, 10.2 Hz, NCOC**H**CHH'), 5.61 (1H, dd, *J* = 10.2, 1.5 Hz, NCOCHCH**H'**), 4.42 (2H, d, *J* = 6.1 Hz, C$\mathbf{H_2}$), 3.99 (2H, s, C$\mathbf{H_2}$), 3.63 – 3.58 (2H, m, C$\mathbf{H_2}$), 3.55 – 3.48 (2H, m, C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$): 169.0 (**C**O), 165.9 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 245.6 Hz), 134.0 (Ar**C**, $^4J_{CF}$ = 3.5 Hz), 132.6 (NCO**C**HCHH'), 129.6 (2 × Ar**C**H, $^3J_{CF}$ = 7.9 Hz), 127.0 (NCOCH**C**HH'), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.8 Hz), 70.7 (**C**H_2), 70.5 (**C**H_2), 42.2 (**C**H_2), 39.3 (**C**H_2); δ_F (376 MHz, $CDCl_3$), -114.75 (1F, m, ArF); HRMS (ESI): calcd. for $C_{14}H_{17}FN_2NaO_3$, 303.1115. Found: $[MNa]^+$, 303.1116 (–0.1 ppm error).

Data for morpholin-3-one : δ_H (400 MHz, $CDCl_3$) 7.06 (1H, br s, N**H**), 4.15 (2H, s, C$\mathbf{H_2}$), 3.85 – 3.80 (2H, m, C$\mathbf{H_2}$), 3.44 – 3.39 (1H, m, C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 169.4 (**C**O), 68.1 (**C**H_2), 63.4 (**C**H_2), 41.7 (**C**H_2).

Methyl 5-acrylamidopentanoate (26)

The synthetic procedure and data for **26** can be found with the information about compound **20d** on page S30.

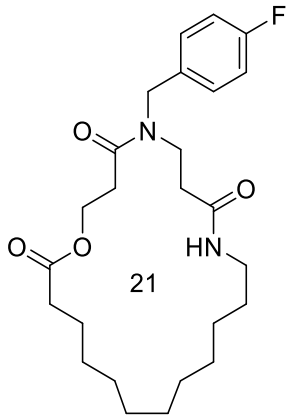
5-Acryloyl-1-oxa-5-azacycloheptadecane-4,17-dione (27)



A stirring solution of 1-oxa-5-azacycloheptadecane-4,17-dione[7] (111 mg, 0.413 mmol) and DIPEA (0.180 mL, 1.03 mmol) in THF (1.6 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.067 mL, 0.825 mmol) in THF (0.8 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 3 hours. It was then allowed to warm to RT and stirred for a further 2

hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (2 mL), extracted with DCM (4 mL), and the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 2 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a colourless oil (21.5 mg, 12%); R_f 0.27 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2927, 2857, 1732, 1687, 1618, 1460, 1404, 1365, 1220, 1133, 1103, 1061, 979, 797, 736; δ_H (300 MHz, $CDCl_3$) 6.73 (1H, dd, *J* = 16.7, 10.3 Hz, NCOC**H**CHH'), 6.41 (1H, dd, *J* = 16.7, 1.7 Hz, NCOCHC**H**H'), 5.80 (1H, dd, *J* = 10.3, 1.7 Hz, NCOCHCH**H'**), 4.43 (2H, t, *J* = 5.9 Hz, $CO_2C\mathbf{H_2}CH_2CON$), 3.75 – 3.65 (2H, m, $CH_2CH_2C\mathbf{H_2}NCO$), 3.07 (2H, t, *J* = 5.9 Hz, $CO_2CH_2C\mathbf{H_2}CON$), 2.35 – 2.25 (2H, m, $CH_2C\mathbf{H_2}CO_2$), 1.72 – 1.51 (4H, m, 2 × C**H₂**), 1.41–1.21 (14H, m, 7 × C**H₂**); δ_C (75 MHz, $CDCl_3$) 173.9 (**C**O), 173.3 (**C**O), 168.9 (**C**O), 130.6 (**C**HCH_2), 130.2 (CH**C**H_2), 59.8 ($CO_2\mathbf{C}H_2CH_2CON$), 44.3 ($CH_2CH_2\mathbf{C}H_2NCO$), 37.2 ($CO_2CH_2\mathbf{C}H_2CON$), 34.2 ($CH_2\mathbf{C}H_2CO_2$), 28.1 (**C**H_2), 27.8 (**C**H_2), 27.7 (**C**H_2), 27.3 (**C**H_2), 27.2 (**C**H_2), 27.0 (**C**H_2), 26.8 (**C**H_2), 25.2 (**C**H_2), 24.7 (**C**H_2); HRMS (ESI): calcd. for $C_{18}H_{29}NNaO_4$, 346.1989. Found: $[MNa]^+$, 346.1993 (–1.2 ppm error).

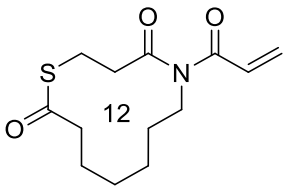
5-(4-Fluorobenzyl)-1-oxa-5,9-diazacyclohenicosane-4,8,21-trione (28)



To a solution of **27** (21.5 mg, 0.066 mmol) in dry methanol (0.13 mL), was added 4-fluorobenzylamine (8 µL, 0.073 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, 2:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a colourless oil (19.3 mg, 65%). In solution in $CDCl_3$, this compound exists as a roughly 2:1 mixture of rotamers; R_f 0.22 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3313, 2927, 2855, 1732, 1638, 1553, 1510, 1460, 1415, 1358, 1222, 1156, 1101, 1016, 824, 732; δ_H (400 MHz, $CDCl_3$) 7.27 – 7.20 (2H, m, Ar**H**, minor rotamer), 7.16 – 7.09 (2H, m, Ar**H**, major rotamer), 7.08 – 7.02 (2H, m, Ar**H**, minor rotamer), 7.01 – 6.95 (2H, m, Ar**H**, minor rotamer), 6.32 (1H, t, *J* = 5.8 Hz, N**H**, major rotamer), 5.64 (1H, t, *J* = 5.8 Hz, N**H**, minor rotamer), 4.56 (4H, s, 2 × C$\mathbf{H}_2$, both rotamers), 4.45 (2H, t, *J* = 6.9 Hz, C$\mathbf{H}_2$, minor rotamer), 4.39 (2H, t, *J* = 6.5 Hz, C$\mathbf{H}_2$, major rotamer), 3.65 – 3.55 (4H, m, C$\mathbf{H}_2$, both rotamers), 3.31 – 3.20 (4H, m, C$\mathbf{H}_2$, both rotamers), 2.77 (2H,

t, *J* = 6.9 Hz, C**H**$_2$, minor rotamer), 2.66 (2H, t, *J* = 6.5 Hz, C**H**$_2$, major rotamer), 2.49 (2H, t, *J* = 6.4 Hz, C**H**$_2$, major rotamer), 2.38 – 2.24 (6H, m, C**H**$_2$, both rotamers), 1.69 – 1.56 (4H, m, C**H**$_2$, both rotamers), 1.55 – 1.43 (4H, m, C**H**$_2$, both rotamers), 1.37 – 1.18 (28H, m, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O, minor rotamer), 173.9 (**C**O, major rotamer), 171.0 (**C**O, major rotamer), 170.9 (**C**O, major rotamer), 170.2 (**C**O, minor rotamer), 169.6 (**C**O, minor rotamer), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz, major rotamer), 161.3 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz, minor rotamer), 133.5 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz, minor rotamer), 132.1 (Ar**C**F, $^4J_{CF}$ = 3.0 Hz, major rotamer), 130.0 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz, minor rotamer), 128.1 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz, major rotamer), 116.1 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz, major rotamer), 115.6 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz, minor rotamer), 61.1 (**C**H$_2$, minor rotamer), 60.4 (**C**H$_2$, major rotamer), 51.6 (**C**H$_2$, major rotamer), 48.4 (**C**H$_2$, minor rotamer), 44.3 (**C**H$_2$, minor rotamer), 43.7 (**C**H$_2$, major rotamer), 39.7 (**C**H$_2$, major rotamer), 39.3 (**C**H$_2$, minor rotamer), 36.0 (**C**H$_2$, minor rotamer), 35.6 (**C**H$_2$, major rotamer), 34.1 (**C**H$_2$, major rotamer), 32.7 (**C**H$_2$, major rotamer), 32.3 (**C**H$_2$, minor rotamer), 29.3 (**C**H$_2$, major rotamer), 28.9 (**C**H$_2$, minor rotamer), 28.8 (**C**H$_2$, major rotamer), 28.4 (**C**H$_2$, rotamer), 28.3 (**C**H$_2$, rotamer), 28.2 (**C**H$_2$, rotamer), 28.10 (**C**H$_2$, rotamer), 28.07 (**C**H$_2$, rotamer), 27.94 (**C**H$_2$, rotamer), 27.93 (**C**H$_2$, rotamer), 27.89 (**C**H$_2$, rotamer), 27.6 (**C**H$_2$, minor rotamer), 27.2 (**C**H$_2$, minor rotamer), 26.4 (**C**H$_2$, major rotamer), 25.7 (**C**H$_2$, minor rotamer), 24.7 (**C**H$_2$, major rotamer), 24.6 (**C**H$_2$, minor rotamer); δ_F (376 MHz, $CDCl_3$), two rotamers in a 2:1 ratio: −114.34 (1F, m, ArF, major rotamer), −114.76 (1F, m, ArF); HRMS (ESI): calcd. for $C_{25}H_{37}FN_2NaO_4$, 471.2630. Found: $[MNa]^+$, 471.2632 (–0.5 ppm error).

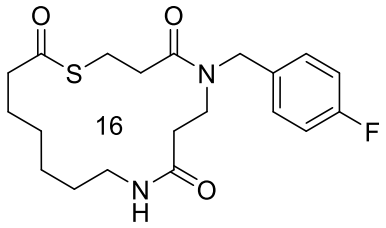
5-Acryloyl-1-thia-5-azacyclododecane-4,12-dione (29)



A stirring solution of 1-thia-5-azacyclododecane-4,12-dione[8] (31.5 mg, 0.147 mmol) and DIPEA (0.064 mL, 0.366 mmol) in THF (0.6 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.024 mL, 0.293 mmol) in THF (0.3 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. It was then allowed to warm to RT and stirred for a further 5 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (1 mL), extracted with DCM (2 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 1 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 diethyl ether: hexane) afforded the *title compound* as a colourless oil (24.5 mg, 62%); R_f 0.29 (1:1 hexane: diethyl ether); ν_{max}/cm^{-1} (thin film) 2938, 1683, 1618, 1404, 1352, 1301, 1276, 1210, 1151, 1072, 1032, 978, 870, 795, 694; δ_H (400 MHz, $CDCl_3$) 6.65 (1H, dd, *J* = 16.7, 10.2 Hz, NCOC**H**CHH'), 6.46 (1H, dd, *J* =

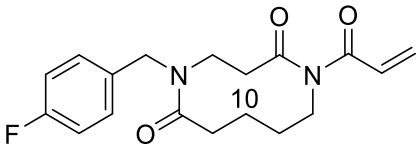
16.7, 1.8 Hz, NCOCHC**H**H'), 5.83 (1H, dd, *J* = 10.2, 1.8 Hz, NCOCHCH**H'**), 3.77 (2H, br s, C**H₂**), 3.60 – 2.90 (4H, m, 2 × C**H₂**), 2.54 – 2.44 (2H, m, C**H₂**), 1.82 (2H, br s, C**H₂**), 1.65 – 1.52 (2H, m, C**H₂**), 1.50 – 1.28 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 200.1 (**C**OS), 175.7 (**C**O), 169.4 (**C**O), 130.5 (CH**C**H_2), 130.3 (**C**HCH_2), 44.3 (**C**H_2), 43.7 (**C**H_2), 38.8 (**C**H_2), 28.3 (**C**H_2), 27.4 (**C**H_2), 25.0 (**C**H_2), 24.8 (**C**H_2), 23.5 (**C**H_2); HRMS (ESI): calcd. for $C_{13}H_{19}NNaO_3S$, 292.0978. Found: $[MNa]^+$, 292.0981 (–1.1 ppm error).

5-(4-Fluorobenzyl)-1-thia-5,9-diazacyclohexadecane-4,8,16-trione (30)



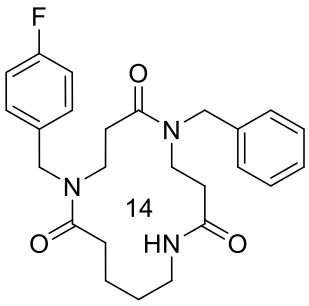
To a solution of **29** (24.5 mg, 0.091 mmol) in dry methanol (0.18 mL), was added 4-fluorobenzylamine (11 µL, 0.100 mmol) in a single portion. The reaction mixture was allowed to stir for 2 h at RT, then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate → 1:2 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* **30** (15.0 mg, 42%) a colourless oil, along with 1-thia-5-azacyclododecane-4,12-dione (2.2 mg, 11%).[8] In solution in $CDCl_3$, compound **30** exists as a roughly 3:1 mixture of rotamers; Data for **30**: R_f 0.22 (ethyl acetate); ν_{max}/cm^{-1} (thin film) 3314, 2931, 2858, 1640, 1548, 1509, 1414, 1364, 1222, 1156, 1098, 982, 823, 731, 597; ^{1}H NMR for the major rotamer: δ_H (400 MHz, $CDCl_3$) 7.31 – 6.95 (4H, m, Ar**H**), 5.89 (1H, t, *J* = 5.6 Hz, N**H**), 4.58 – 4.45 (2H, m, C**H₂**), 3.69 – 3.53 (2H, m, C**H₂**), 3.32 – 3.21 (2H, m, C**H₂**), 3.21 – 3.08 (2H, m, C**H₂**), 2.74 – 2.34 (6H, m, C**H₂**), 1.97 – 1.66 (2H, m, C**H₂**), 1.58 – 1.42 (2H, m, C**H₂**), 1.40 – 1.21 (4H, m, C**H₂**). Diagnostic ^{1}H NMR shifts for the minor rotamers can be seen at: 7.31 – 7.19 (1H, m, Ar**H**, minor rotamer), 4.55 (2H, s, ArC**H₂**, minor rotamer), 7.10 – 7.04 (1H, m, Ar**H**, major rotamer), 4.49 (2H, s, ArC**H₂**, major rotamer); δ_C (100 MHz, $CDCl_3$) ^{13}C peaks for the major rotamer: 200.6 (**C**OS), 171.51 (**C**O), 171.45 (**C**O), 162.3 (Ar**C**F, $^1J_{CF}$ = 246.1 Hz), 132.7 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 128.1 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 116.0 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 52.9 (**C**H_2), 45.1 (**C**H_2), 42.5 (**C**H_2), 39.1 (**C**H_2), 35.3 (**C**H_2), 33.1 (**C**H_2), 29.5 (**C**H_2), 27.8 (**C**H_2), 25.9 (**C**H_2), 25.2 (**C**H_2), 25.0 (**C**H_2). ^{13}C peaks for the minor rotamer: 133.53 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 129.9 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 115.7 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 48.7 (**C**H_2), 44.7 (**C**H_2), 43.7 (**C**H_2), 39.6 (**C**H_2), 36.7 (**C**H_2), 33.8 (**C**H_2), 29.8 (**C**H_2), 28.0 (**C**H_2), 27.2 (**C**H_2), 26.2 (**C**H_2), 23.7 (**C**H_2); δ_F (376 MHz, $CDCl_3$), −114.77 (1F, m, ArF, both rotamers, overlapping); HRMS (ESI): calcd. for $C_{20}H_{27}FN_2NaO_3S$, 417.1619. Found: $[MNa]^+$, 417.1620 (–0.3 ppm error).

1-Acryloyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (S1)



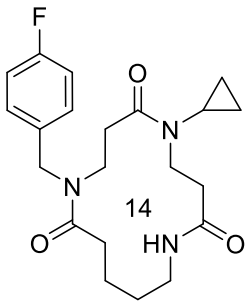
A stirring solution of **14a** (1.20 g, 4.30 mmol) and DIPEA (1.87 mL, 10.8 mmol) in THF (20 mL) was cooled to 0°C. To this was added a 0 °C cooled solution of acryloyl chloride (0.524 mL, 6.45 mmol) in THF (5.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 18 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (15 mL), extracted with Et_2O (25 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 15 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:2 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* as a pale-yellow oil (997 mg, 70%). In solution in $CDCl_3$, this compound exists largely as a single rotamer, along with a minor rotamer (most clearly seen in the ^{19}F NMR data). The ^1H NMR spectrum is significantly affected by rotameric broadening; R_f 0.49 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2943, 1681, 1631, 1509, 1457, 1406, 1342, 1245, 1220, 1158, 1141, 1092, 1063, 981, 905, 816, 767, 730, 582, 498, 474; δ_H (400 MHz, $CDCl_3$) 7.19 – 7.13 (2H, m, Ar**H**), 6.96 – 6.89 (2H, m, Ar**H**), 6.62 (1H, dd, *J* = 16.6, 10.3 Hz, NCOC**H**CHH'), 6.42 (1H, dd, *J* = 16.6, 1.5 Hz, NCOCHC**H**H'), 5.85 (1H, dd, *J* = 10.3, 1.5 Hz, NCOCHCH**H'**), 4.91 – 4.15 (2H, m, C**H₂**), 3.84 (2H, br s, C**H₂**), 3.56 (2H, br s, C**H₂**), 3.24 (2H, br s, C**H₂**), 2.39 (2H, br s, C**H₂**), 1.90 (2H, br s, C**H₂**), 1.66 (2H, br p, *J* = 5.4Hz, C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.4 (**C**O), 172.9 (**C**O), 168.8 (**C**O), 162.1 (Ar**C**F, $^1J_{CF}$ = 245.6 Hz), 133.0 (Ar**C**, $^4J_{CF}$ = 3.1 Hz), 132.1 (NCOCH=**C**HH'), 129.9 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 129.4 (NCO**C**H=CHH'), 115.4 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 46.8 (**C**H_2), 45.6 (**C**H_2), 43.8 (**C**H_2), 38.0 (**C**H_2), 29.1 (**C**H_2), 24.1 (**C**H_2), 24.0 (**C**H_2); δ_F (376 MHz, $CDCl_3$), −114.32 (1F, m, ArF, minor rotamer), −115.01 (1F, m, ArF, major rotamer); HRMS (ESI): calcd. for $C_{18}H_{21}FN_2NaO_3$, 355.1428. Found: $[MNa]^+$, 355.1423 (1.5 ppm error).

5-Benzyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (31a)



To a solution of **S1** (179 mg, 0.537 mmol) in dry methanol (1.07 mL), was added benzylamine (65 µL, 0.591 mmol) in a single portion. After 30 min of stirring a white precipitate formed which turned the solution into a slurry. The reaction mixture was allowed to stir for 3 h in total at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 1:49 methanol: ethyl acetate → 1:16 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate) afforded the *title compound* as a white solid (180 mg, 76%). This compounds exists as a complex mixture of rotamers at RT in $CDCl_3$, with 4 main rotamers visible in a ratio of roughly 7:5:4:1, based on the ^{19}F NMR data and the NH signals in the ^{1}H NMR spectrum; m.p. 188–190 °C; R_f 0.34 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3301, 2933, 1626, 1552, 1509, 1450, 1363, 1221, 1157, 1096, 915, 823, 729, 699, 646; δ_H (400 MHz, $CDCl_3$) 7.39 – 6.91 (9H, m, Ar**H**), 6.88 (1H, br t, *J* = 5.7 Hz, N**H**), 6.76 (1H, br t, *J* = 6.0 Hz, N**H**), 6.46 (1H, br t, *J* = 5.5 Hz, N**H**), 6.05 (1H, br t, *J* = 6.1 Hz, N**H**), 4.69 (2H, s, ArC**H₂**), 4.62 (2H, s, ArC**H₂**), 4.56 (2H, s, ArC**H₂**), 4.55 (2H, s, ArC**H₂**), 4.48 (2H, s, ArC**H₂**), 4.38 (2H, s, ArC**H₂**), 3.74 – 3.47 (4H, m, 2 × C**H₂**), 3.36 – 3.26 (2H, m, C**H₂**), 2.66 – 2.23 (6H, m, 6 × C**H₂**), 1.80 – 1.50 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.9 (**C**O), 173.6 (**C**O), 173.4 (**C**O), 172.9 (**C**O), 172.8 (**C**O), 171.2 (**C**O), 171.1 (**C**O), 170.6 (**C**O), 170.2 (**C**O), 162.3 (Ar**C**F, $^{1}J_{CF}$ = 246.0 Hz), 162.1 (Ar**C**F, $^{1}J_{CF}$ = 246.0 Hz), 138.0 (Ar**C**), 137.4 (Ar**C**), 136.9 (Ar**C**), 137.8 (Ar**C**), 133.5 (Ar**C**, $^{4}J_{CF}$ = 3.0 Hz), 133.4 (Ar**C**, $^{4}J_{CF}$ = 3.0 Hz), 132.8 (Ar**C**, $^{4}J_{CF}$ = 3.0 Hz), 129.8 (Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 129.3 (2 × Ar**C**H), 129.0 (2 × Ar**C**H), 128.8 (Ar**C**H), 129.31 (Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 128.32 (Ar**C**H), 128.0 (Ar**C**H), 127.7 (Ar**C**H), 127.6 (Ar**C**H), 126.2 (2 × Ar**C**H), 126.0 (2 × Ar**C**H), 116.0 (Ar**C**H, $^{2}J_{CF}$ = 21.5 Hz), 115.6 (Ar**C**H, $^{2}J_{CF}$ = 21.5 Hz), 115.5 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 53.4 (Ar**C**H_2), 53.0 (Ar**C**H_2), 51.5 (Ar**C**H_2), 48.3 (Ar**C**H_2), 48.0 (Ar**C**H_2), 47.9 (Ar**C**H_2), 44.5 (**C**H_2), 43.9 (**C**H_2), 43.7 (**C**H_2), 42.9 (**C**H_2), 42.4 (**C**H_2), 39.6 (**C**H_2), 38.5 (**C**H_2), 38.3 (**C**H_2), 35.4 (**C**H_2), 35.2 (**C**H_2), 35.0 (**C**H_2), 33.6 (**C**H_2), 33.2 (**C**H_2), 32.5 (**C**H_2), 31.7 (**C**H_2), 29.1 (**C**H_2), 28.1 (**C**H_2), 27.8 (**C**H_2), 24.0 (**C**H_2), 23.3 (**C**H_2), 23.0 (**C**H_2); δ_F (376 MHz, $CDCl_3$), four rotamers in a 7:5:1:4 ratio: −114.49 (1F, m, ArF, major rotamer), −114.69 (1F, m, ArF), −114.87 (1F, m, ArF), −115.15 (1F, m, ArF); HRMS (ESI): calcd. for $C_{25}H_{30}FN_3NaO_3$, 462.2163. Found: $[MNa]^+$, 462.2160 (0.7 ppm error).

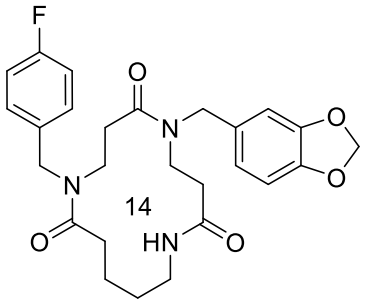
5-Cyclopropyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (31b)



To a solution of **S1** (320 mg, 0.963 mmol) in dry methanol (2.0 mL), was added cyclopropyl amine (73 µL, 1.06 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 → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 3:17 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (279 mg, 74%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 4 main rotamers based on the carbonyl region of the ^{13}C NMR spectrum. Due to overlapping signals in the ^{1}H and ^{19}F NMR, it is difficult to confidently quote a rotamer ratio; R_f 0.26 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3303, 2937, 1736, 1638, 1549, 1509, 1413, 1366, 1221, 1158, 827; δ_H (400 MHz, $CDCl_3$) 7.38 (1H, t, *J* = 5.6 Hz, N**H**, rotamer), 7.33 (1H, t, *J* = 5.7 Hz, N**H**, rotamer), 7.14 – 6.98 (2H, m, Ar**H**), 6.96 – 6.83 (2H, m, Ar**H**), 6.80 (1H, t, *J* = 5.4 Hz, N**H**, rotamer), 4.70 – 4.37 (2H, m, C$\mathbf{H}_2$), 3.63 – 3.54 (2H, m, C$\mathbf{H}_2$), 3.52 (1H, d, *J* = 6.6 Hz, C**H**, rotamer), 3.49 – 3.40 (1H, m, C$\mathbf{H}_2$), 3.20 – 2.99 (2H, m, C$\mathbf{H}_2$), 2.84 – 2.67 (1H, m, C$\mathbf{H}_2$), 2.61 – 2.16 (6H, m, C**H** (rotamer) and C$\mathbf{H}_2$), 1.64 – 1.25 (4H, m, C$\mathbf{H}_2$), 0.80 – 0.66 (1H, m, cyclopropyl C$\mathbf{H}_2$, major rotamer), 0.60 – 0.48 (1H, m, cyclopropyl C$\mathbf{H}_2$, major rotamer), 0.44 – 0.36 (1H, m, cyclopropyl C$\mathbf{H}_2$, minor rotamer), 0.32 – 0.23 (1H, m, cyclopropyl C$\mathbf{H}_2$, minor rotamer); δ_C (100 MHz, $CDCl_3$) 174.2 (**C**O), 173.9 (**C**O), 173.7 (**C**O), 173.3 (**C**O), 173.0 (**C**O), 172.8 (**C**O), 172.34 (**C**O), 172.31 (**C**O), 172.2 (**C**O), 171.2 (**C**O), 170.9 (**C**O), 170.7 (**C**O), 162.0 (Ar**C**F, $^{1}J_{CF}$ = 245.6 Hz), 161.92 (Ar**C**F, $^{1}J_{CF}$ = 245.6 Hz), 162.89 (Ar**C**F, $^{1}J_{CF}$ = 245.6 Hz), 133.4 (Ar**C**F, $^{4}J_{CF}$ = 3.2 Hz), 133.2 (Ar**C**F, $^{4}J_{CF}$ = 3.2 Hz), 133.1 (Ar**C**F, $^{4}J_{CF}$ = 3.2 Hz), 132.3 (Ar**C**F, $^{4}J_{CF}$ = 3.2 Hz), 129.6 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 129.3 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 129.1 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 127.8 (2 × Ar**C**H, $^{3}J_{CF}$ = 8.0 Hz), 115.7 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.5 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.3 (2 × Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 53.4 (**C**H_2), 53.1 (**C**H_2), 51.8 (**C**H_2), 51.54 (**C**H), 51.51 (**C**H), 51.2 (**C**H_2), 48.0 (**C**H_2), 47.5 (**C**H_2), 43.5 (**C**H_2), 43.3 (**C**H_2), 43.0 (**C**H_2), 42.5 (**C**H_2), 41.8 (**C**H_2), 38.7 (**C**H_2), 38.6 (**C**H_2), 38.0 (**C**H_2), 36.5 (**C**H), 34.9 (**C**H_2), 34.8 (**C**H_2), 34.6 (**C**H_2), 33.9 (**C**H_2), 33.5 (**C**H_2), 33.4 (**C**H_2), 33.1 (**C**H_2), 32.8 (**C**H_2), 32.6 (**C**H_2), 32.5 (**C**H_2), 32.3 (**C**H_2), 32.2 (**C**H_2), 30.7 (**C**H), 29.2 (**C**H), 28.8 (**C**H_2), 28.7 (**C**H_2), 28.6 (**C**H_2), 28.0 (**C**H_2), 23.2 (**C**H_2), 22.9 (**C**H_2), 22.4 (**C**H_2), 22.2 (**C**H_2), 9.5 (cyclopropyl **C**H_2), 9.0 (cyclopropyl **C**H_2), 6.4 (cyclopropyl **C**H_2); δ_F (376 MHz, $CDCl_3$), 114.98 (1F, m, ArF),

–114.62 (1F, m, ArF); HRMS (ESI): calcd. for $C_{21}H_{28}FN_3NaO_3$, 412.2007. Found: $[MNa]^+$, 412.2008 (–0.2 ppm error).

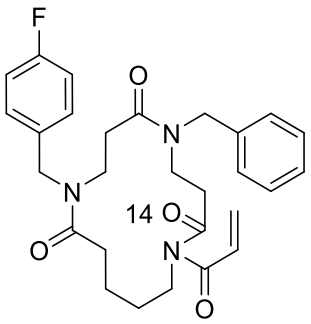
5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (31c)



To a solution of **S1** (332 mg, 0.998 mmol) in dry methanol (2.0 mL), was added piperonylamine (166 mg, 1.10 mmol) in a single portion. The reaction mixture was allowed to stir for 10 min at RT at which point a white precipitate formed which impeded stirring. To the crude reaction mixture was added DCM (2 mL) 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 → ethyl acetate → 1:49 methanol: ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:4 methanol: ethyl acetate) afforded the *title compound* as a white solid (256 mg, 53%). This compounds exists as a complex mixture of rotamers at RT in $CDCl_3$, with 3 main rotamers visible in a ratio of roughly 12:8:6 based on the ^{19}F NMR data and the OC**H$_2$**O signals in the ^1H NMR spectrum. A more minor fourth rotamer can also be seen in the ^{19}F NMR spectrum; m.p. 216–220°C; R_f 0.23 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2933, 1633, 1508, 1490, 1443, 1244, 1157, 1038, 928, 705, 503; δ_H (600 MHz, $CDCl_3$) 7.26 – 7.11 (2H, m, Ar**H**), 7.07 – 6.93 (2H, m, Ar**H**), 6.79 – 6.67 (2H, m, Ar**H**), 6.61 (1H, br t, *J* = 5.9 Hz, N**H**, rotamer), 6.59 – 6.46 (1H, m, Ar**H**), 6.01 – 5.87 (2H, s, OC**H$_2$**O), 5.67 (1H, br t, *J* = 6.2 Hz, N**H**, rotamer), 4.85 – 4.23 (4H, m, ArC**H$_2$**), 3.74 – 3.46 (4H, m, C**H$_2$**), 3.37 – 3.21 (2H, m, C**H$_2$**), 2.69 – 2.40 (5H, m, C**H$_2$**), 1.91 – 1.49 (5H, m, C**H$_2$**), Diagnostic ^1H NMR signals for the 3 major rotamers: 5.97 (2H, s, OC**H$_2$**O, rotamer B), 5.94 (2H, s, OC**H$_2$**O, major rotamer A), 5.93 (2H, s, OC**H$_2$**O, rotamer C); δ_C (151 MHz, $CDCl_3$) 173.9 (**C**O, major rotamer), 173.6 (**C**O), 173.4 (**C**O), 172.8 (**C**O, major rotamer), 172.7 (**C**O), 171.2 (**C**O, major rotamer), 171.0 (**C**O), 170.6 (**C**O), 170.2 (**C**O), 162.4 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz, major rotamer), 162.3 (2 × Ar**C**F, $^1J_{CF}$ = 246.0 Hz, two minor rotamers overlapping), 148.6 (Ar**C**OCH$_2$), 148.4 (Ar**C**OCH$_2$, major rotamer), 148.2 (Ar**C**OCH$_2$), 147.5 (Ar**C**OCH$_2$), 147.3 (Ar**C**OCH$_2$), 147.2 (Ar**C**OCH$_2$, major rotamer), 133.6 (Ar**C**), 133.5 (Ar**C**), 132.9 (Ar**C**, $^4J_{CF}$ = 2.8 Hz, major rotamer), 131.3 (Ar**C**), 130.8 (Ar**C**, major rotamer), 129.9 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 129.6 (Ar**C**), 128.4 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.2 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 121.7 (Ar**C**H), 119.6 (Ar**C**H), 119.5 (Ar**C**H), 116.0 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.7 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.6

(Ar**C**H, $^{2}J_{CF}$ = 21.5 Hz), 108.9 (Ar**C**H), 108.8 (Ar**C**H), 108.7 (Ar**C**H, major rotamer), 108.4 (Ar**C**H), 106.8 (Ar**C**H, major rotamer), 106.6 (Ar**C**H), 101.5 (O**C**H$_2$O), 101.32 (O**C**H$_2$O, major rotamer), 101.26 (O**C**H$_2$O), 53.2 (**C**H$_2$), 53.1 (**C**H$_2$), 51.4 (**C**H$_2$), 48.4 (**C**H$_2$), 48.1 (**C**H$_2$), 47.8 (**C**H$_2$), 44.5 (**C**H$_2$), 44.3 (**C**H$_2$), 43.8 (**C**H$_2$), 43.7 (**C**H$_2$), 43.0 (**C**H$_2$), 42.2 (**C**H$_2$), 39.6 (**C**H$_2$), 38.54 (**C**H$_2$), 38.51 (**C**H$_2$), 35.5 (**C**H$_2$), 35.3 (**C**H$_2$), 35.2 (**C**H$_2$), 33.6 (**C**H$_2$), 33.3 (**C**H$_2$), 33.2 (**C**H$_2$), 32.7 (**C**H$_2$), 31.8 (**C**H$_2$), 29.1 (**C**H$_2$), 28.2 (**C**H$_2$), 27.8 (**C**H$_2$), 24.0 (**C**H$_2$), 23.3 (**C**H$_2$), 23.0 (**C**H$_2$); δ_F (376 MHz, $CDCl_3$), four rotamers in a 12:8:3:6 ratio: –114.48 (1F, m, ArF, major rotamer), –114.73 (1F, m, ArF), –114.84 (1F, m, ArF, minor rotamer), –115.19 (1F, m, ArF); HRMS (ESI): calcd. for $C_{26}H_{30}FN_3NaO_5$, 506.2062. Found: $[MNa]^+$, 506.2061 (0.2 ppm error).

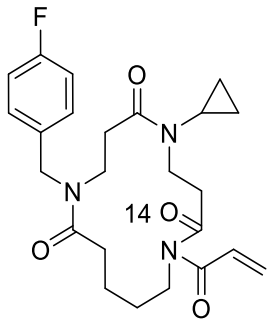
1-Acryloyl-5-benzyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (S2)



To a stirring solution of **31a** (277 mg, 0.630 mmol) and DIPEA (0.27 mL, 1.58 mmol) in DCM (10 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.077 mL, 0.945 mmol) in DCM (3.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 18 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (40 mL), extracted with Et_2O (40 mL), then the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 40 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:2 ethyl acetate: hexane → 1:1 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a colorless oil (265 mg, 85%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with at least 3 significant rotameric forms based on the carbonyl region of the ^{13}C NMR spectrum. Due to overlapping signals in the ^{1}H and ^{19}F NMR, it is difficult to confidently quote a rotamer ratio; R_f 0.12 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 1681, 1634, 1509, 1408, 1365, 1221, 1141, 1064, 974, 910, 822, 726, 646, 499; δ_H (400 MHz, $CDCl_3$) 7.41 – 7.01 (9H, m, Ar**H**), 6.84 (1H, dd, *J* = 16.6, 10.3 Hz, NCOC**H**CHH') [overlapping]), 6.80 (1H, dd, *J* = 16.6, 10.3 Hz, NCOC**H**CHH'), major rotamer, [overlapping]), 6.40 (1H, dd, *J* = 16.6, 1.5 Hz, NCOCHC**H**H' H-26, major rotamer, [overlapping]), 6.36 (1H, dd, *J* = 16.6, 1.5 Hz, NCOCHC**H**H' H-26, [overlapping]), 5.77 (1H, dd, *J* = 10.3, 1.5 Hz, NCOCHCH**H'** H-25, major rotamer, [overlapping]), 5.74 (1H, dd, *J* = 10.3, 1.5 Hz, NCOCHCH**H'** H-25, [overlapping]), 4.82 (2H, s, ArC**H$_2$**, major rotamer), 4.71

(2H, s, ArC**H₂**), 4.69 (2H, s, ArC**H₂**, major rotamer), 4.56 (2H, s, ArC**H₂**), 4.43 (2H, s, ArC**H₂**), 3.97 – 3.60 (5H, m, 2.5 × C**H₂**), 3.52 – 3.40 (1H, m, 0.5 × C**H₂**), 3.14 – 3.03 (1H, m, 0.5 × C**H₂**), 2.92 – 2.74 (2H, m, C**H₂**), 2.56 – 2.39 (2H, m, C**H₂**), 1.86 – 1.55 (5H, m, 2.5 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 175.24 (**C**O), 174.66 (**C**O), 173.70 (**C**O), 173.55 (**C**O), 173.23 (**C**O), 173.10 (**C**O), 172.69 (**C**O), 172.22 (**C**O), 171.73 (**C**O), 170.06 (**C**O), 169.44 (**C**O), 168.91 (**C**O), 168.64 (**C**O), 168.49 (**C**O), 161.98 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 137.53 (Ar**C**), 137.07 (Ar**C**), 136.88 (Ar**C**), 133.34 (Ar**C**F, $^4J_{CF}$ = 3.1 Hz), 133.03 (Ar**C**F, $^4J_{CF}$ = 3.1 Hz), 132.89 (Ar**C**F, $^4J_{CF}$ = 3.1 Hz), 132.08 (Ar**C**H), 131.31 (Ar**C**H), 131.09 (Ar**C**H), 130.47 (Ar**C**H), 129.71 (Ar**C**H), 129.63 (Ar**C**H), 129.10 (Ar**C**H), 128.90 (Ar**C**H), 129.67 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.53 (Ar**C**H), 128.51 (Ar**C**H), 128.19 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.07 (Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.01 (Ar**C**H), 127.45 (Ar**C**H), 127.41 (Ar**C**H), 127.35 (Ar**C**H), 126.18 (Ar**C**H), 125.99 (Ar**C**H), 115.62 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 115.58 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 115.24 (Ar**C**H, $^2J_{CF}$ = 21.6 Hz), 53.45 (**C**H_2), 53.18 (**C**H_2), 53.09 (**C**H_2), 51.91 (**C**H_2), 49.88 (**C**H_2), 48.13 (**C**H_2), 47.72 (**C**H_2), 47.57 (**C**H_2), 44.21 (**C**H_2), 44.13 (**C**H_2), 43.45 (**C**H_2), 43.37 (**C**H_2), 43.15 (**C**H_2), 43.04 (**C**H_2), 42.38 (**C**H_2), 36.41 (**C**H_2), 35.55 (**C**H_2), 34.98 (**C**H_2), 33.83 (**C**H_2), 32.76 (**C**H_2), 32.54 (**C**H_2), 31.72 (**C**H_2), 31.24 (**C**H_2), 30.80 (**C**H_2), 30.77 (**C**H_2), 28.65 (**C**H_2), 28.29 (**C**H_2), 28.16 (**C**H_2), 27.22 (**C**H_2), 22.77 (**C**H_2), 22.60 (**C**H_2), 21.32 (**C**H_2), Characteristic peaks for major rotamer: 175.24 (**C**O), 168.91 (**C**O), 137.07 (Ar**C**), 133.03 (Ar**C**F, $^4J_{CF}$ = 3.1 Hz), 131.09 (Ar**C**H), 53.45 (**C**H_2), 53.18 (**C**H_2), 44.21 (**C**H_2), 43.37 (**C**H_2), 43.15 (**C**H_2), 34.98 (**C**H_2), 33.83 (**C**H_2), 30.77 (**C**H_2), 28.65 (**C**H_2), 22.77 (**C**H_2); δ_F (376 MHz, $CDCl_3$), three signals are visible in a 11:23:3 ratio: –114.72 (1F, m, ArF), –114.80 (1F, m, ArF, major rotamer), –115.07 (1F, m, ArF); HRMS (ESI): calcd. for $C_{28}H_{32}FN_3NaO_4$, 516.2269. Found: $[MNa]^+$, 516.2273 (–0.8 ppm error).

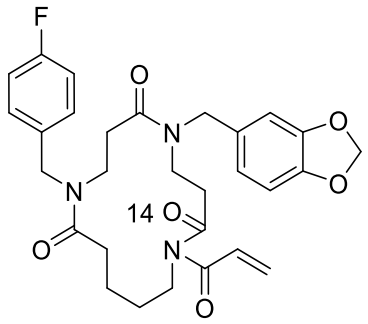
1-Acryloyl-5-cyclopropyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (S3)



A stirring solution of **31b** (278 mg, 0.713 mmol) and DIPEA (0.31 mL, 1.78 mmol) in THF (4.0 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.087 mL, 1.07 mmol) in THF (1.0 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 2 hours. At this stage additional THF (4 mL) was added to aid solubility and the mixture was allowed to stir for an additional 2 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (25 mL), extracted with Et_2O (15 mL), then

the organic layer washed with washed with sat. aq. $NaHCO_3$ (2 × 25 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate) afforded the *title compound* a colourless oil (105 mg, 33%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 4 main rotamers visible in a ratio of roughly 10:8:5:1, based on the ^{19}F NMR data; R_f 0.30 and 0.46 (1:4 methanol: ethyl acetate) – the 2 R_f values shows that rotamer interconversion is sufficiently slow that some rotamer separation is possible using chromatography, although for the purpose of this synthetic reaction, the product was isolated and used as a rotameric mixture; ν_{max}/cm^{-1} (thin film) 2937, 1682, 1639, 1509, 1405, 1367, 1221, 1148, 1064, 1036, 977, 917, 823, 798, 729, 646, 533, 499; δ_H (400 MHz, $CDCl_3$) 7.20 – 7.07 (2H, m, Ar**H**), 7.06 – 6.92 (2H, m, Ar**H**), 6.75 – 6.57 (1H, m, NCOC**H**CHH'), 6.43 – 6.32 (1H, m, NCOCHC**H**H'), 5.82 – 5.72 (1H, m, NCOCHCH**H'**), 4.86 – 4.47 (2H, m, ArC$\mathbf{H}_2$), 3.74 – 3.47 (6H, m, C**H** (rotamer) and C$\mathbf{H}_2$),3.03 – 2.87 (3H, m, C**H** (rotamer) and C$\mathbf{H}_2$), 2.58 (1H, t, *J* = 6.8 Hz, C$\mathbf{H}_2$), 2.54 – 2.28 (3H, m, C$\mathbf{H}_2$), 1.72 – 1.45 (4H, m, C$\mathbf{H}_2$), 0.39 – 0.27 (4H, m, cyclopropyl C$\mathbf{H}_2$). For a diagnostic ^1H NMR signal for one of the individual rotamers: 2.53 (1H, tt, *J* = 6.8, 3.9 Hz, cyclopropyl C**H**); δ_C (100 MHz, $CDCl_3$) 175.5 (**C**O), 174.7 (**C**O), 174.2 (**C**O), 173.4 (**C**O), 172.9 (**C**O), 172.60 (**C**O), 172.54 (**C**O), 171.4 (**C**O), 168.9 (**C**O), 168.8 (**C**O), 162.28 (Ar**C**F, $^1J_{CF}$ = 245.5 Hz), 162.22 (Ar**C**F, $^1J_{CF}$ = 245.5 Hz), 162.15 (Ar**C**F, $^1J_{CF}$ = 245.5 Hz), 133.6 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 133.4 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 132.6 (Ar**C**, $^4J_{CF}$ = 3.2 Hz), 130.62 (NCO**C**HCHH', one rotamer), 130.57 (NCO**C**HCHH', two rotamers), 130.1 (NCOCH**C**HH', two rotamers), 129.0 (NCOCH**C**HH', one rotamer), 129.7 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.3 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 128.0 (2 × Ar**C**H, $^3J_{CF}$ = 8.1 Hz), 116.0 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.8 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.6 (2 × Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 53.6 (**C**H_2), 52.0 (**C**H), 51.8 (**C**H), 51.5 (**C**H_2), 50.8 (**C**H_2), 47.7 (**C**H_2), 44.30 (**C**H_2), 44.25 (**C**H_2), 43.8 (**C**H_2), 43.6 (**C**H_2), 42.9 (**C**H_2), 42.7 (**C**H_2), 41.8 (**C**H_2), 36.0 (**C**H_2), 35.6 (**C**H_2), 35.5 (**C**H), 33.4 (**C**H_2), 32.8 (**C**H_2), 32.7 (**C**H_2), 32.4 (**C**H_2), 32.3 (**C**H_2), 29.9 (**C**H), 29.0 (**C**H_2), 28.9 (**C**H_2), 28.4 (**C**H_2), 22.5 (**C**H_2), 22.35 (**C**H_2), 22.3 (**C**H_2), 9.7 (cyclopropyl **C**H_2), 7.1 (cyclopropyl **C**H_2, two rotamers); δ_F (376 MHz, $CDCl_3$), four major rotamers in a 10:1:8:5 ratio: –114.61 (1F, m, ArF, major rotamer), –114.78 (1F, m, ArF), –115.00 (1F, m, ArF), –115.17 (1F, m, ArF); HRMS (ESI): calcd. for $C_{24}H_{30}FN_3NaO_4$, 466.2113. Found: $[MNa]^+$, 466.2114 (–0.4 ppm error).

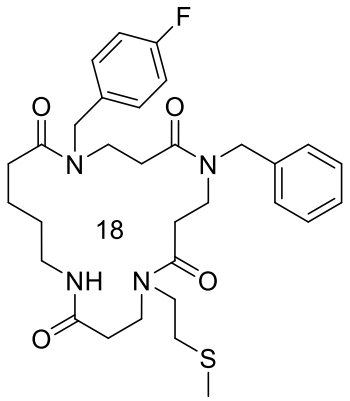
1-Acryloyl-5-(benzo[*d*][1,3]dioxol-5-ylmethyl)-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (S4)



A stirring solution of **31c** (73.1 mg, 0.151 mmol) and DIPEA (0.065 mL, 0.37 mmol) in DCM (2.5 mL) was cooled to 0 °C. To this was added a 0 °C cooled solution of acryloyl chloride (0.018 mL, 0.22 mmol) in DCM (0.5 mL) dropwise. Under an argon atmosphere this mixture was stirred at 0 °C for 2 hours. Afterwards it was allowed to warm to RT and stirred for a further 15 hours. The reaction mixture was then quenched with sat. aq. NH_4Cl (8 mL), extracted with Et_2O (10 mL), then the organic layer was washed with sat. aq. $NaHCO_3$ (2 × 5 mL). The organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:2 ethyl acetate: hexane → 2:1 ethyl acetate: hexane → ethyl acetate) afforded the *title compound* a colorless oil (22.0 mg, 27%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 2 major rotameric forms (≈3:2) based on the carbonyl region of the ^{13}C NMR spectrum, and a third more minor rotamer based on the ^{19}F NMR data. Due to overlapping signals in the ^{1}H and ^{19}F NMR, it is difficult to confidently quote a rotamer ratio; R_f 0.68 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 2932, 1682, 1637, 1508, 1490, 1443, 1410, 1374, 1223, 1143, 1038, 923, 812, 732; δ_H (400 MHz, $CDCl_3$) 7.24 – 7.10 (2H, m, Ar**H**), 7.07 – 6.94 (2H, m, Ar**H**), 6.84 – 6.65 (3H, m, Ar**H** and C**H**CH_2), 6.63 – 6.57 (1H, m, Ar**H**), 6.37 (1H, dd, *J* = 16.8, 1.7 Hz, CHC**H**H', major rotamer), 5.95 – 5.91 (2H, m, OC**H₂**O), 5.74 (1H, dd, *J* = 10.3, 1.7 Hz, CHCH**H**', major rotamer), 4.83 – 4.46 (4H, m, ArC**H**$_2$), 3.92 – 3.57 (4H, m, C**H**$_2$), 3.42 (1H, br s, C**H**$_2$), 3.03 (1H, br s, C**H**$_2$), 2.91 – 2.67 (2H, m, C**H**$_2$), 2.53 – 2.33 (2H, m, C**H**$_2$), 1.89 – 1.48 (4H, m, C**H**$_2$). Diagnostic ^{1}H NMR signals for the minor rotamer: 6.34 (1H, dd, *J* = 16.8, 1.7 Hz, CHC**H**H', minor rotamer), 5.73 (1H, dd, *J* = 10.4, 1.6 Hz, CHCH**H**', minor rotamer [overlapping]); δ_C (100 MHz, $CDCl_3$) 175.5 (**C**O), 173.9 (**C**O), 173.7 (**C**O), 173.6 (**C**O), 172.4 (**C**O), 172.1 (**C**O), 169.2 (**C**O), 168.8 (**C**O), 162.3 (Ar**C**F, $^{1}J_{CF}$ = 246.0 Hz), 148.3 (Ar**C**OCH$_2$), 148.0 (Ar**C**OCH$_2$), 147.18 (Ar**C**OCH$_2$), 147.15 (Ar**C**OCH$_2$) 134.8 (**C**H$_2$), 133.1 (Ar**C**, $^{4}J_{CF}$ = 3.1 Hz), 133.0 (Ar**C**, $^{4}J_{CF}$ = 3.1 Hz), 132.12 (Ar**C**), 132.02 (**C**H$_2$), 131.6 (**C**H), 131.5 (**C**H), 131.3 (**C**H), 131.0 (Ar**C**), 129.9 (Ar**C**H, $^{3}J_{CF}$ = 8.2 Hz), 129.0 (**C**H$_2$), 128.9 (**C**H$_2$), 128.4 (Ar**C**H, $^{3}J_{CF}$ = 8.2 Hz), 128.3 (Ar**C**H, $^{3}J_{CF}$ = 8.2 Hz), 127.6 (Ar**C**H), 121.8 (Ar**C**H), 119.8 (Ar**C**H), 115.92 (Ar**C**H, $^{2}J_{CF}$ = 21.5 Hz), 115.89 (Ar**C**H, $^{2}J_{CF}$ = 21.5 Hz), 108.8 (Ar**C**H), 108.6 (Ar**C**H), 108.3 (Ar**C**H), 107.0 (Ar**C**H), 106.6 (Ar**C**H), 101.3

(O**C**H_2O), 101.2 (O**C**H_2O), 53.8 (**C**H_2), 53.6 (**C**H_2), 53.2 (**C**H_2), 50.0 (**C**H_2), 44.6 (**C**H_2), 44.5 (**C**H_2), 43.9 (**C**H_2), 43.7 (**C**H_2), 43.2 (**C**H_2), 36.7 (**C**H_2), 35.2 (**C**H_2), 34.1 (**C**H_2), 31.6 (**C**H_2), 31.2 (**C**H_2), 31.1 (**C**H_2), 29.8 (**C**H_2), 28.9 (**C**H_2), 27.5 (**C**H_2), 23.0 (**C**H_2), 21.6 (**C**H_2); δ_F (376 MHz, $CDCl_3$), three signals in a 20:14:1 ratio: –114.74 (1F, m, ArF), –114.77 (1F, m, ArF, major rotamer),–115.05 (1F, m, ArF), –115.19 (1F, m, ArF); HRMS (ESI): calcd. for $C_{29}H_{32}FN_3NaO_6$, 560.2167. Found: $[MNa]^+$, 560.2185 (–3.1 ppm error).

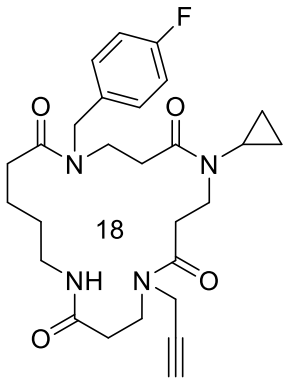
9-Benzyl-13-(4-fluorobenzyl)-5-(2-(methylthio)ethyl)-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (32a)



To a solution of **S2** (258 mg, 0.523 mmol) in dry methanol (1.04 mL), was added 2-(methylthio)ethylamine (53 µL, 0.575 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 → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a white solid (196 mg, 64%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 8 rotameric forms observable in the ^{19}F NMR data, and 32 (*i.e*. 4 × 8) signals consistent with CO groups in the ^{13}C NMR. Due to overlapping signals in the NMR data, it is not possible to confidently quote a rotamer ratio; m.p. 43–57 °C; R_f 0.11 (1:9 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3310, 2928, 1626, 1551, 1509, 1424, 1364, 1220, 1157, 921, 823, 730, 700, 499; δ_H (400 MHz, $CDCl_3$) 8.08 (1H, br t, *J* = 4.6 Hz, N**H**), 7.61 (1H, br t, *J* = 5.0 Hz, N**H**, rotamer), 7.52 (1H, br t, *J* = 5.6 Hz, N**H**), 7.47 (1H, br t, *J* = 6.0 Hz, N**H**), 7.42 – 6.89 (9H, m, Ar**H**), 4.86 – 4.35 (4H, m, 2 × ArC**H₂**), 3.81 – 3.13 (10H, m, 5 × C**H₂**), 2.95 – 2.26 (10H, m, 5 × C**H₂**), 2.16 – 2.02 (3H, m, C**H₃**), 1.91 – 1.44 (4H, m, 2 × C**H₂**); δ_C (100 MHz, $CDCl_3$) 174.21 (**C**O), 174.10 (**C**O), 174.02 (**C**O), 173.94 (**C**O), 173.78 (**C**O), 173.70 (**C**O), 173.41 (**C**O), 173.11 (**C**O), 172.69 (**C**O), 172.61 (**C**O), 172.16 (**C**O), 172.08 (**C**O), 172.05 (**C**O), 171.88 (**C**O), 171.52 (**C**O), 171.44 (**C**O), 171.41 (**C**O), 171.29 (**C**O), 171.24 (**C**O), 171.19 (**C**O), 171.16 (**C**O), 171.11 (**C**O), 170.97 (**C**O), 170.72 (**C**O), 170.68 (**C**O), 170.62 (**C**O), 170.49 (**C**O), 170.47 (**C**O), 170.44 (**C**O), 170.32 (**C**O), 170.12 (**C**O), 169.96 (**C**O), 161.97 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.92 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.88 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.83 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.80 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 161.73 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 137.51 (Ar**C**), 137.38

(Ar**C**), 137.34 (Ar**C**), 137.13 (Ar**C**), 136.96 (Ar**C**), 136.86 (Ar**C**), 136.78 (Ar**C**), 136.38 (Ar**C**), 136.31 (Ar**C**), 135.84 (Ar**C**), 135.71 (Ar**C**), 133.64 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 133.43 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 133.18 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 133.07 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 132.70 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 132.32 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 132.19 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 132.10 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 129.63 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 129.48 (Ar**C**H), 129.43 (Ar**C**H), 129.39 (Ar**C**H), 129.13 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 128.98 (Ar**C**H), 128.90 (Ar**C**H), 128.86 (Ar**C**H), 128.68 (Ar**C**H), 128.63 (Ar**C**H), 128.52 (Ar**C**H), 128.43 (Ar**C**H), 128.33 (Ar**C**H), 128.06 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 127.94 (Ar**C**H), 127.88 (Ar**C**H), 127.82 (Ar**C**H), 127.80 (Ar**C**H), 127.71 (Ar**C**H), 127.50 (Ar**C**H), 127.30 (Ar**C**H), 127.14 (Ar**C**H), 126.27 (Ar**C**H), 126.08 (Ar**C**H), 125.91 (Ar**C**H), 125.75 (Ar**C**H), 125.73 (Ar**C**H), 126.27 (Ar**C**H), 126.08 (Ar**C**H), 125.91 (Ar**C**H), 125.75 (Ar**C**H), 115.65 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 115.58 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 115.54 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 115.23 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 115.54 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 115.23 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 115.12 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 114.99 (Ar**C**H, $^{2}J_{CF}$ = 21.1 Hz), 55.86 (**C**H_2), 53.22 (**C**H_2), 52.93 (**C**H_2), 52.67 (**C**H_2), 52.33 (**C**H_2), 51.92 (**C**H_2), 51.83 (**C**H_2), 51.23 (**C**H_2), 49.96 (**C**H_2), 49.11 (**C**H_2), 49.01 (**C**H_2), 48.81 (**C**H_2), 48.59 (**C**H_2), 48.28 (**C**H_2), 48.25 (**C**H_2), 48.10 (**C**H_2), 47.80 (**C**H_2), 47.49 (**C**H_2), 47.18 (**C**H_2), 46.91 (**C**H_2), 46.79 (**C**H_2), 46.42 (**C**H_2), 45.89 (**C**H_2), 45.60 (**C**H_2), 45.45 (**C**H_2), 45.33 (**C**H_2), 45.02 (**C**H_2), 44.89 (**C**H_2), 44.62 (**C**H_2), 44.26 (**C**H_2), 44.17 (**C**H_2), 44.03 (**C**H_2), 43.75 (**C**H_2), 43.65 (**C**H_2), 43.58 (**C**H_2), 43.54 (**C**H_2), 43.48 (**C**H_2), 43.36 (**C**H_2), 43.23 (**C**H_2), 43.11 (**C**H_2), 42.87 (**C**H_2), 42.68 (**C**H_2), 42.47 (**C**H_2), 42.33 (**C**H_2), 42.25 (**C**H_2), 41.20 (**C**H_2), 40.24 (**C**H_2), 39.41 (**C**H_2), 39.22 (**C**H_2), 39.13 (**C**H_2), 38.66 (**C**H_2), 38.58 (**C**H_2), 38.20 (**C**H_2), 38.06 (**C**H_2), 37.56 (**C**H_2), 37.51 (**C**H_2), 37.33 (**C**H_2), 36.91 (**C**H_2), 36.20 (**C**H_2), 35.33 (**C**H_2), 35.27 (**C**H_2), 34.93 (**C**H_2), 34.79 (**C**H_2), 34.15 (**C**H_2), 33.99 (**C**H_2), 33.52 (**C**H_2), 33.44 (**C**H_2), 33.23 (**C**H_2), 33.05 (**C**H_2), 32.78 (**C**H_2), 32.74 (**C**H_2), 32.64 (**C**H_2), 32.53 (**C**H_2), 32.49 (**C**H_2), 32.41 (**C**H_2), 32.32 (**C**H_2), 32.24 (**C**H_2), 32.14 (**C**H_2), 32.05 (**C**H_2), 31.98 (**C**H_2), 31.81 (**C**H_2), 31.75 (**C**H_2), 31.65 (**C**H_2), 31.56 (**C**H_2), 31.52 (**C**H_2), 31.44 (**C**H_2), 31.34 (**C**H_2), 31.24 (**C**H_2), 31.20 (**C**H_2), 31.05 (**C**H_2), 30.93 (**C**H_2), 30.76 (**C**H_2), 30.67 (**C**H_2), 30.58 (**C**H_2), 29.34 (**C**H_2), 28.76 (**C**H_2), 28.56 (**C**H_2), 27.96 (**C**H_2), 27.87 (**C**H_2), 27.73 (**C**H_2), 27.61 (**C**H_2), 27.41 (**C**H_2), 27.20 (**C**H_2), 27.03 (**C**H_2), 23.60 (**C**H_2), 23.12 (**C**H_2), 22.99 (**C**H_2), 22.68 (**C**H_2), 22.18 (**C**H_2), 22.08 (**C**H_2), 22.03 (**C**H_2), 20.65 (**C**H_2), 20.49 (**C**H_2), 15.58 (**C**H_3), 15.22 (**C**H_3); δ_F (376 MHz, $CDCl_3$), eight signals in a 14:24:19:7:16:7:7:6 ratio: –114.33 (1F, m, ArF), –114.47 (1F, m, ArF, major rotamer), –114.59 (1F, m, ArF), –114.72 (1F, m, ArF), –114.79 (1F, m, ArF), –115.04 (1F, m, ArF), –115.15 (1F, m, ArF), –115.47 (1F, m, ArF); HRMS (ESI): calcd. for $C_{31}H_{41}FN_4NaO_4S$, 607.2725. Found: $[MNa]^+$, 607.2708 (2.8 ppm error).

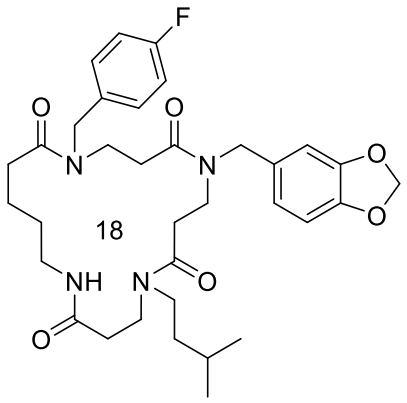
9-Cyclopropyl-13-(4-fluorobenzyl)-5-(prop-2-yn-1-yl)-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (32b)



To a solution of **S3** (98.1 mg, 0.221 mmol) in dry methanol (0.44 mL), was added propargyl amine (16 µL, 0.243mmol) 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 → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate → 1:6 methanol: ethyl acetate → 1:4 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (27.6 mg, 25%). This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 6 rotameric forms observable in the ^{19}F NMR data. Due to overlapping signals in the NMR data, it is not possible to confidently quote a rotamer ratio; R_f 0.33 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3295, 2941, 1733, 1634, 1552, 1510, 1438, 1369, 1219, 1017, 826, 731; δ_H (700 MHz, $CDCl_3$), 7.23 – 7.13 (2H, m, Ar**H**), 7.10 (1H, t, *J* = 6.6 Hz, N**H**, rotamer), 7.06 – 6.95 (2H, m, Ar**H**), 6.92 (1H, t, *J* = 6.0 Hz, N**H**, rotamer), 6.66 (1H, t, *J* = 5.5 Hz, N**H**, rotamer), 4.63 – 4.48 (2H, m, C**H**$_2$), 4.22 – 4.11 (2H, m, C**H**$_2$), 3.81 – 3.50 (4H, m, C**H**$_2$), 3.45 – 3.13 (2H, m, C**H**$_2$), 2.96 – 2.16 (12H, m, C**H**$_2$ and C**H**), 1.87 – 1.43 (4H, m, C**H**$_2$), 0.96 – 0.55 (4H, m, cyclopropyl C**H**$_2$); δ_C (176 MHz, $CDCl_3$), 174.36 (**C**O), 174.10 (**C**O), 173.94 (**C**O), 173.81 (**C**O), 173.78 (**C**O), 173.71 (**C**O), 172.58 (**C**O), 172.49 (**C**O), 171.64 (**C**O), 171.54 (**C**O), 171.50 (**C**O), 171.48 (**C**O), 171.06 (**C**O), 170.37 (**C**O), 170.26 (**C**O), 169.89 (**C**O), 162.35 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.31 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.24 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.20 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 162.18 (Ar**C**F, $^1J_{CF}$ = 246.0 Hz), 133.99 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 133.91 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 133.39 (Ar**C**F), 132.70 (Ar**C**F, $^4J_{CF}$ = 3.2 Hz), 132.54 (Ar**C**F), 129.96 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 129.50 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 129.22 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.32 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.23 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 128.09 (Ar**C**H, $^3J_{CF}$ = 8.0 Hz), 116.05 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 116.02 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.95 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.60 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 115.55 (Ar**C**H, $^2J_{CF}$ = 21.5 Hz), 79.22 (**C**CH), 78.98 (**C**CH), 78.80 (**C**CH), 78.63 (**C**CH), 72.85 (C**C**H), 72.45 (C**C**H), 72.06 (C**C**H), 71.89 (C**C**H), 51.50 (**C**H$_2$), 51.44 (**C**H$_2$), 50.05 (**C**H$_2$), 47.94 (**C**H$_2$), 47.82 (**C**H$_2$), 45.92 (**C**H$_2$), 45.52 (**C**H$_2$), 45.48 (**C**H$_2$), 43.99 (**C**H$_2$), 43.93 (**C**H$_2$), 43.82 (**C**H$_2$), 43.64 (**C**H$_2$), 43.15 (**C**H$_2$), 42.97 (**C**H$_2$), 42.47 (**C**H$_2$), 40.58 (**C**H$_2$), 39.65 (**C**H$_2$), 39.55 (**C**H$_2$), 39.43 (**C**H$_2$), 39.32 (**C**H$_2$),

39.09 (**C**H_2), 37.53 (**C**H_2), 37.22 (**C**H_2), 35.75 (**C**H_2), 35.11 (**C**H_2), 34.81 (**C**H_2), 33.42 (**C**H_2), 33.27 (**C**H_2), 33.25 (**C**H_2), 32.84 (**C**H_2), 32.73 (**C**H_2), 32.69 (**C**H_2), 32.64 (**C**H_2), 32.40 (**C**H_2), 32.11 (**C**H_2), 31.94 (**C**H_2), 31.87 (**C**H_2), 31.51 (**C**H_2), 30.90 (**C**H_2), 30.53 (**C**H), 30.37 (**C**H), 30.31 (**C**H), 29.79 (**C**H_2), 29.71 (**C**H), 28.67 (**C**H_2), 28.46 (**C**H_2), 28.30 (**C**H_2), 27.96 (**C**H_2), 27.24 (**C**H_2), 23.40 (**C**H_2), 22.67 (**C**H_2), 22.58 (**C**H_2), 22.31 (**C**H_2), 9.87 (cyclopropyl **C**H_2), 9.67 (cyclopropyl **C**H_2), 9.31 (cyclopropyl **C**H_2), 9.25 (cyclopropyl **C**H_2); δ_F (376 MHz, $CDCl_3$), six rotamers in a 7:5:9:1:12:4 ratio: –114.42 (1F, m, ArF), –114.57 (1F, m, ArF), –114.65 (1F, m, ArF), –114.80 (1F, m, ArF), –114.92 (1F, m, ArF, major rotamer), –115.08 (1F, m, ArF); HRMS (ESI): calcd. for $C_{27}H_{35}FN_4NaO_4$, 521.2535. Found: $[MNa]^+$, 521.2536 (–0.3 ppm error).

9-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-13-(4-fluorobenzyl)-5-isopentyl-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (32c)



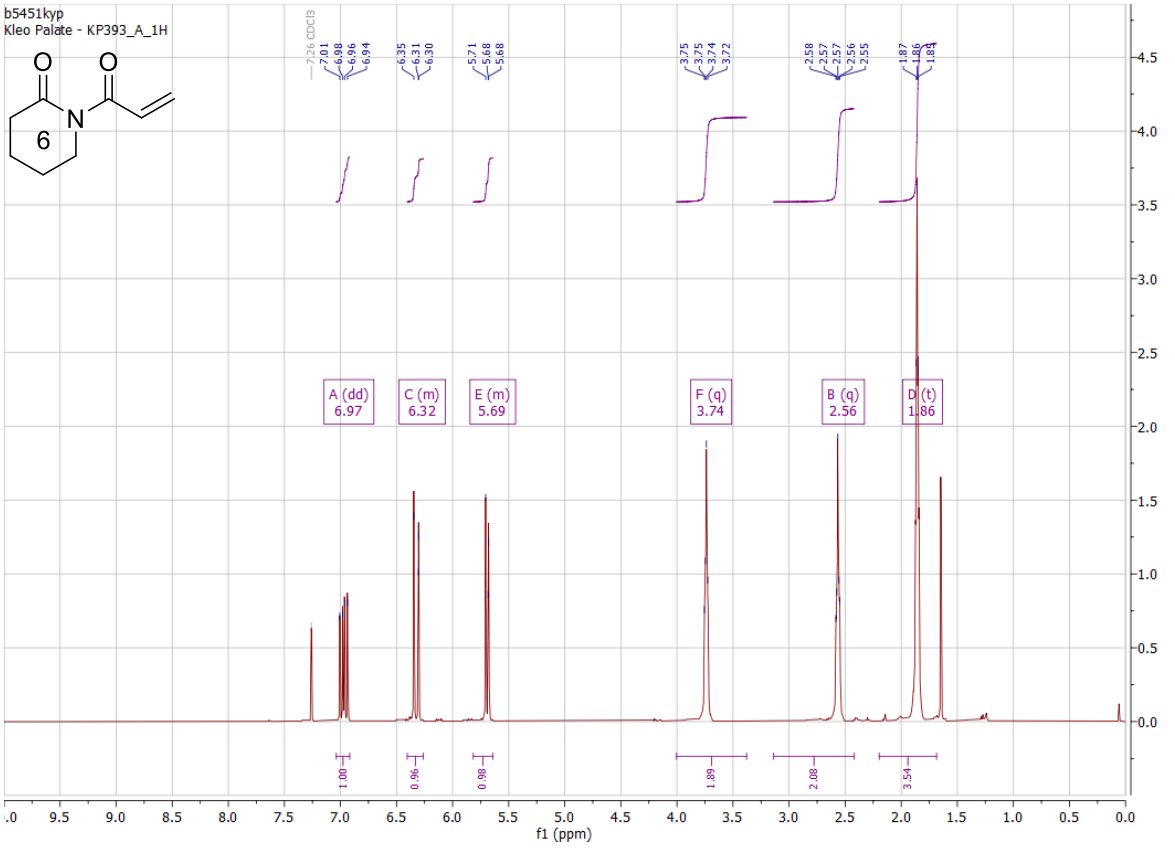
To a solution of **S4** (53.3 mg, 0.099 mmol) in dry methanol (0.24 mL), was added isopentylamine (15 µL, 0.130 mmol) in a single portion. The reaction mixture was allowed to stir for 4 h at RT and then the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 1:19 methanol: ethyl acetate → 1:9 methanol: ethyl acetate) afforded the *title compound* as a colourless oil (37.1 mg, 60%); R_f 0.45 (1:4 methanol: ethyl acetate); ν_{max}/cm^{-1} (thin film) 3308, 2942, 1628, 1557, 1508, 1489, 1442, 1368, 1243, 1221, 1097, 1038, 924, 813, 731; δ_H (600 MHz, $CDCl_3$) 8.01 (1H, br t, *J* = 5.1 Hz N**H**, rotamer), 7.40 – 7.36 (1H, m, N**H**, rotamer), 7.34 (1H, br t, *J* = 5.6 Hz N**H**, rotamer), 7.25 – 7.07 (2H, m, Ar**H**), 7.07 – 6.90 (2H, m, Ar**H**), 6.81 – 6.44 (3H, m, Ar**H**), 5.96 – 5.87 (2H, m, OC**H₂**O), 4.77 – 4.19 (4H, m, 2 × ArC**H₂**), 3.76 – 3.46 (6H, m, 3 × C**H₂**), 3.40 – 2.98 (4H, m, 2 × C**H₂**), 2.87 – 2.24 (8H, m, 4 × C**H₂**), 1.86 – 1.12 (7H, m, 3 × C**H₂**and C**H**, [overlapping]), 0.92 – 0.83 (6H, m, 2 × C**H₃**); δ_C (151 MHz, $CDCl_3$) 174.49 (**C**O), 174.14 (**C**O), 174.05 (**C**O), 173.96 (**C**O), 173.86 (**C**O), 173.84 (**C**O), 173.39 (**C**O), 173.60 (**C**O), 173.39 (**C**O), 173.12 (**C**O), 172.71 (**C**O), 172.64 (**C**O), 172.32 (**C**O), 172.14 (**C**O), 172.02 (**C**O), 171.98 (**C**O), 171.63 (**C**O), 171.46 (**C**O), 171.39 (**C**O), 171.22 (**C**O), 171.01 (**C**O), 170.85 (**C**O), 170.75 (**C**O), 170.55 (**C**O), 170.53 (**C**O), 170.43 (**C**O), 170.37 (**C**O), 170.30 (**C**O), 170.19 (**C**O), 170.04 (**C**O), 170.03 (**C**O), 169.77 (**C**O), 162.36 (Ar**C**F, $^1J_{CF}$

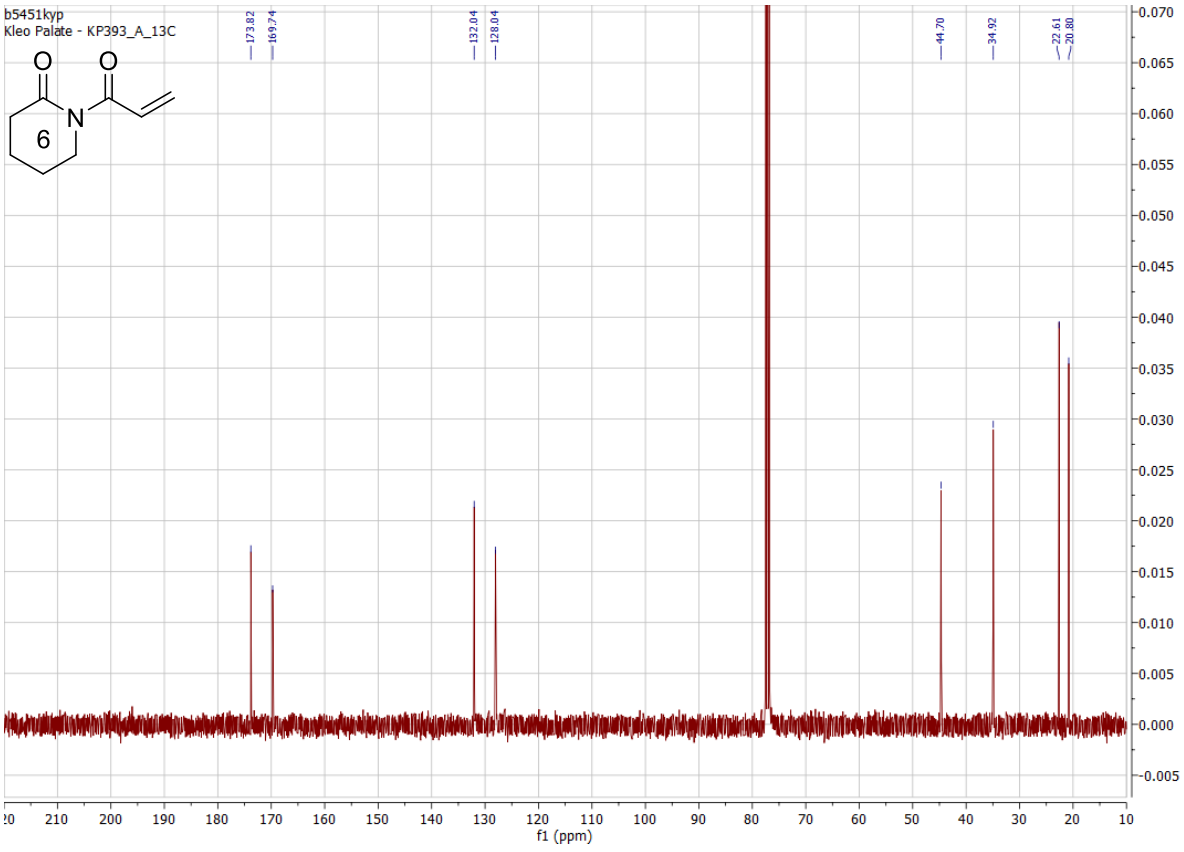
= 246.5 Hz), 162.34 (Ar**C**F, $^{1}J_{CF}$ = 246.5 Hz), 162.30 (Ar**C**F, $^{1}J_{CF}$ = 246.5 Hz), 162.23 (Ar**C**F, $^{1}J_{CF}$ = 246.5 Hz), 148.55 (Ar**C**OCH$_2$), 148.33 (Ar**C**OCH$_2$), 148.27 (Ar**C**OCH$_2$), 148.20 (Ar**C**OCH$_2$), 148.05 (Ar**C**OCH$_2$), 147.94 (Ar**C**OCH$_2$), 147.51 (Ar**C**OCH$_2$), 147.29 (Ar**C**OCH$_2$), 147.19 (Ar**C**OCH$_2$), 147.10 (Ar**C**OCH$_2$), 147.06 (Ar**C**OCH$_2$), 147.00 (Ar**C**OCH$_2$), 133.90 (Ar**C**), 133.74 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 133.50 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 133.41 (Ar**C**), 132.83 (Ar**C**), 132.59 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz),1 32.38 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz), 132.34 (Ar**C**F, $^{4}J_{CF}$ = 3.0 Hz),131.83 (Ar**C**), 131.72 (Ar**C**), 131.52 (Ar**C**), 131.18 (Ar**C**), 130.71 (Ar**C**), 130.35 (Ar**C**), 130.03 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 129.86 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 129.83 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 129.70 (Ar**C**), 129.53 (Ar**C**), 129.48 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 129.31 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 128.31 (Ar**C**H, $^{3}J_{CF}$ = 8.1 Hz), 128.20 (Ar**C**H), 128.15 (Ar**C**H), 128.10 (Ar**C**H), 128.05 (Ar**C**H), 121.68 (Ar**C**H), 121.61 (Ar**C**H), 121.43 (Ar**C**H), 121.01 (Ar**C**H), 119.84 (Ar**C**H), 119.54 (Ar**C**H), 119.49 (Ar**C**H), 119.42 (Ar**C**H), 116.05 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 116.02 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.95 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.62 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.57 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 115.46 (Ar**C**H, $^{2}J_{CF}$ = 21.6 Hz), 108.80 (Ar**C**H), 108.76 (Ar**C**H), 108.66 (Ar**C**H), 108.64 (Ar**C**H), 108.59 (Ar**C**H), 108.55 (Ar**C**H), 108.34 (Ar**C**H), 108.26 (Ar**C**H), 108.21 (Ar**C**H), 107.12 (Ar**C**H), 106.94 (Ar**C**H), 106.79 (Ar**C**H), 106.60 (Ar**C**H), 106.55 (Ar**C**H), 115.53 (O**C**H$_2$O), 115.38 (O**C**H$_2$O), 101.46 (O**C**H$_2$O), 101.43 (O**C**H$_2$O), 101.29 (O**C**H$_2$O), 101.26 (O**C**H$_2$O), 101.22 (O**C**H$_2$O), 101.13 (O**C**H$_2$O), 101.06 (O**C**H$_2$O), 53.52 (**C**H$_2$), 53.12 (**C**H$_2$), 53.03 (**C**H$_2$), 52.62 (**C**H$_2$), 52.50 (**C**H$_2$), 52.27 (**C**H$_2$), 52.16 (**C**H$_2$), 52.06 (**C**H$_2$), 51.81 (**C**H$_2$), 51.53 (**C**H$_2$), 50.56 (**C**H$_2$), 49.80 (**C**H$_2$), 49.42 (**C**H$_2$), 49.26 (**C**H$_2$), 49.11 (**C**H$_2$), 48.63 (**C**H$_2$), 48.27 (**C**H$_2$), 47.99 (**C**H$_2$), 47.85 (**C**H$_2$), 47.68 (**C**H$_2$), 47.23 (**C**H$_2$), 46.94 (**C**H$_2$), 46.74 (**C**H$_2$), 46.33 (**C**H$_2$), 46.15 (**C**H$_2$), 45.82 (**C**H$_2$), 45.34 (**C**H$_2$), 45.25 (**C**H$_2$), 44.96 (**C**H$_2$), 44.89 (**C**H$_2$), 44.85 (**C**H$_2$), 44.74 (**C**H$_2$), 44.52 (**C**H$_2$), 44.25 (**C**H$_2$), 44.09 (**C**H$_2$), 44.04 (**C**H$_2$), 43.85 (**C**H$_2$), 43.74 (**C**H$_2$), 43.68 (**C**H$_2$), 43.52 (**C**H$_2$), 43.23 (**C**H$_2$), 43.07 (**C**H$_2$), 42.98 (**C**H$_2$), 42.77 (**C**H$_2$), 42.39 (**C**H$_2$), 41.88 (**C**H$_2$), 39.65 (**C**H$_2$), 39.51 (**C**H$_2$), 39.18 (**C**H$_2$), 38.94 (**C**H$_2$), 38.49 (**C**H$_2$), 38.34 (**C**H$_2$), 38.07 (**C**H$_2$), 37.83 (**C**H$_2$), 37.68 (**C**H$_2$), 37.64 (**C**H$_2$), 37.52 (**C**H$_2$), 37.28 (**C**H$_2$), 36.96 (**C**H$_2$), 36.75 (**C**H$_2$), 36.68 (**C**H$_2$), 36.57 (**C**H$_2$), 36.22 (**C**H$_2$), 35.88 (**C**H$_2$), 35.86 (**C**H$_2$), 35.79 (**C**H$_2$), 35.37 (**C**H$_2$), 35.12 (**C**H$_2$), 33.60 (**C**H$_2$), 33.52 (**C**H$_2$), 33.46 (**C**H$_2$), 33.21 (**C**H$_2$), 33.11 (**C**H$_2$), 32.96 (**C**H$_2$), 32.83 (**C**H$_2$), 32.65 (**C**H$_2$), 32.53 (**C**H$_2$), 32.31 (**C**H$_2$), 32.19 (**C**H$_2$), 32.12 (**C**H$_2$), 32.02 (**C**H$_2$), 31.98 (**C**H$_2$), 31.94 (**C**H$_2$), 31.91 (**C**H$_2$), 31.84 (**C**H$_2$), 31.69 (**C**H$_2$), 31.34 (**C**H$_2$), 31.10 (**C**H$_2$), 30.95 (**C**H$_2$), 29.69 (**C**H$_2$), 29.07 (**C**H$_2$), 28.78 (**C**H$_2$), 28.12 (**C**H$_2$), 27.95 (**C**H$_2$), 27.74 (**C**H$_2$), 27.23 (**C**H$_2$), 27.05 (**C**H$_2$), 26.38 (**C**H), 26.32 (**C**H), 26.23 (**C**H), 26.14 (**C**H), 26.10 (**C**H), 26.04 (**C**H), 26.00 (**C**H), 25.97 (**C**H), 23.87 (**C**H$_2$), 23.48 (**C**H$_2$), 23.25 (**C**H$_2$), 22.97 (**C**H$_2$), 22.61 (**C**H$_3$), 22.59 (**C**H$_3$), 22.48 (**C**H$_3$), 22.42 (**C**H$_3$), 22.39 (**C**H$_2$), 20.77 (**C**H$_2$); δ_F (376 MHz, $CDCl_3$), eight rotamers in a 42:8:14:13:6:8:5:3 ratio: −114.34 (1F, m, ArF, major rotamer), −114.50 (1F, m, ArF), −114.57 (1F, m, ArF), −114.71 (1F, m, ArF), −114.83 (1F, m, ArF), −115.12 (1F, m, ArF), −115.19 (1F, m, ArF), −115.50 (1F, m, ArF). HRMS (ESI): calcd. for $C_{34}H_{45}FN_4NaO_6$, 647.3215. Found: $[MNa]^+$, 647.3223 (–1.2 ppm error).

NMR data for were also collected in d_6-DMSO at 120 °C to reduce the number of rotameric forms, leading greatly simplified NMR spectra:

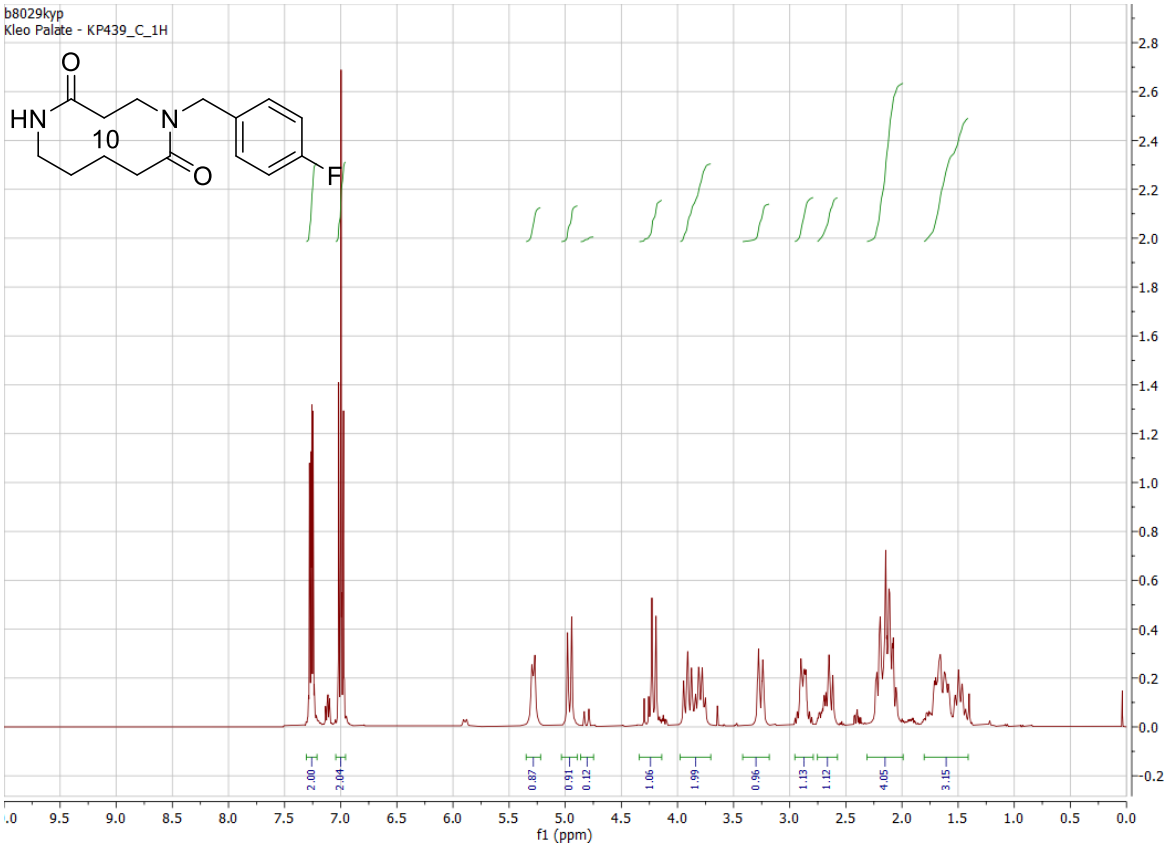
δ_H (500 MHz, d_6-DMSO, 120 °C) 2 major rotamers were observed under these conditions, with most signals broadened; 7.60 (1H, br s, N**H**, minor rotamer), 7.52 (1H, br s, N**H**, major rotamer), 7.31 – 7.23 (2H, m, Ar**H**), 7.15 – 7.06 (2H, m, Ar**H**), 6.65 – 6.68 (3H, m, Ar**H**), 5.96 (2H, s, OC**H₂**O), 4.60 – 4.52 (2H, m, ArC**H₂**), 4.47 – 4.41 (2H, m, ArC**H₂**), 3.65 – 3.43 (6H, m, 3 × C**H₂**), 3.30 – 3.20 (2H, m, C**H₂**), 3.19 – 3.05 (3H, m, 1.5 × C**H₂**), 2.72 – 2.53 (3H, m, 1.5 × C**H₂**), 2.45 – 2.30 (4H, m, 2 × C**H₂**), 1.68 – 1.44 (4H, m, 2 × C**H₂**), [overlapping]), 1.54 (1H, dt, *J* = 13.4, 6.7 Hz, C**H**, [overlapping]), 1.40 – 1.32 (2H, m, C**H₂**), 0.91 (6H, d, *J* = 6.7 Hz, 2 × C**H₃**); Diagnostic ^{13}C resonances are provided; there is clear evidence for rotemric broadening in the ^{13}C NMR spectrum, which explains why all carbons are not accounted for: δ_C (126 MHz, d_6-DMSO, 120 °C); 173.1 (**C**O), 171.1 (**C**O), 170.6 (**C**O), 162.0 (Ar**C**F, $^1J_{CF}$ = 243.2 Hz), 148.1 (Ar**C**OCH$_2$), 147.0 (Ar**C**OCH$_2$), 135.0 (Ar**C**), 129.7 (Ar**C**H), 115.53 (Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 115.46 (Ar**C**H, $^2J_{CF}$ = 21.3 Hz), 108.5 (Ar**C**H), 101.3 (O**C**H$_2$O), 43.8 (**C**H$_2$), 32.2 (**C**H$_2$), 26.1 (**C**H), 22.7 (**C**H$_3$); δ_F (471 MHz, d_6-DMSO, 120 °C) two rotamers (broadened, and overlapping) in a 8:5 ratio: −115.99 (1F, m, ArF, major rotamer), −116.07 (1F, m, ArF).

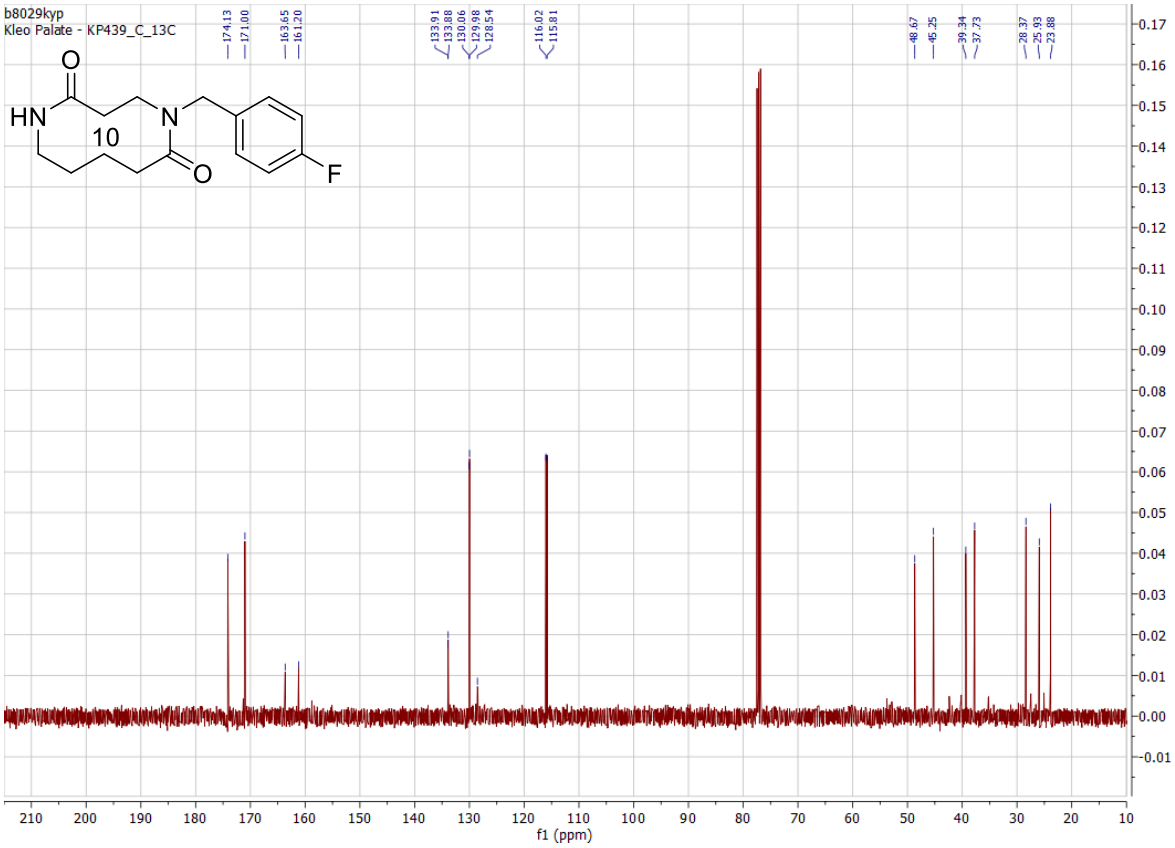
1-Acryloyl-piperidin-2-one (11a)

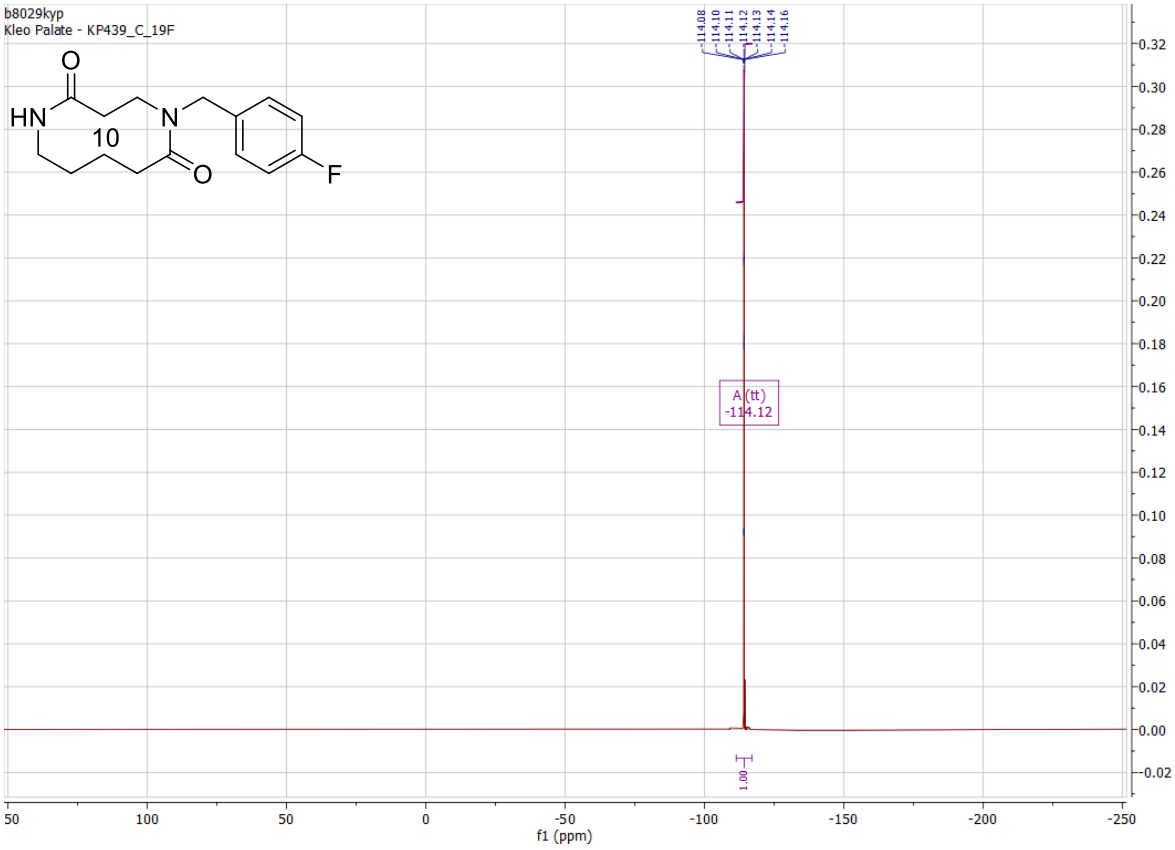




5-(4-Fluorobenzyl)-1,5-diazecane-2,6-dione (14a) 2:15 mixture of rotamers.



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O
N
10
O
F
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-114.12
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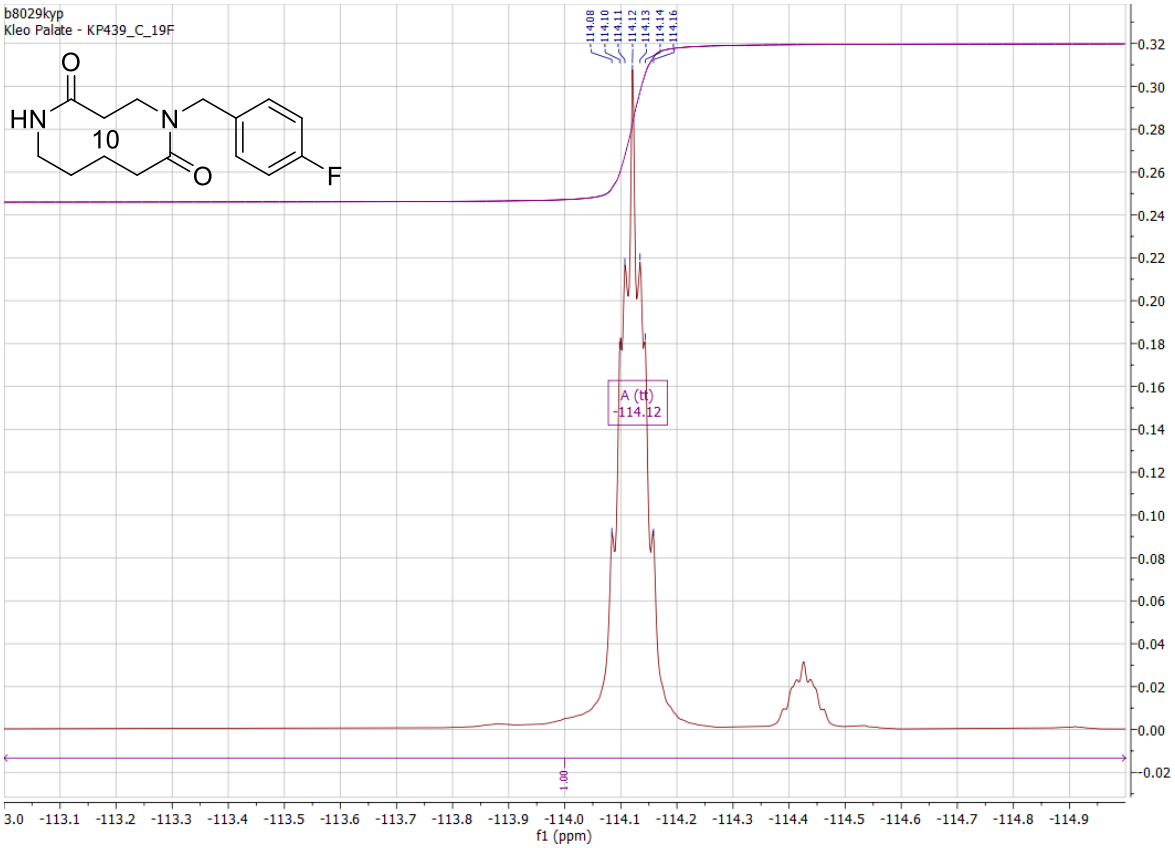
-114.16
A (tt)
-114.12
1.00
f1 (ppm)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Kleo Palate - KP439_C_19F
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-114.12
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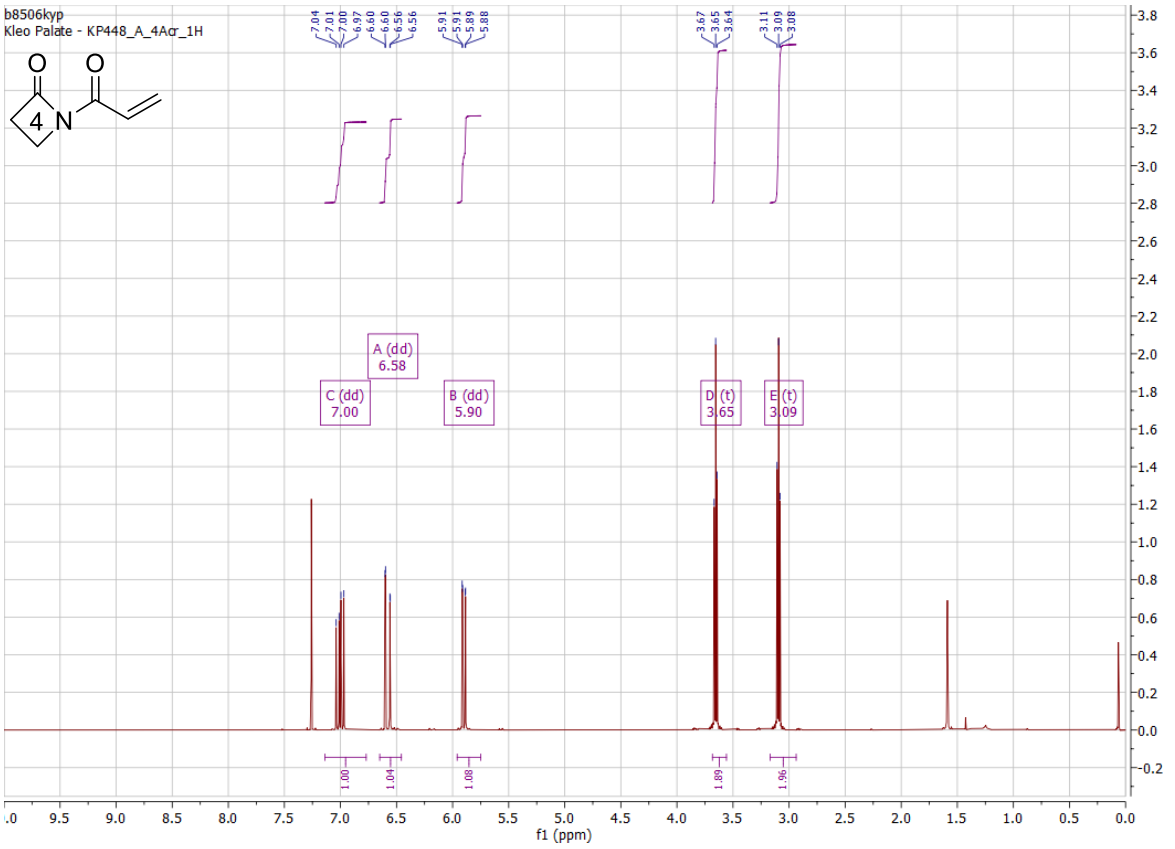
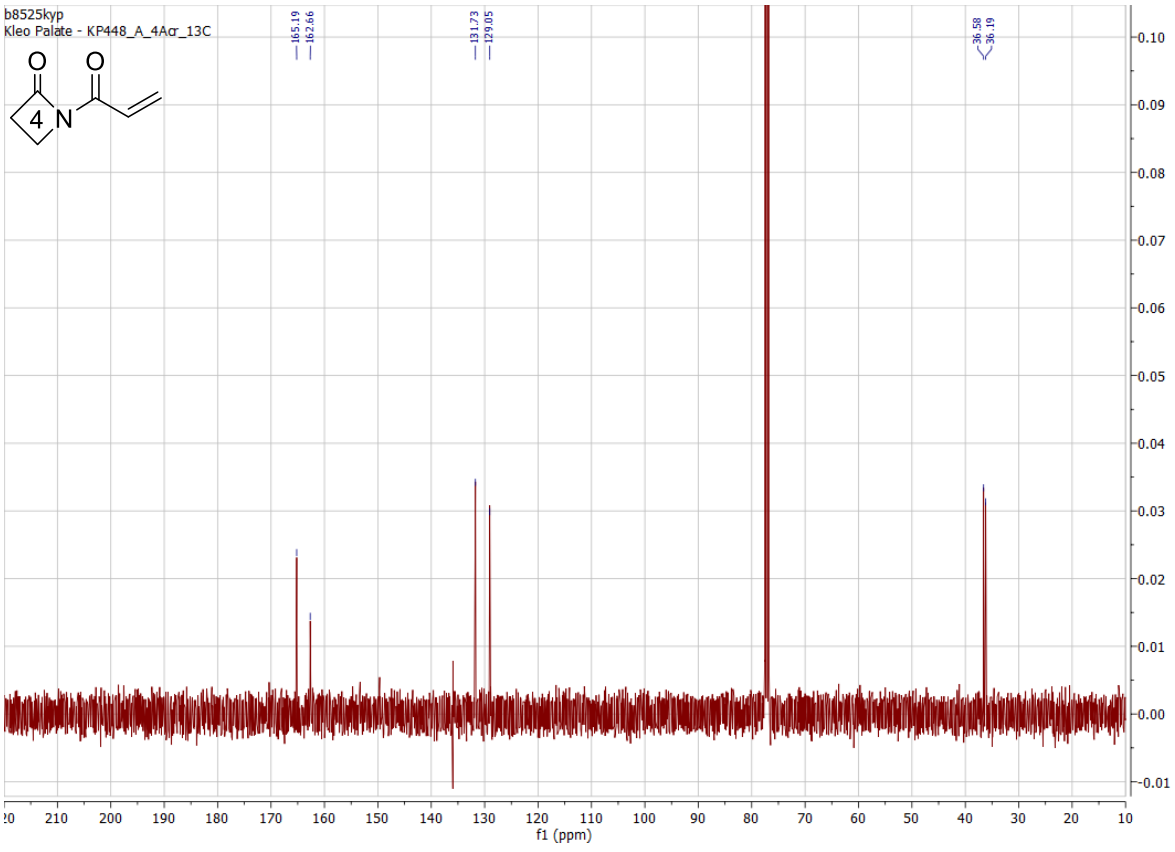
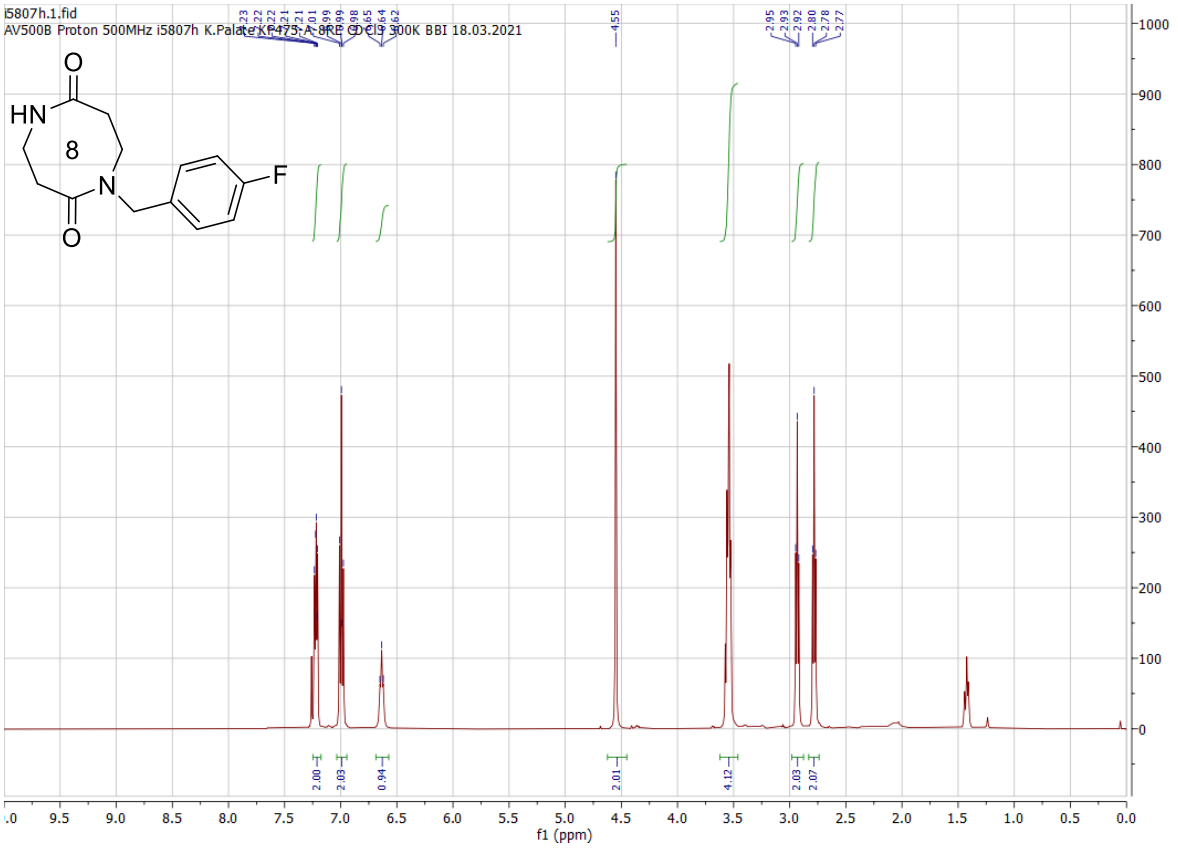
-114.16
A (tt)
-114.12
1.00
f1 (ppm)

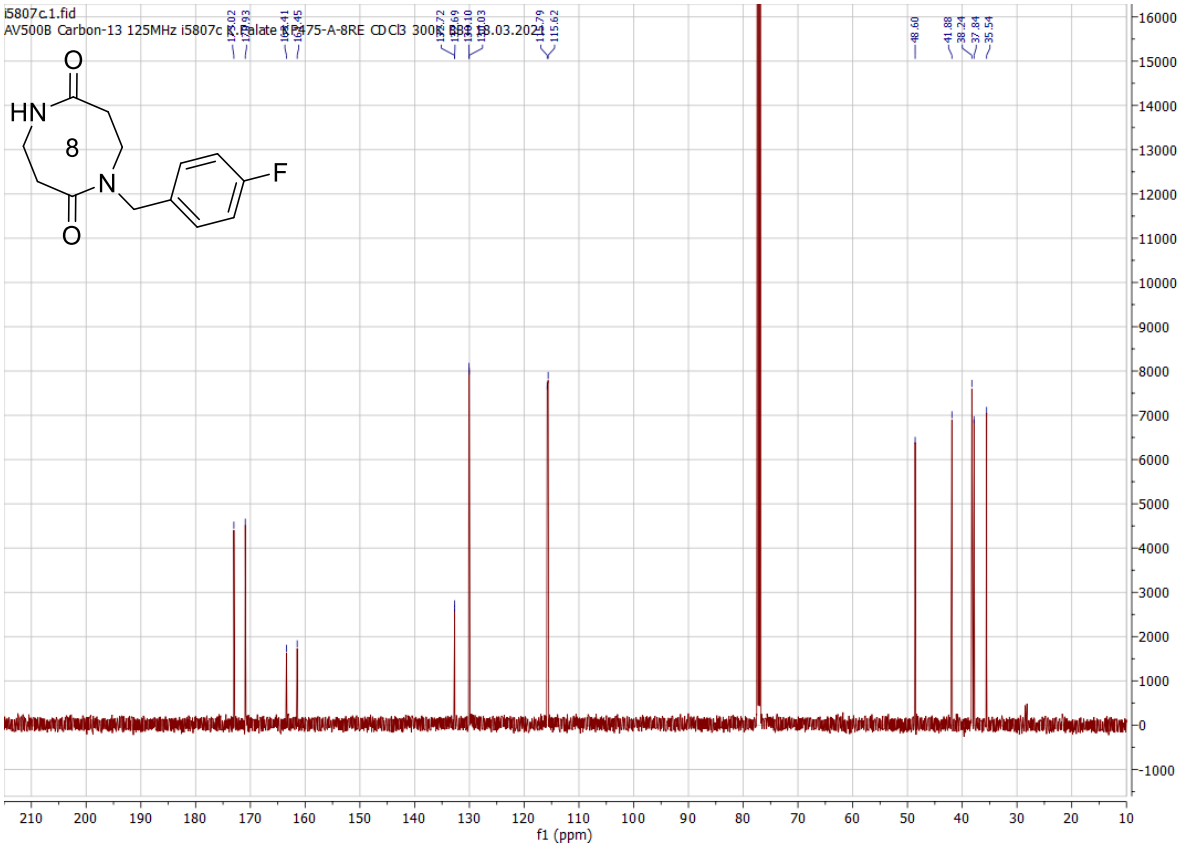
1-acryloyl-azetidin-2-one (11b)

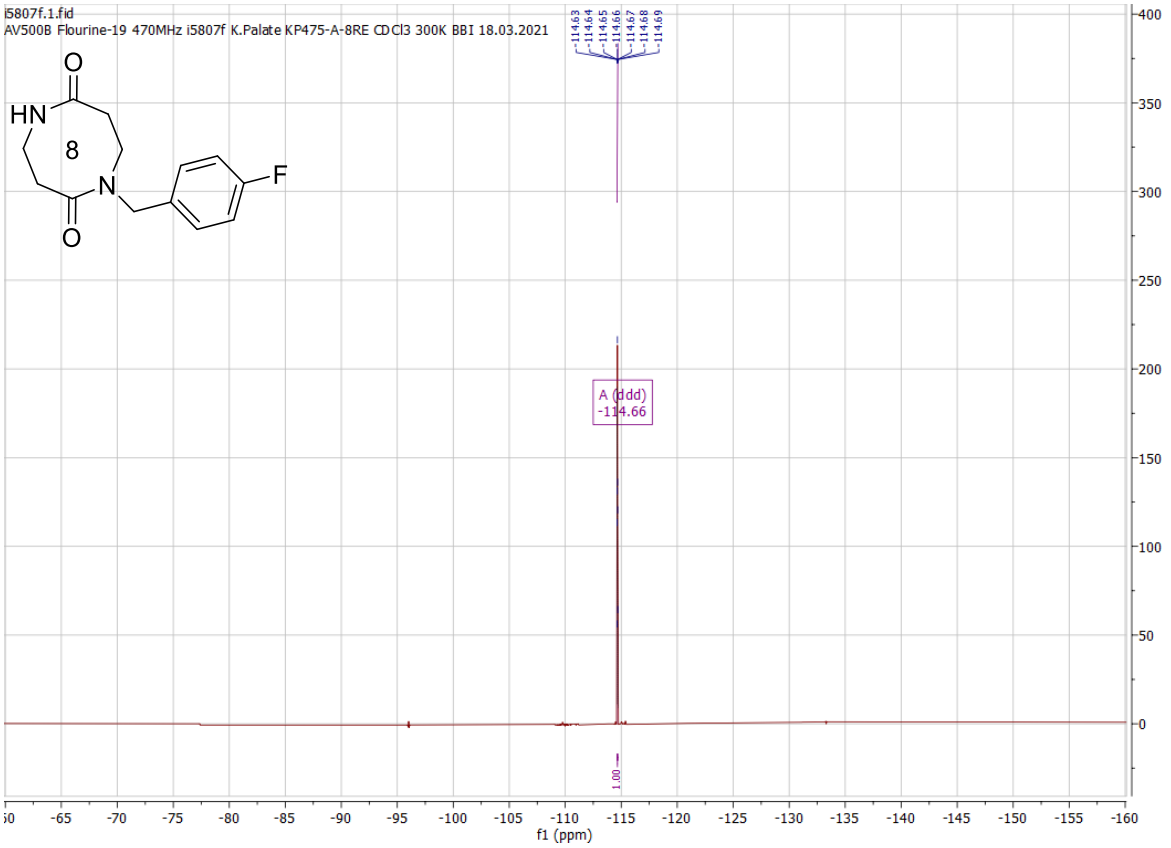




1-(4-Fluorobenzyl)-1,5-diazocane-2,6-dione (14b)



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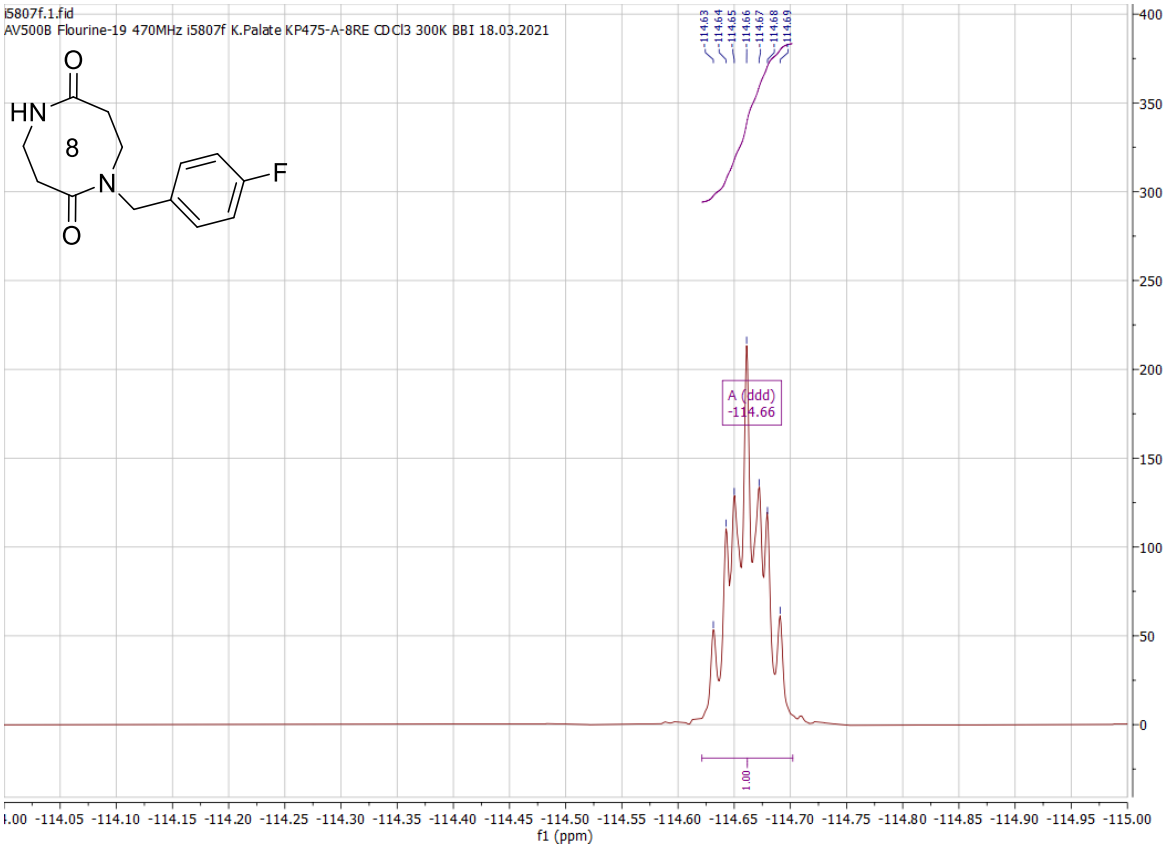
N
O
F
A (ddd)
-114.66
f1 (ppm)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AV500B Flourine-19 470MHz i5807f K.Palate KP475-A-8RE CDCl3 300K BBI 18.03.2021
HN
O
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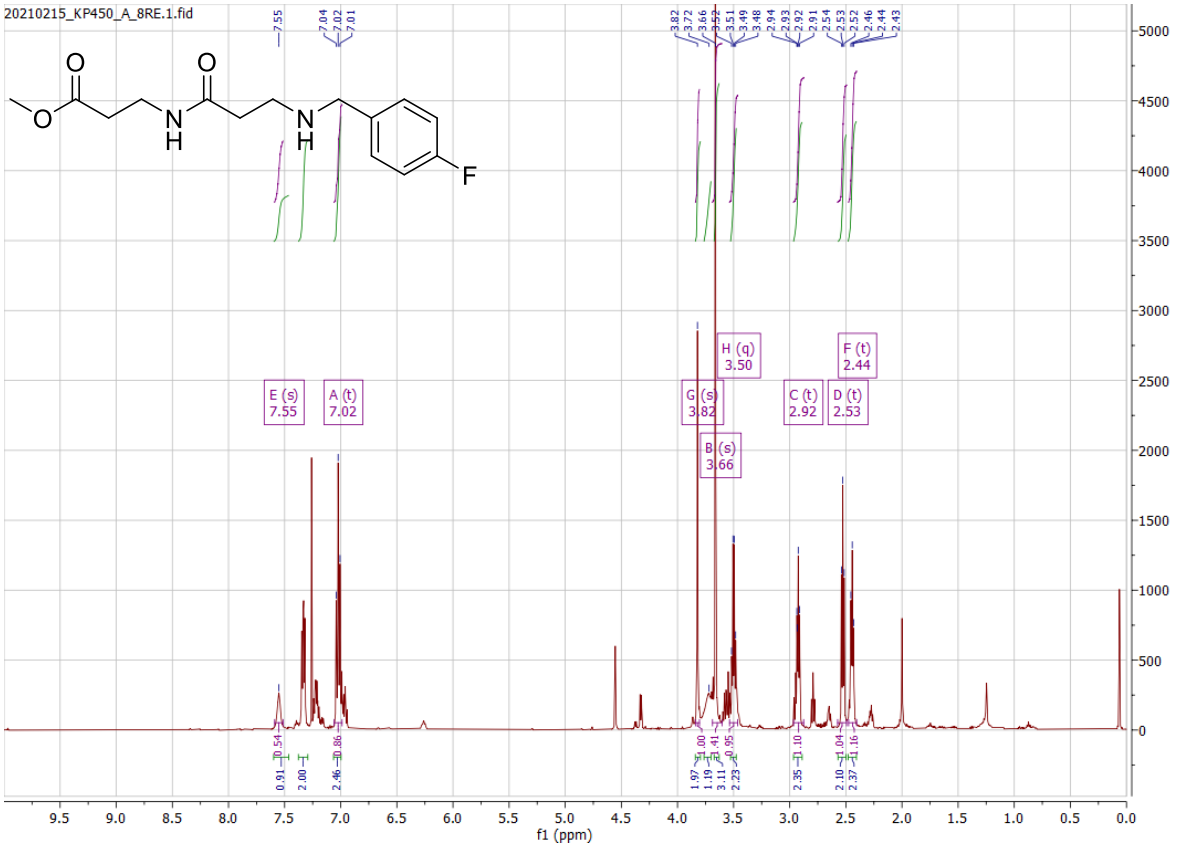
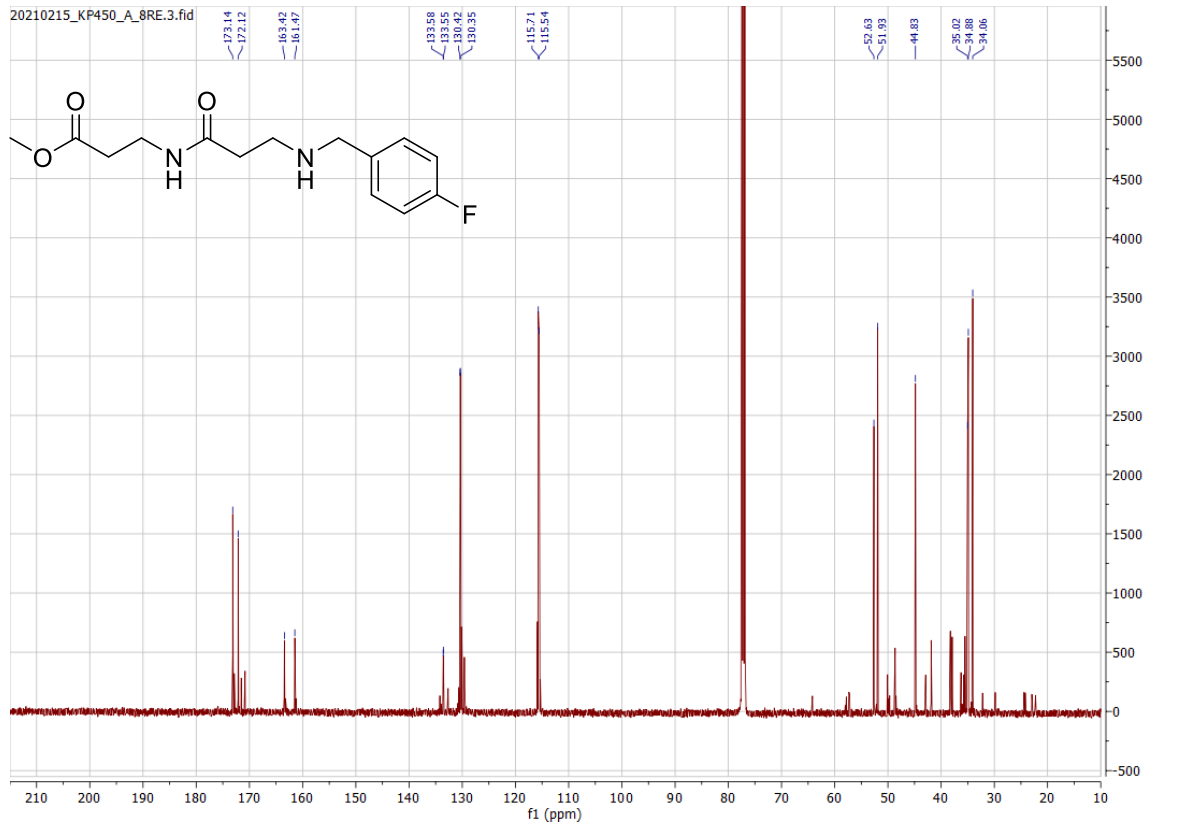
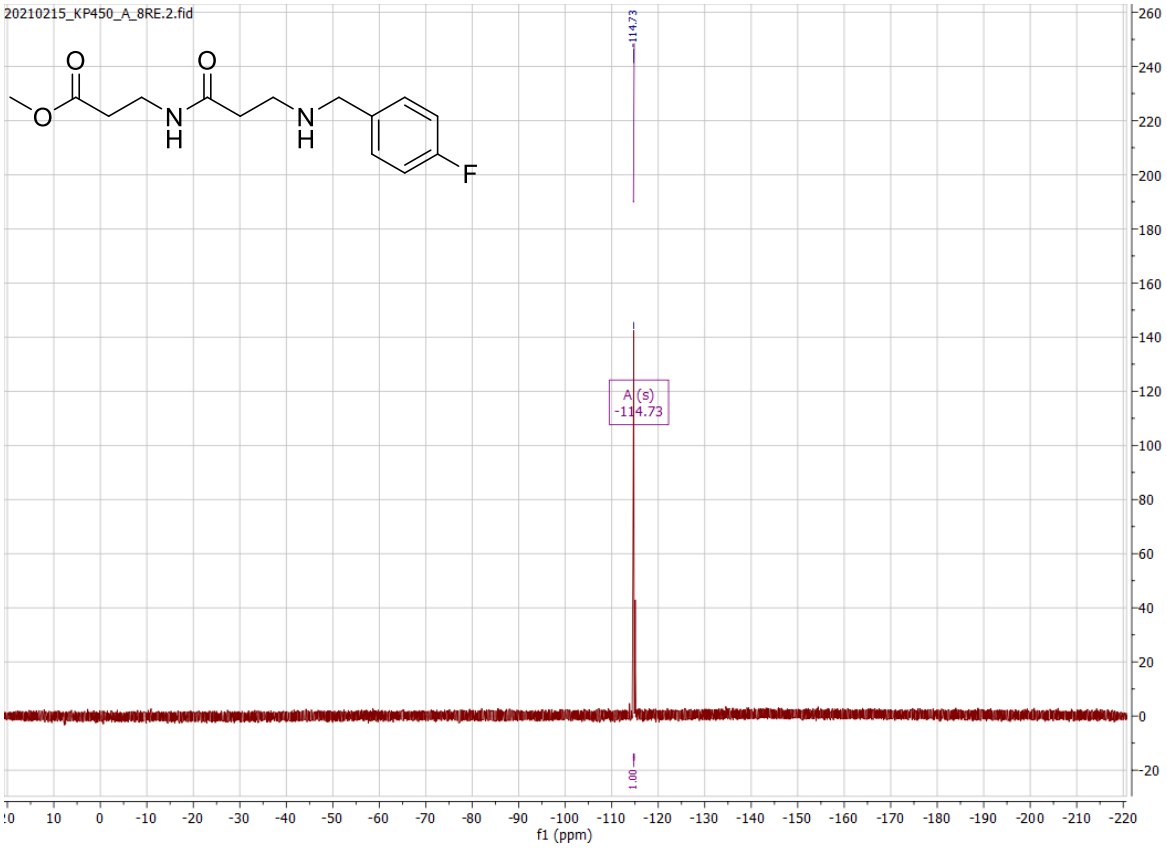
N
O
F
A (ddd)
-114.66
f1 (ppm)

Methyl 3-(3-((4-fluorobenzyl)amino)propanamido)propanoate. The isolated material contained minor unidentified impurities, but the NMR data obtained were sufficient to identify this unwanted side product.



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O
N
H
N
H
F
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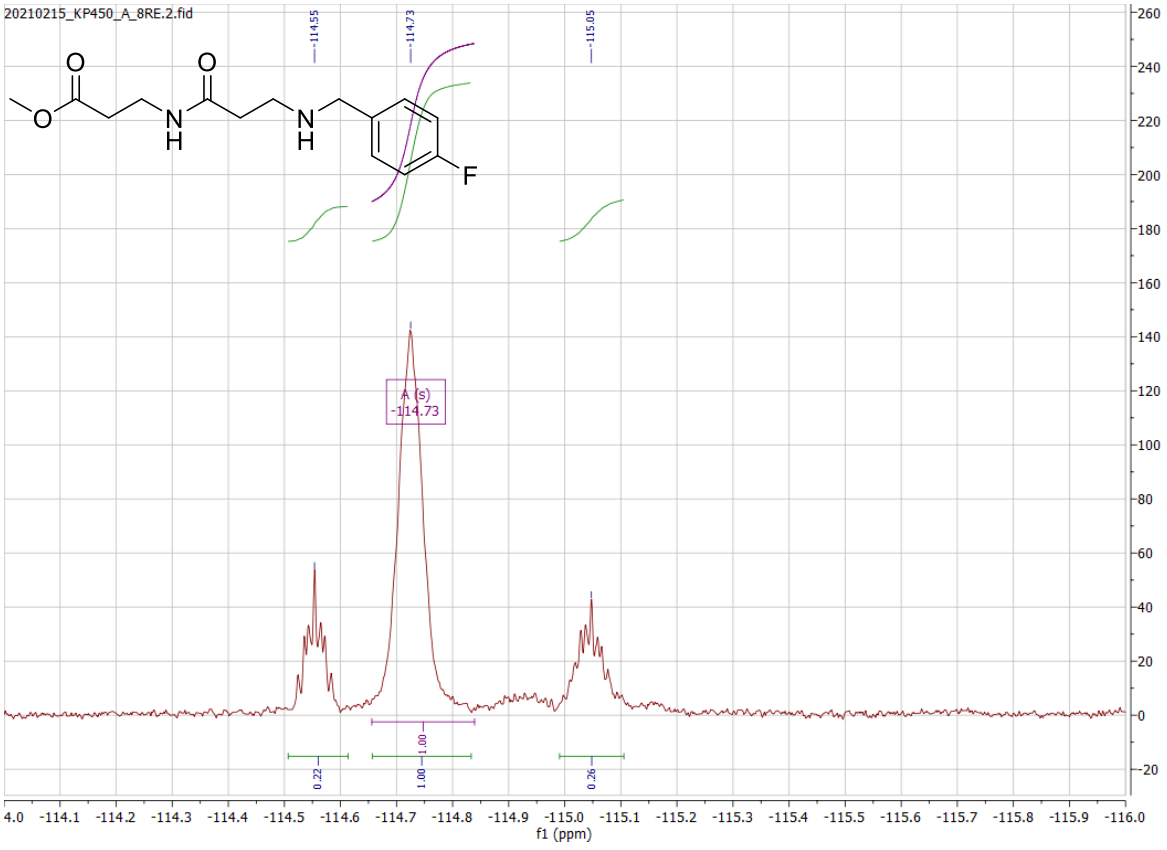
A (s)
-114.73
1.00
f1 (ppm)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O
N
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N
H
F
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-114.73
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A (s)
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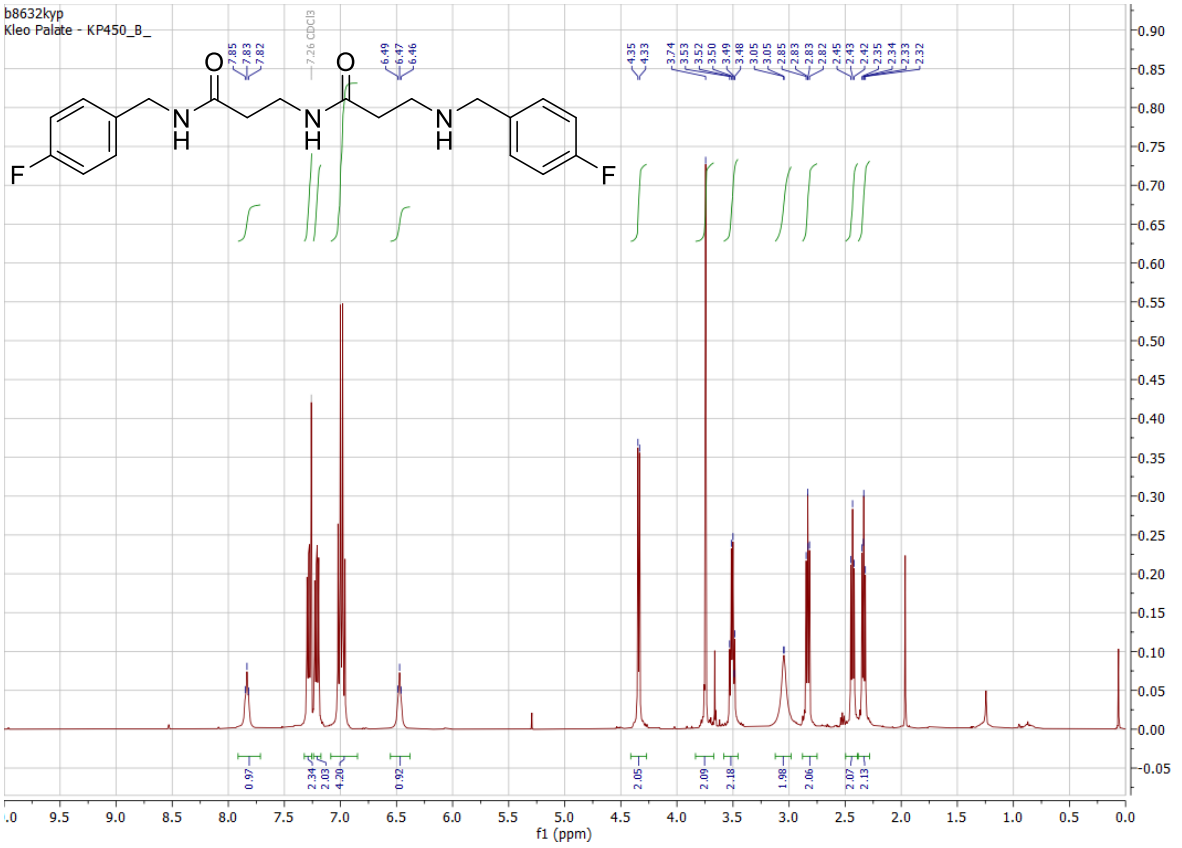
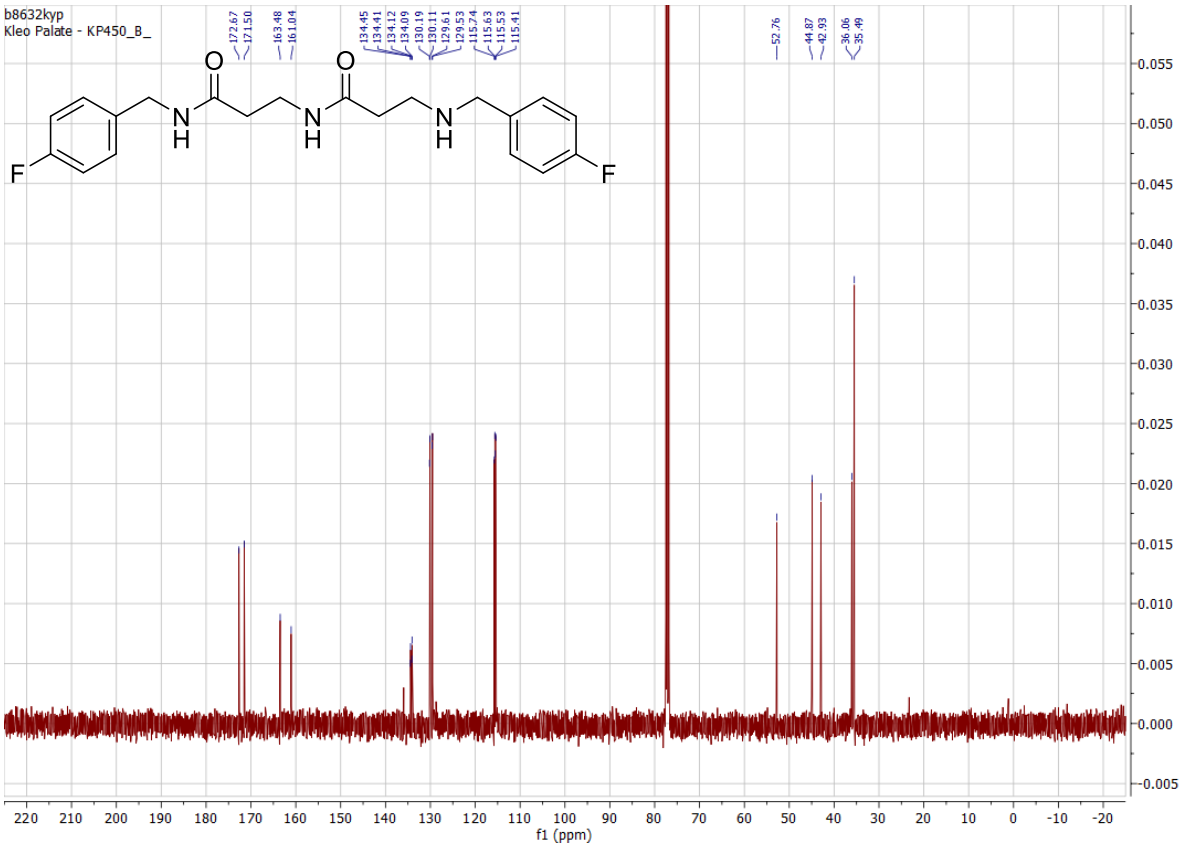
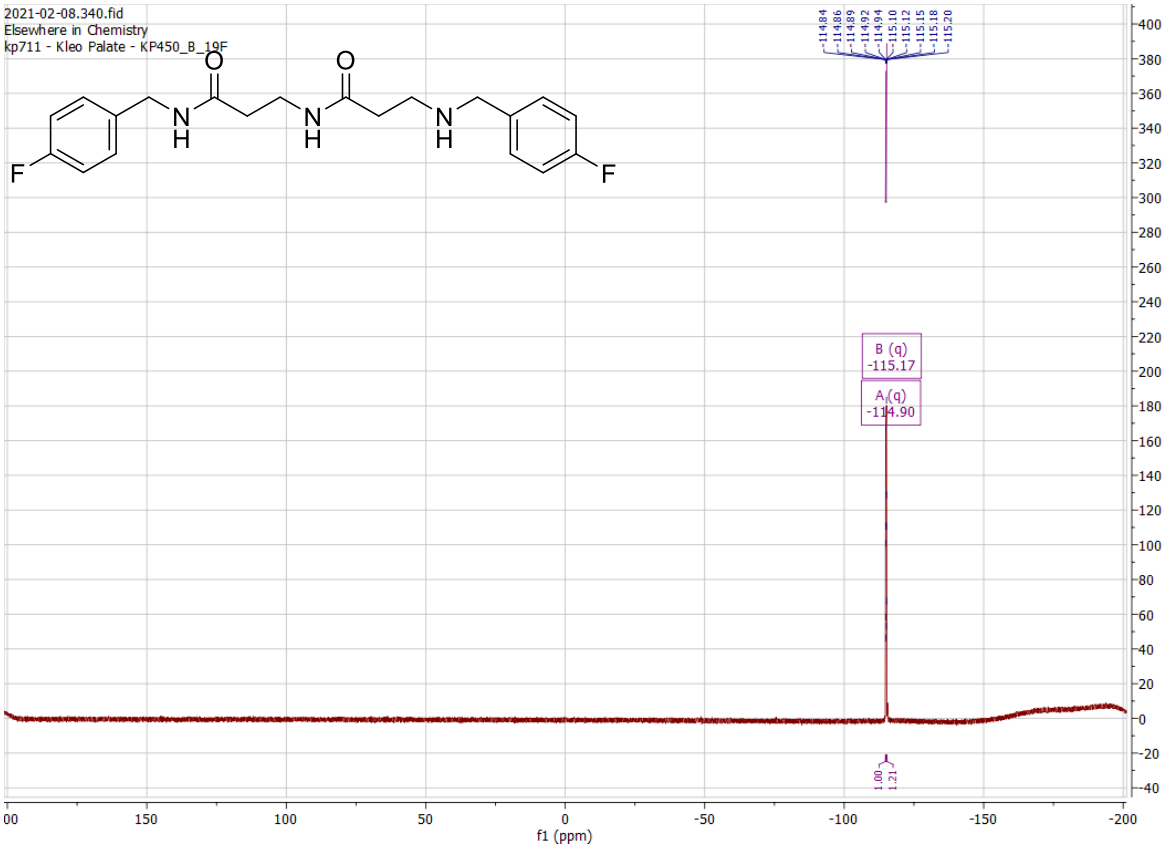
0.26
f1 (ppm)

***N*-(4-fluorobenzyl)-3-(3-((4-fluorobenzyl)amino)propanamido)propanamide**.



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Elsewhere in Chemistry
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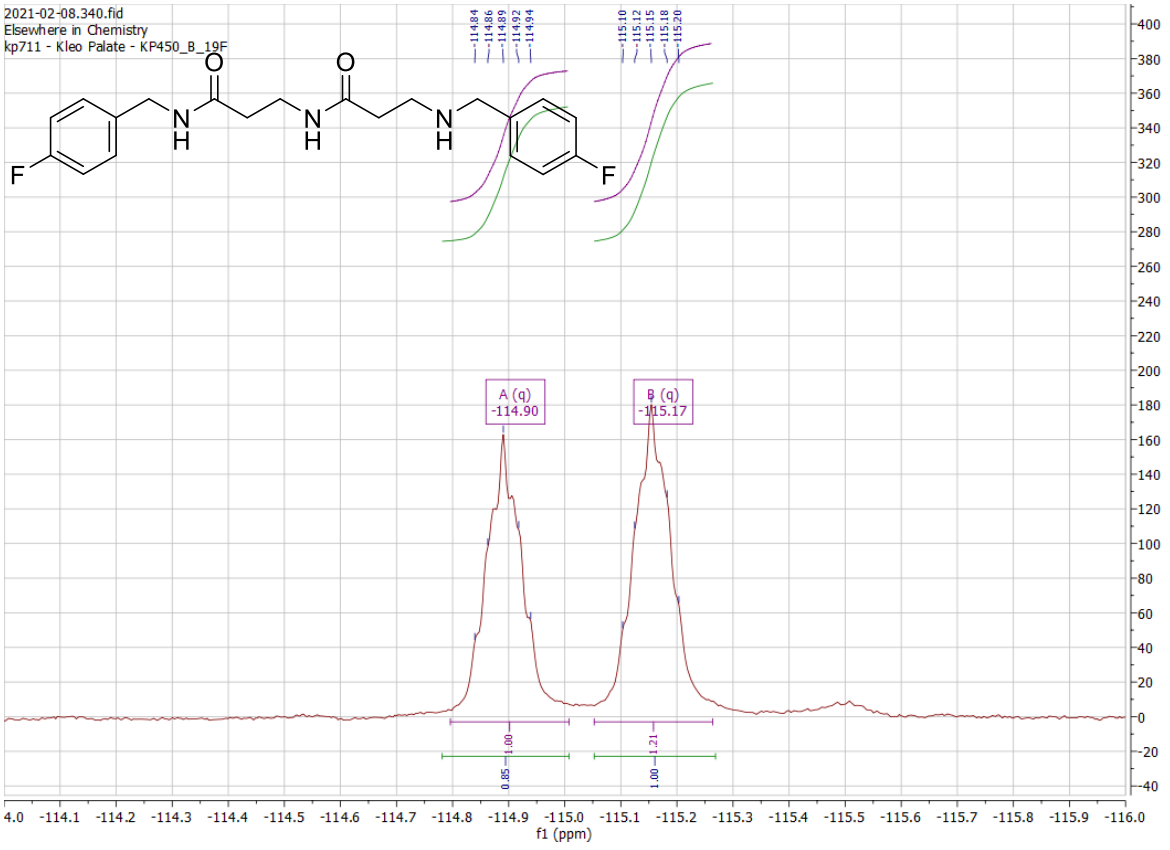
A (q)
-114.90
f1 (ppm)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B (q)
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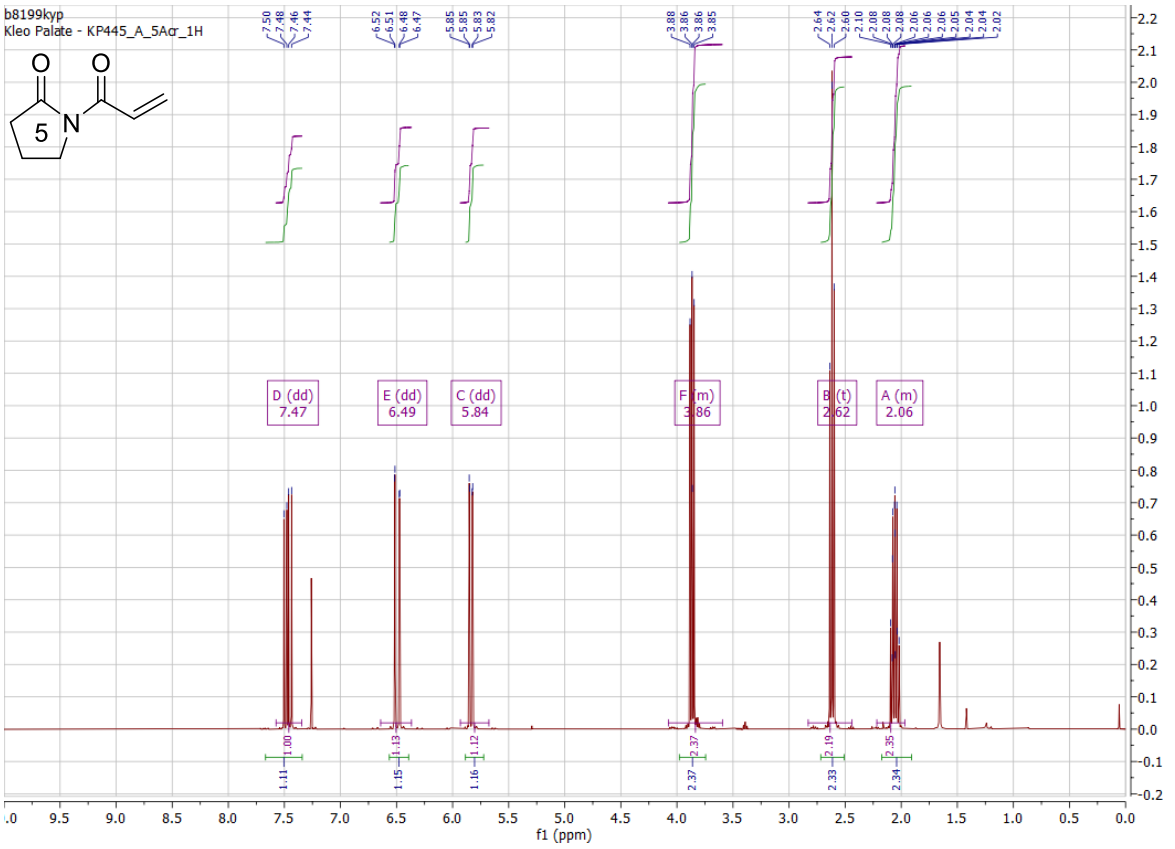
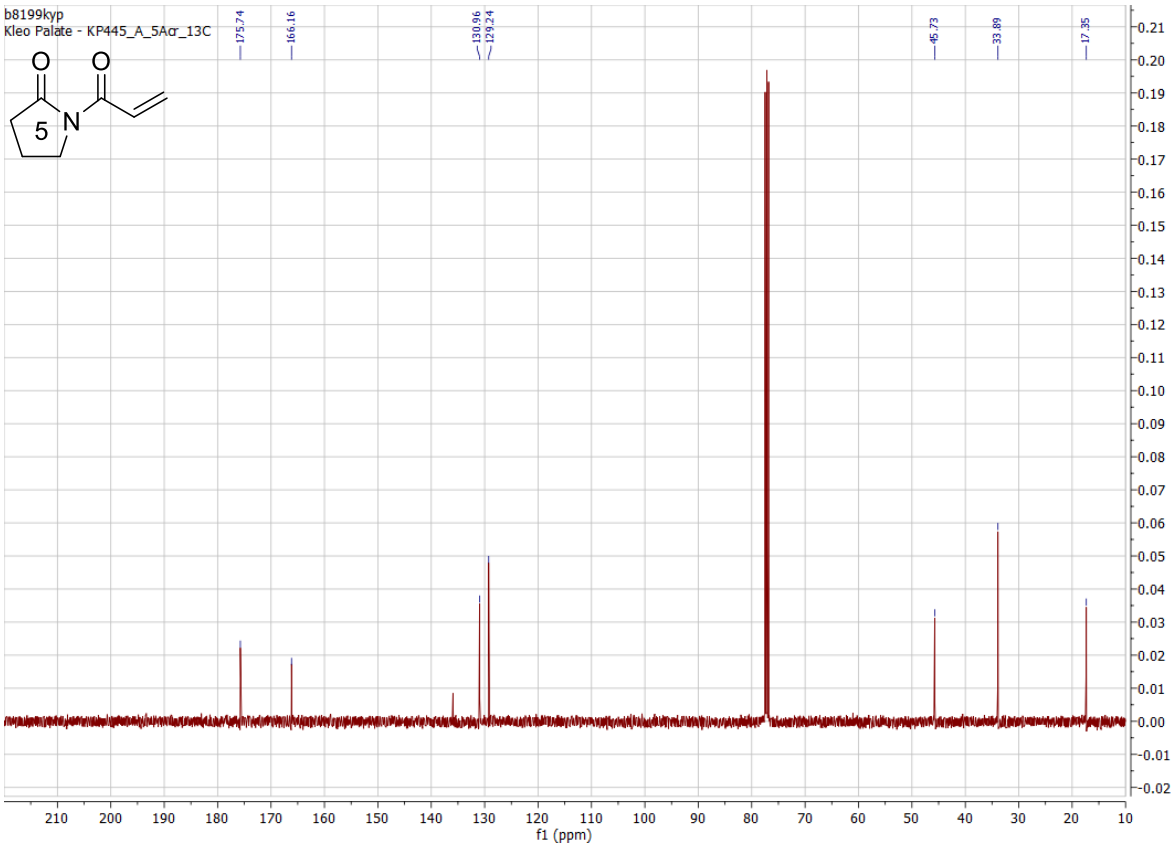
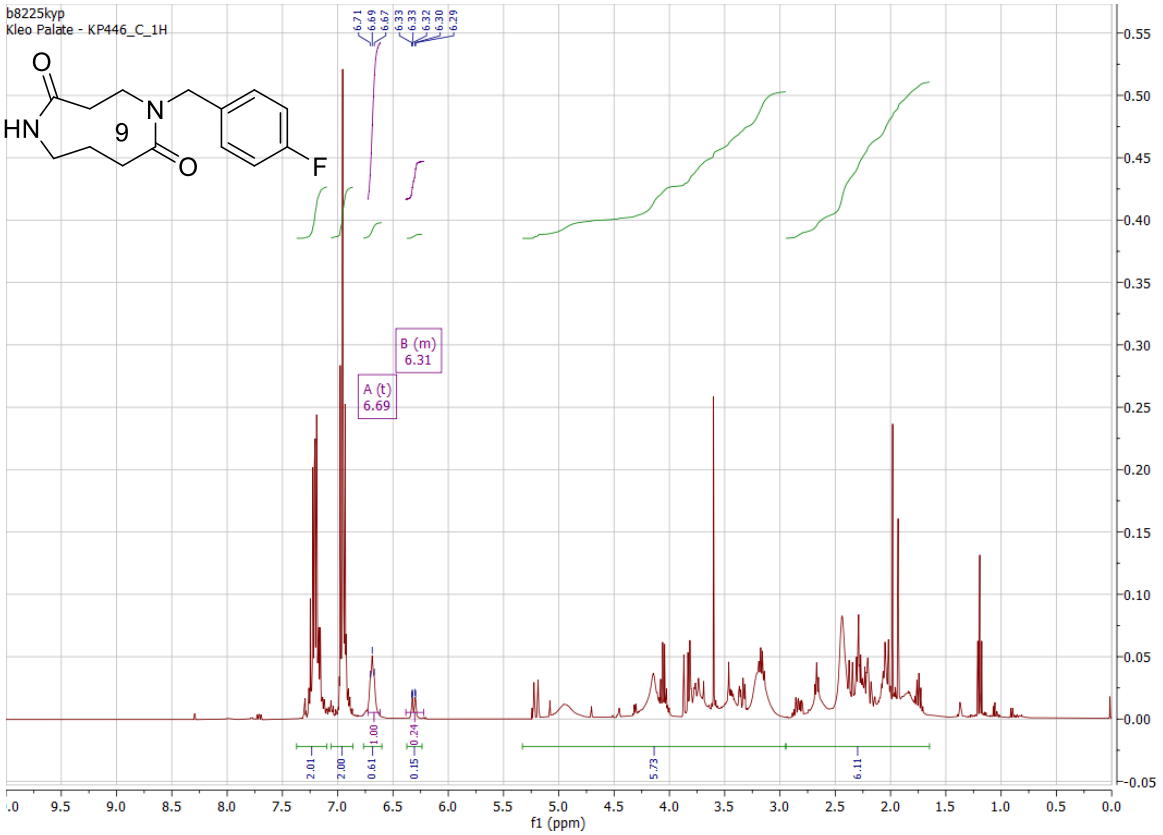
f1 (ppm)

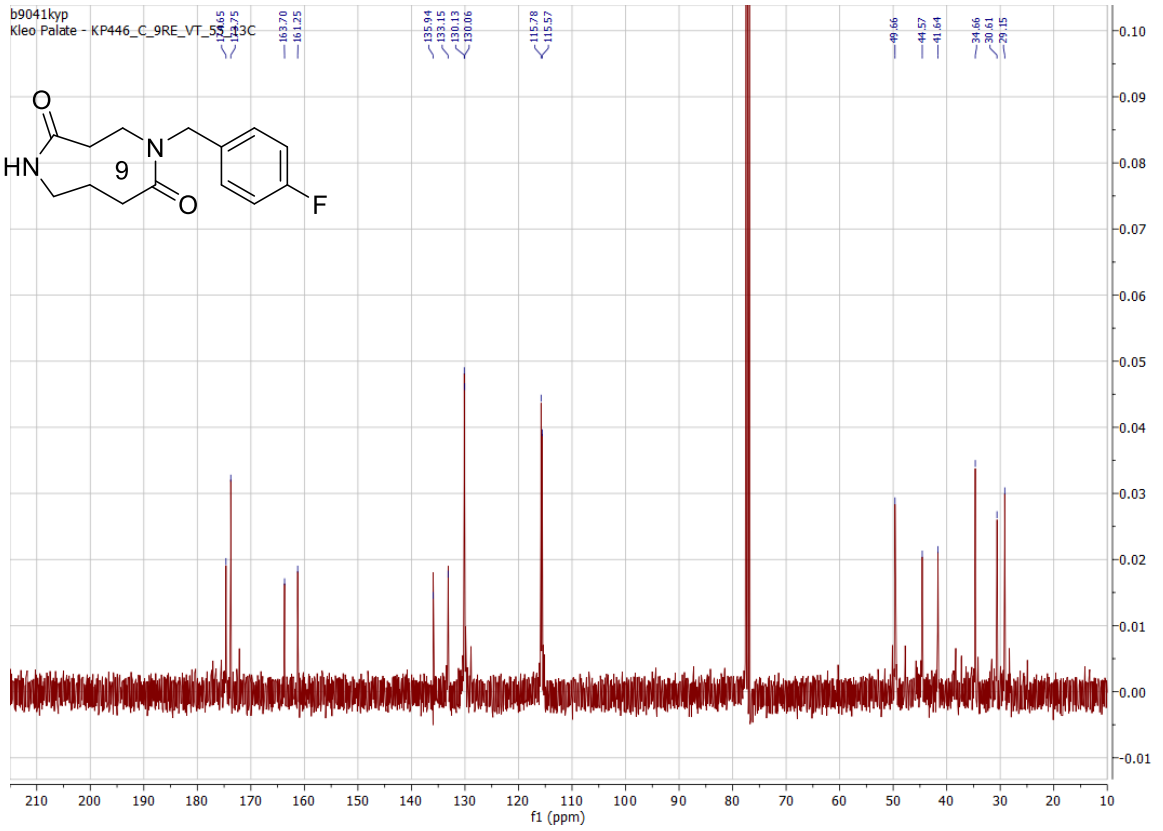
1-Acryloyl-pyrrolidin-2-one (11c)

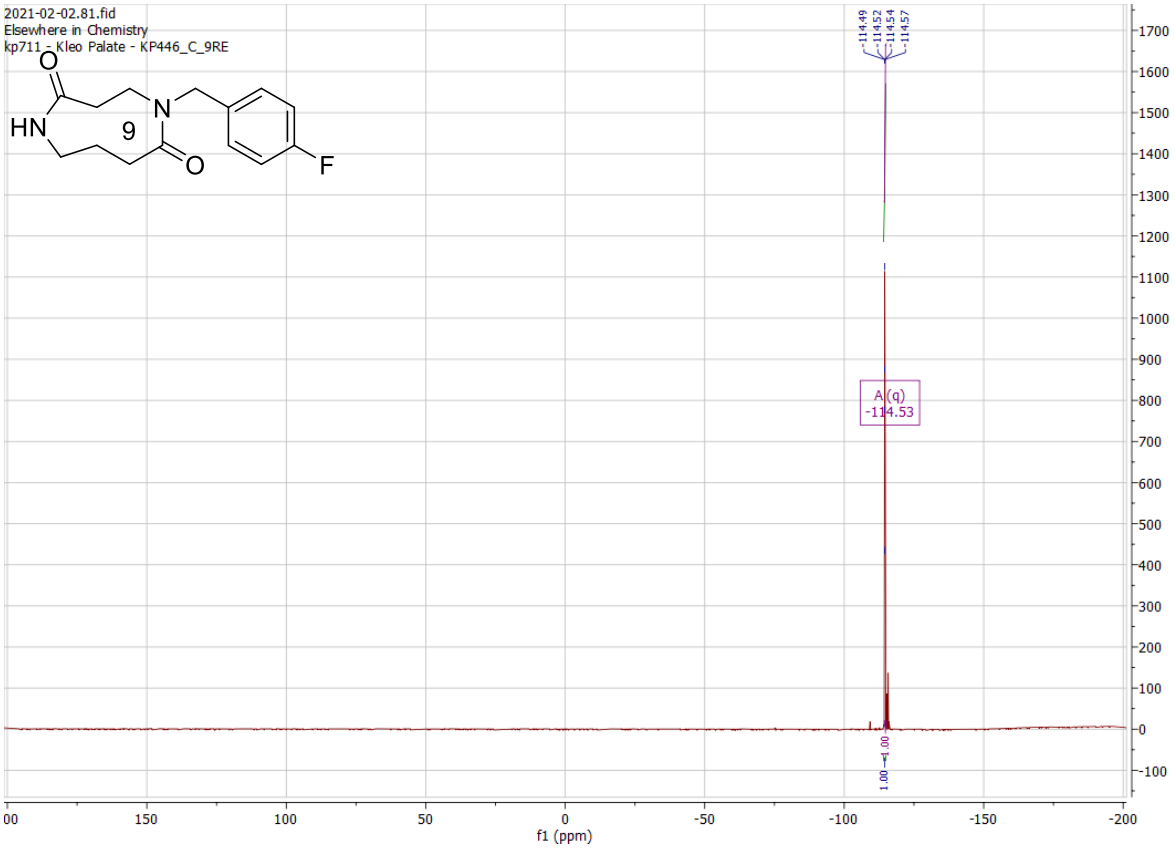


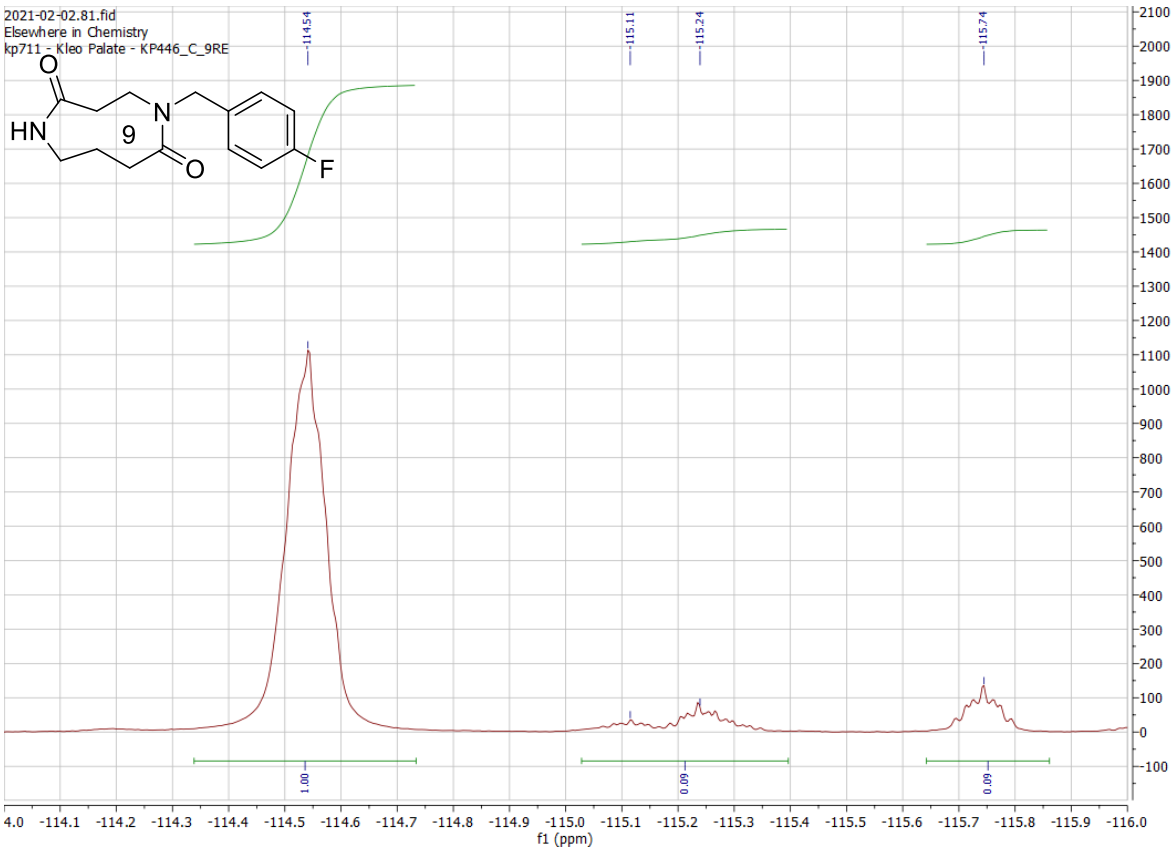


5-(4-Fluorobenzyl)-1,5-diazonane-2,6-dione (14c). In solution in $CDCl_3$, this compound exists as a mixture of rotameric forms (1 major rotamer and 3 minor rotamers, best seen in the ^{19}F NMR). The ^{1}H NMR data is complicated by rotameric broadening, with product identity and purity best determined using the ^{13}C NMR data collected at 55 °C.

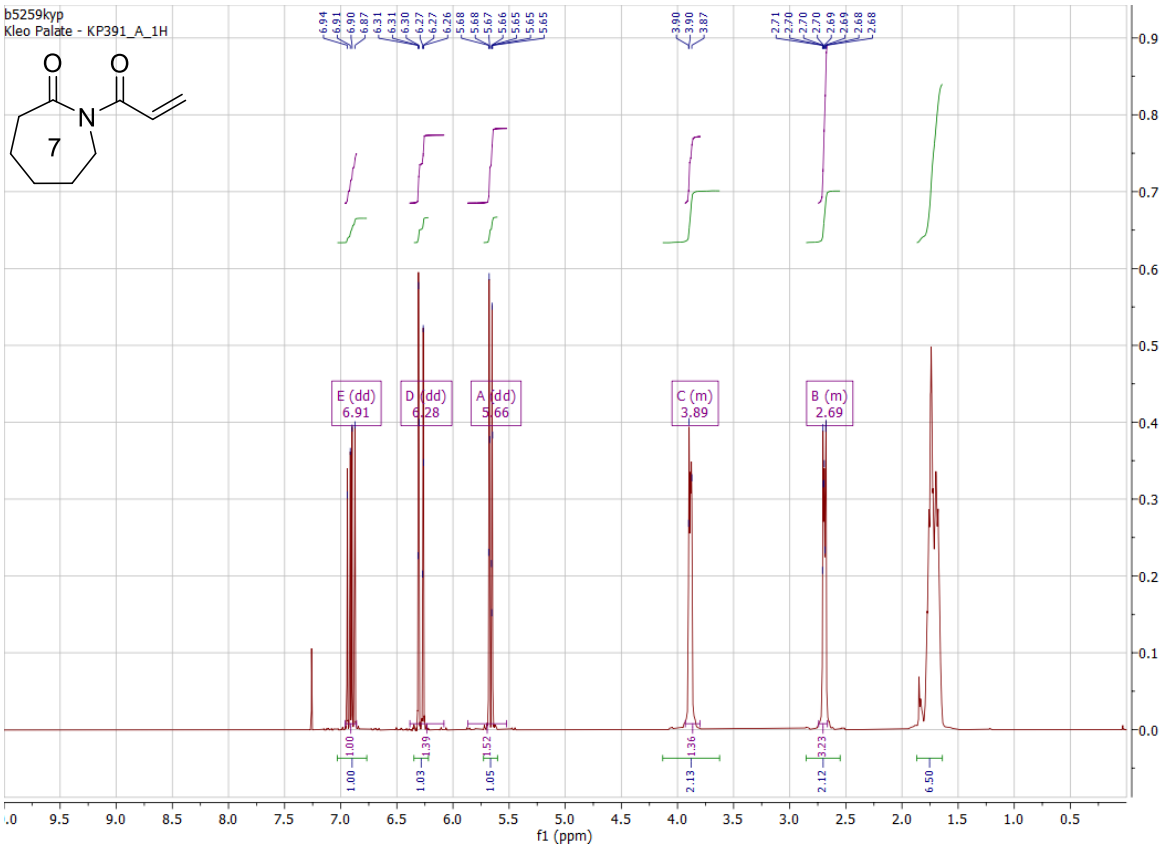


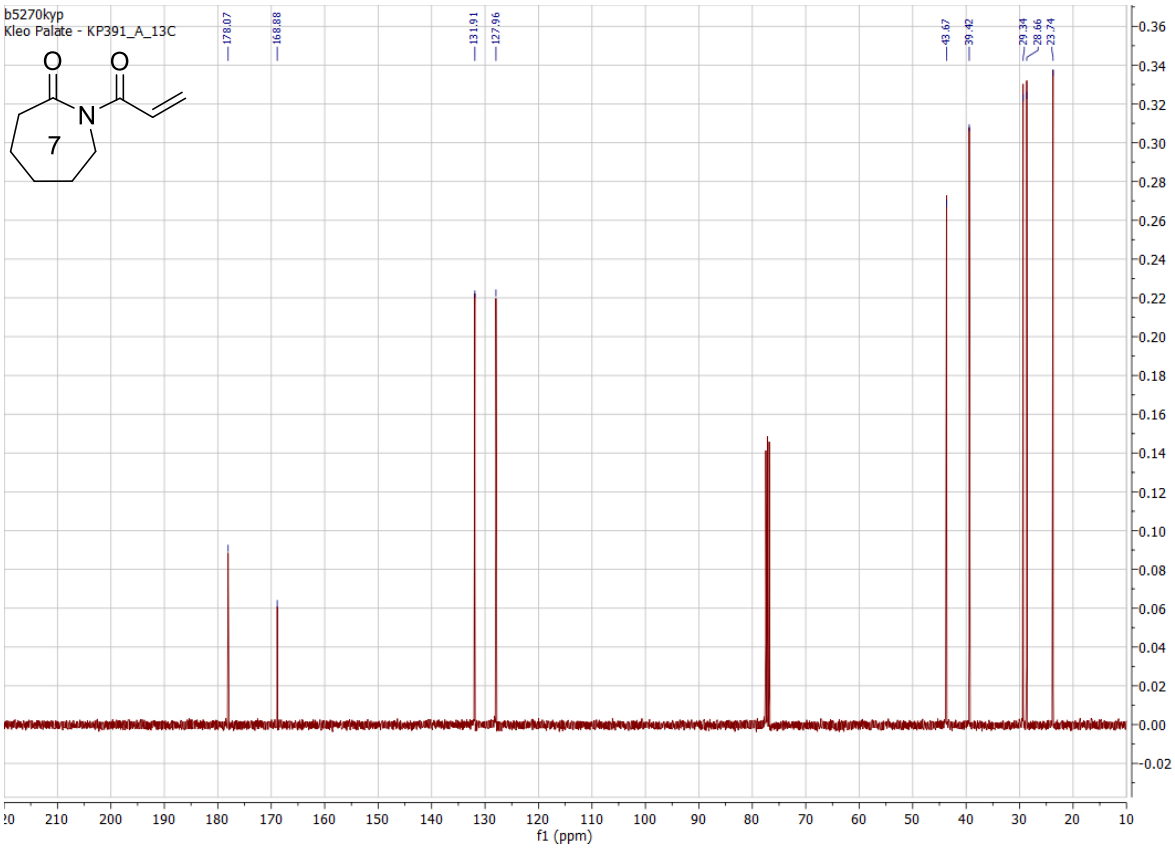



2021-02-02.81.fid
Elsewhere in Chemistry
kp711 - Kleo Palate - KP446_C_9RE
O
HN
9
N
O
F
-114.49
-114.52
-114.54
-114.57
A (q)
-114.53
1.00
f1 (ppm)

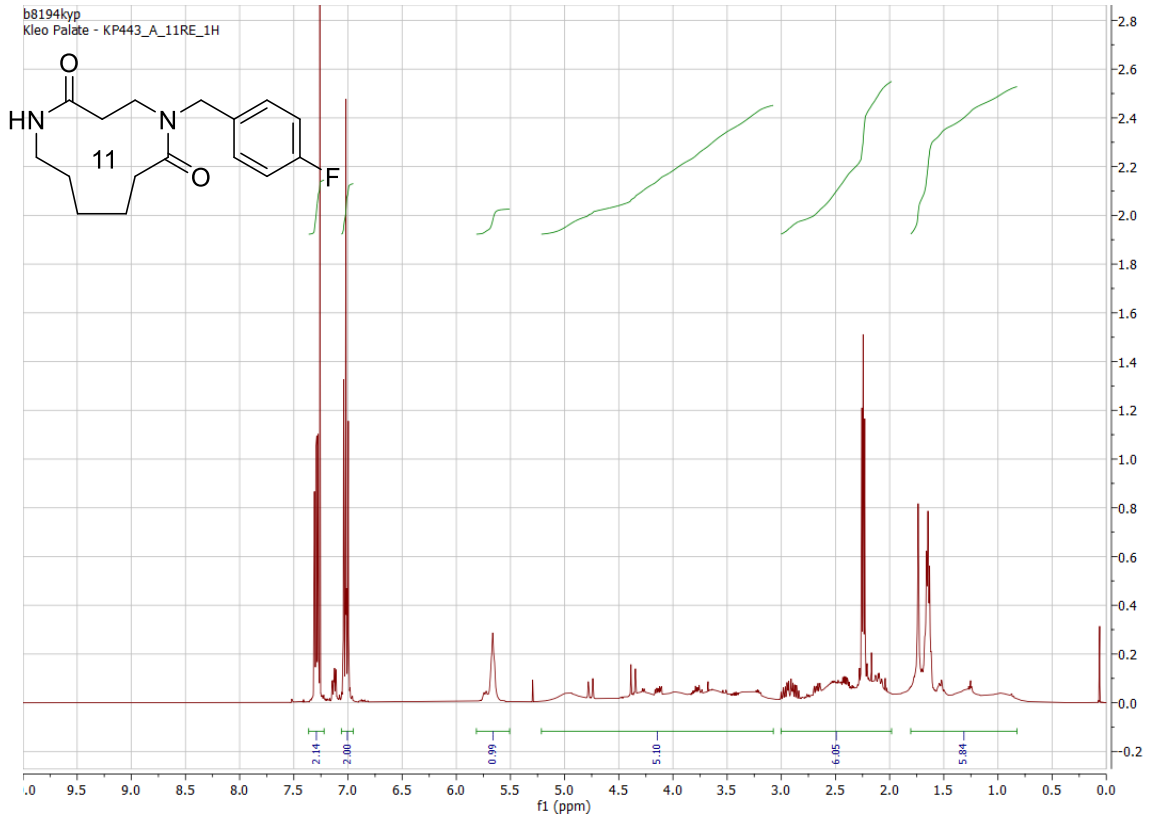

2021-02-02.81.fid
Elsewhere in Chemistry
kp711 - Kleo Palate - KP446_C_9RE
O
HN
9
N
O
F
-114.54
-115.11
-115.24
-115.74
1.00
0.09
0.09
f1 (ppm)

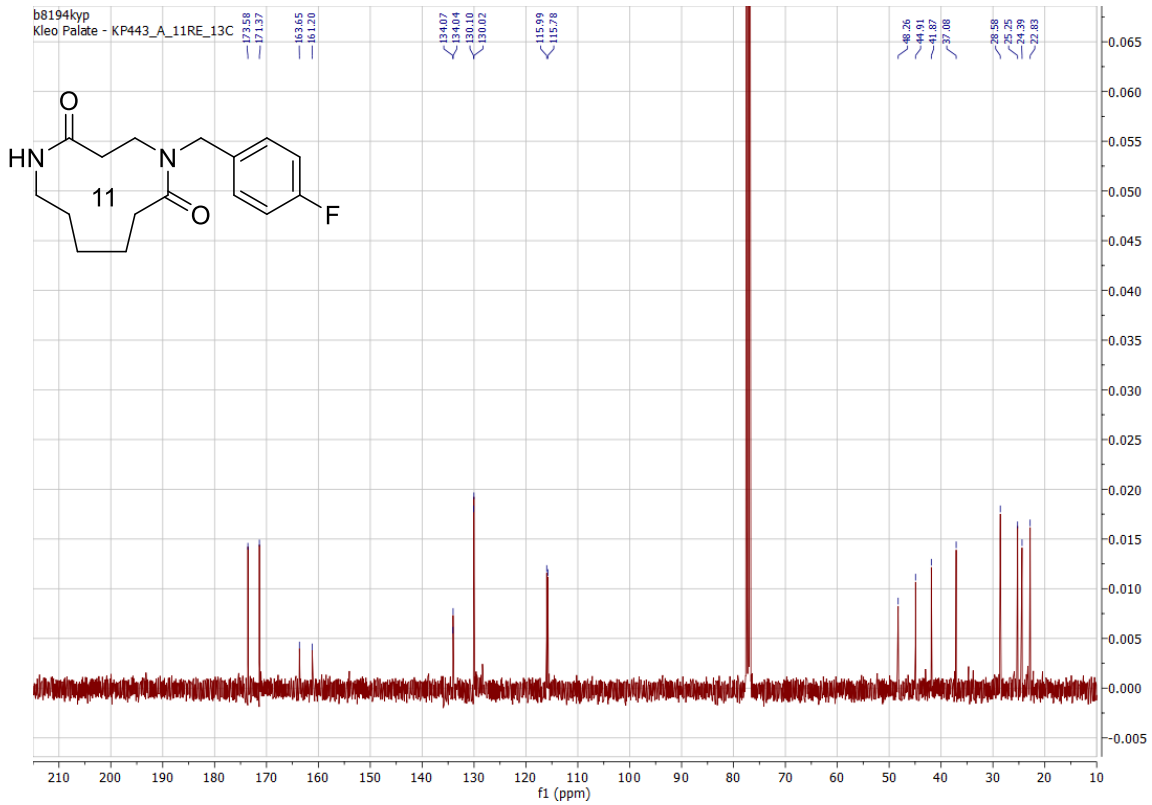
1-Acryloyl-azepan-2-one (11d)

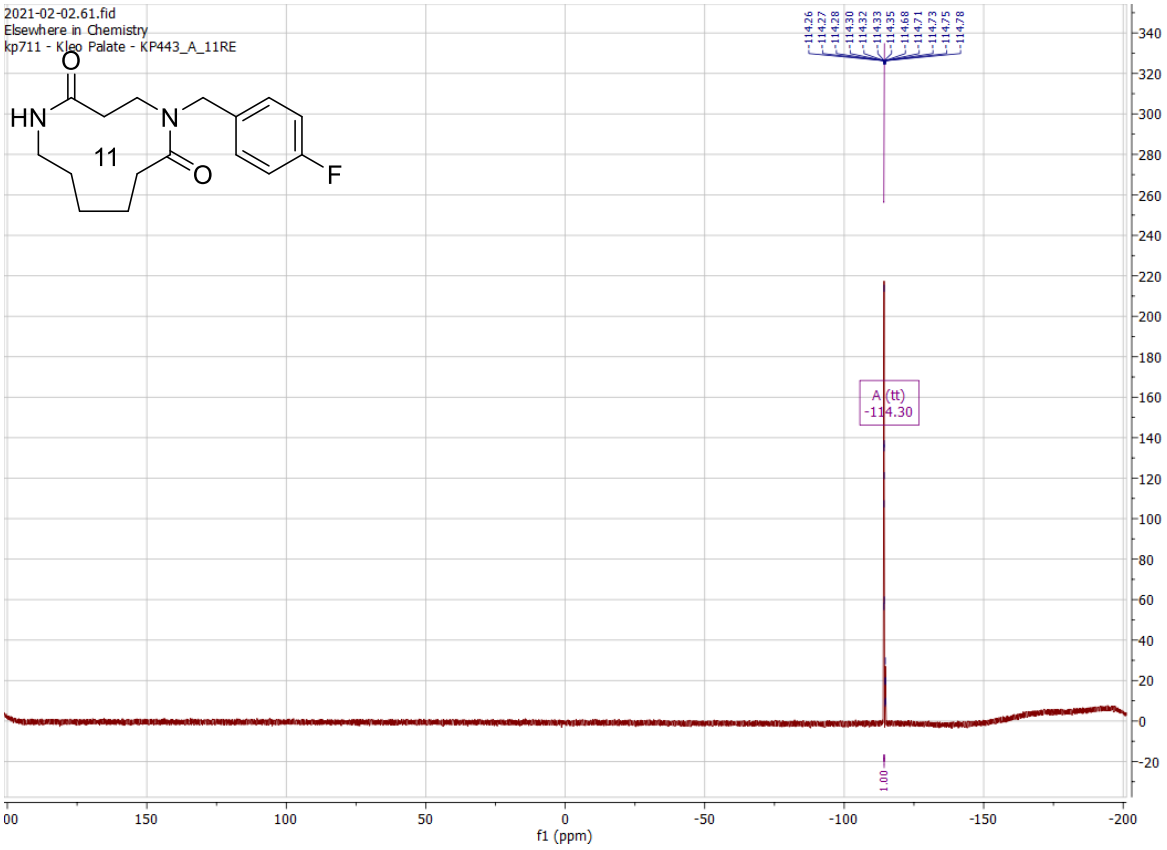


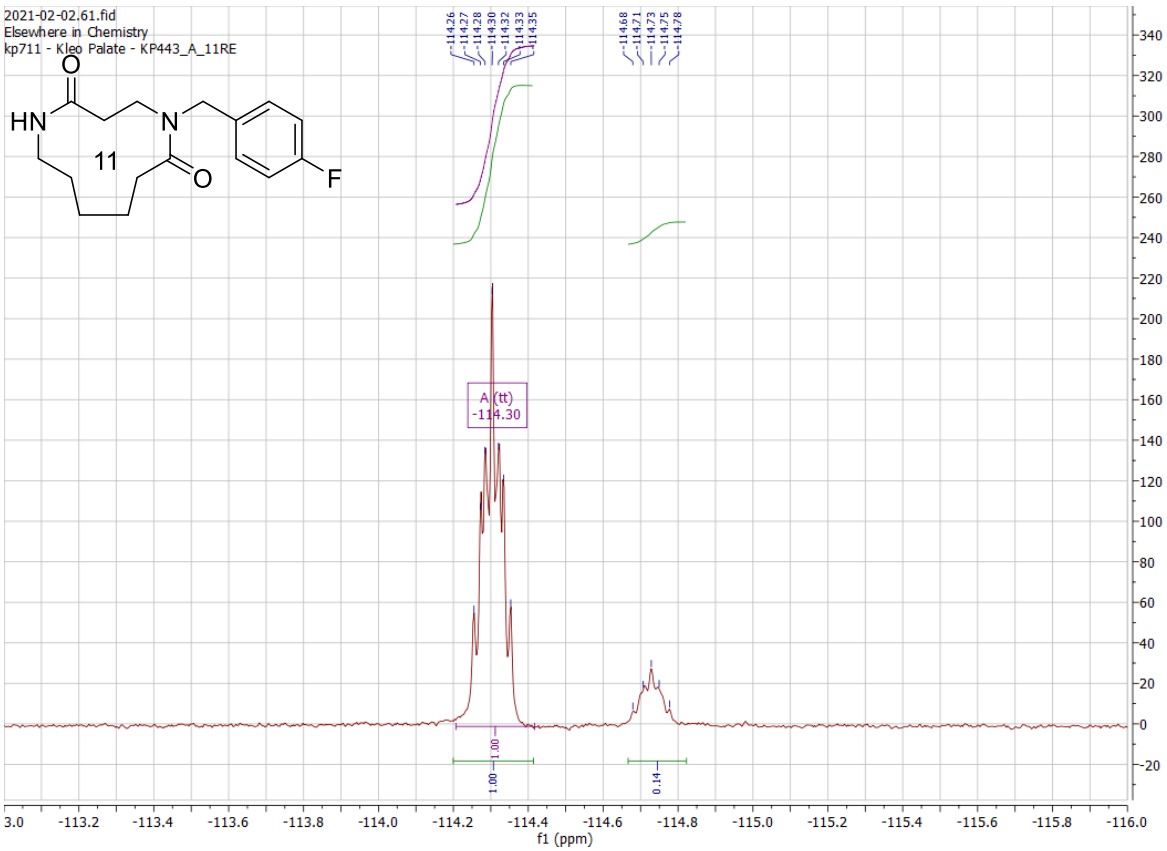


5-(4-Fluorobenzyl)-1,5-diazacycloundecane-2,6-dione (14d) Note, in solution in $CDCl_3$, this compound exists as a mixture of rotameric forms (1 major rotamer and 1 minor based on the ^{19}F NMR data). The ^{1}H NMR spectrum is severely complicated by rotameric broadening, with product identity and purity best determined using ^{13}C NMR data.

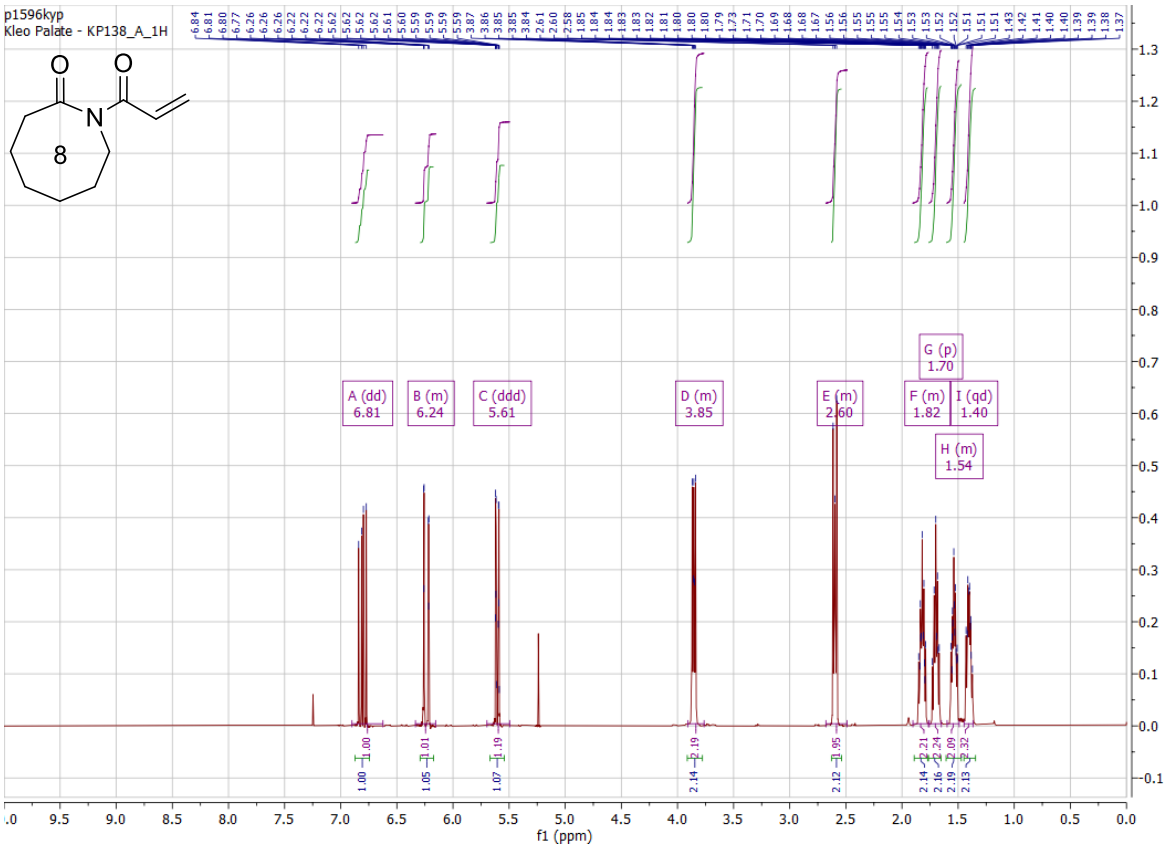


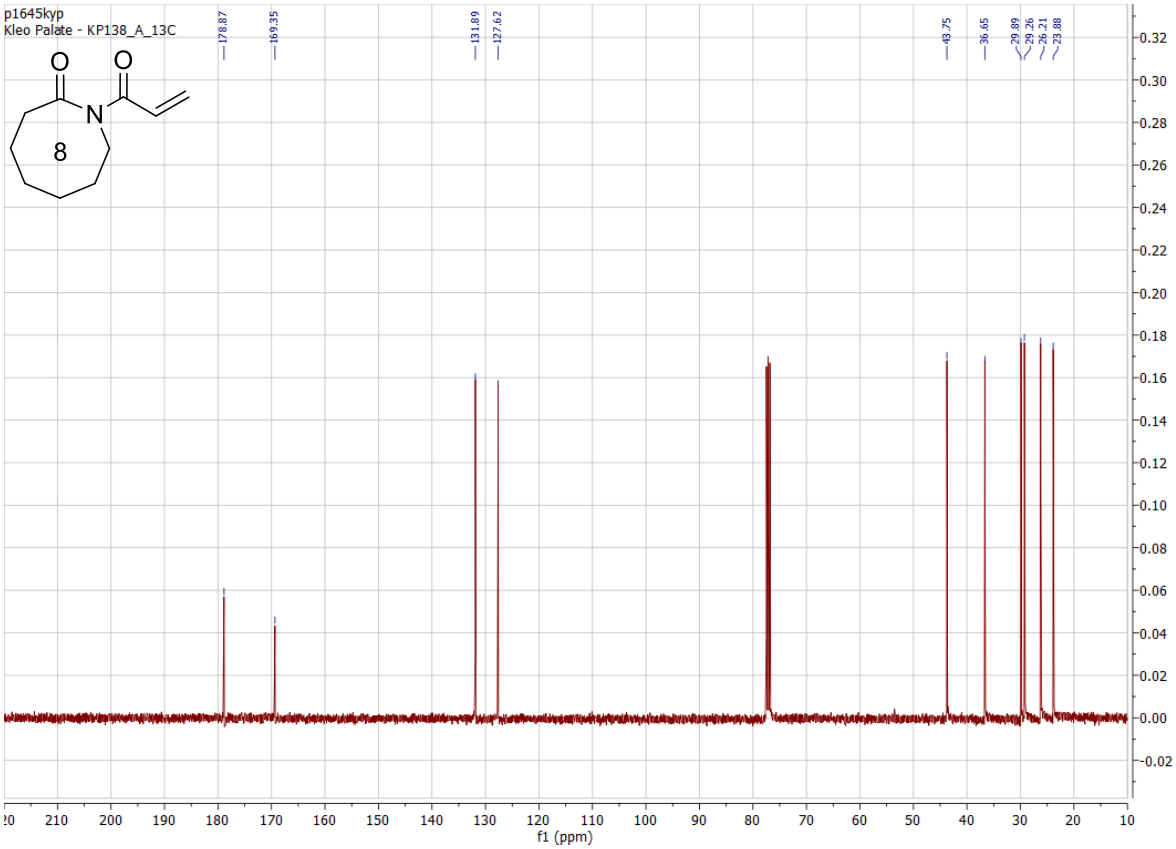



2021-02-02.61.fid
Elsewhere in Chemistry
kp711 - Kleo Palate - KP443_A_11RE
HN
O
N
11
O
F
A (tt)
-114.30
f1 (ppm)

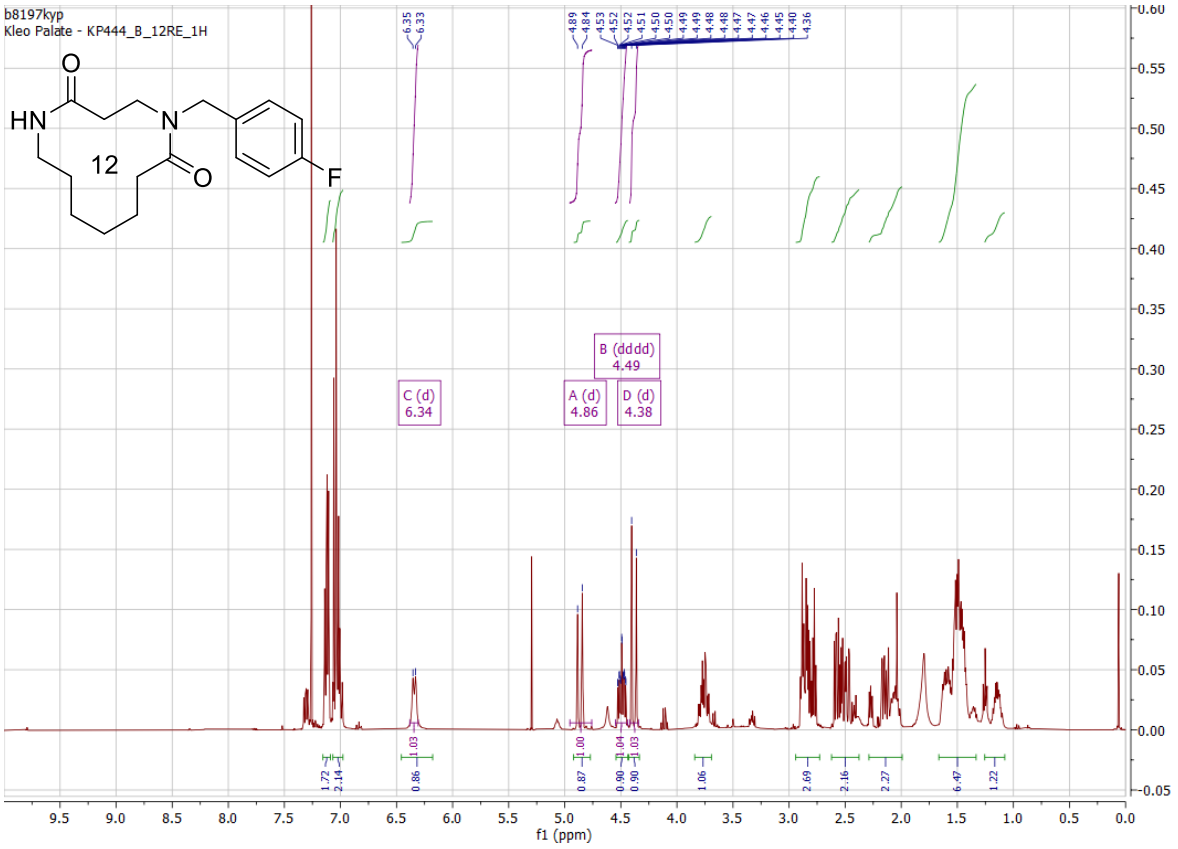

2021-02-02.61.fid
Elsewhere in Chemistry
kp711 - Kleo Palate - KP443_A_11RE
HN
O
N
11
O
F
A (tt)
-114.30
1.00
1.00
0.14
f1 (ppm)

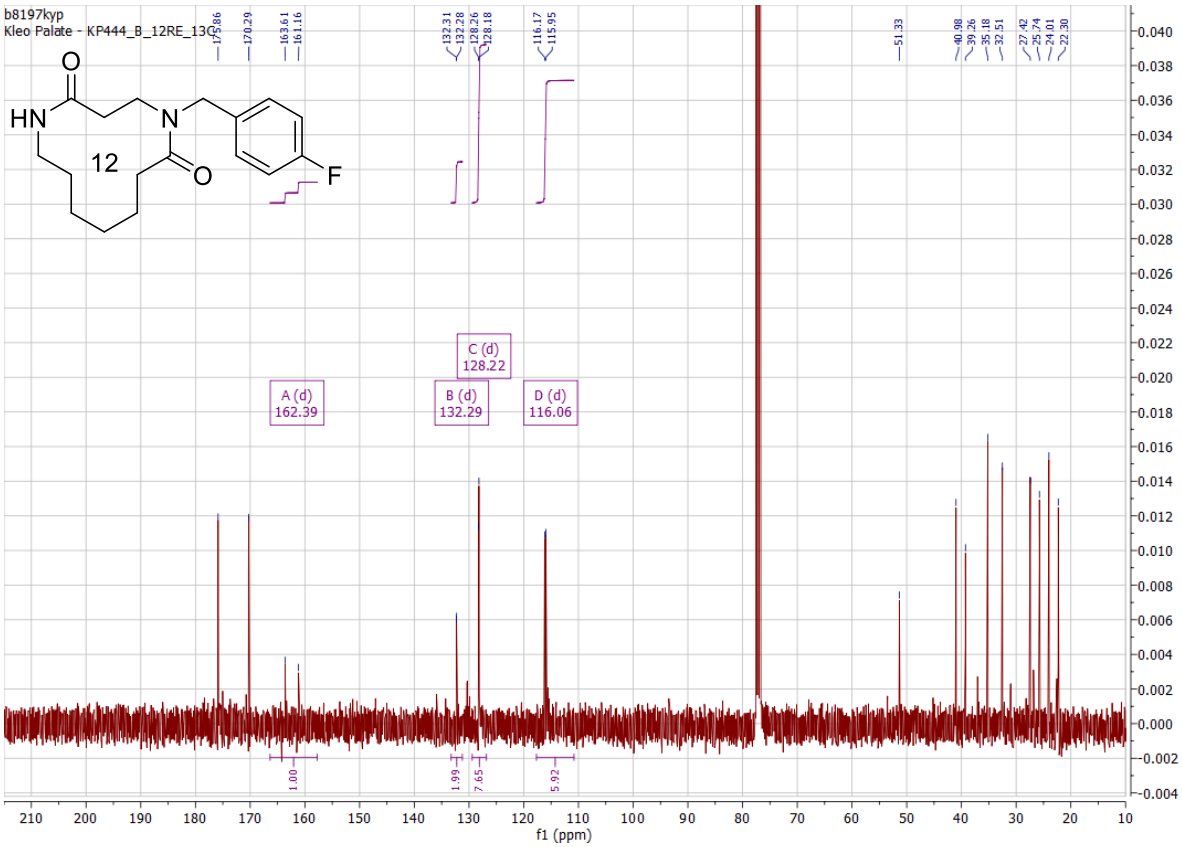
1-Acryloyl-azocan-2-one (11e)

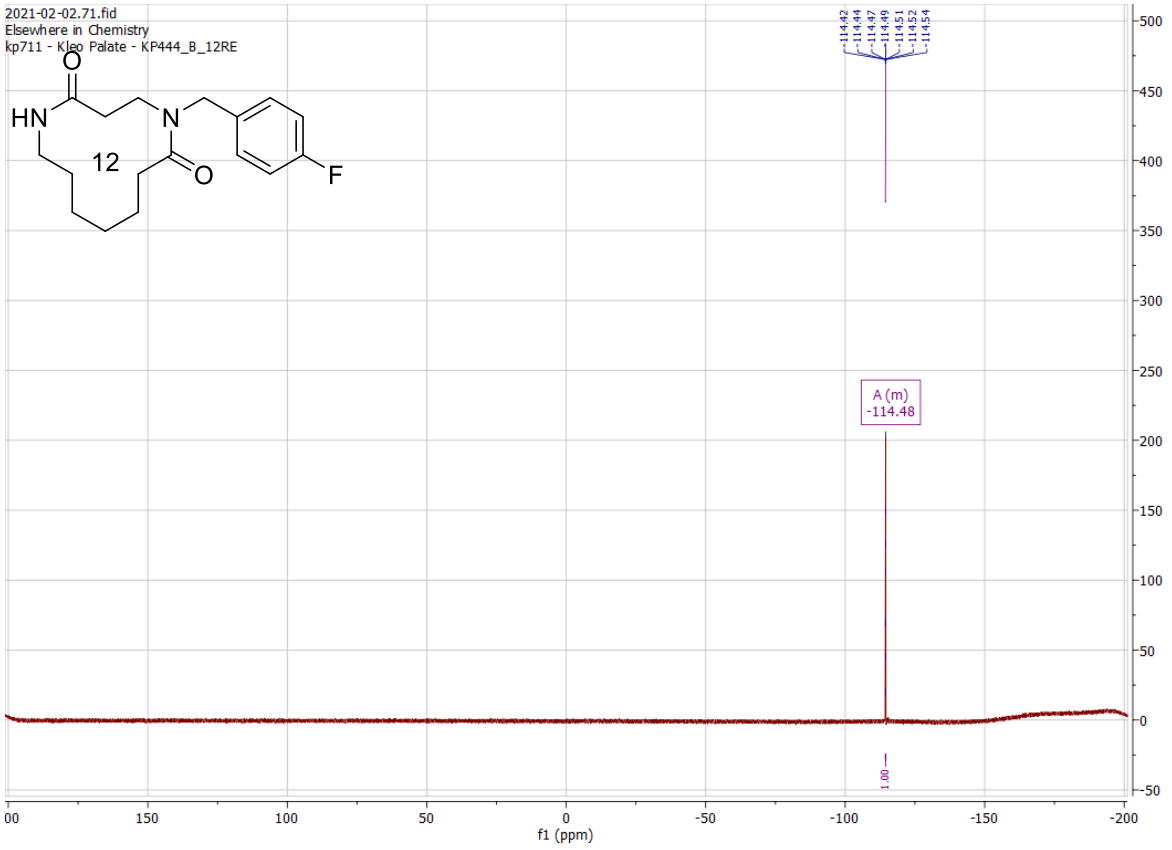


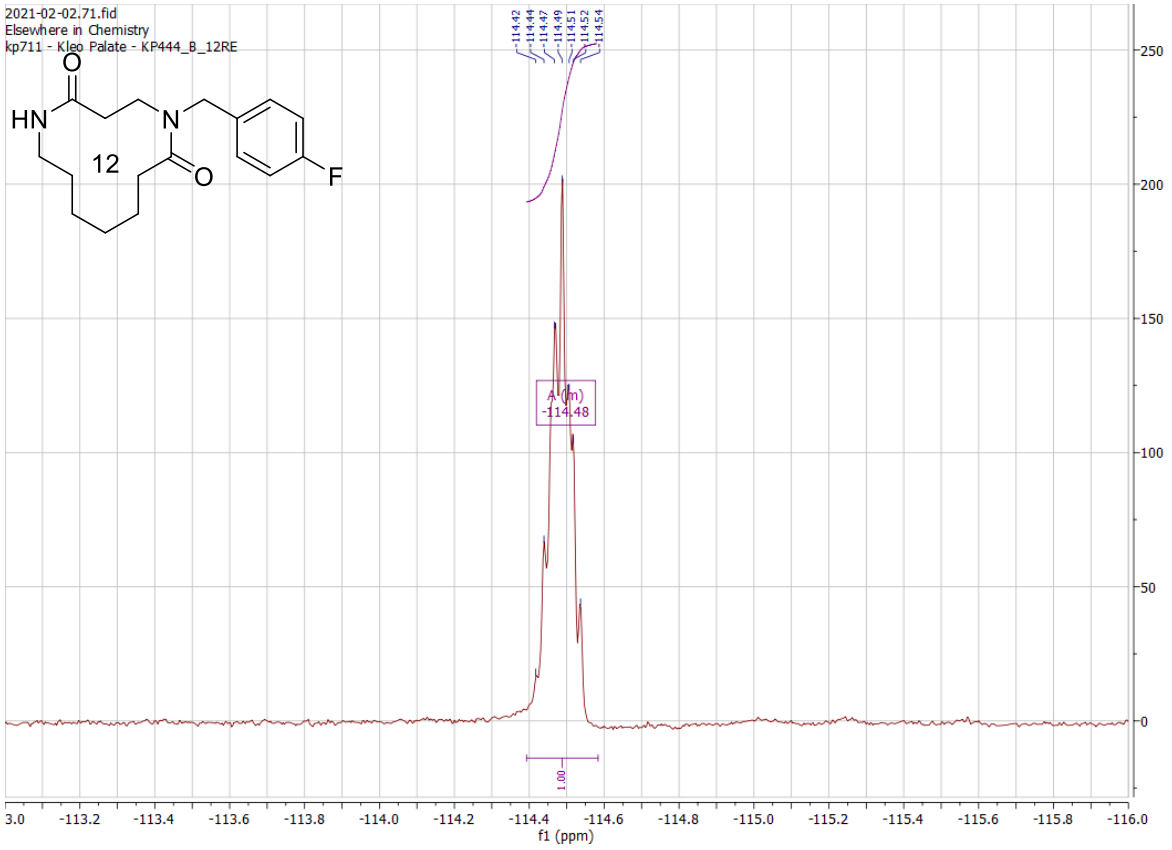


5-(4-Fluorobenzyl)-1,5-diazacyclododecane-2,6-dione (14e)

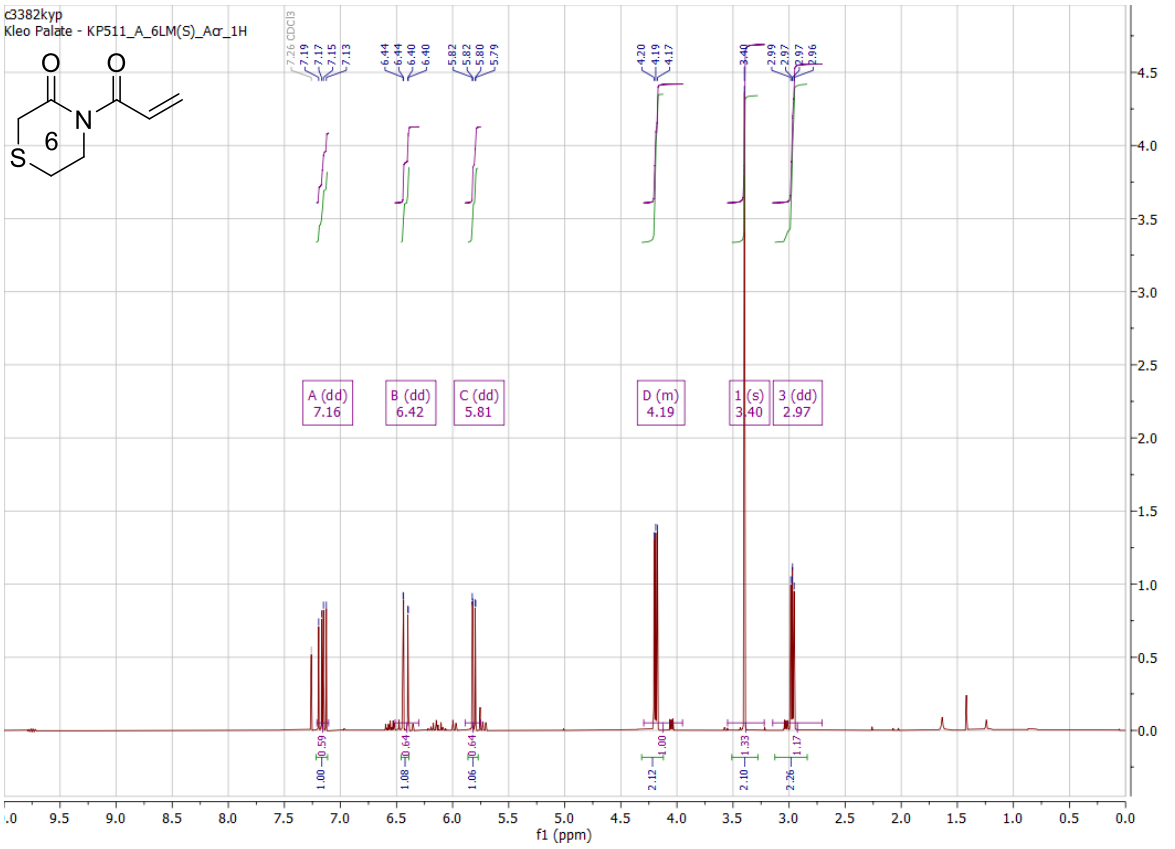


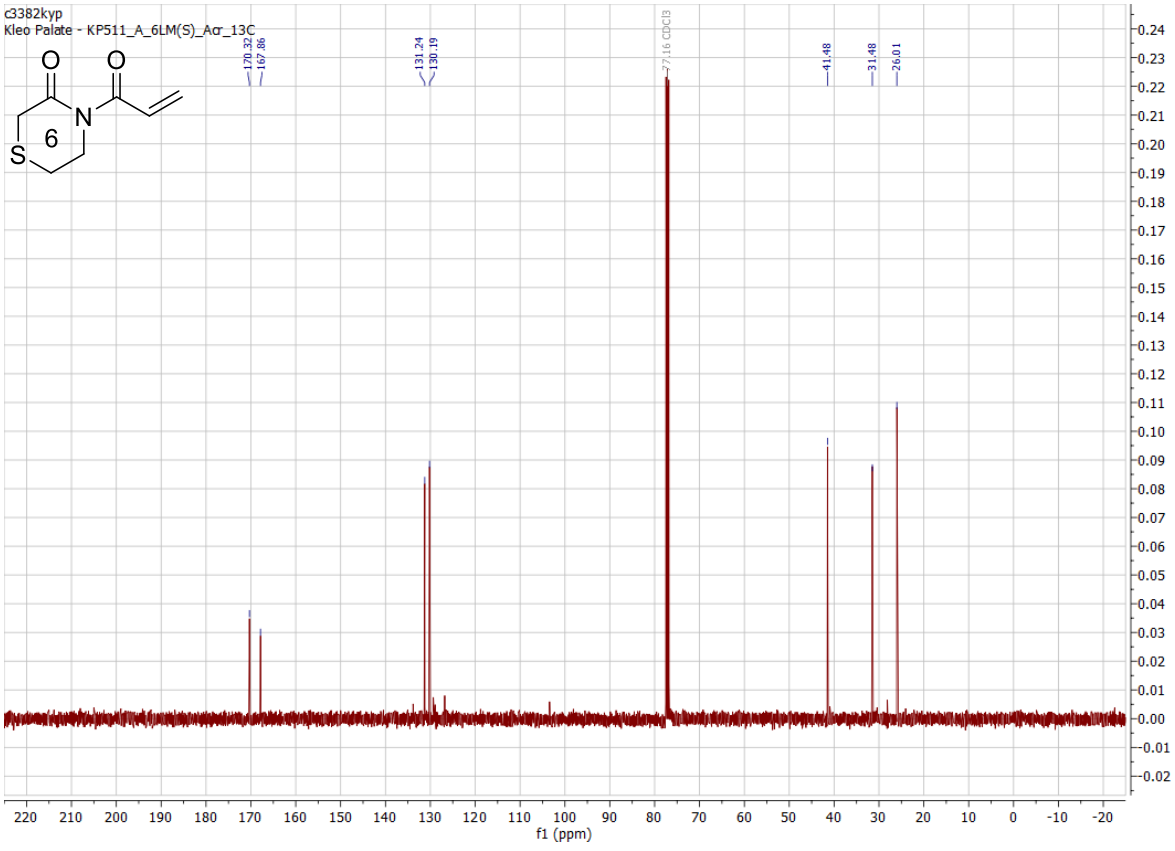



2021-02-02.71.fid
Elsewhere in Chemistry
kp711 - Kleo Palate - KP444_B_12RE
HN
O
N
12
O
F
-114.42
-114.44
-114.47
-114.49
-114.51
-114.52
-114.54
A (m)
-114.48
1.00
f1 (ppm)

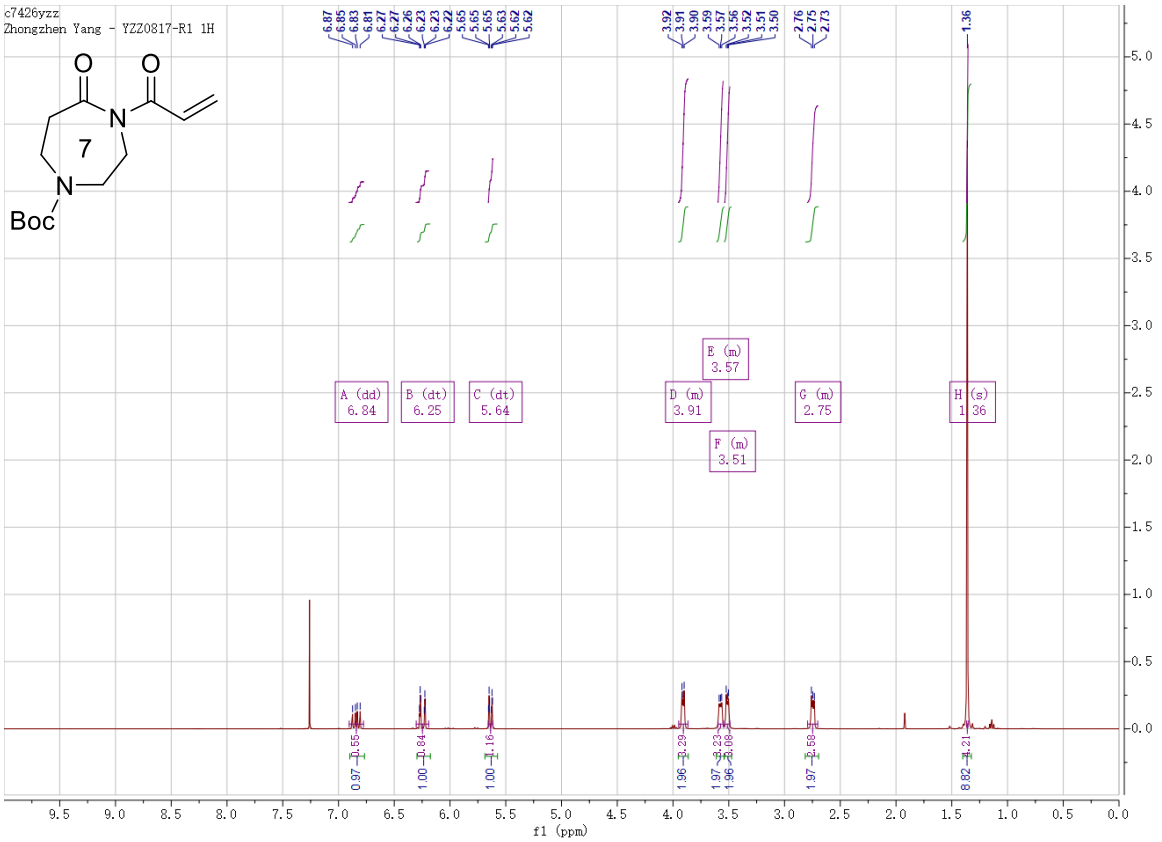

2021-02-02.71.fid
Elsewhere in Chemistry
kp711 - Kleo Palate - KP444_B_12RE
HN
O
N
12
O
F
-114.42
-114.44
-114.47
-114.49
-114.51
-114.52
-114.54
A (m)
-114.48
1.00
f1 (ppm)

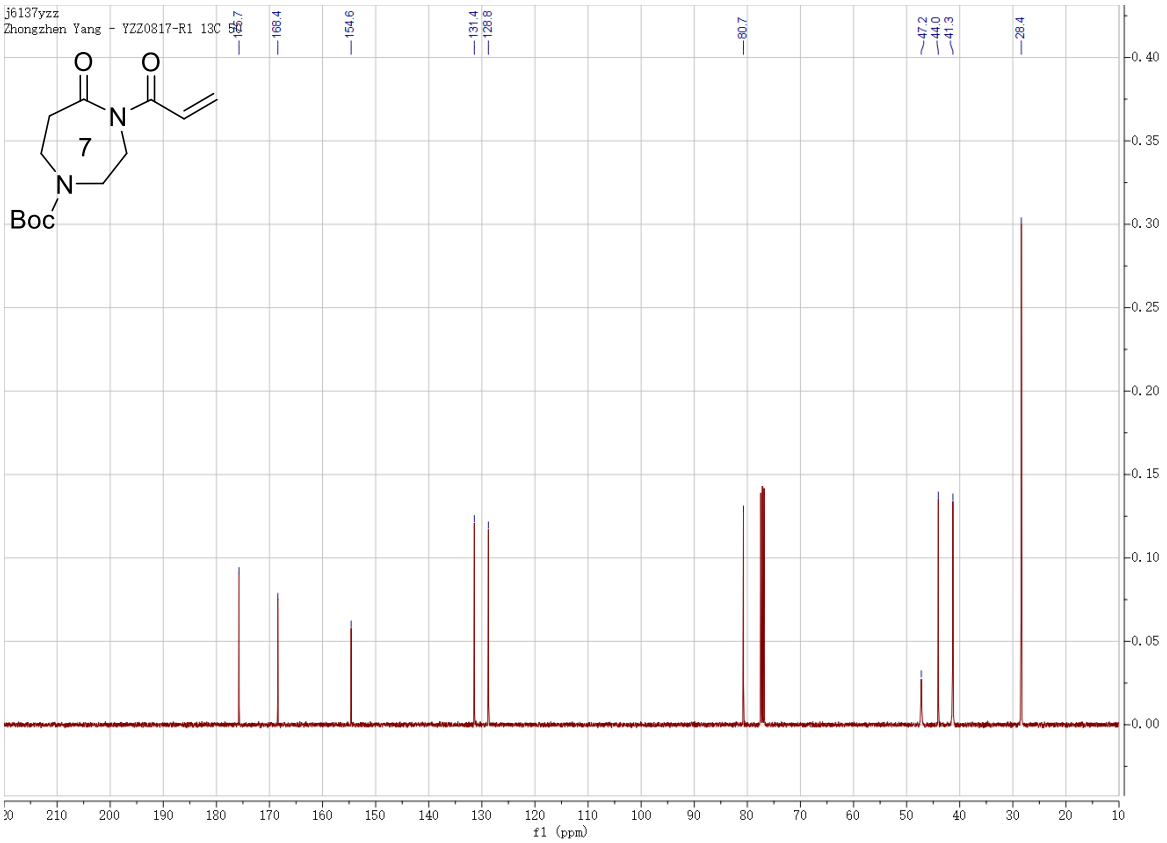
4-(Acryloyl)thiomorpholin-3-one (16a)



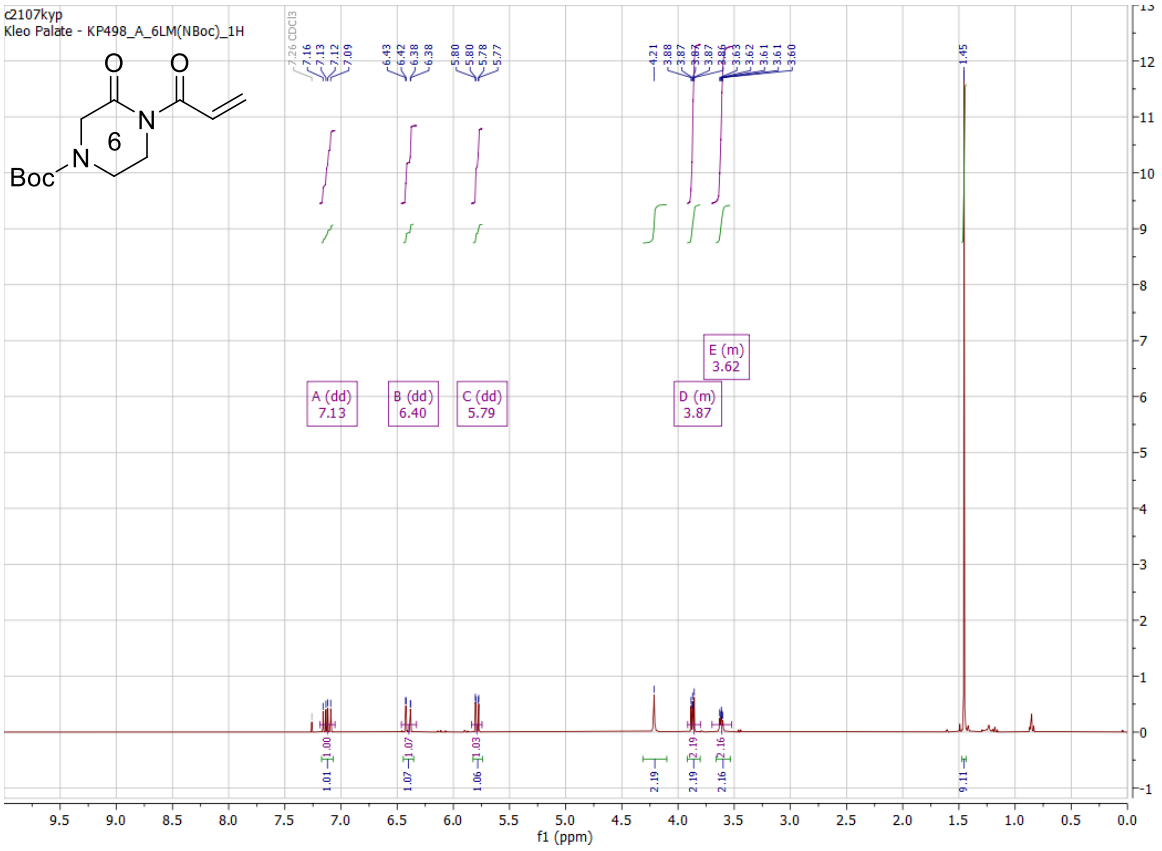


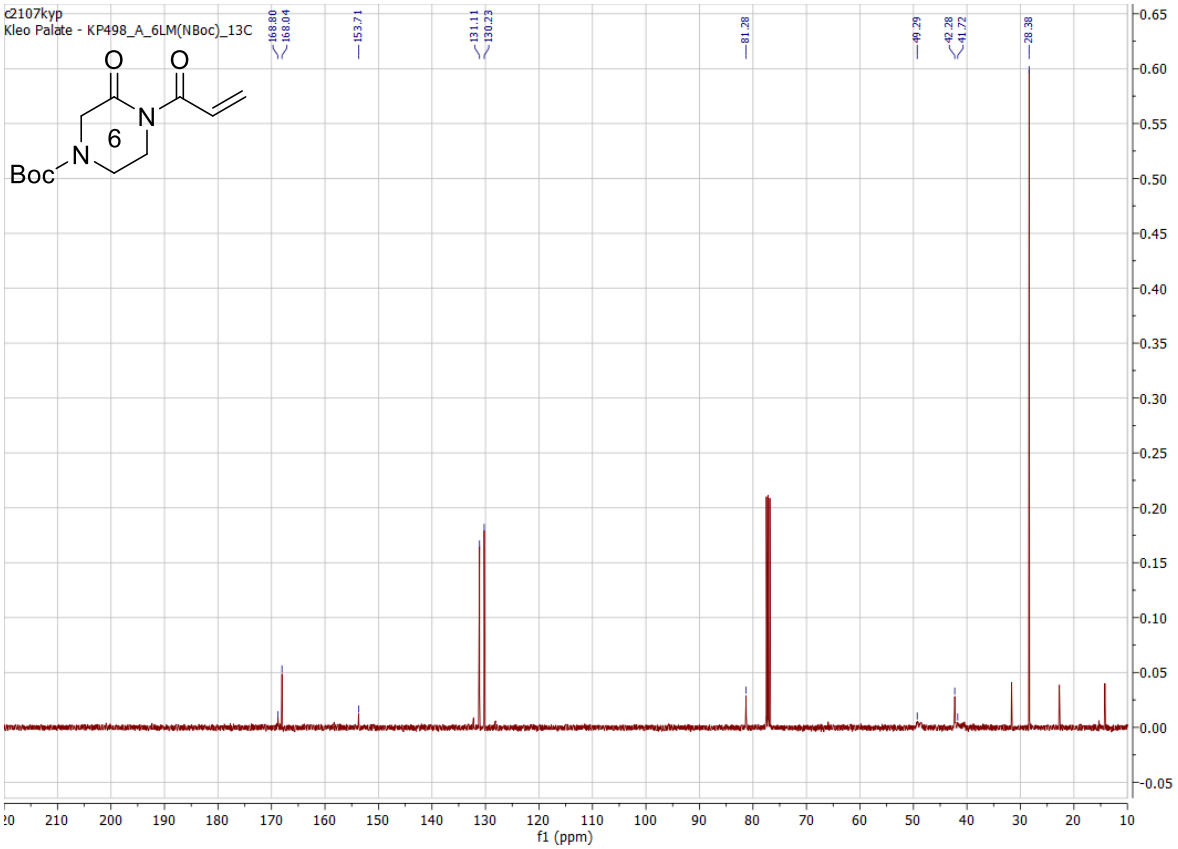
tert-Butyl 4-acryloyl-5-oxo-1,4-diazepane-1-carboxylate (16b)



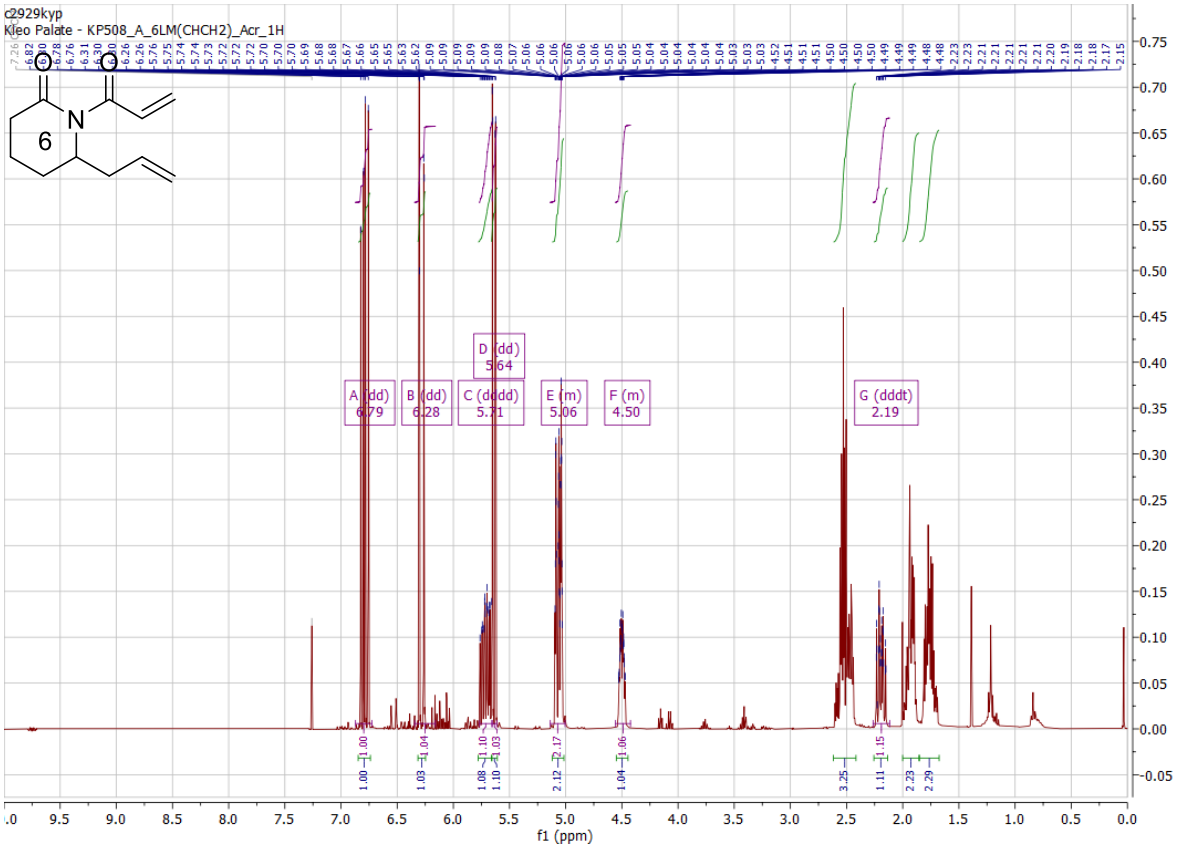


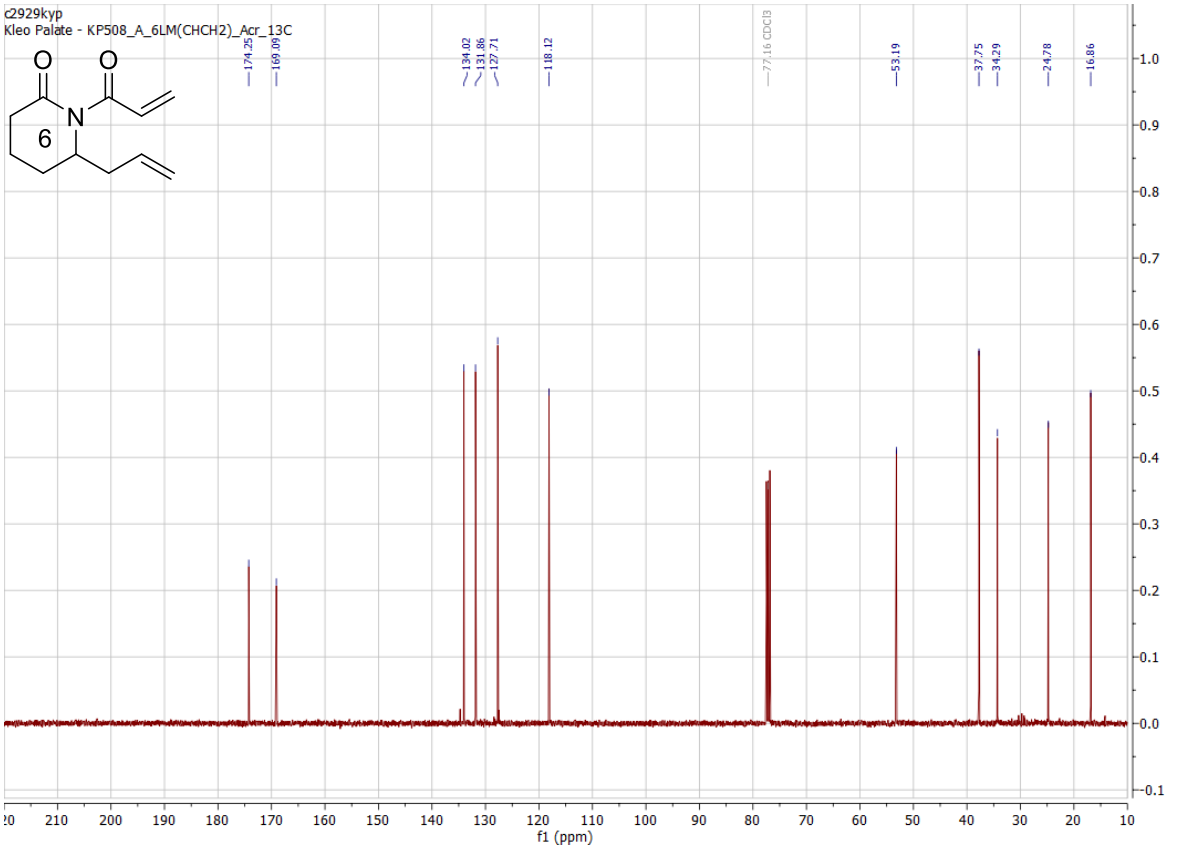
tert-Butyl 4-acryloyl-3-oxopiperazine-1-carboxylate (16c)



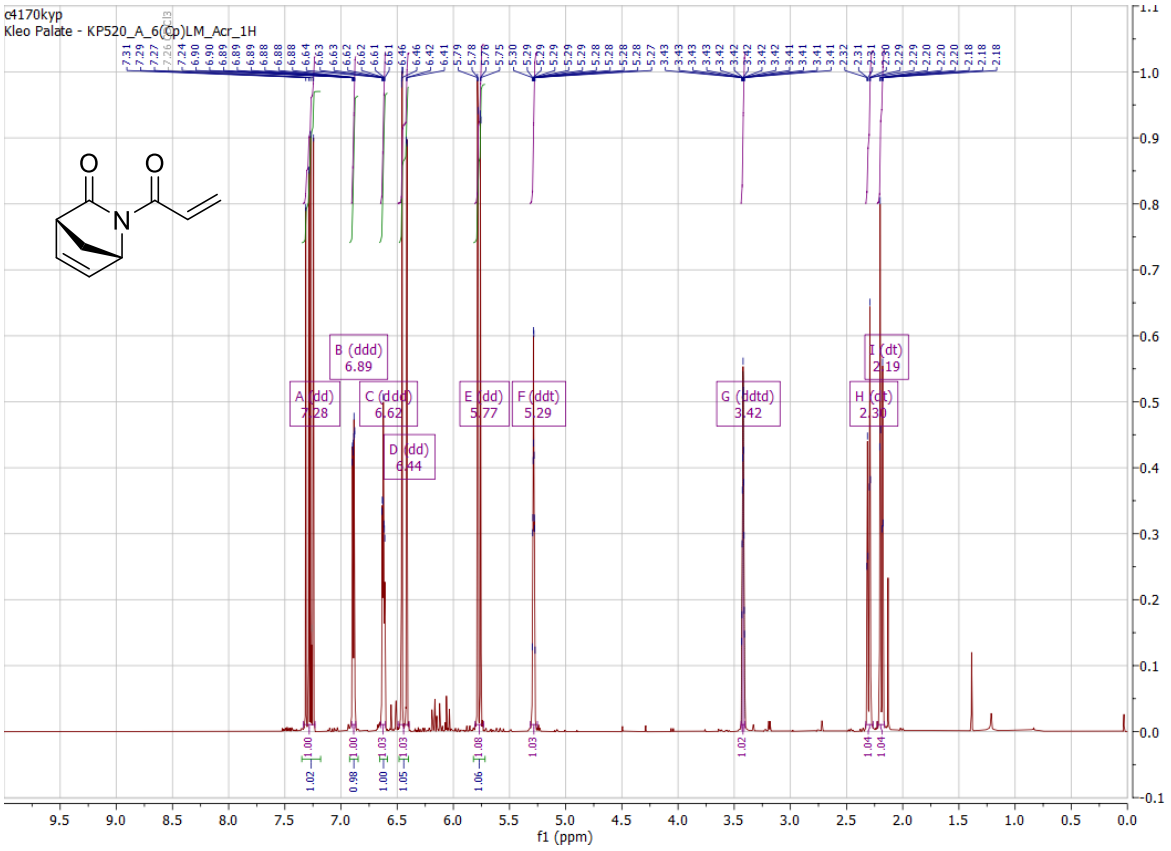


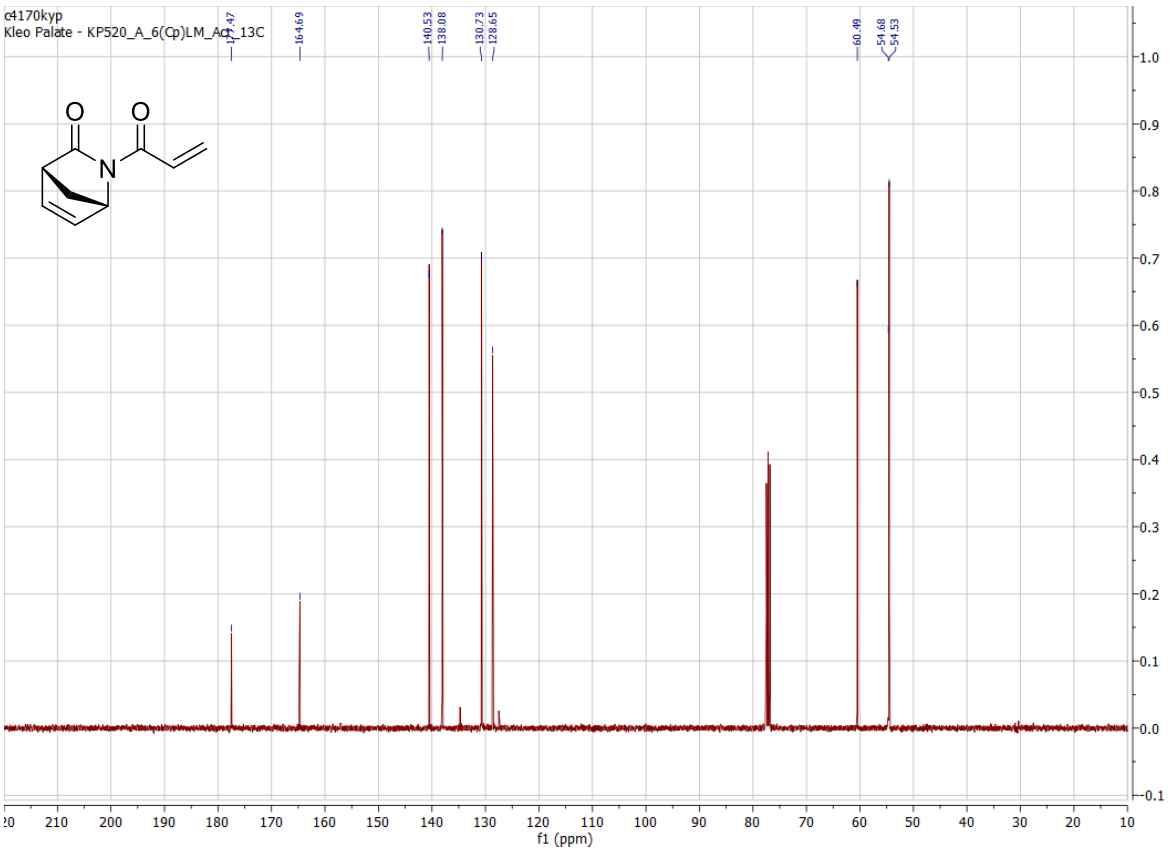
1-Acryloyl-6-allylpiperidin-2-one (16d)



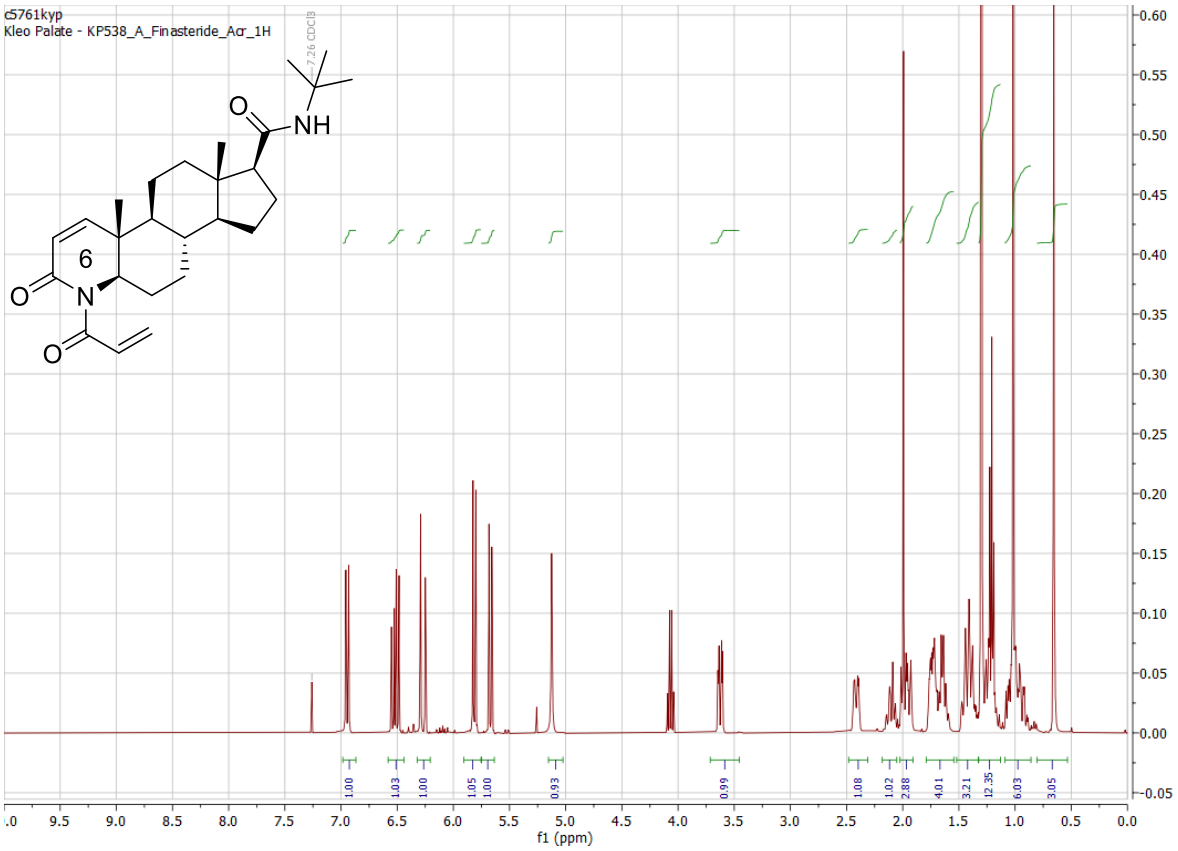


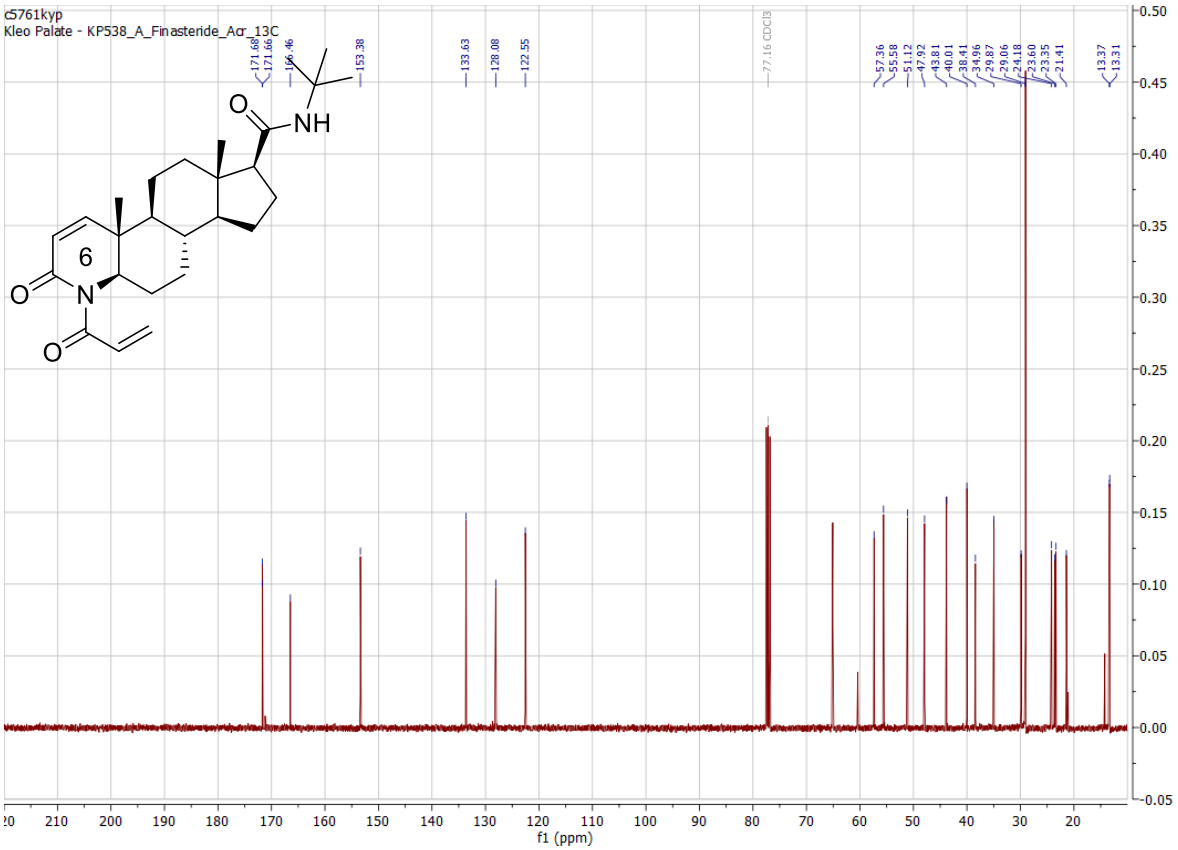
(1*SR*,4*RS*)-2-Acryloyl-2-azabicyclo[2.2.1]hept-5-en-3-one (16e)



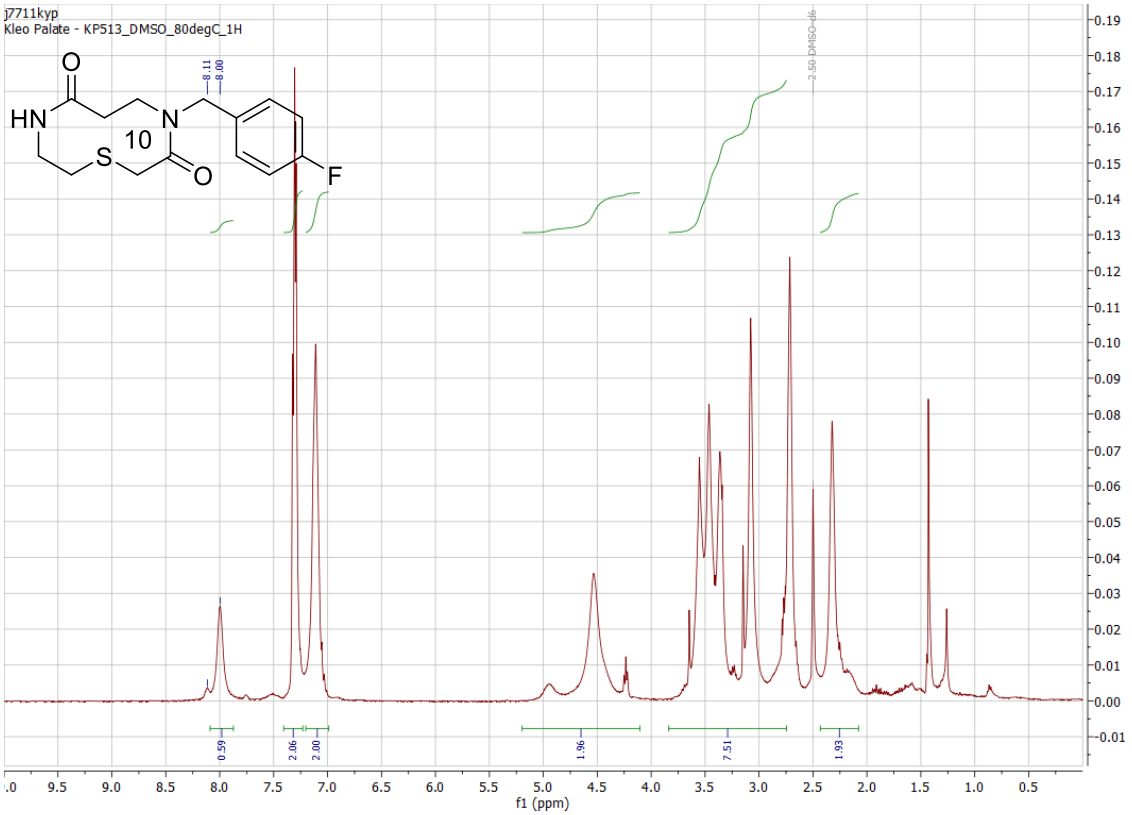


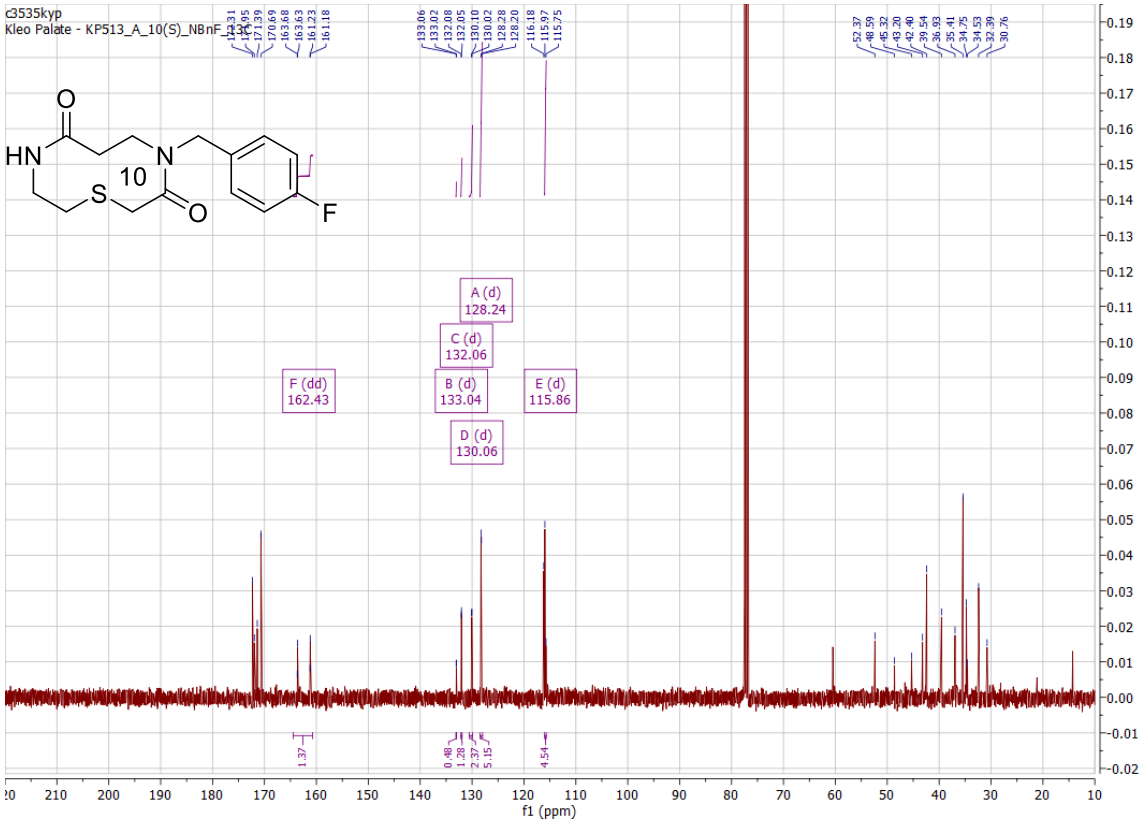
4a*R*,4b*S*,6a*S*,7*S*,9a*S*,9b*S*,11a*R*)-1-Acryloyl-*N*-(*tert*-butyl)-4a,6a-dimethyl-2-oxo-2,4a,4b,5,6,6a,7,8,9,9a,9b,10,11,11a-tetradecahydro-1*H*-indeno[5,4-*f*]quinoline-7-carboxamide (16f)

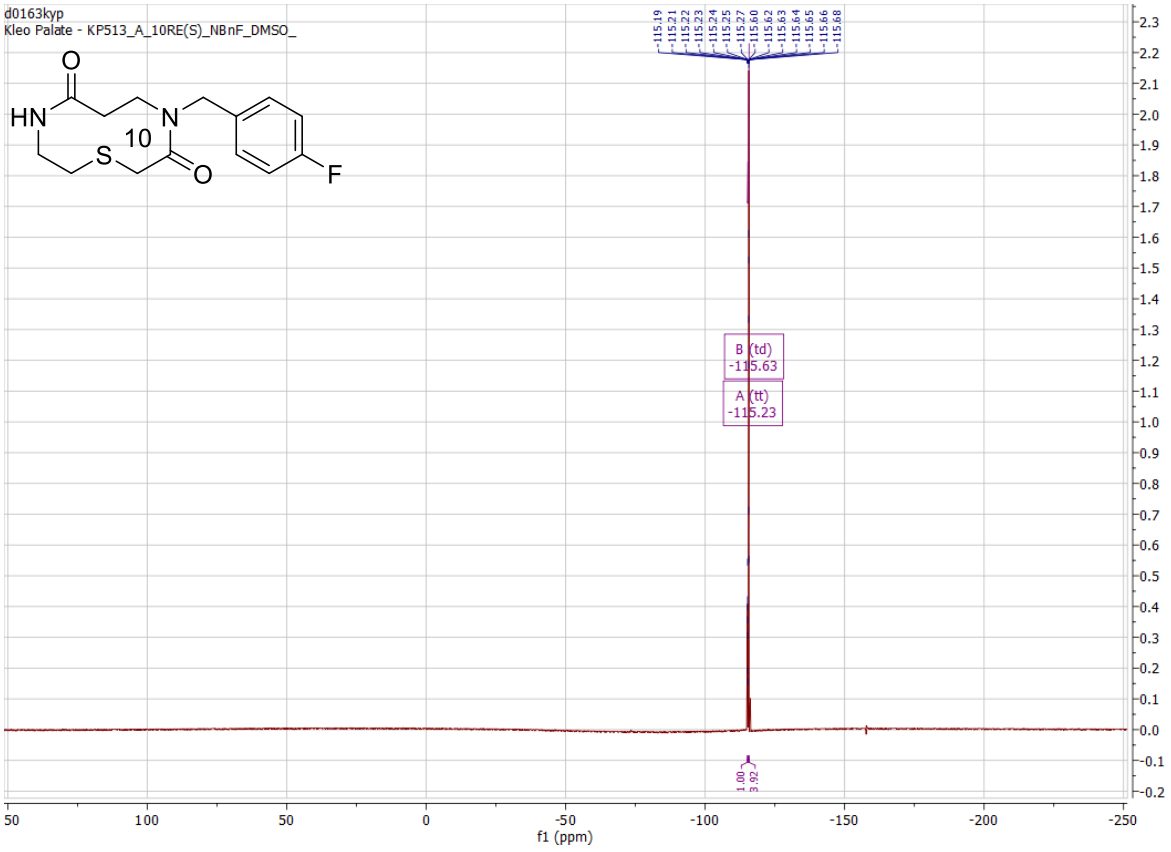


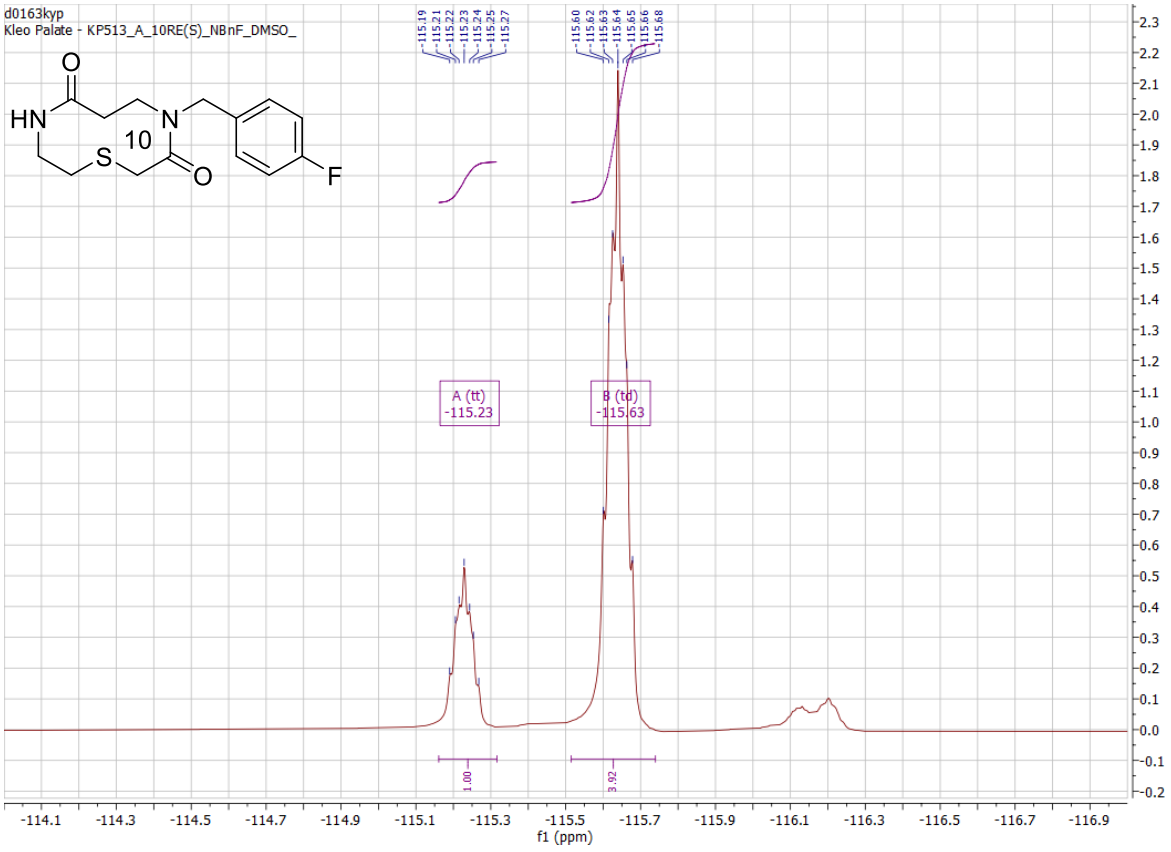


4-(4-Fluorobenzyl)-1,4,8-thiadiazecane-3,7-dione (17a) In solution in $CDCl_3$, this compound exists as a mixture of 2 rotameric forms (4:1 ratio, best seen in the ^{19}F NMR). The ^{1}H NMR spectrum is difficult to interpret due rotameric broadening, even when recorded at 80 °C in DMSO-d6, with product identity and purity best determined using ^{13}C NMR data in $CDCl_3$ at RT.

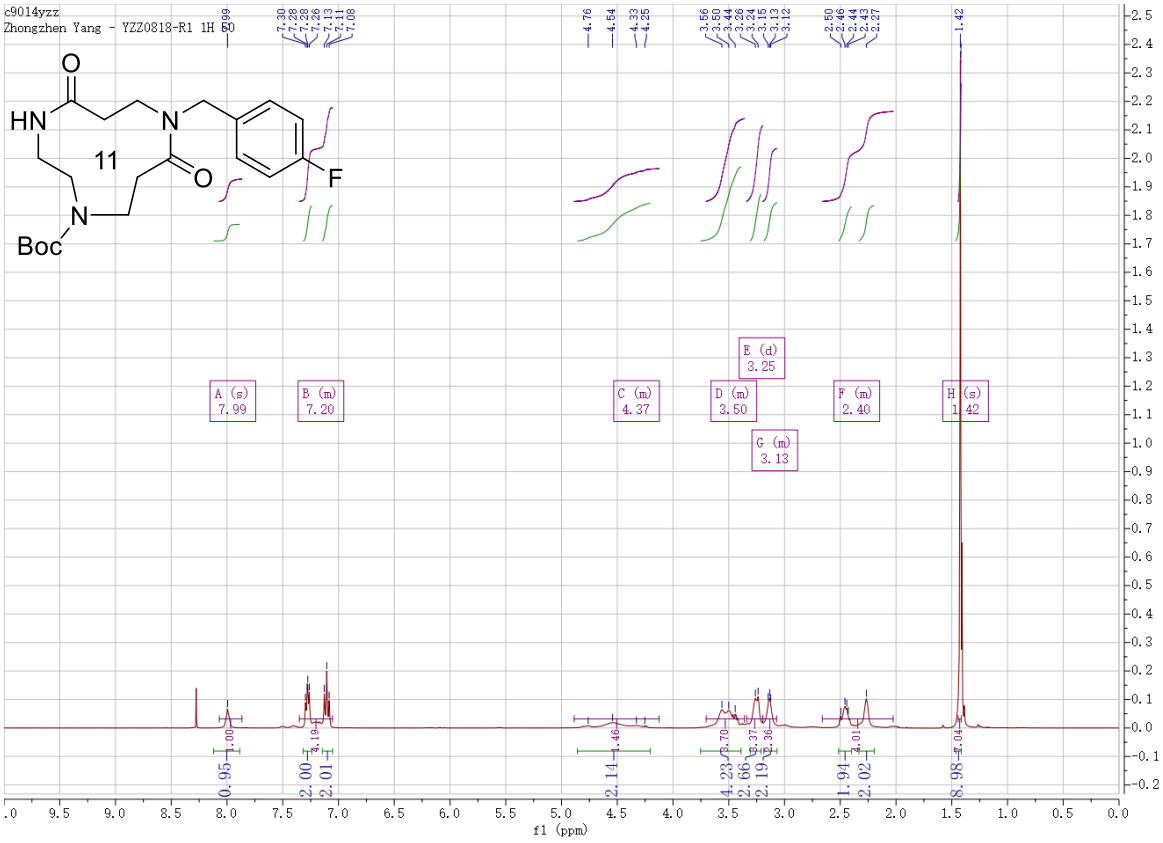


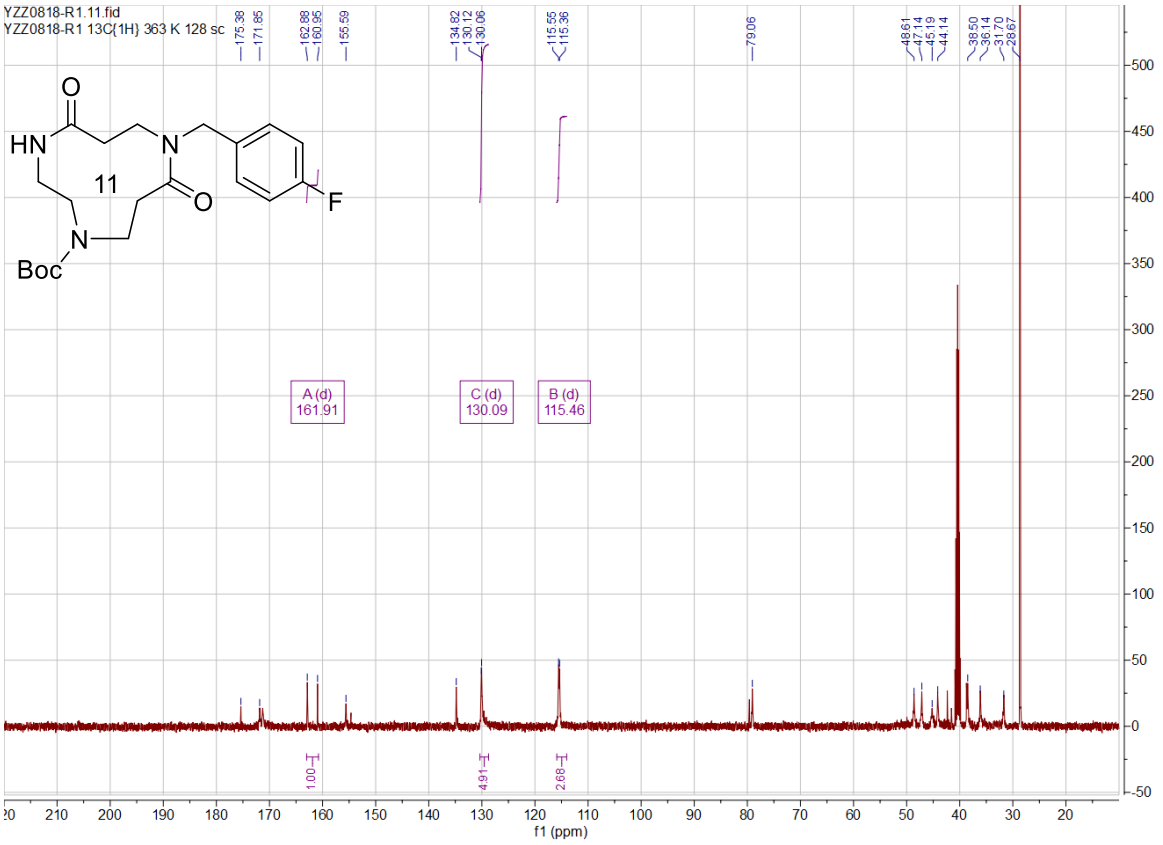


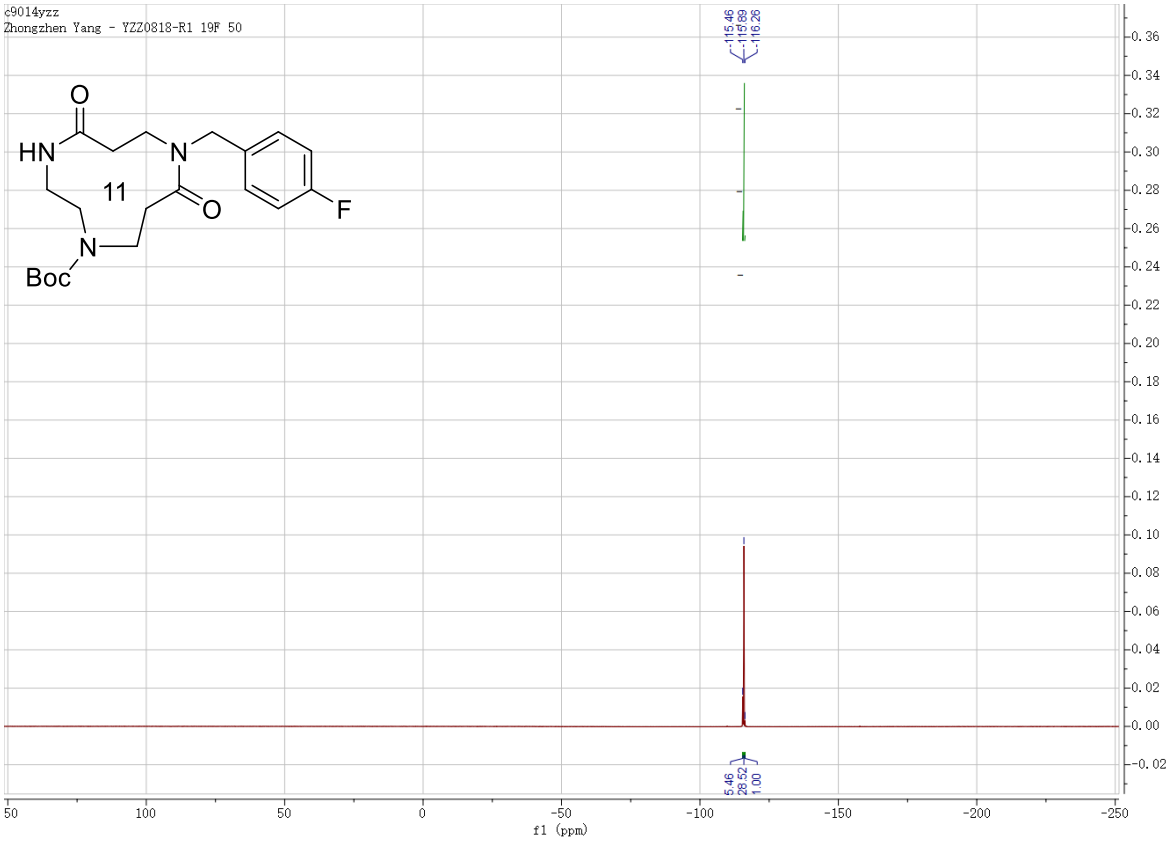

d0163kyp
Kleo Palate - KP513_A_10RE(S)_NBnF_DMSO_
HN
O
N
10
S
O
F
B (td)
-115.63
A (tt)
-115.23
1.00
3.92
f1 (ppm)

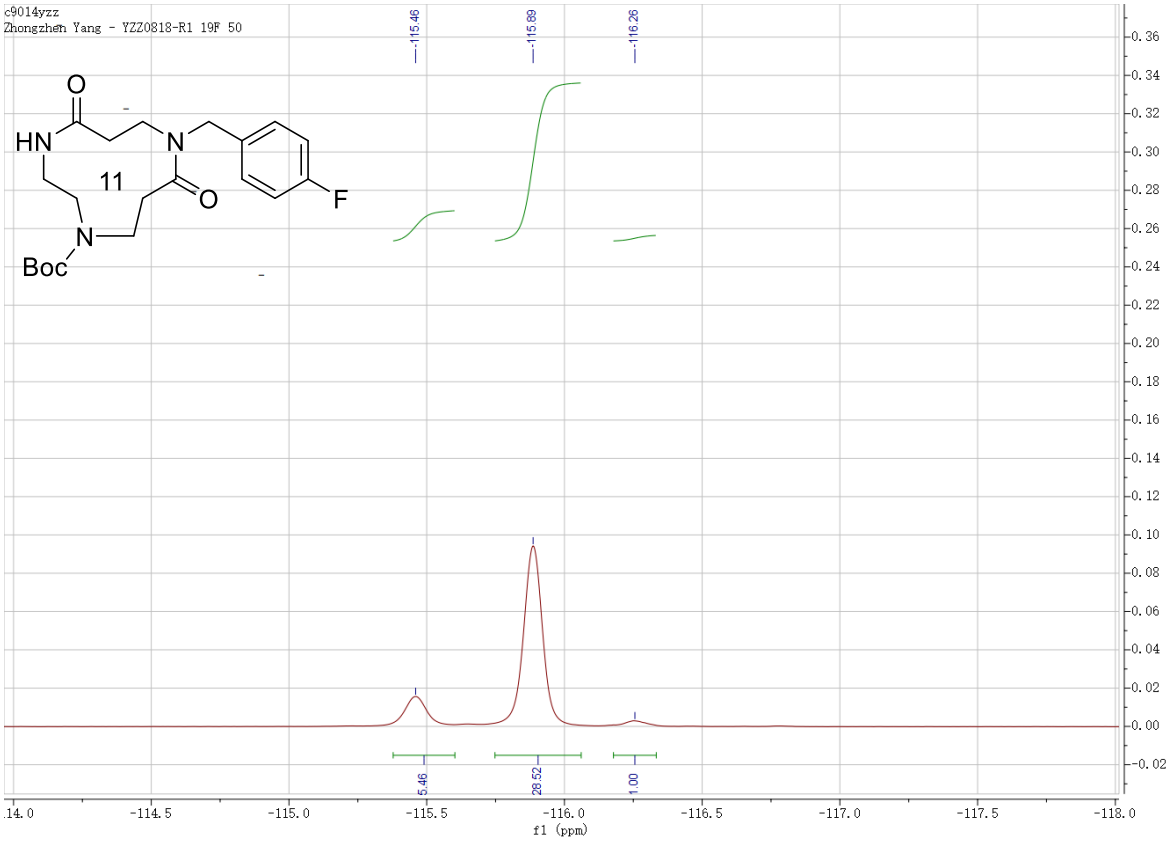

d0163kyp
Kleo Palate - KP513_A_10RE(S)_NBnF_DMSO_
HN
O
N
10
S
O
F
A (tt)
-115.23
B (td)
-115.63
1.00
3.92
f1 (ppm)

***tert*-Butyl 8-(4-fluorobenzyl)-5,9-dioxo-1,4,8-triazacycloundecane-1-carboxylate (17b)** The ^{1}H NMR and 13C NMR spectra are both affected by rotameric broadening, even when recorded at elevated temperatures.

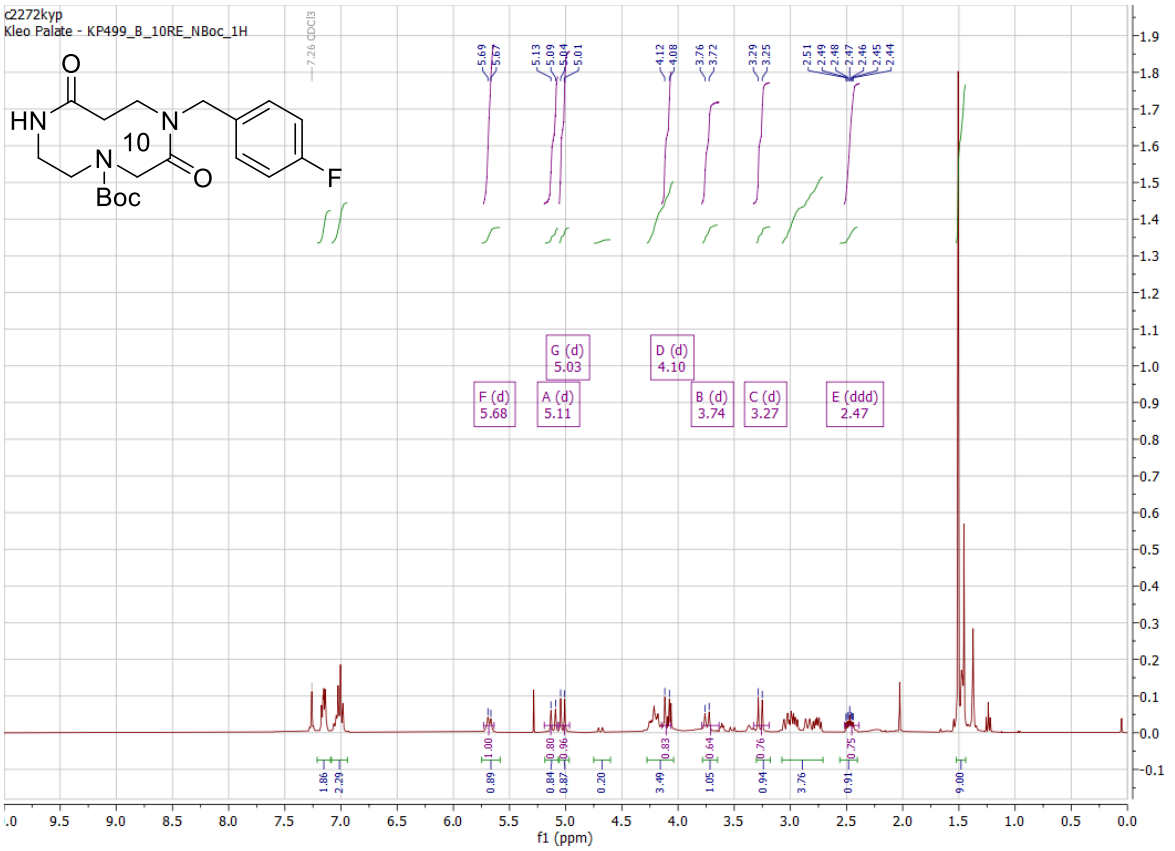


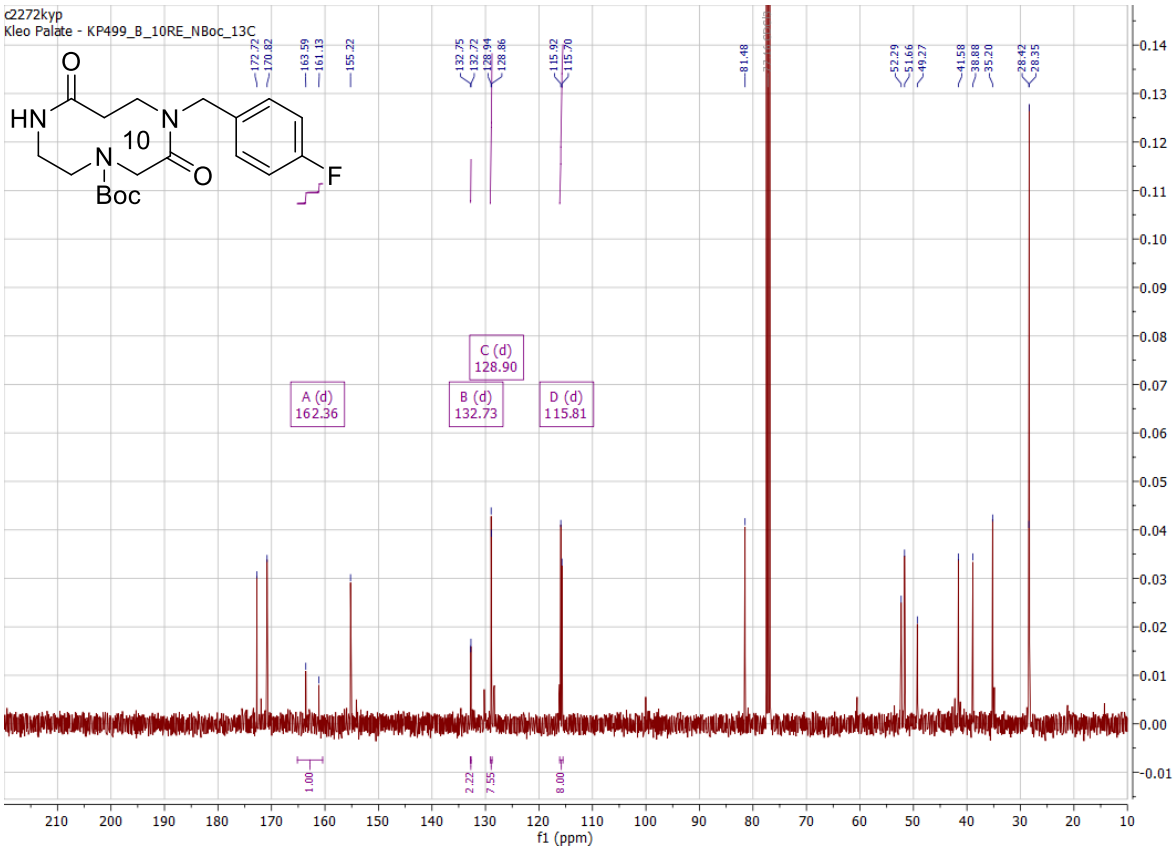


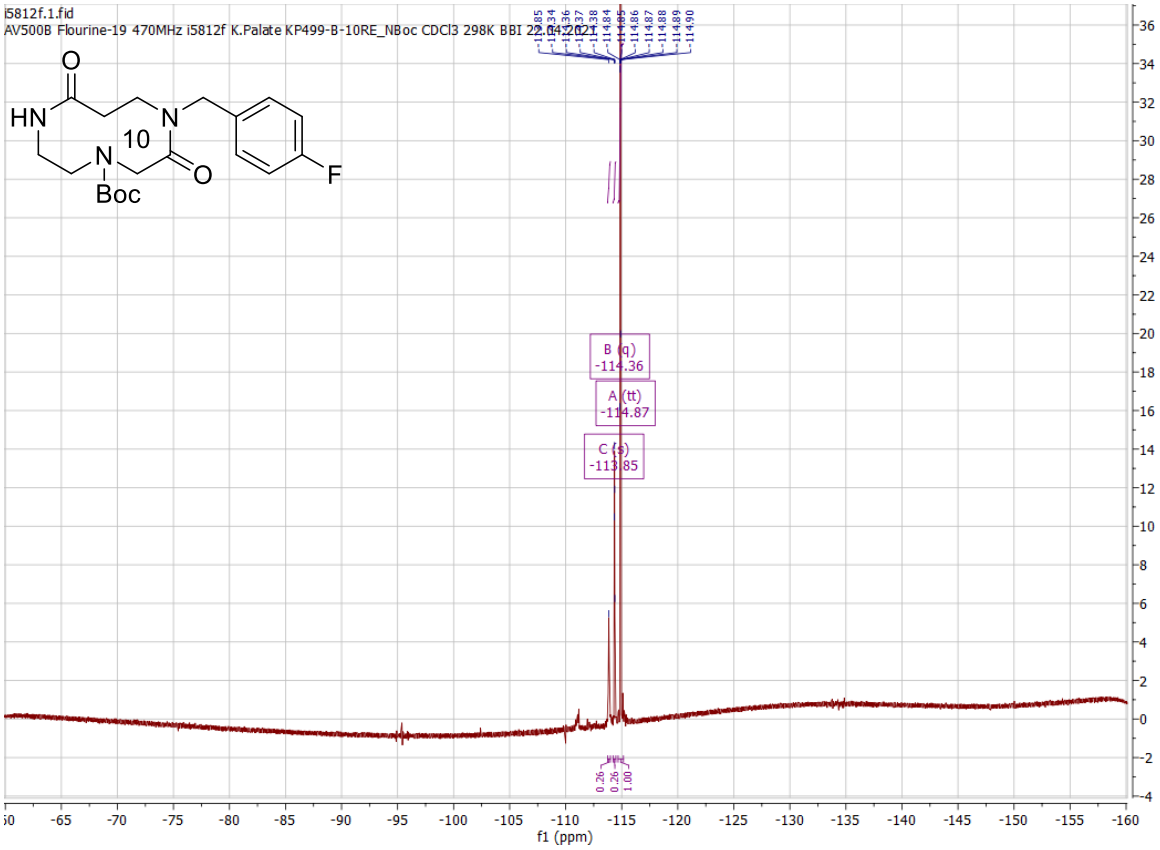

c9014yzz
Zhongzhen Yang - YZZ0818-R1 19F 50
O
HN
N
11
O
F
N
Boc
-115.46
-115.89
-116.26
5.46
28.52
1.00
f1 (ppm)

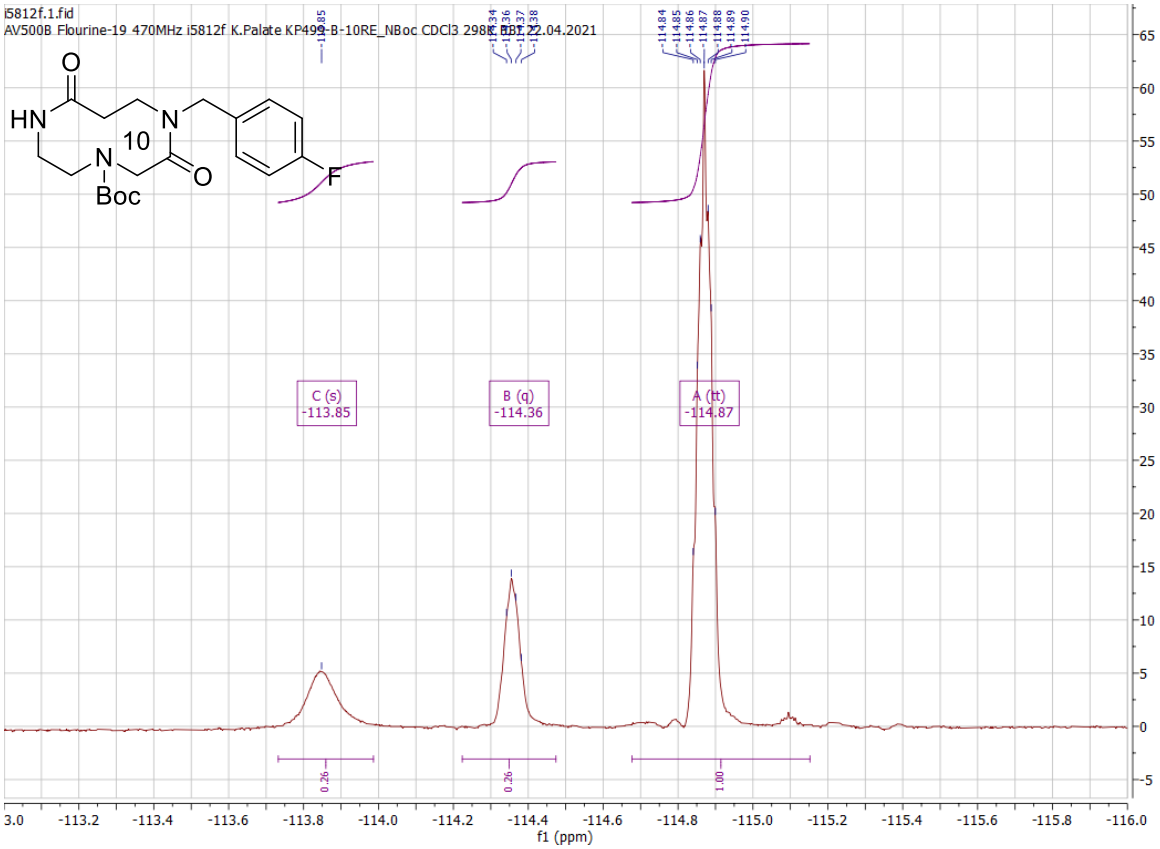

c9014yzz
Zhongzhen Yang - YZZ0818-R1 19F 50
O
HN
N
11
O
F
N
Boc
-115.46
-115.89
-116.26
5.46
28.52
1.00
f1 (ppm)

***tert*-Butyl 1-(4-fluorobenzyl)-2,8-dioxo-1,4,7-triazecane-4-carboxylate (17c)** In solution in $CDCl_3$, this compound exists as a mixture of 3 rotameric forms (4:5:20 ratio, best seen in the ^{19}F NMR)

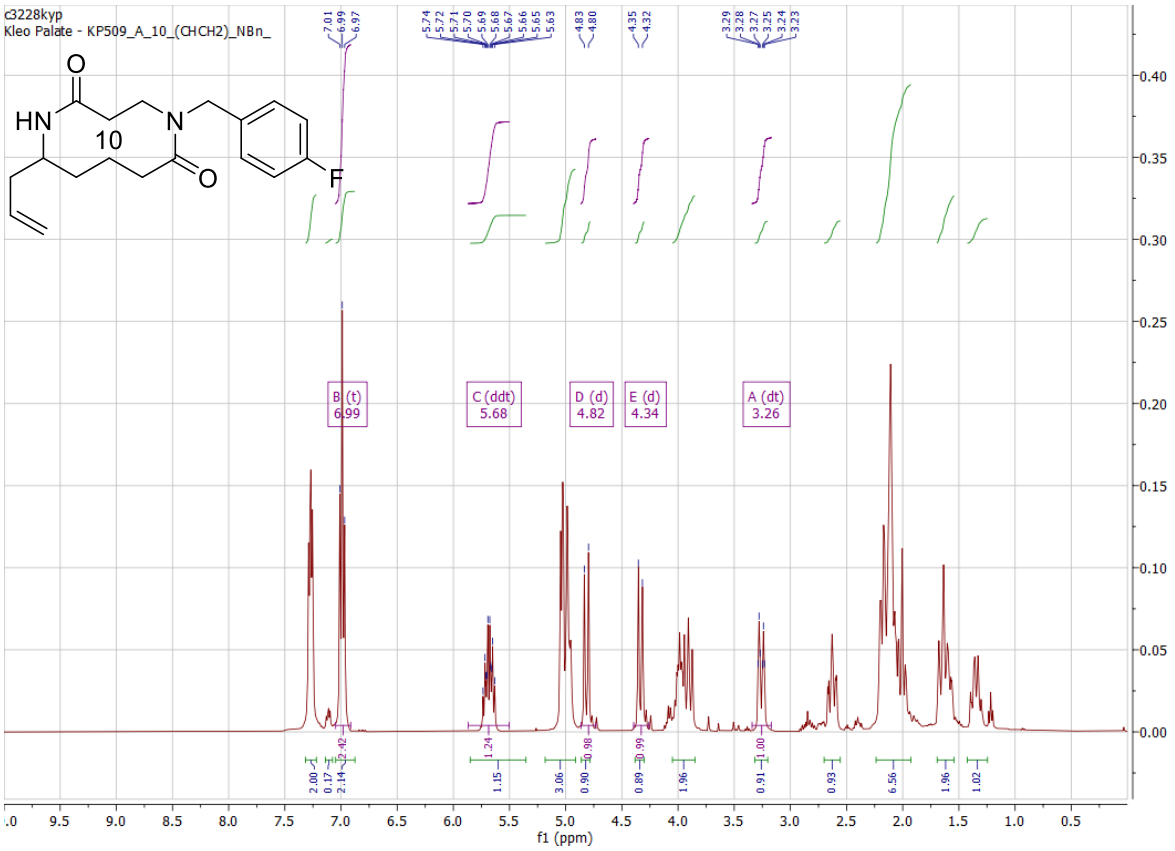


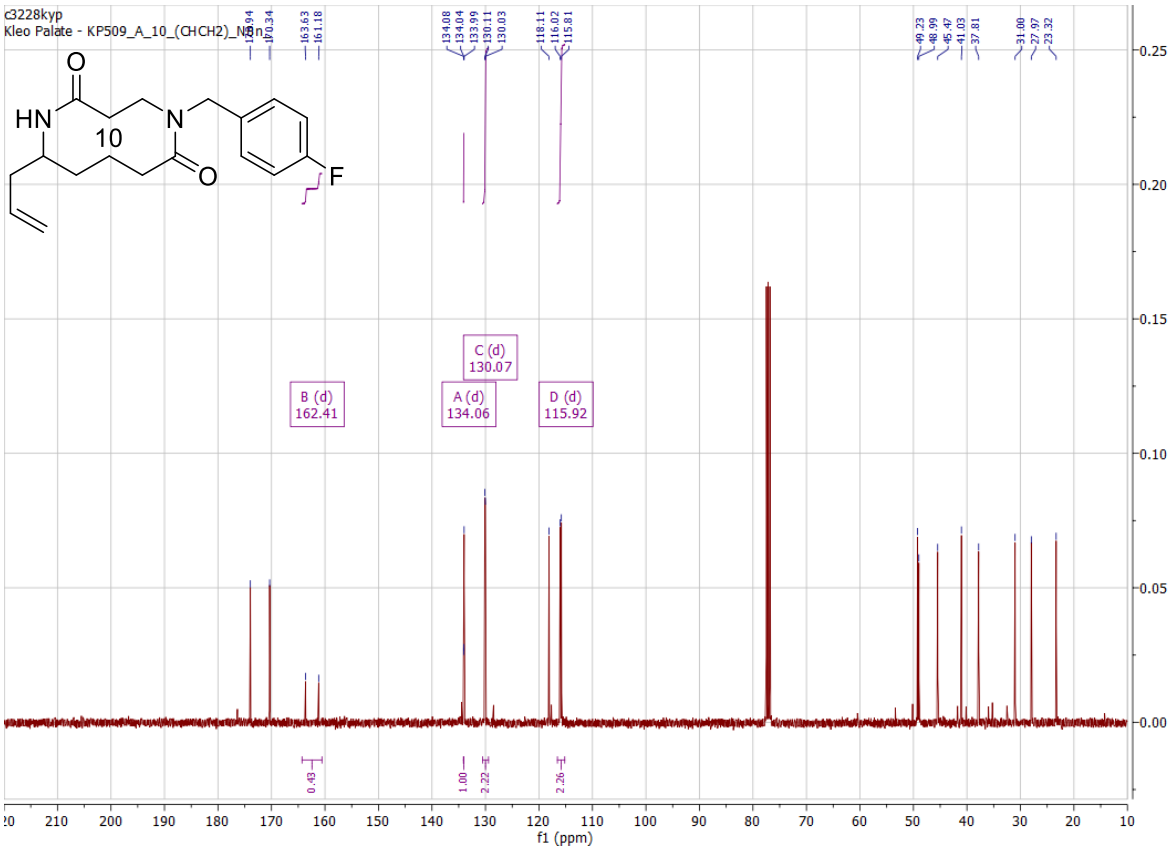


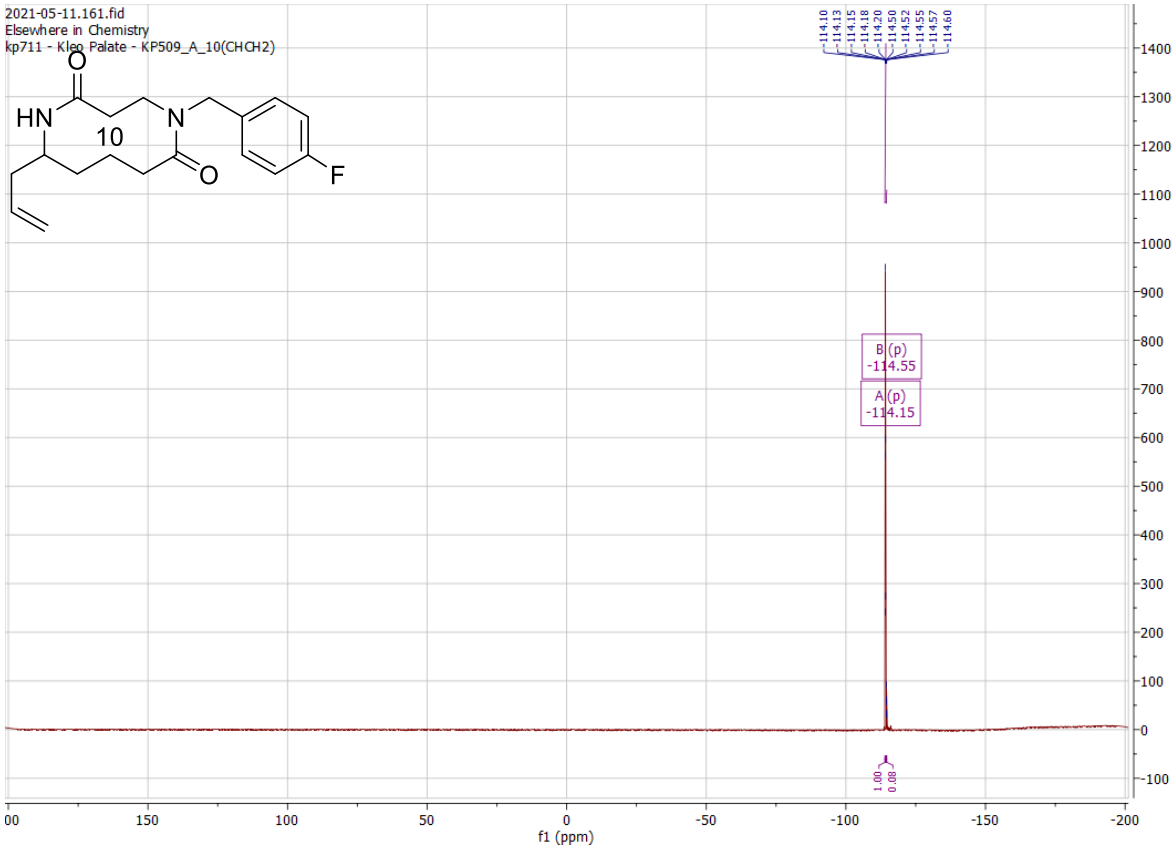

i5812f.1.fid
AV500B Flourine-19 470MHz i5812f K.Palate KP499-B-10RE_NBoc CDCl3 298K BBI 22.04.2021
O
HN
N
10
N
O
Boc
F
B (q)
-114.36
A (tt)
-114.87
C (s)
-113.85
0.26
0.26
1.00
f1 (ppm)

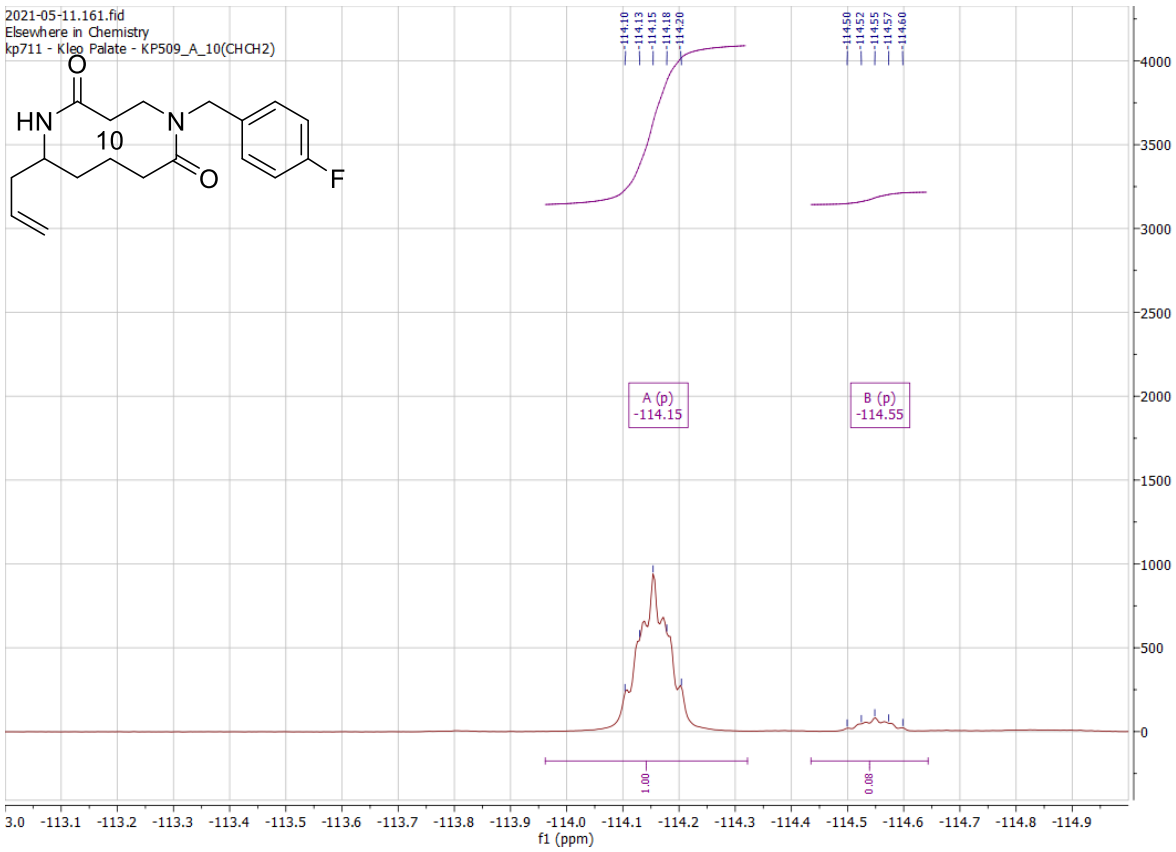

i5812f.1.fid
AV500B Flourine-19 470MHz i5812f K.Palate KP499-B-10RE_NBoc CDCl3 298K BBI 22.04.2021
O
HN
N
10
N
O
Boc
F
C (s)
-113.85
B (q)
-114.36
A (tt)
-114.87
0.26
0.26
1.00
f1 (ppm)

10-Allyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (17d) In solution in $CDCl_3$, this compound exists as a mixture of 2 rotameric forms (12:1 ratio, best seen in the ^{19}F NMR).

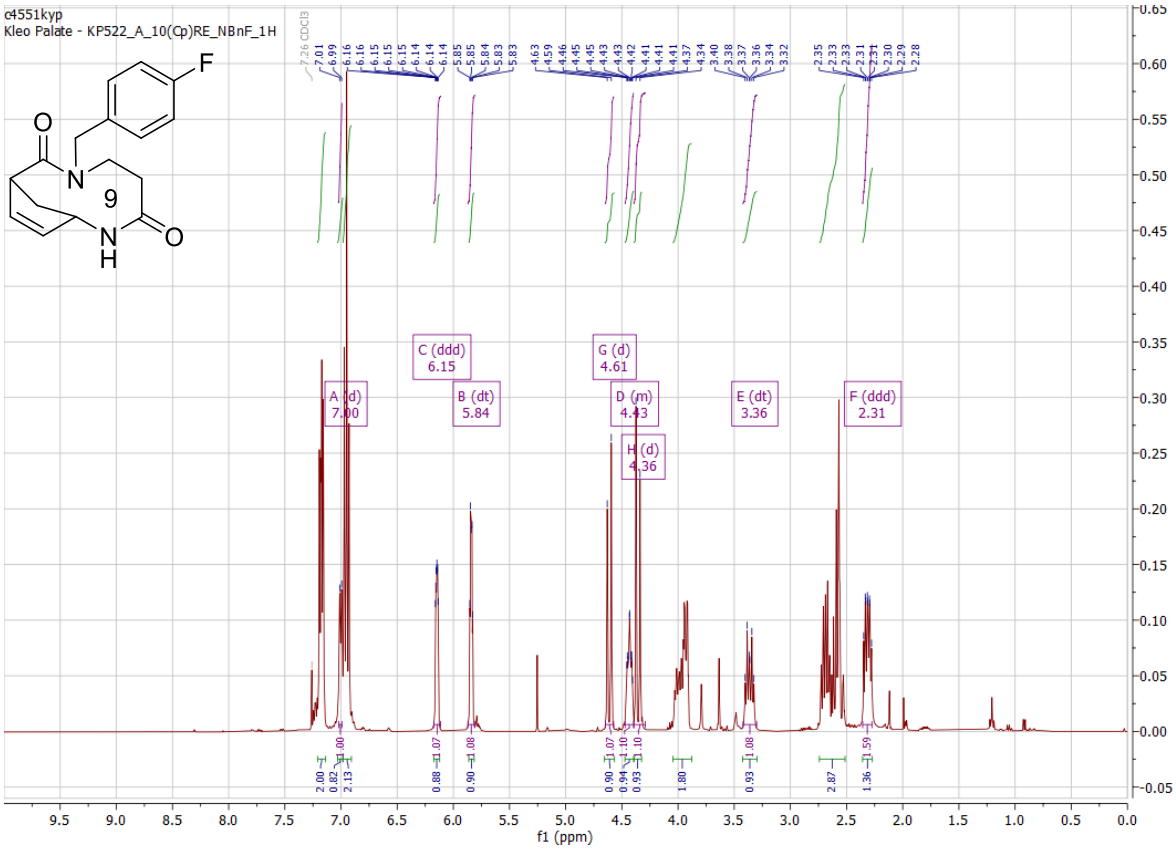


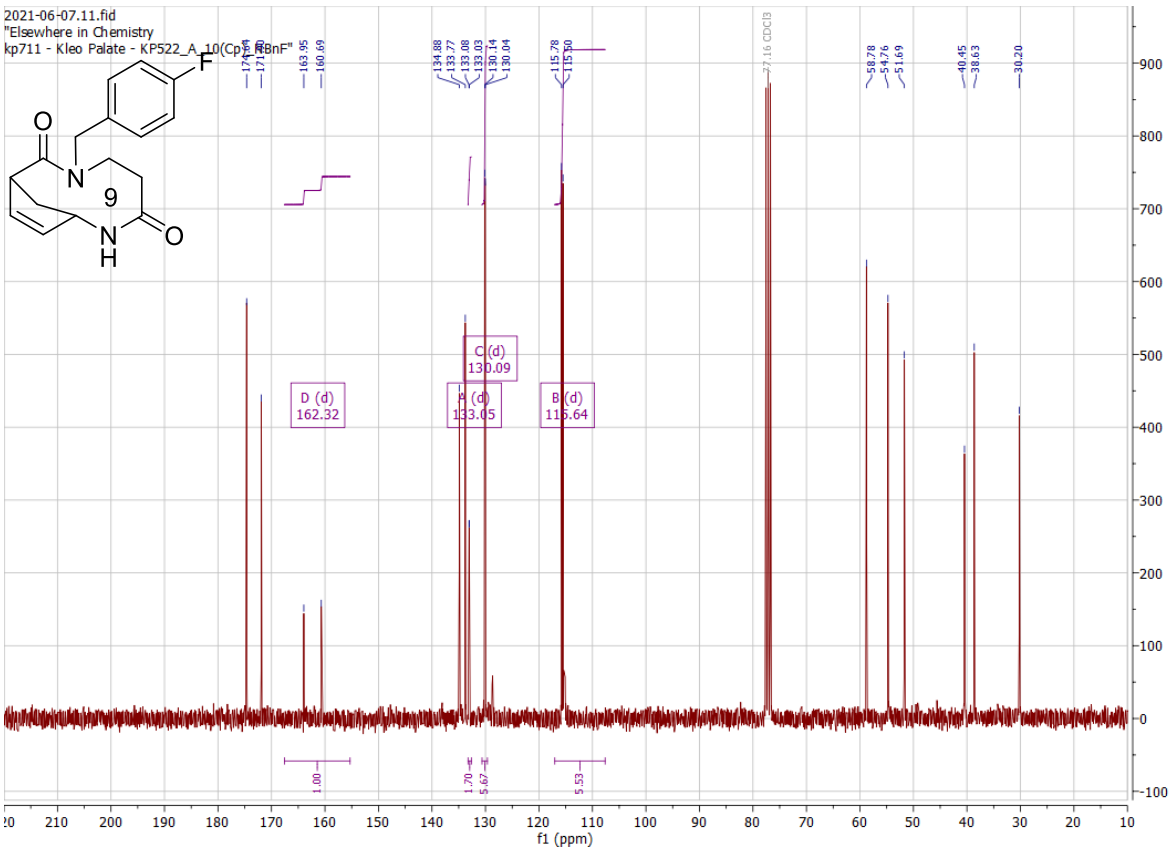


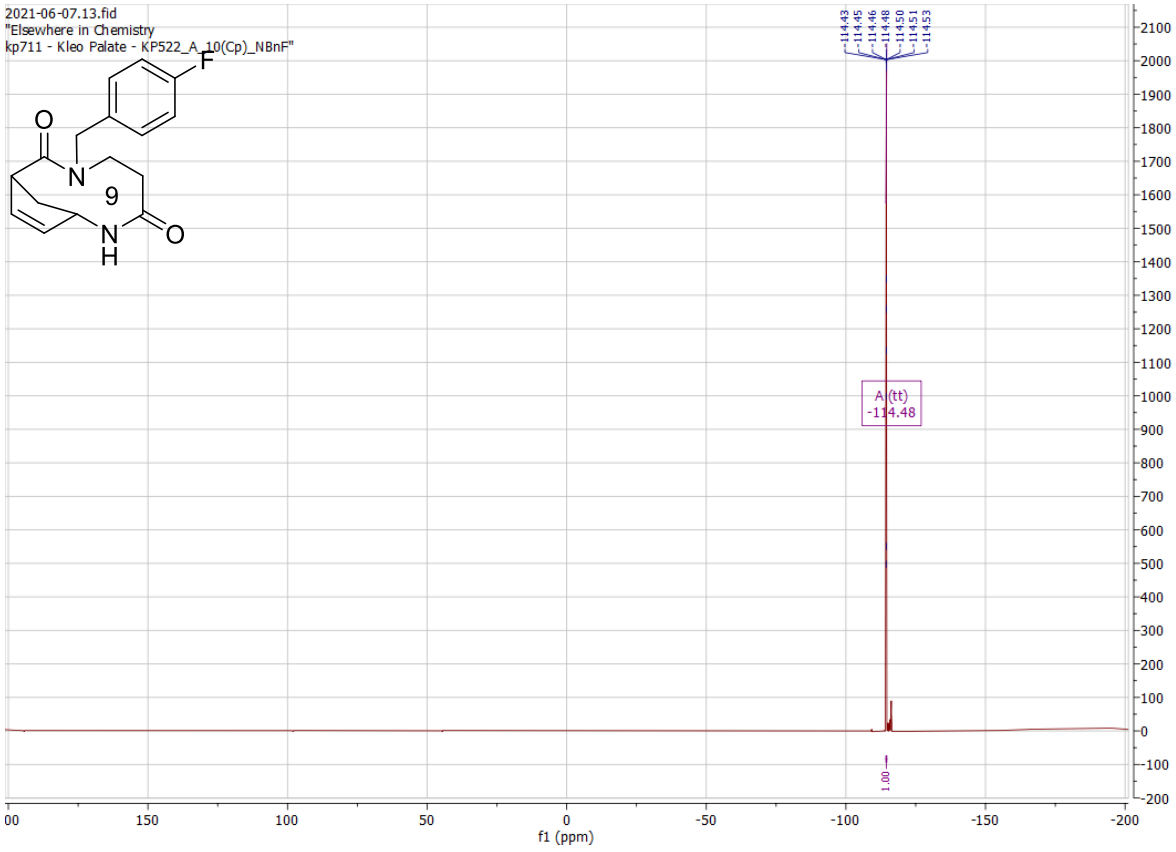

2021-05-11.161.fid
Elsewhere in Chemistry
kp711 - Kleo Palate - KP509_A_10(CHCH2)
HN
O
10
N
O
F
-114.10
-114.13
-114.15
-114.18
-114.20
-114.50
-114.52
-114.55
-114.57
-114.60
B (p)
-114.55
A (p)
-114.15
1.00
0.08
f1 (ppm)

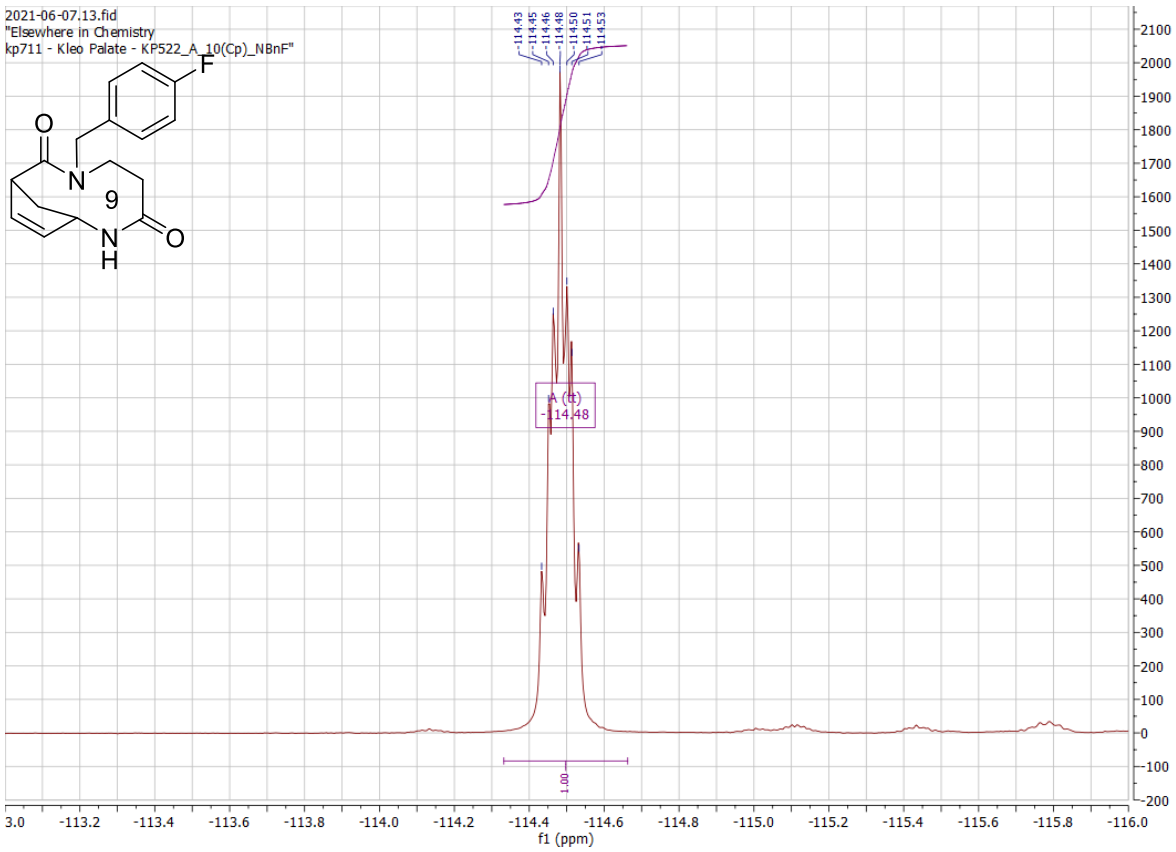

2021-05-11.161.fid
Elsewhere in Chemistry
kp711 - Kleo Palate - KP509_A_10(CHCH2)
HN
O
10
N
O
F
-114.10
-114.13
-114.15
-114.18
-114.20
-114.50
-114.52
-114.55
-114.57
-114.60
A (p)
-114.15
B (p)
-114.55
1.00
0.08
f1 (ppm)

(1*SR*,8*SR*)-6-(4-fluorobenzyl)-2,6-diazabicyclo[6.2.1]undec-9-ene-3,7-dione (17e)

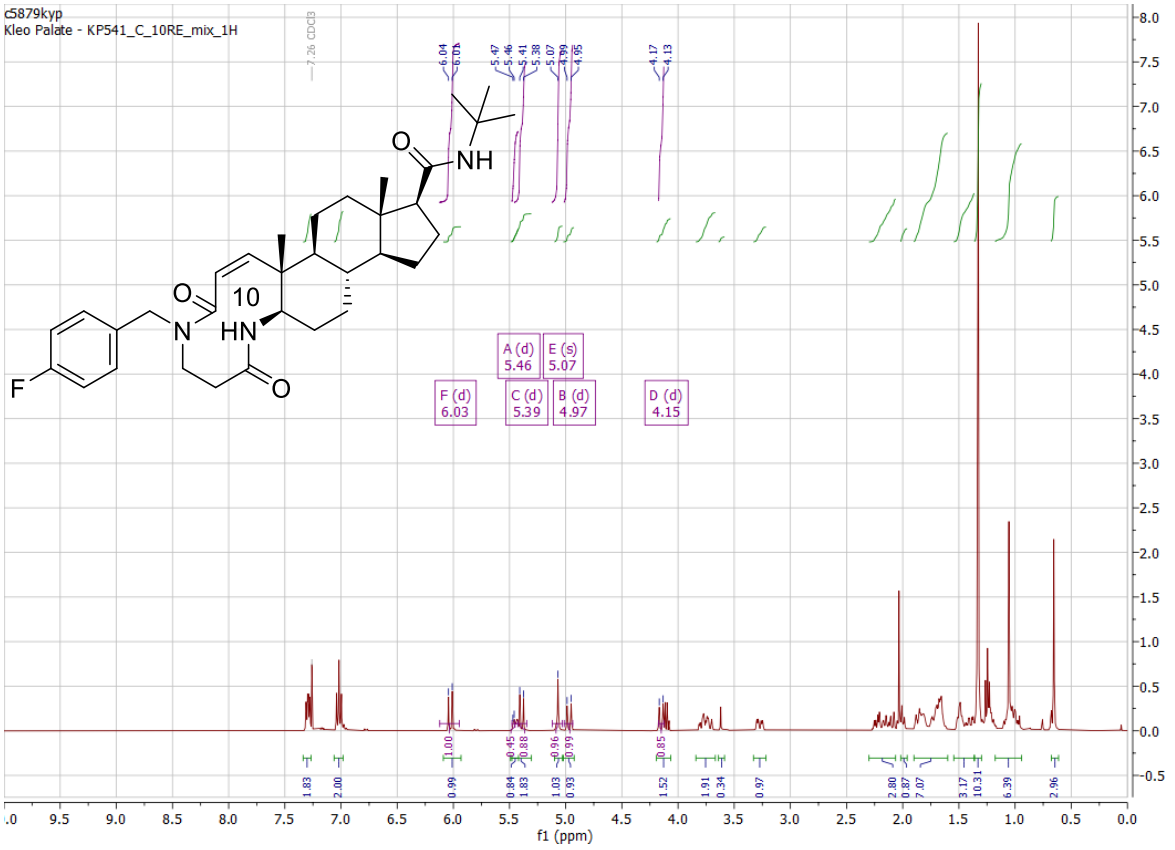


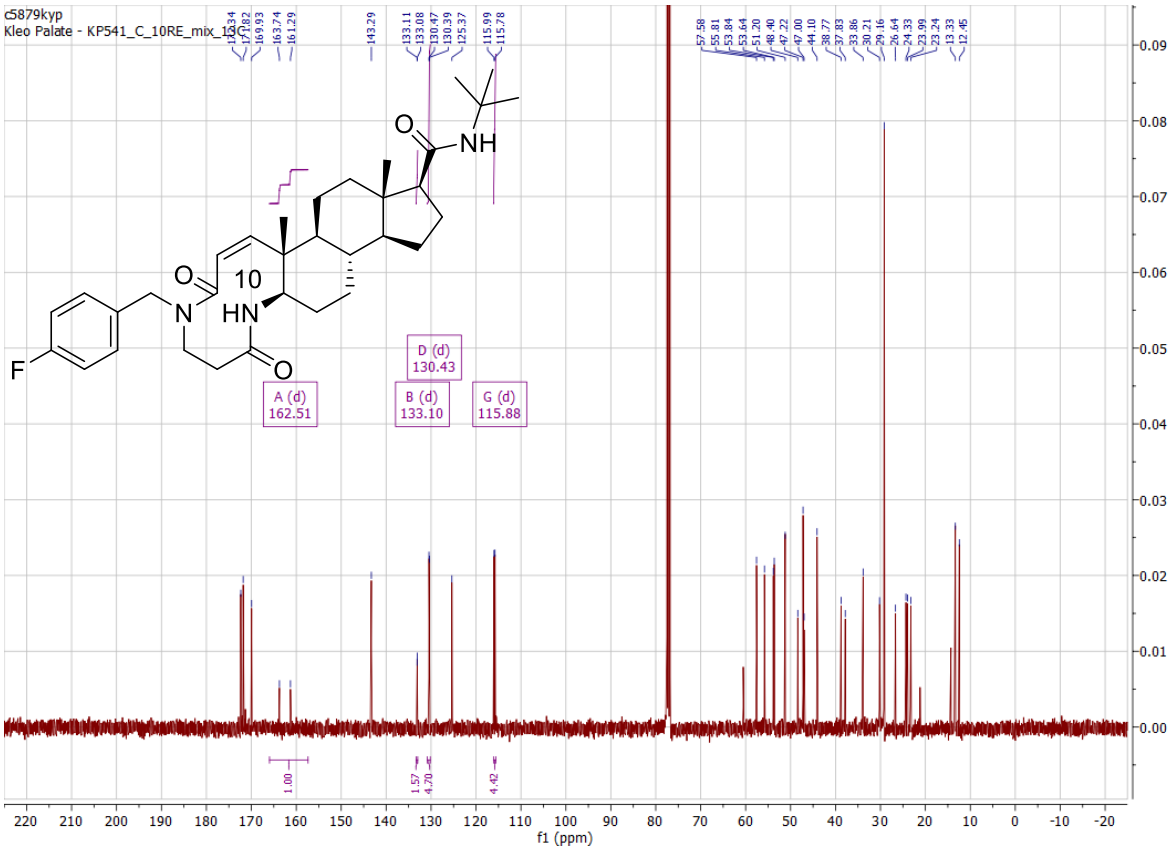


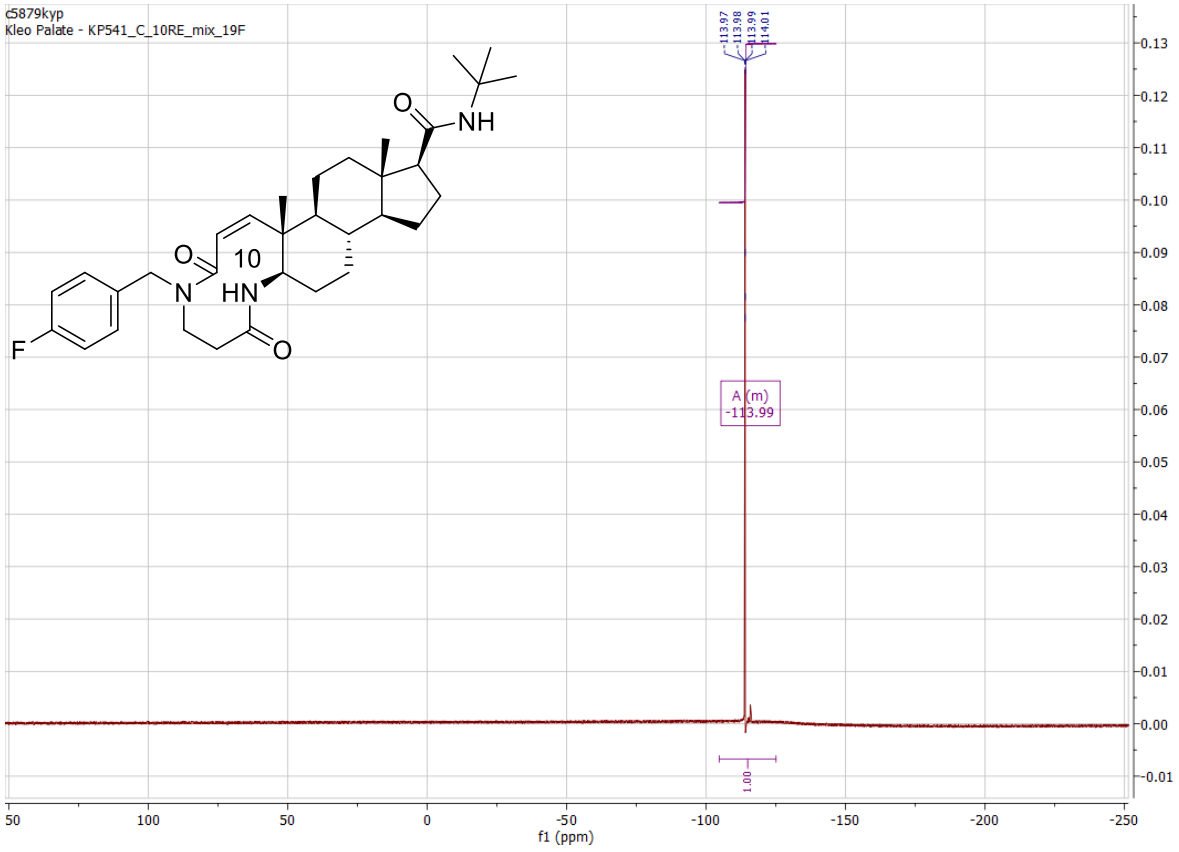

2021-06-07.13.fid
"Elsewhere in Chemistry
kp711 - Kleo Palate - KP522_A_10(Cp)_NBnF"
F
O
N
9
N
H
O
-114.43
-114.45
-114.46
-114.48
-114.50
-114.51
-114.53
A (tt)
-114.48
1.00
f1 (ppm)

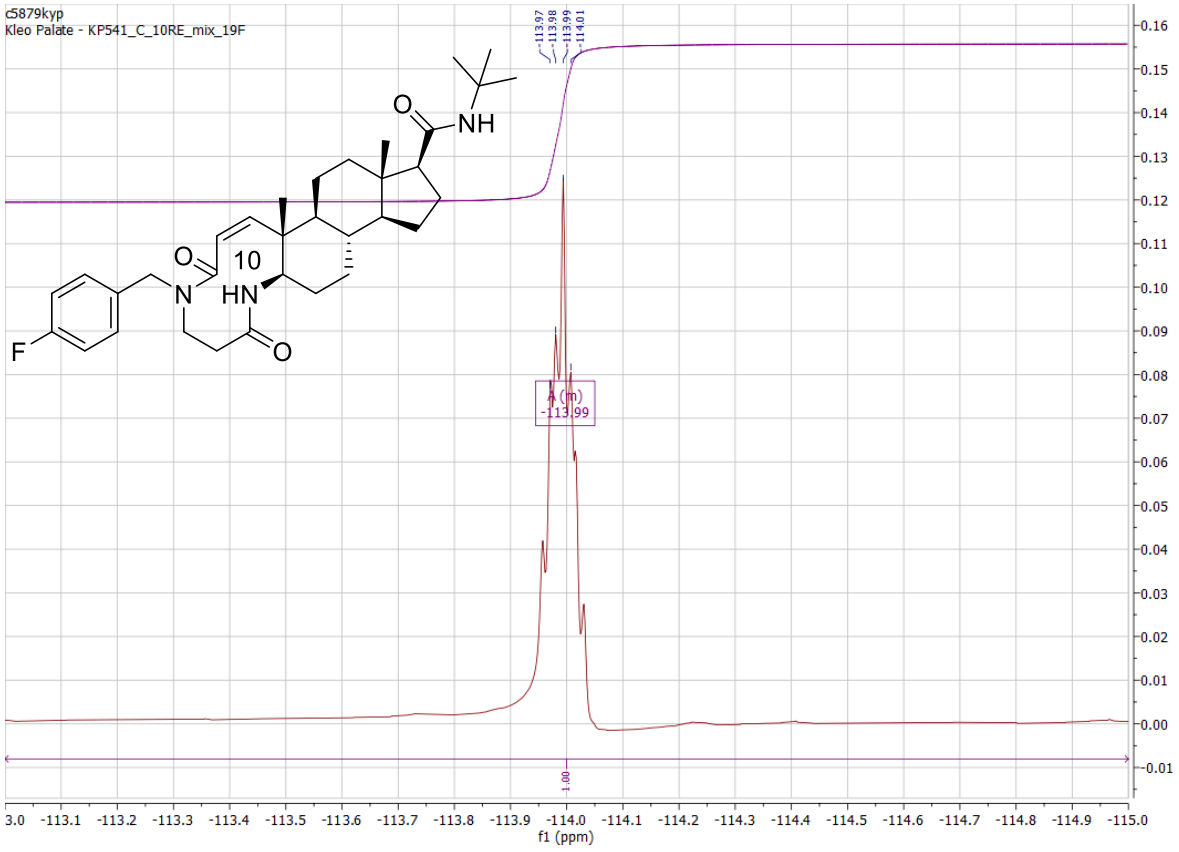

2021-06-07.13.fid
"Elsewhere in Chemistry
kp711 - Kleo Palate - KP522_A_10(Cp)_NBnF"
F
O
N
9
N
H
O
-114.43
-114.45
-114.46
-114.48
-114.50
-114.51
-114.53
A (tt)
-114.48
1.00
f1 (ppm)

(8a*R*,8b*S*,10a*S*,11*S*,13a*S*,13b*S*,15a*R*,Z)-*N*-(*tert*-butyl)-5-(4-fluorobenzyl)-8a,10a-dimethyl-2,6-dioxo-2,3,4,5,6,8a,8b,9,10,10a,11,12,13,13a,13b,14,15,15a-octadecahydro-1*H*-cyclopenta[5,6]naphtho[2,1-*f*][1,5]diazecine-11-carboxamide trione (17f)

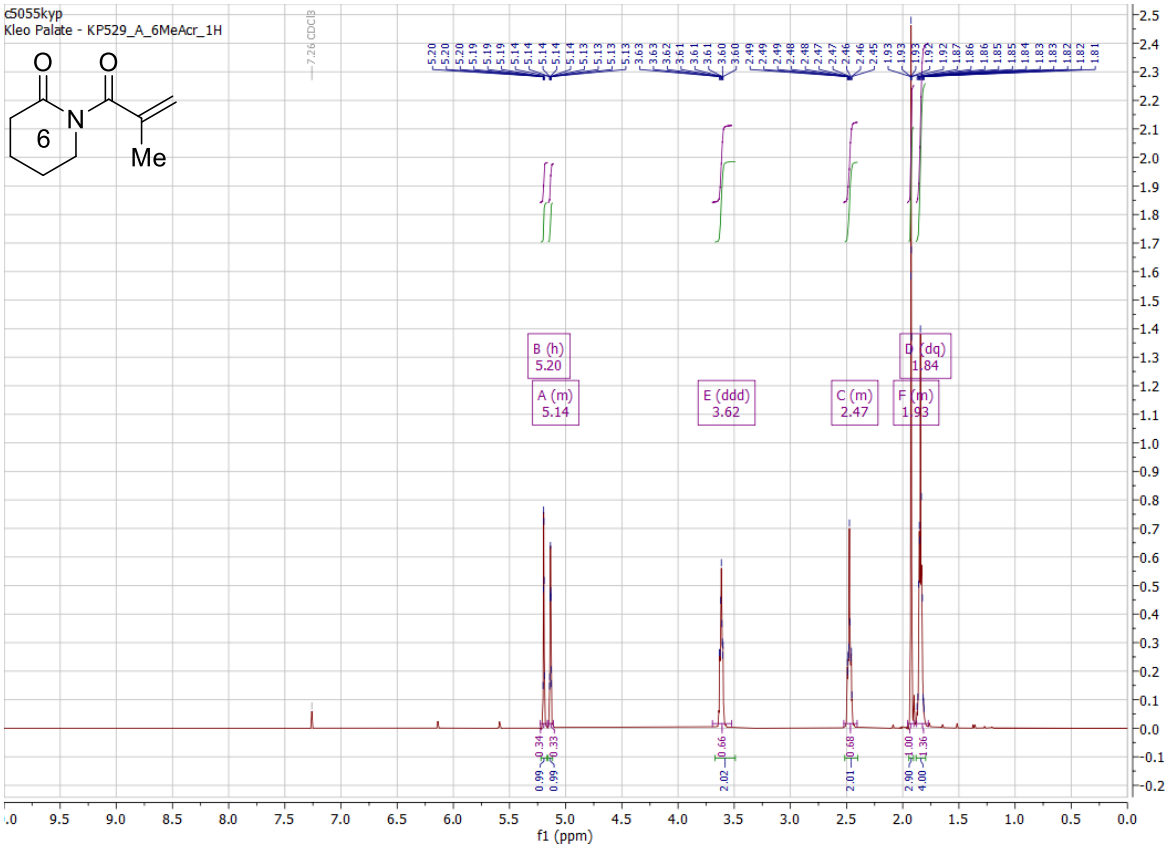


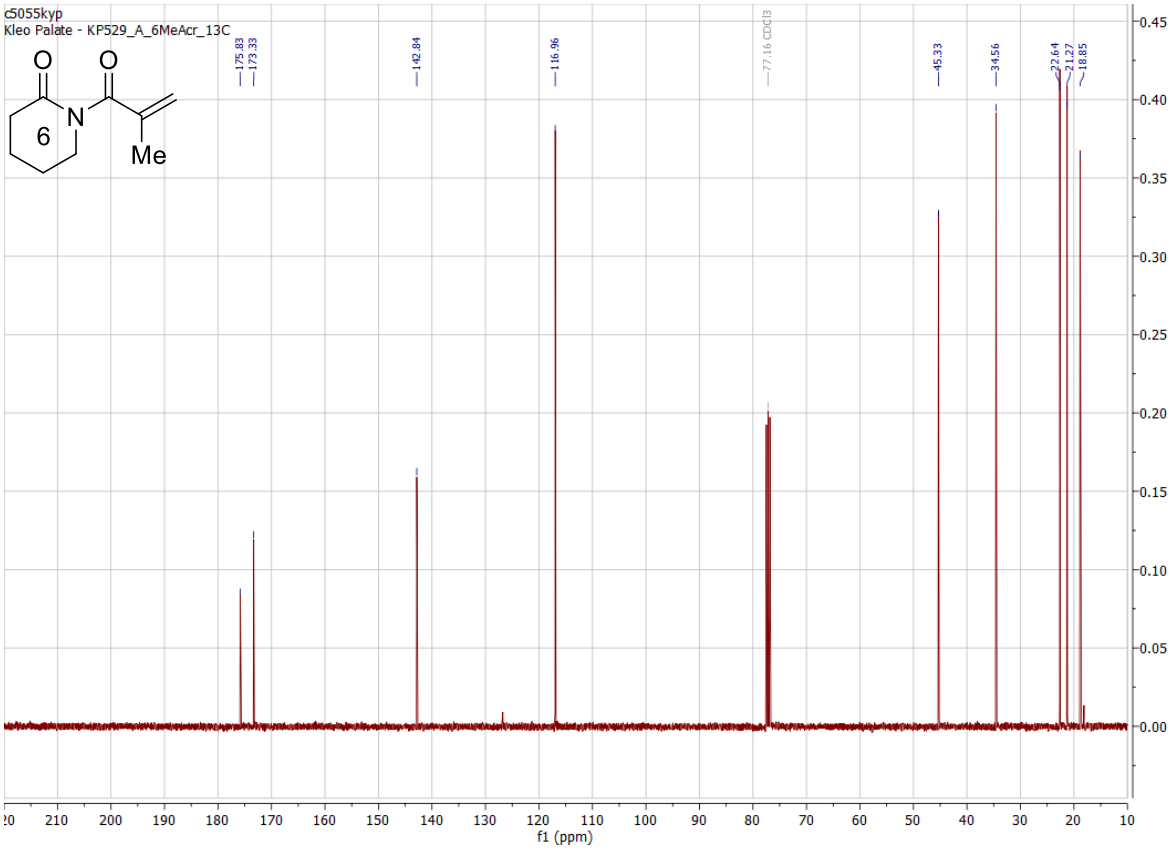



c5879kyp
Kleo Palate - KP541_C_10RE_mix_19F
O
NH
O
10
N
HN
O
F
A (m)
-113.99
1.00
f1 (ppm)

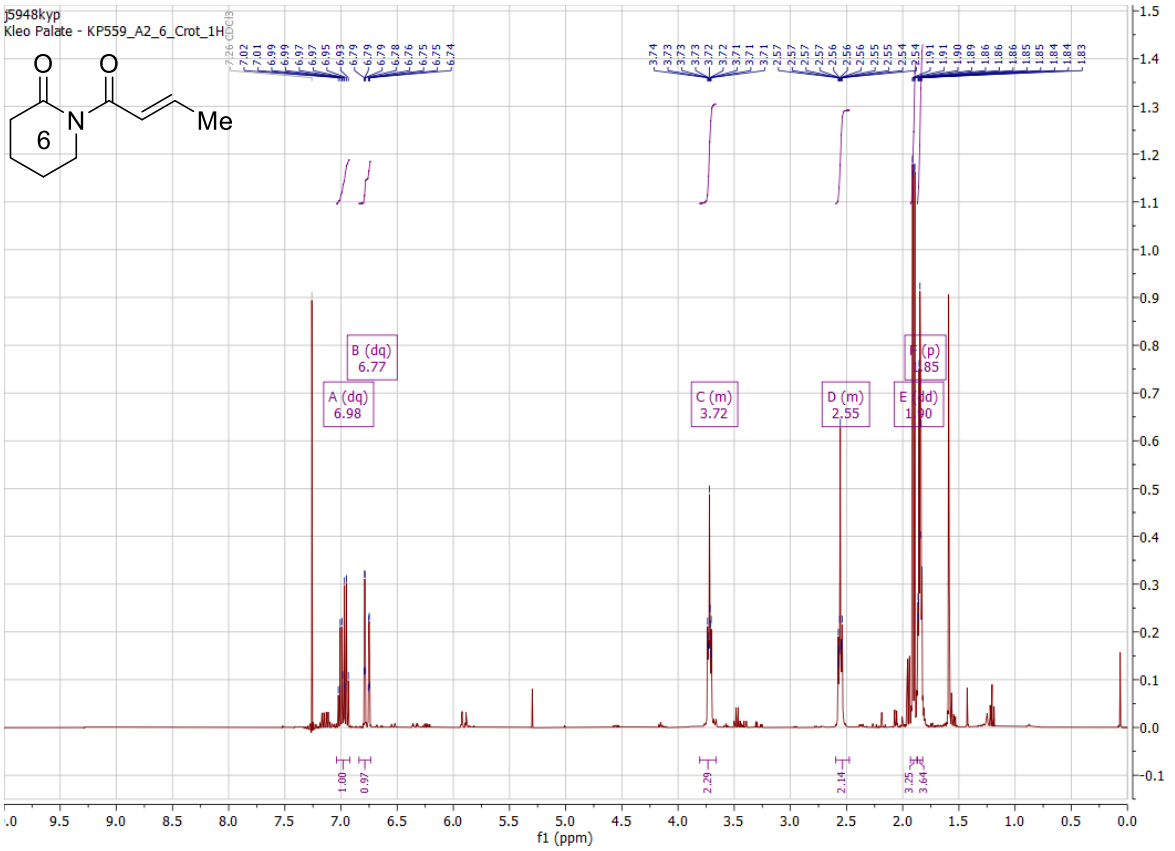

c5879kyp
Kleo Palate - KP541_C_10RE_mix_19F
O
NH
O
10
N
HN
O
F
A (m)
-113.99
1.00
f1 (ppm)

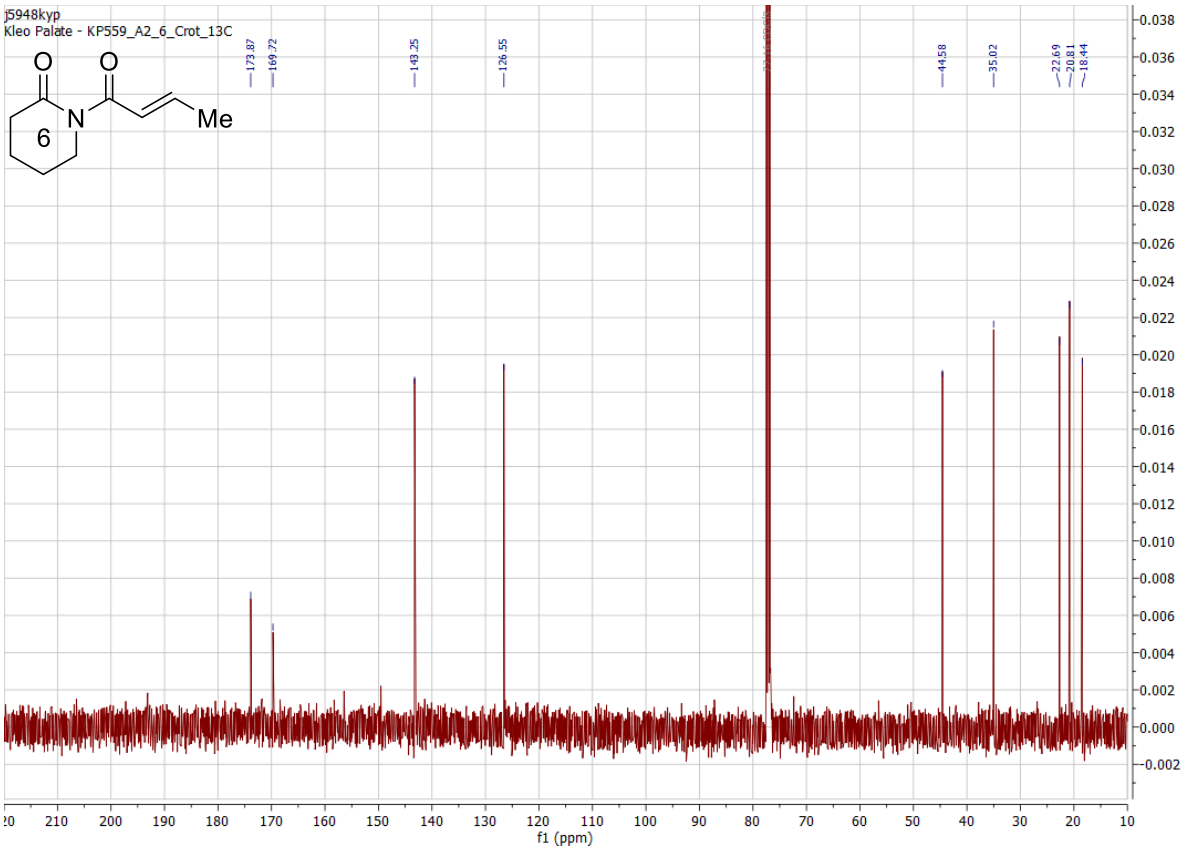
1-Methacryloylpiperidin-2-one (18a)



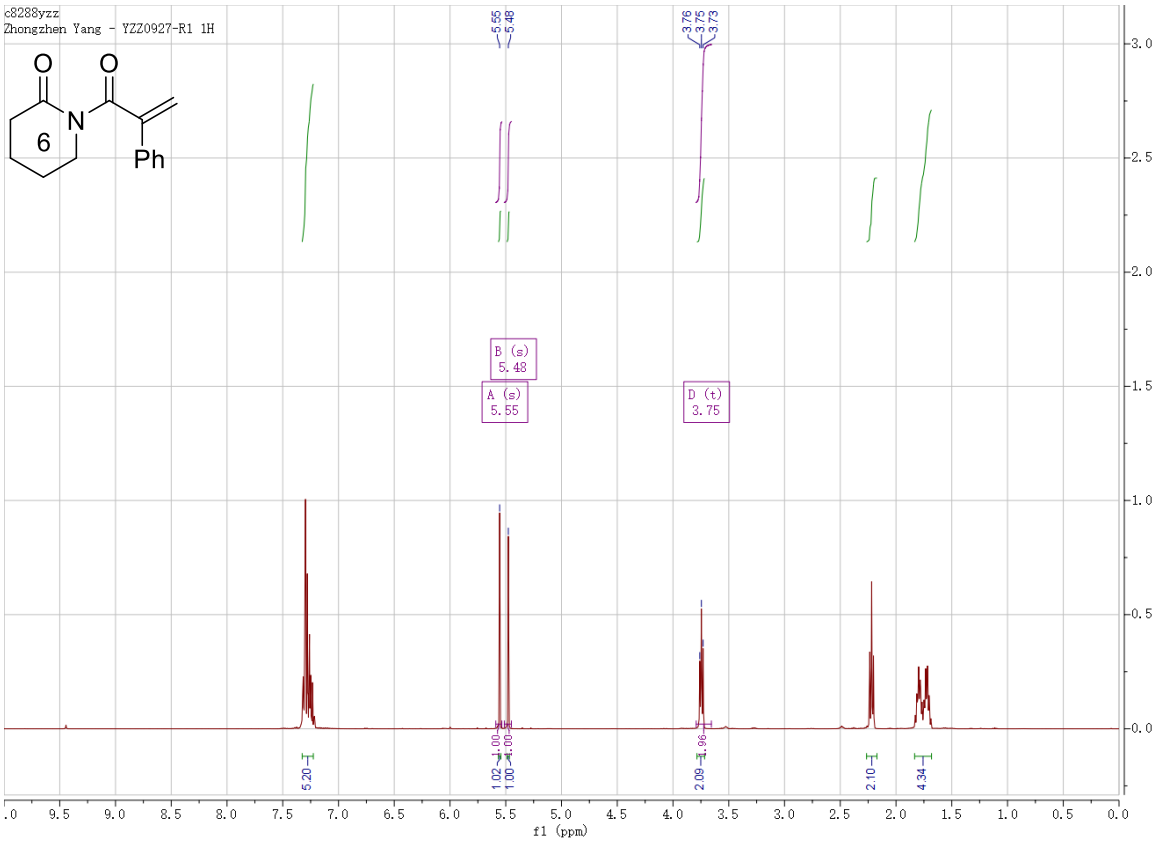


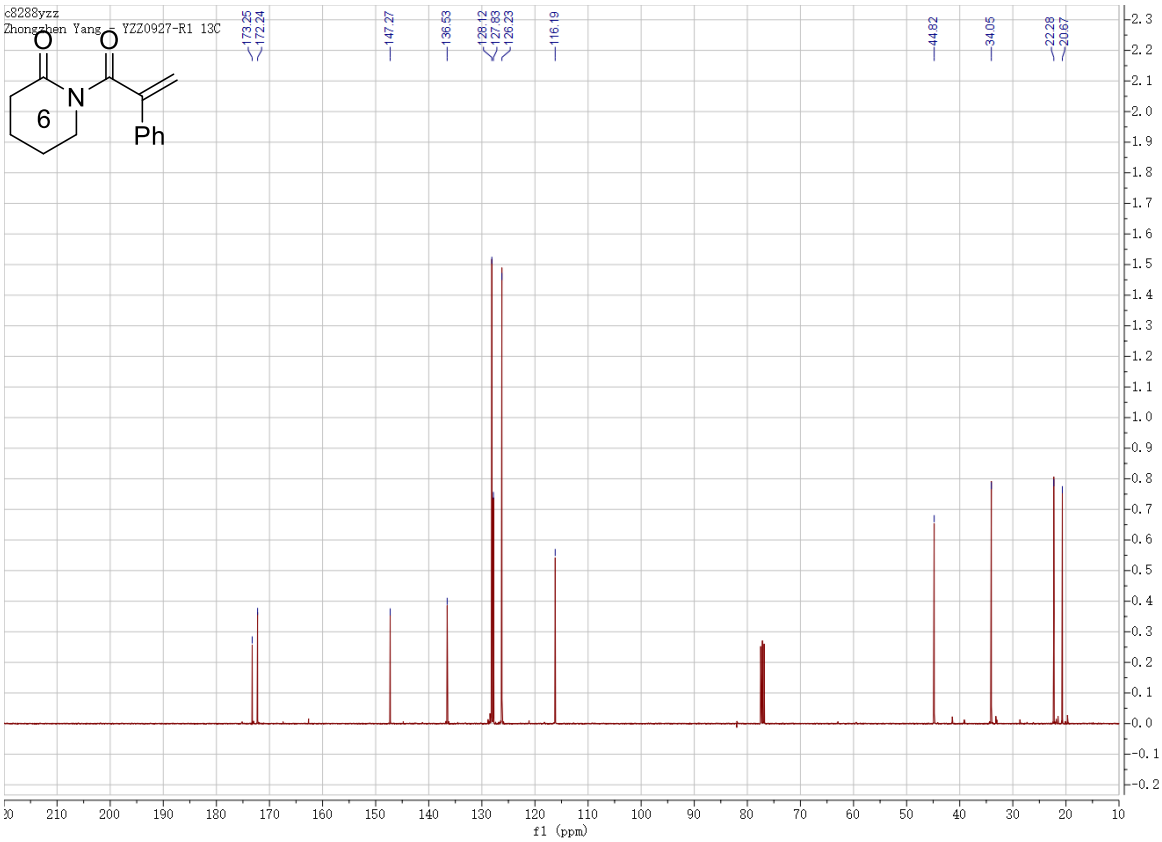
(*E*)-1-(But-2-enoyl)piperidin-2-one (18b) Contains trace impurities; used in this form in the subsequent CARE step.



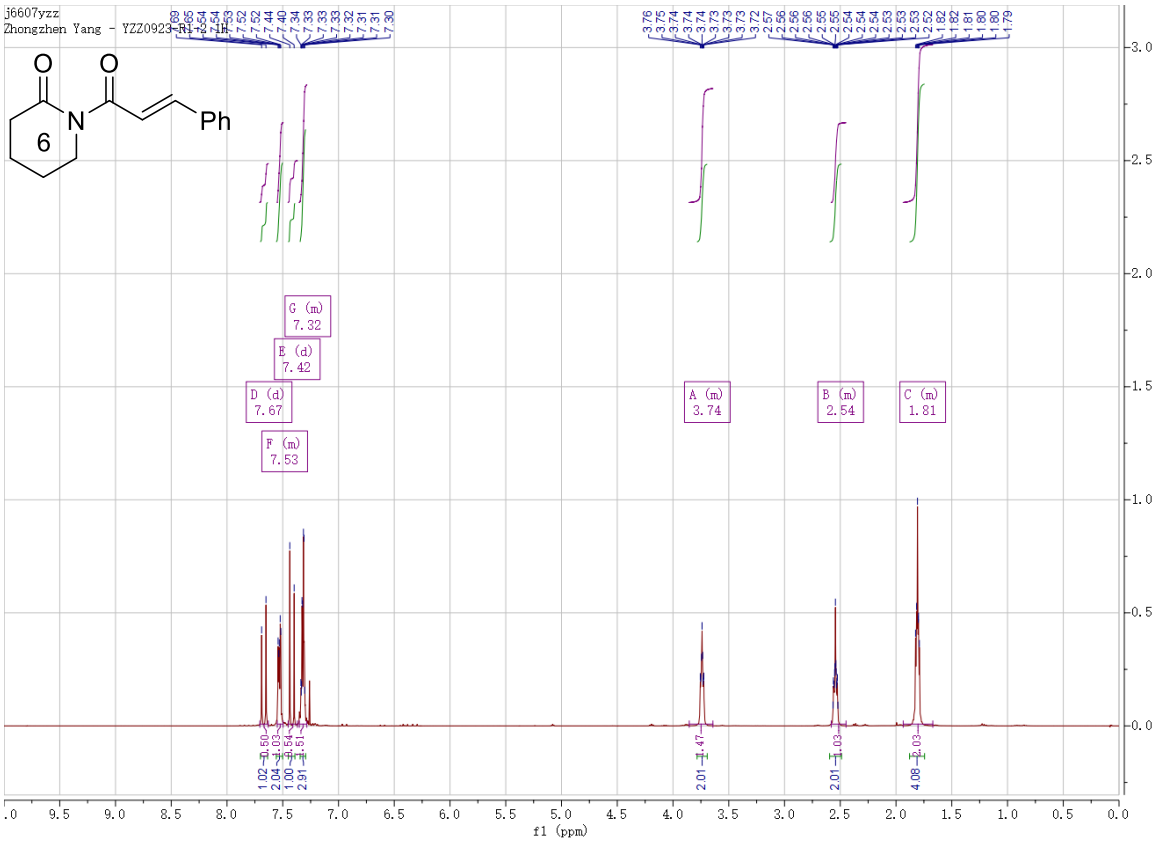


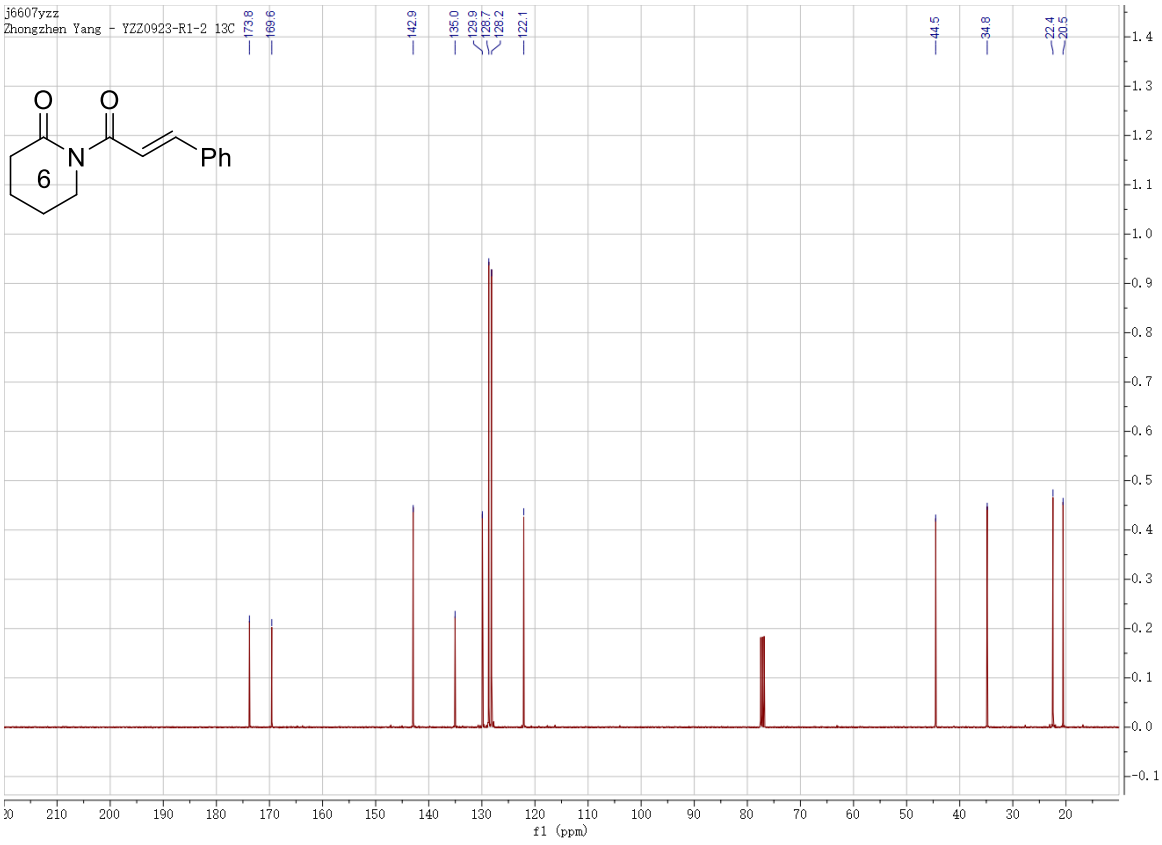
1-(2-Phenylacryloyl)piperidin-2-one (18c)



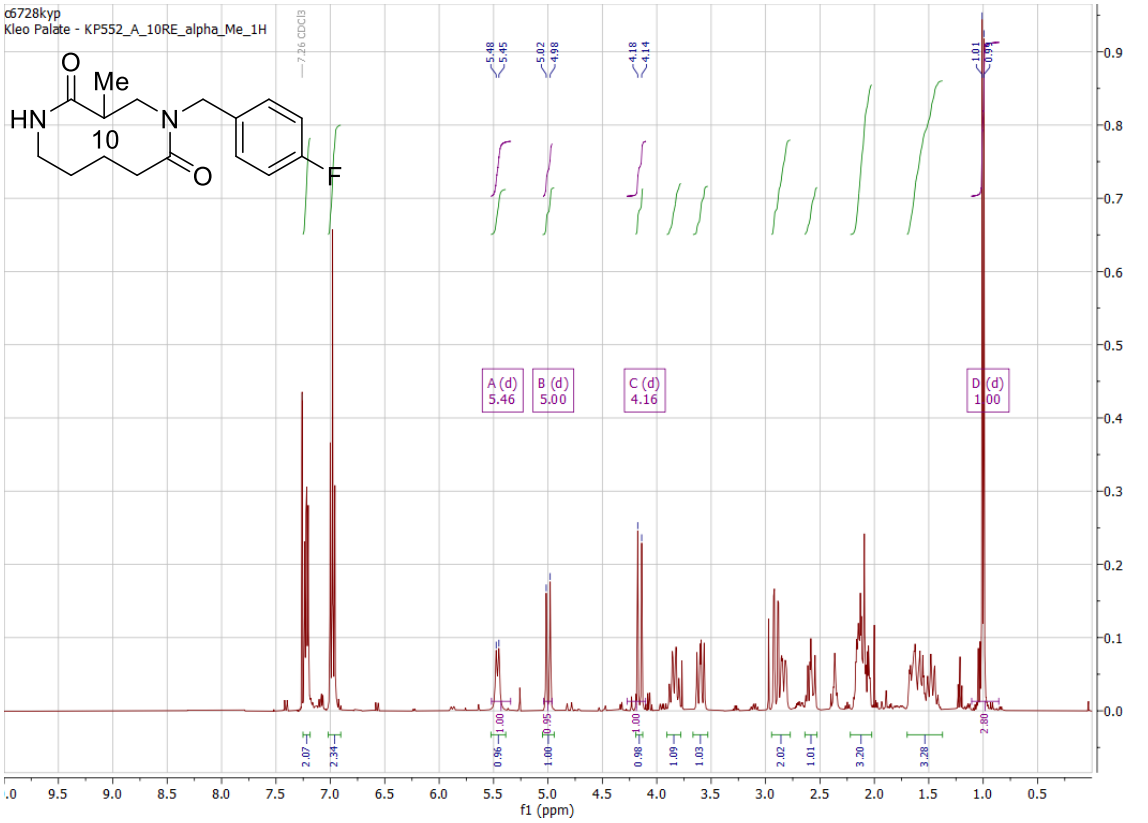


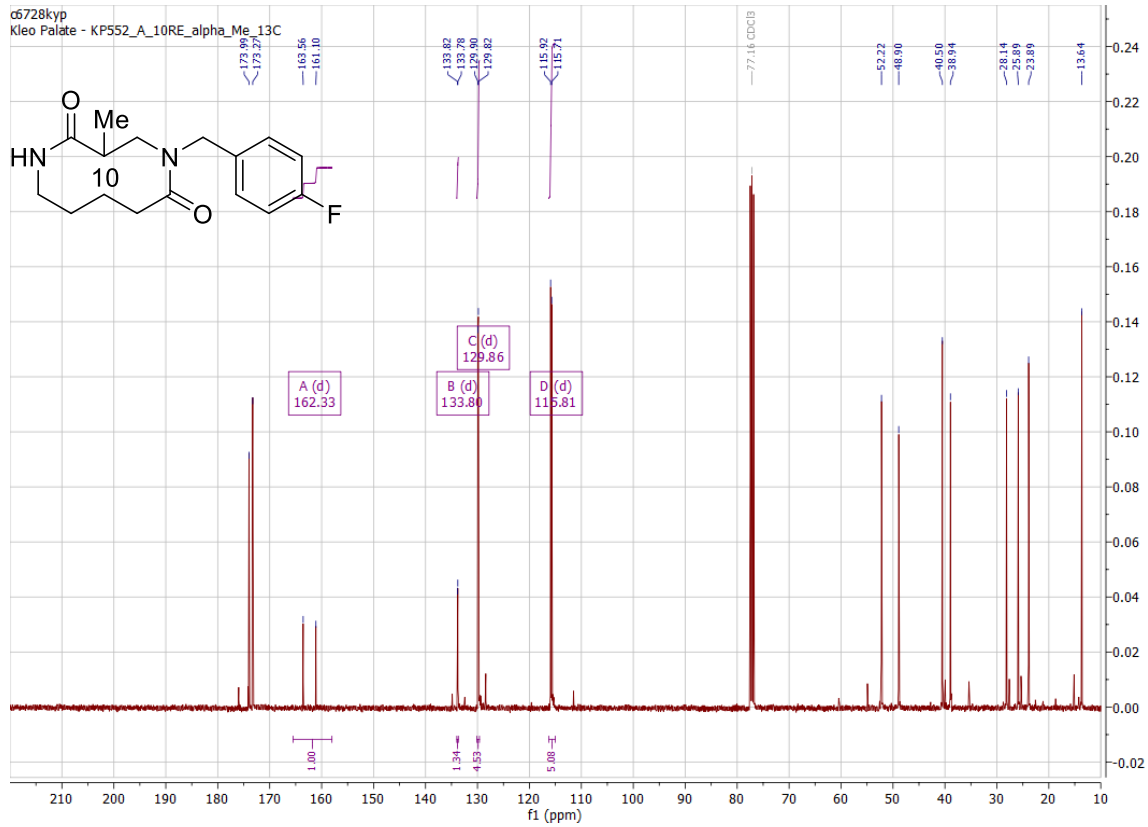
1-Cinnamoylpiperidin-2-one (18d)

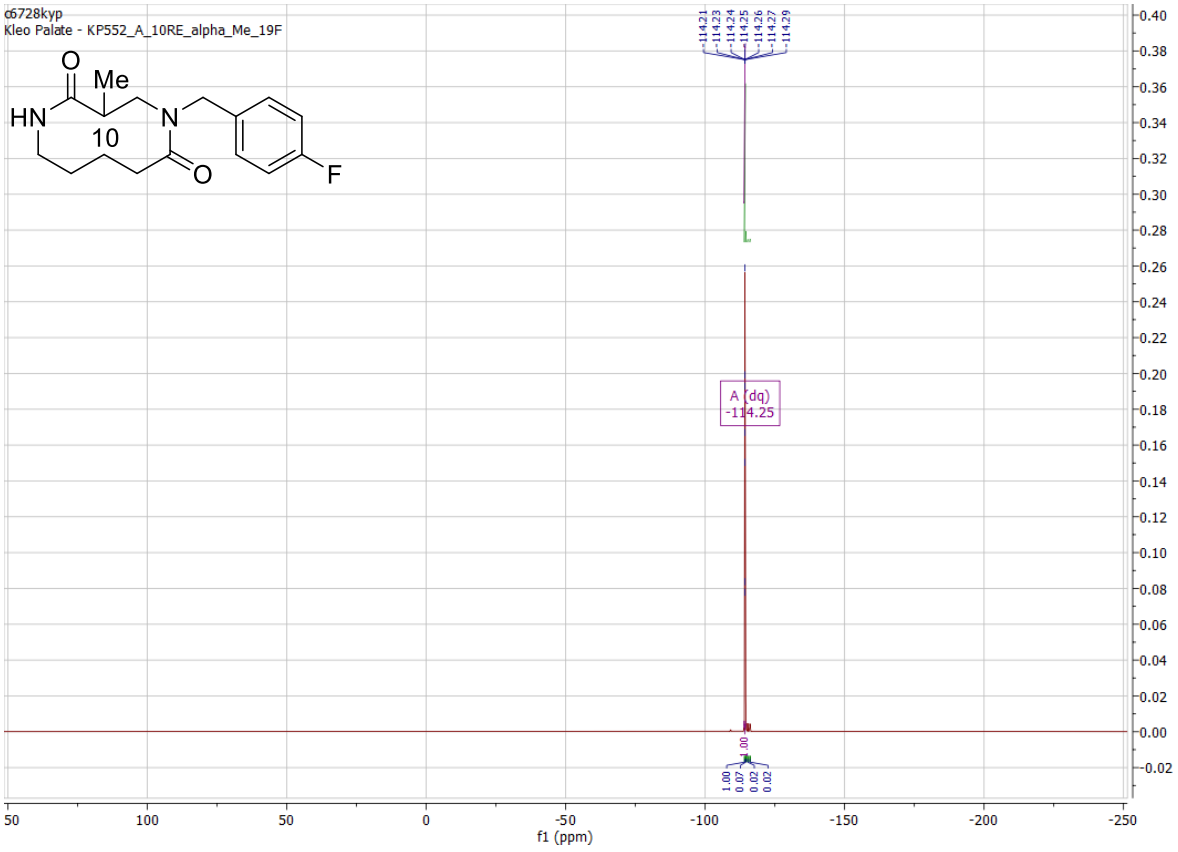


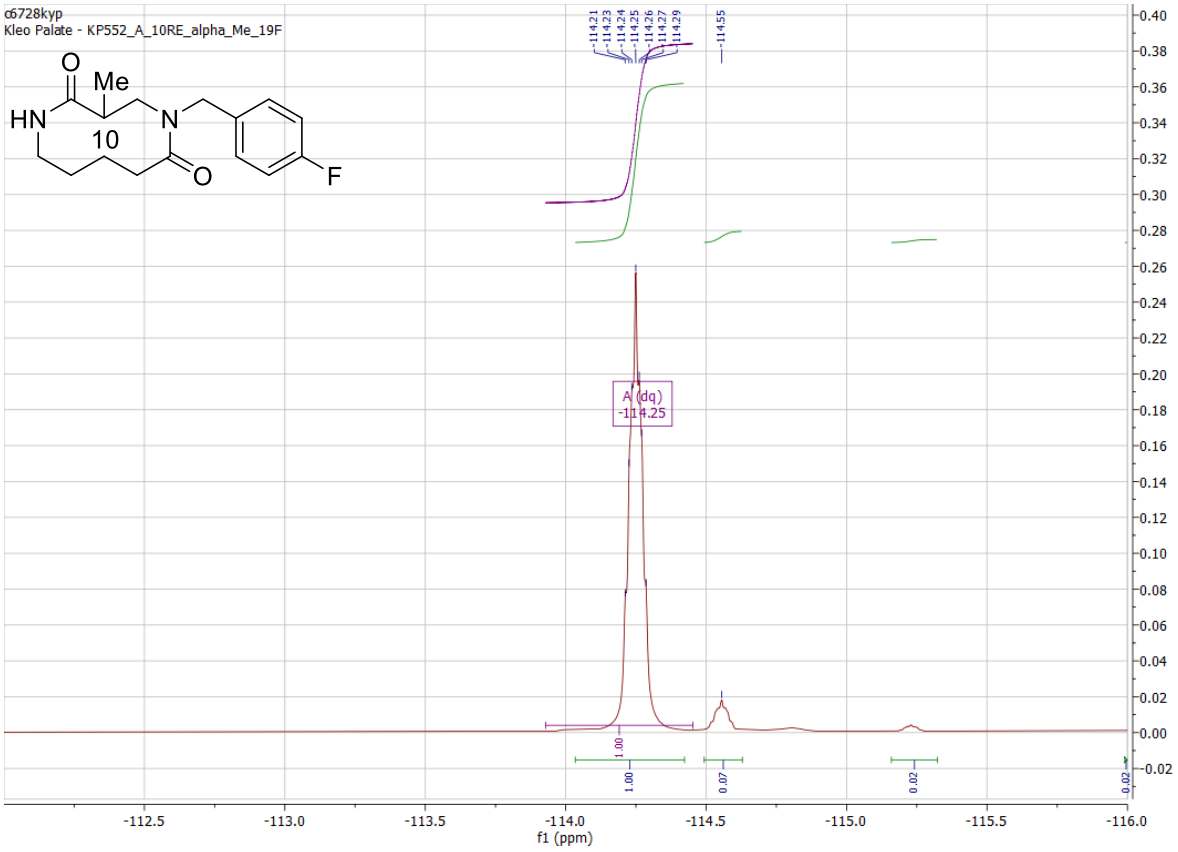


5-(4-Fluorobenzyl)-3-methyl-1,5-diazecane-2,6-dione (19a) In solution in $CDCl_3$, this compound exists largely as a single rotamer, along with 2 minor rotamers (most clearly seen in the ^{19}F NMR data).

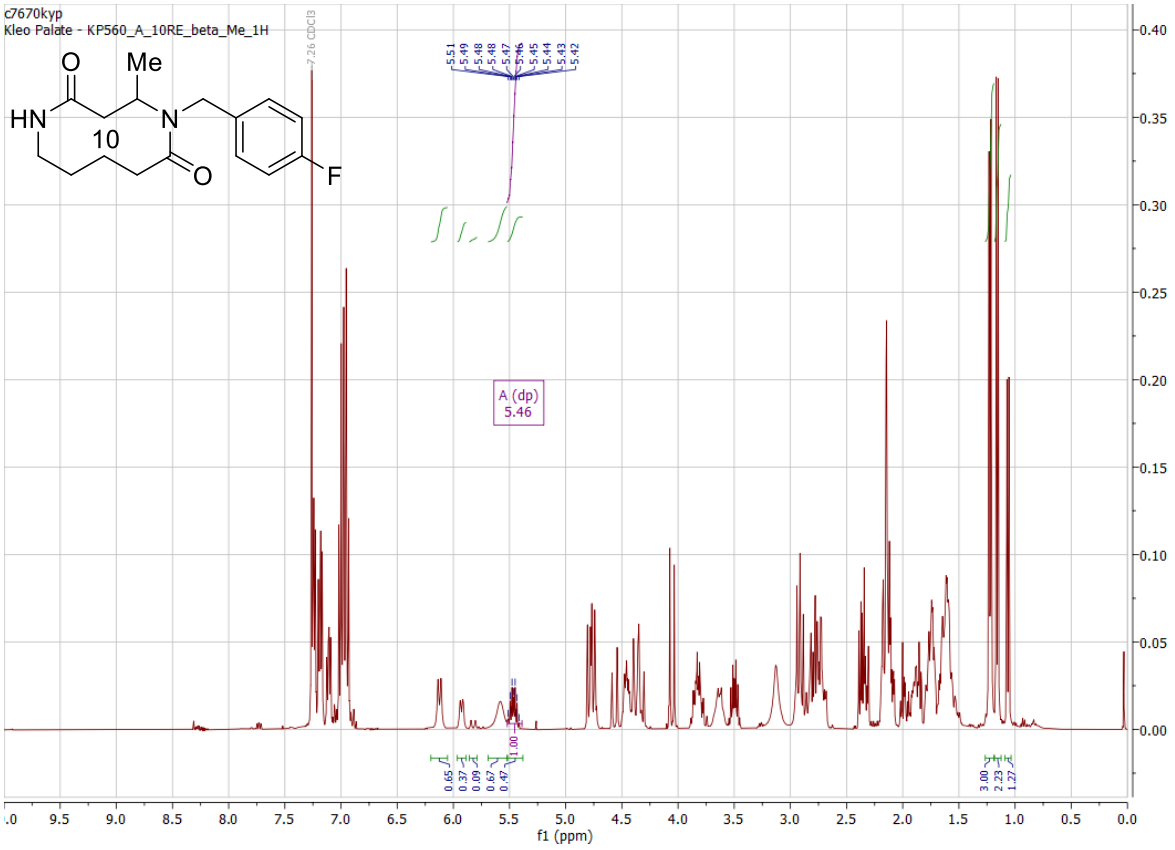


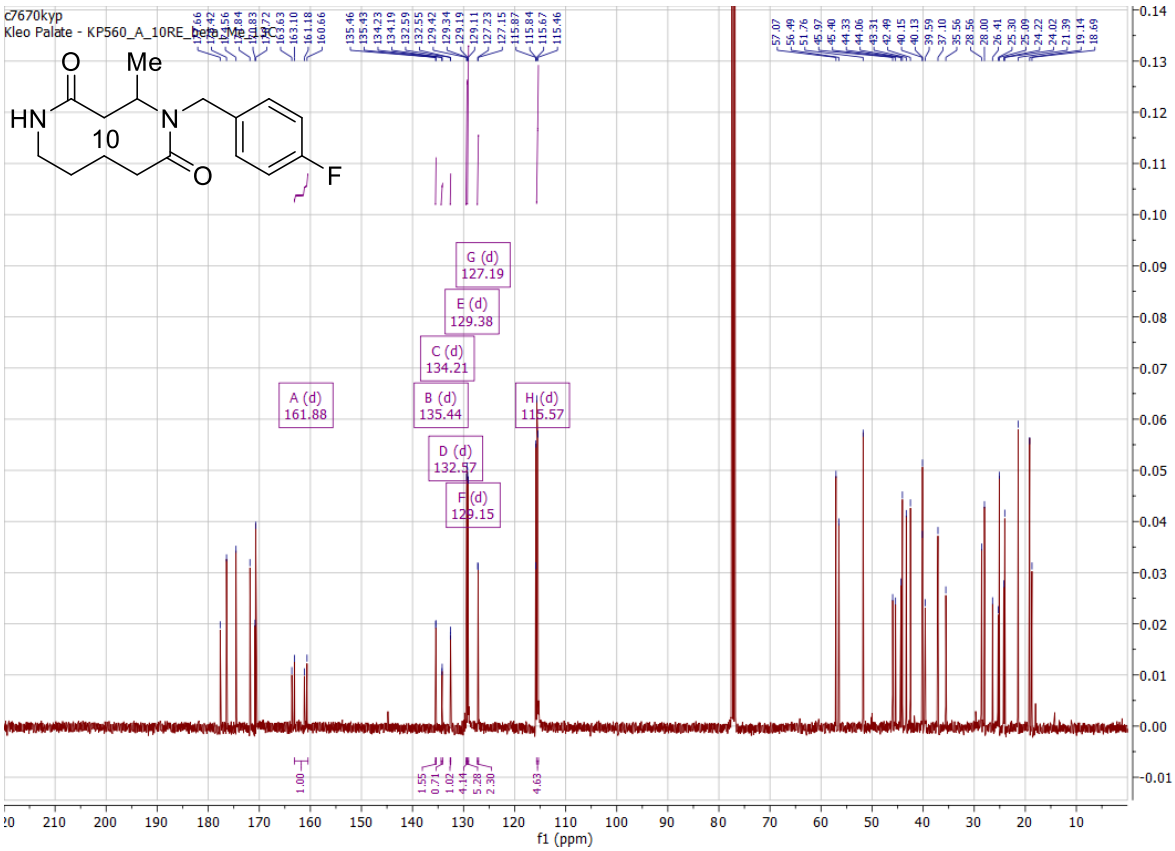


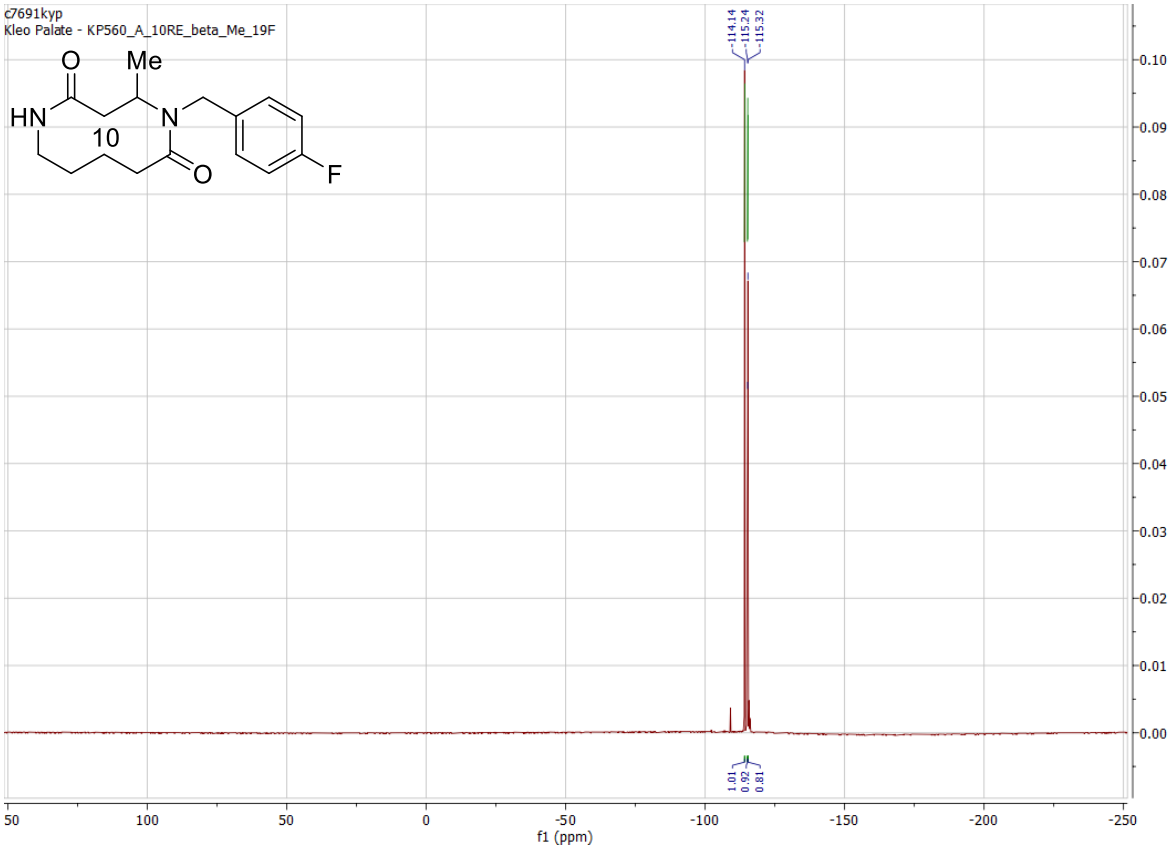

d6728kyp
Kleo Palate - KP552_A_10RE_alpha_Me_19F
O
Me
HN
10
N
O
F
-114.21
-114.23
-114.24
-114.25
-114.26
-114.27
-114.29
A (dq)
-114.25
1.00
0.07
0.02
0.02
f1 (ppm)

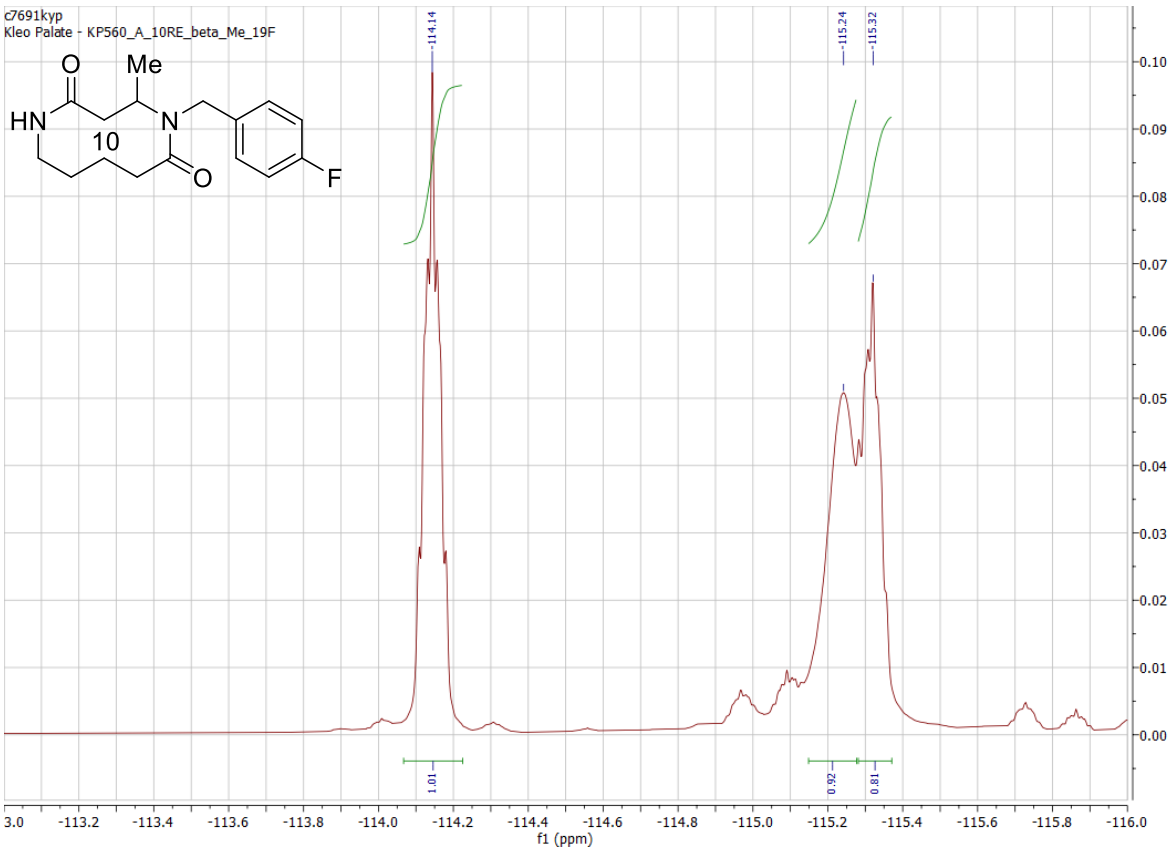

d6728kyp
Kleo Palate - KP552_A_10RE_alpha_Me_19F
O
Me
HN
10
N
O
F
-114.21
-114.23
-114.24
-114.25
-114.26
-114.27
-114.29
-114.55
A (dq)
-114.25
1.00
1.00
0.07
0.02
0.02
f1 (ppm)

5-(4-Fluorobenzyl)-4-methyl-1,5-diazecane-2,6-dione (19b)

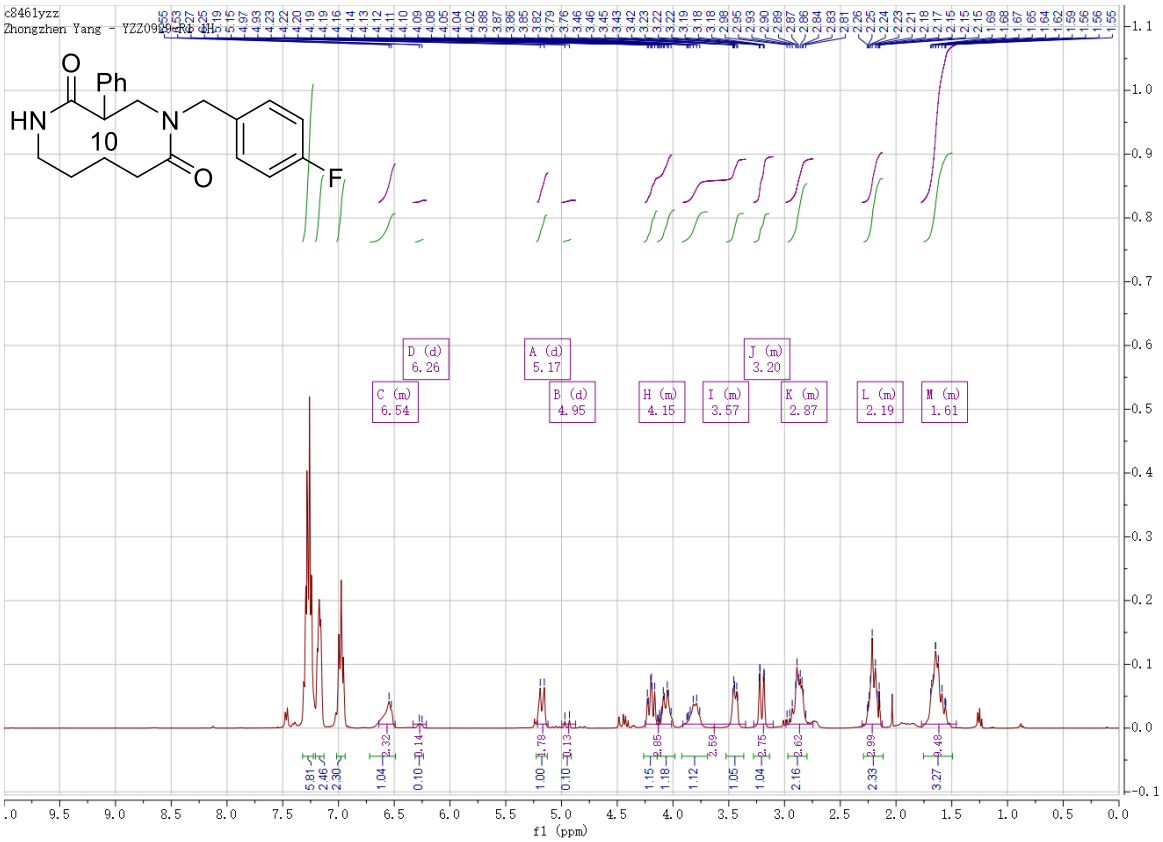


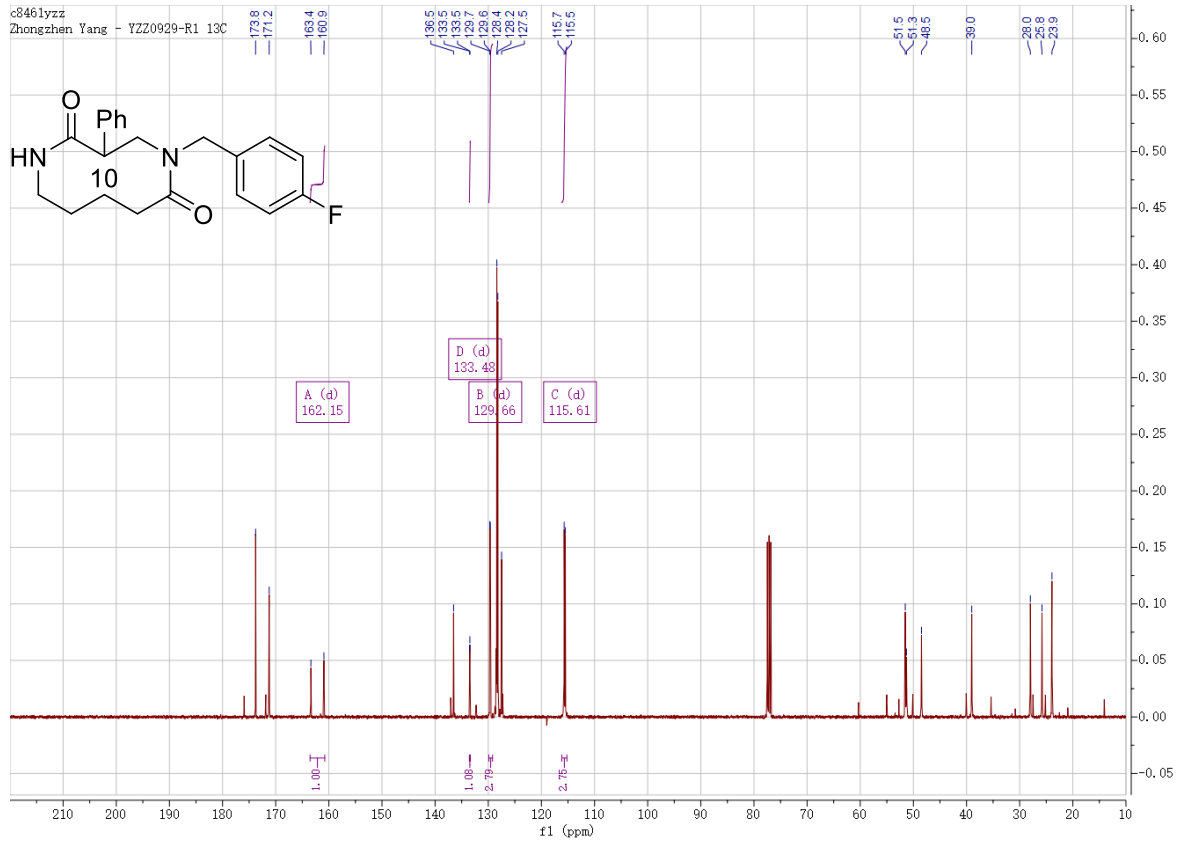



c7691kyp
Kleo Palate - KP560_A_10RE_beta_Me_19F
O
Me
HN
10
N
O
F
-114.14
-115.24
-115.32
1.01
0.92
0.81
f1 (ppm)

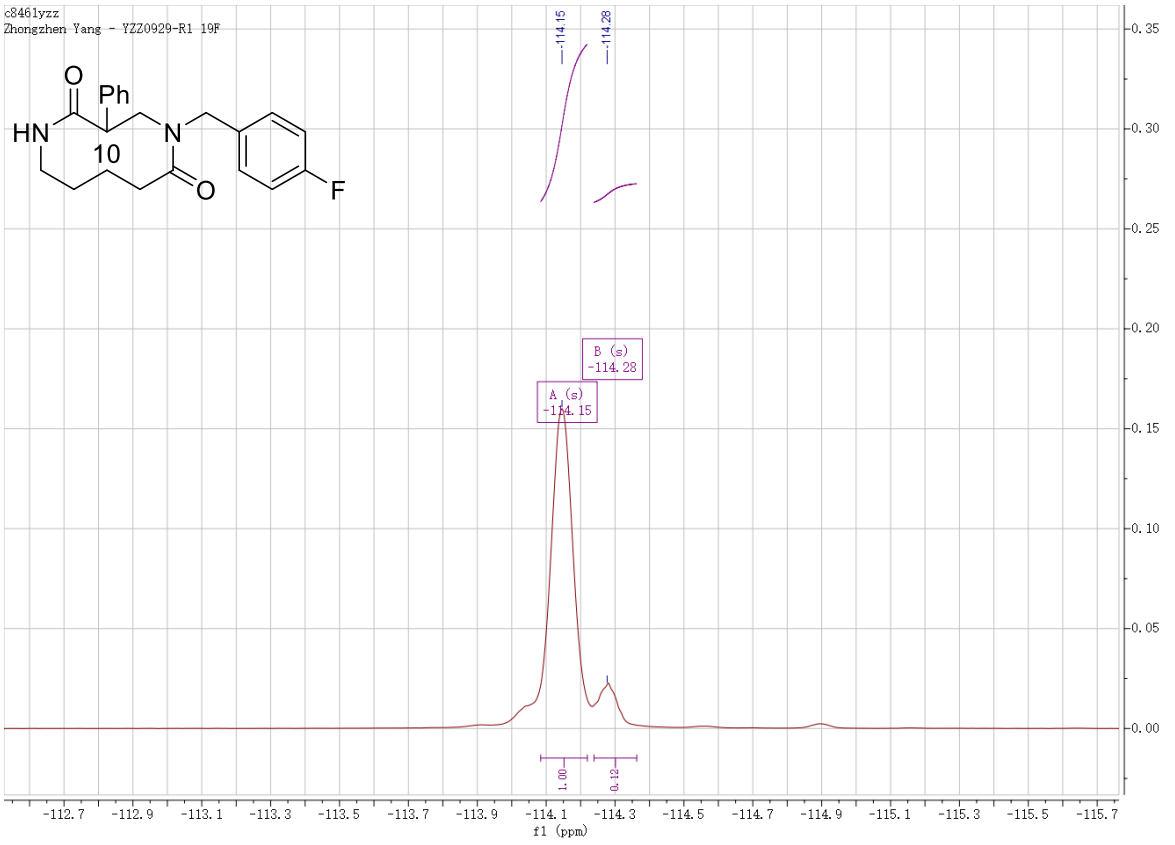

c7691kyp
Kleo Palate - KP560_A_10RE_beta_Me_19F
O
Me
HN
10
N
O
F
-114.14
-115.24
-115.32
1.01
0.92
0.81
f1 (ppm)

5-(4-Fluorobenzyl)-3-phenyl-1,5-diazecane-2,6-dione (19c) 10:1 mixture of rotamers.

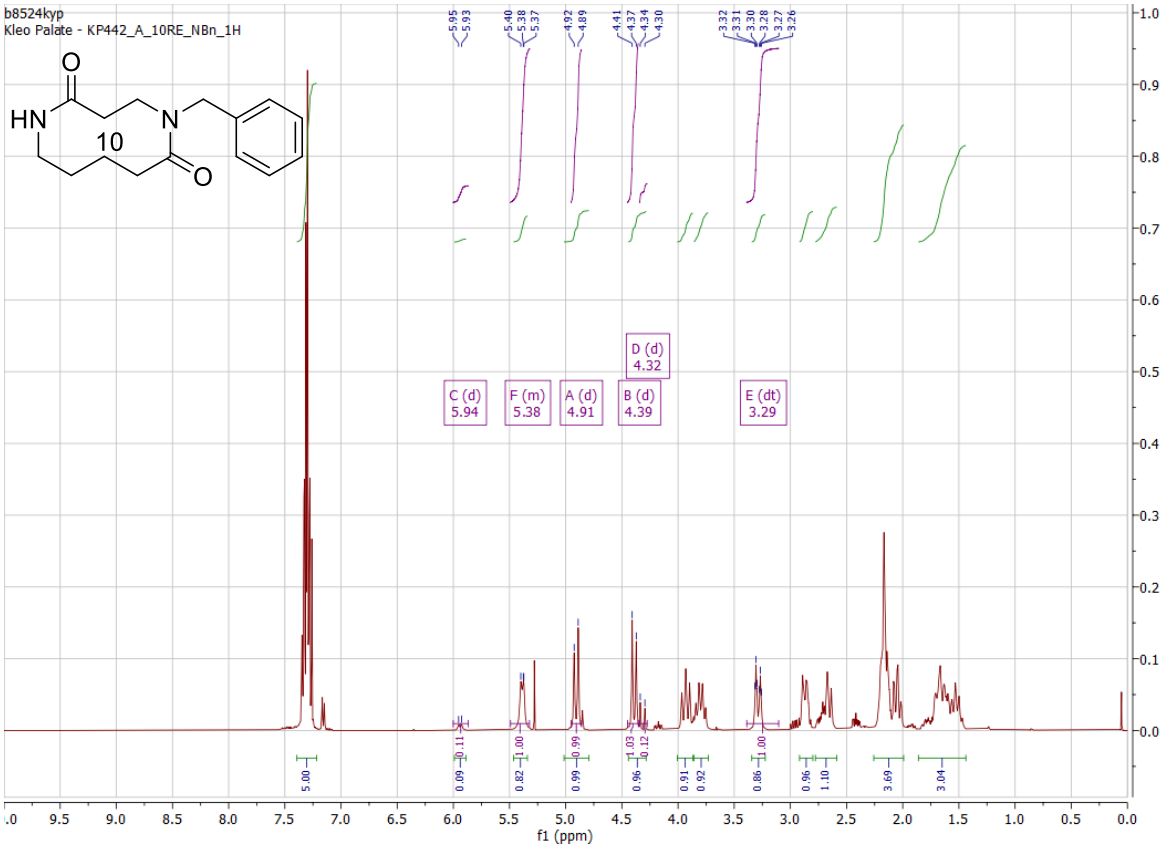


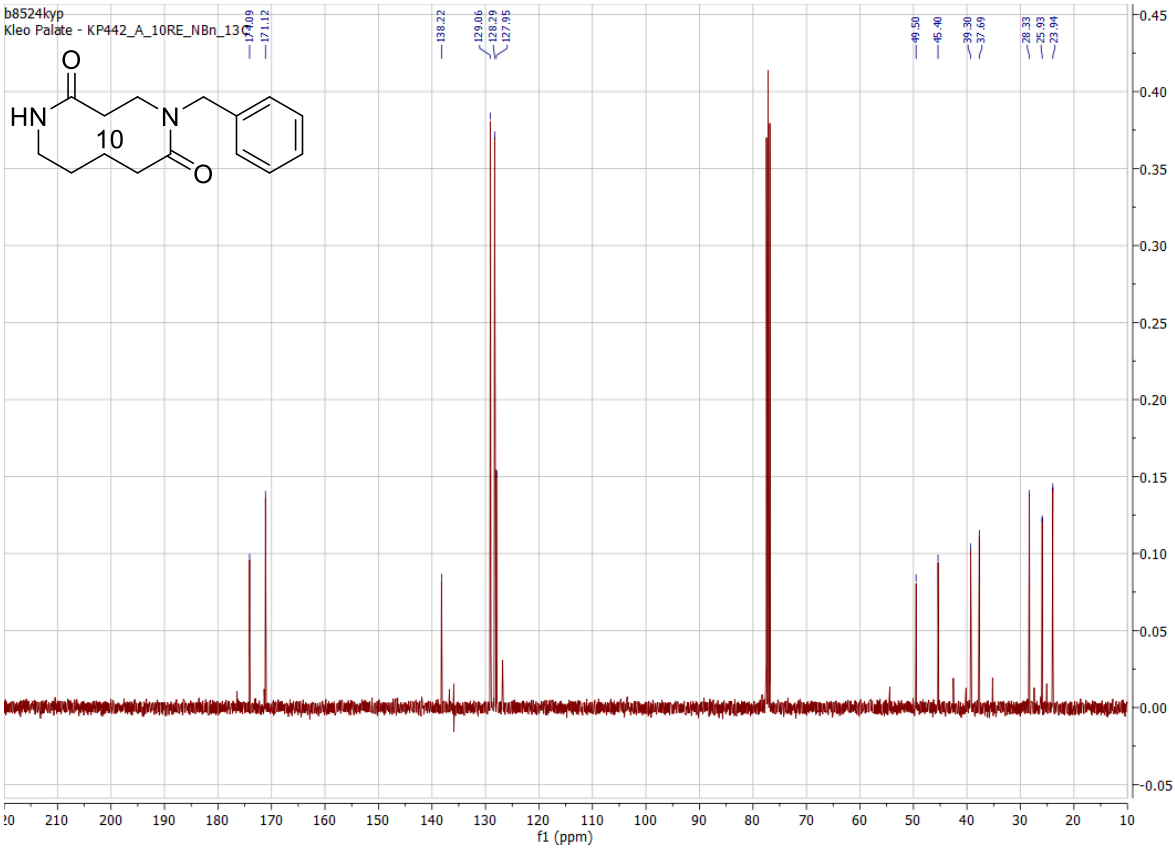



c8461yzz
Zhongzhen Yang - YZZ0929-R1 19F
O
Ph
HN
10
N
O
F
-114.15
-114.28
B (s)
-114.28
A (s)
-114.15
1.00
0.12
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
50
100
50
0
-50
-100
-150
-200
-250
f1 (ppm)

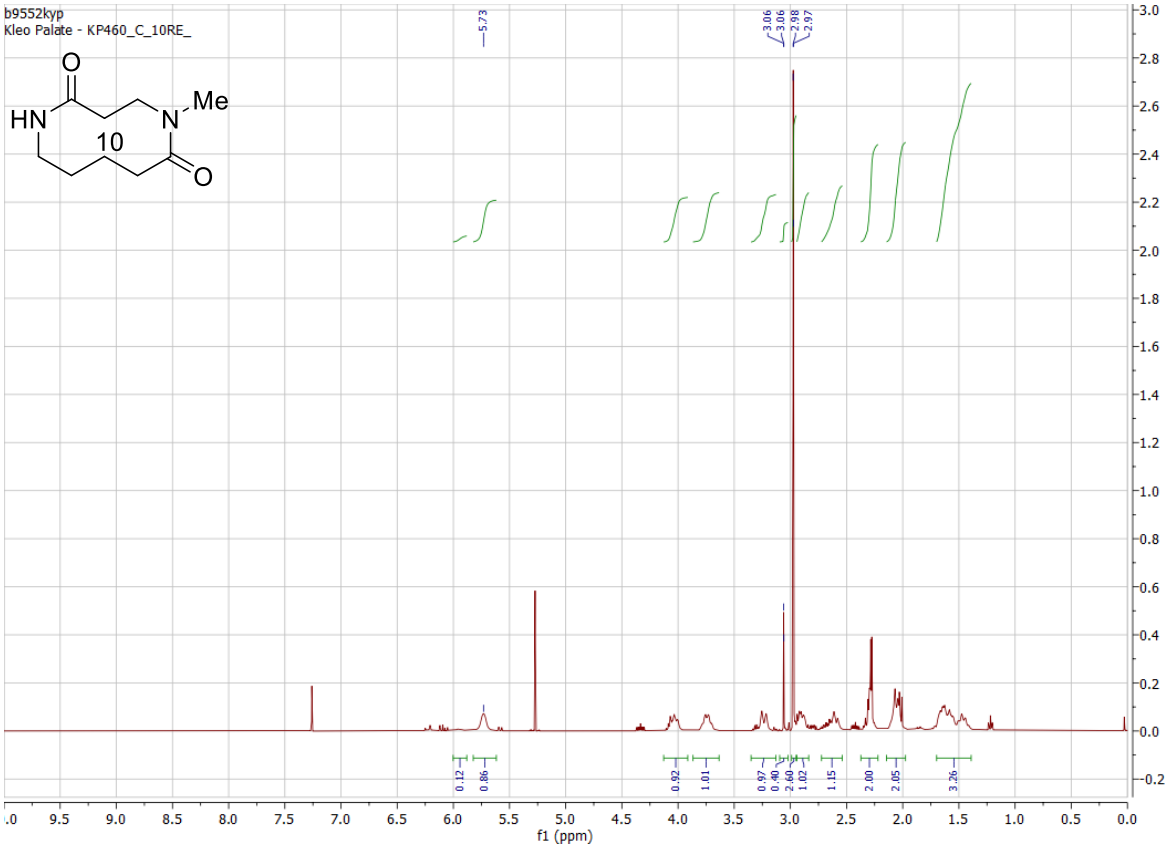

c8461yzz
Zhongzhen Yang - YZZ0929-R1 19F
O
Ph
HN
10
N
O
F
-114.15
-114.28
B (s)
-114.28
A (s)
-114.15
1.00
0.12
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-112.7
-112.9
-113.1
-113.3
-113.5
-113.7
-113.9
-114.1
-114.3
-114.5
-114.7
-114.9
-115.1
-115.3
-115.5
-115.7
f1 (ppm)

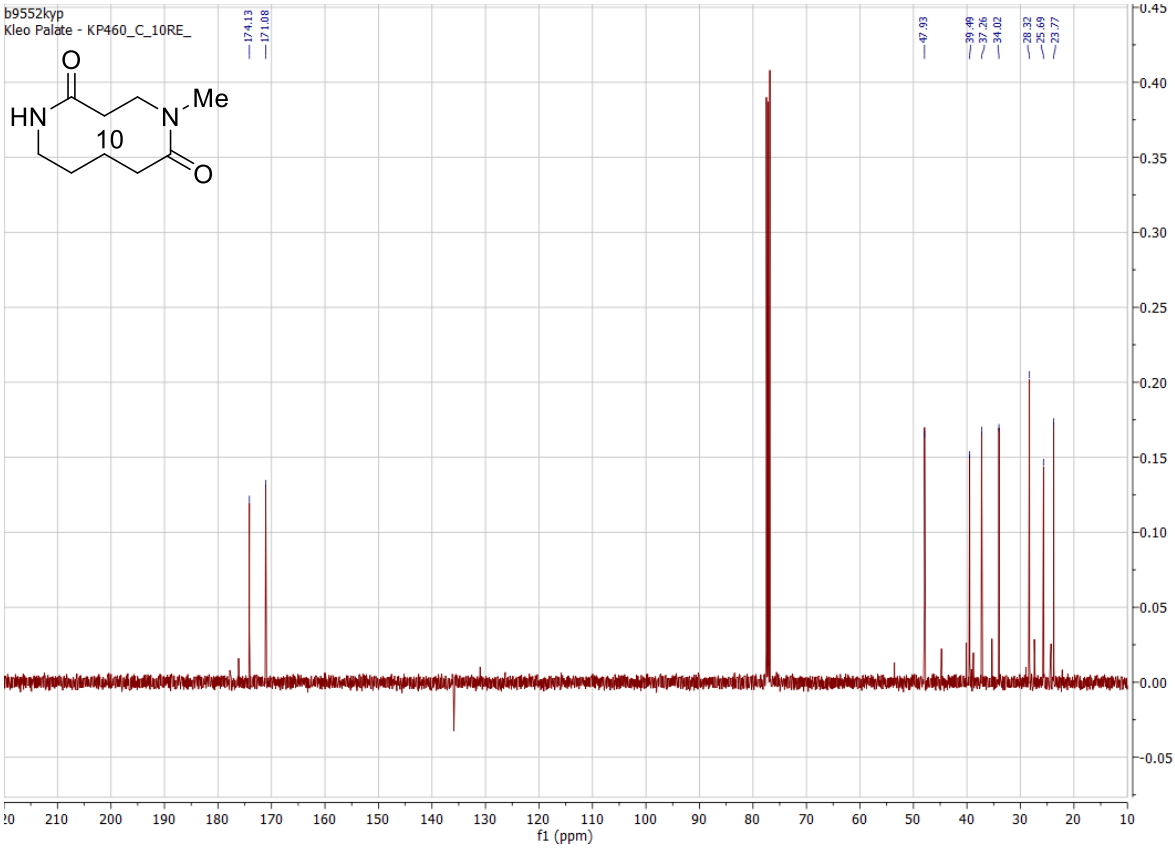
5-Benzyl-1,5-diazecane-2,6-dione (20a) 10:1 mixture of rotamers.



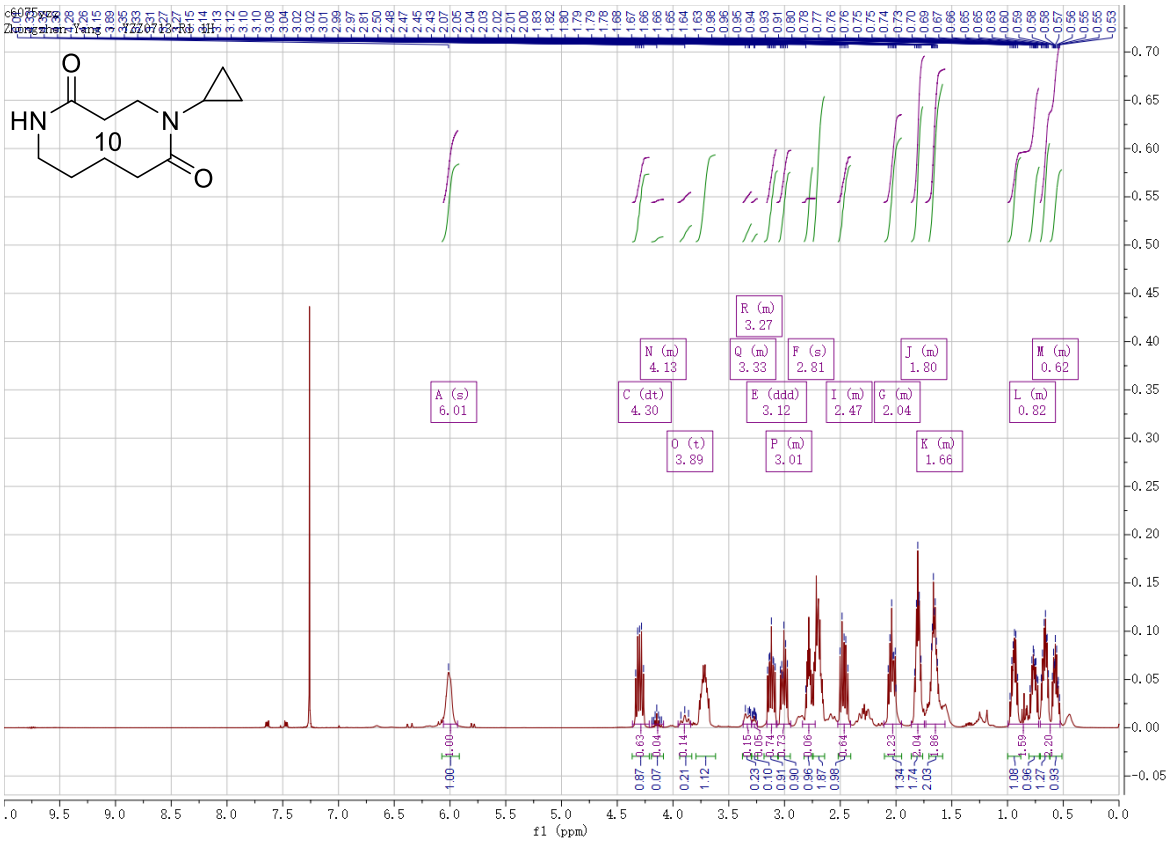


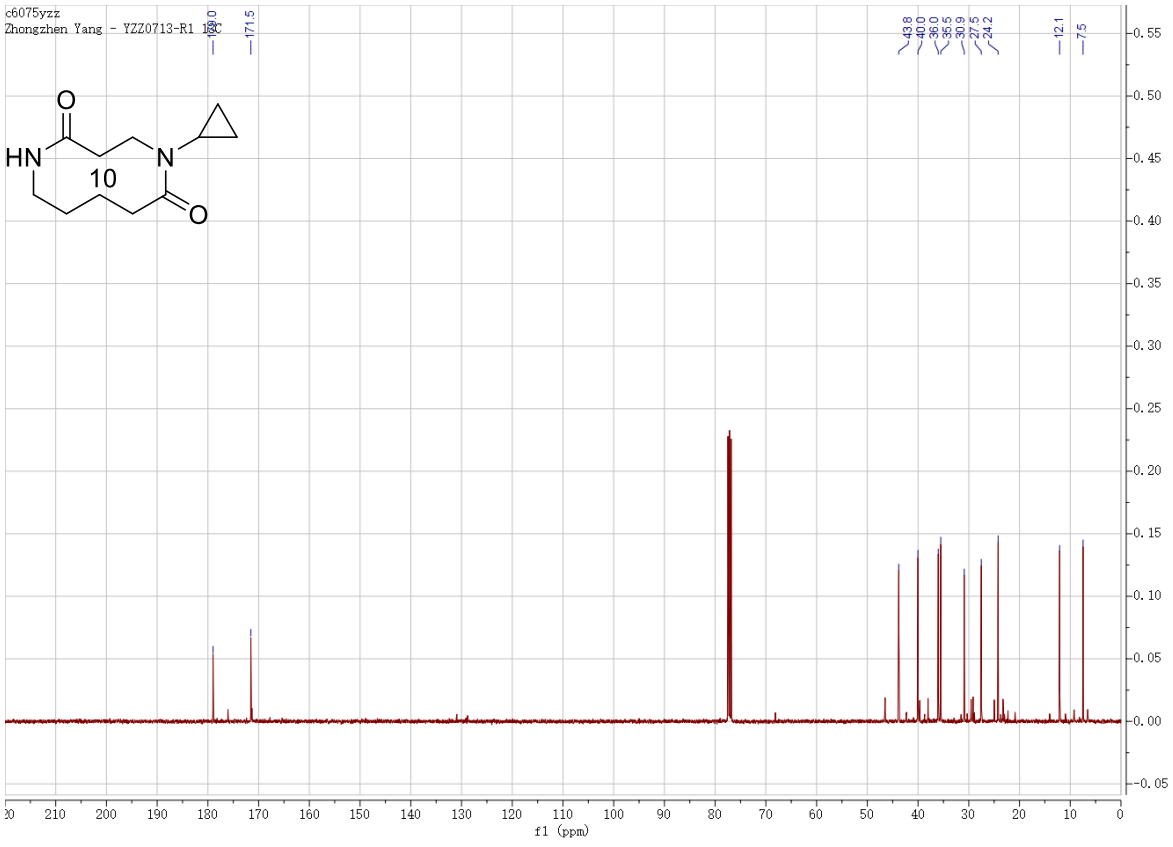
5-Methyl-1,5-diazecane-2,6-dione (20b) 7:1 mixture of rotamers.



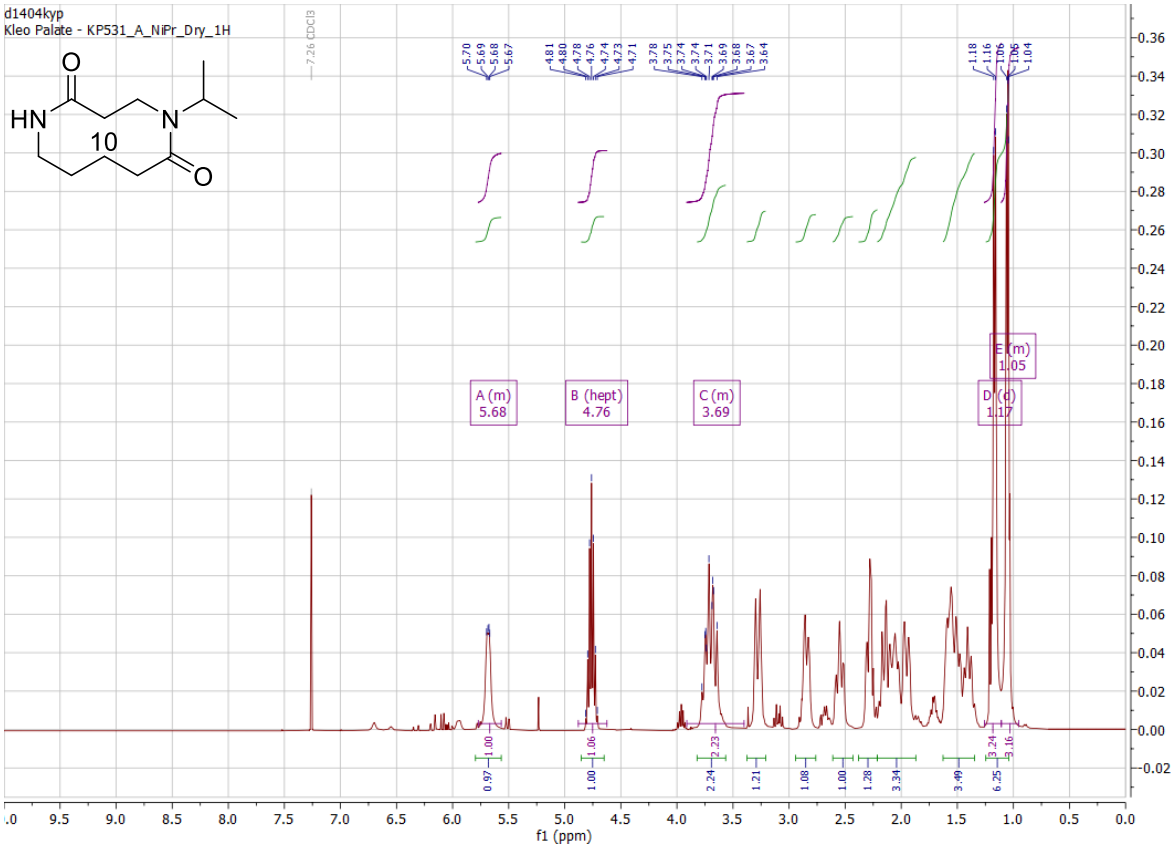


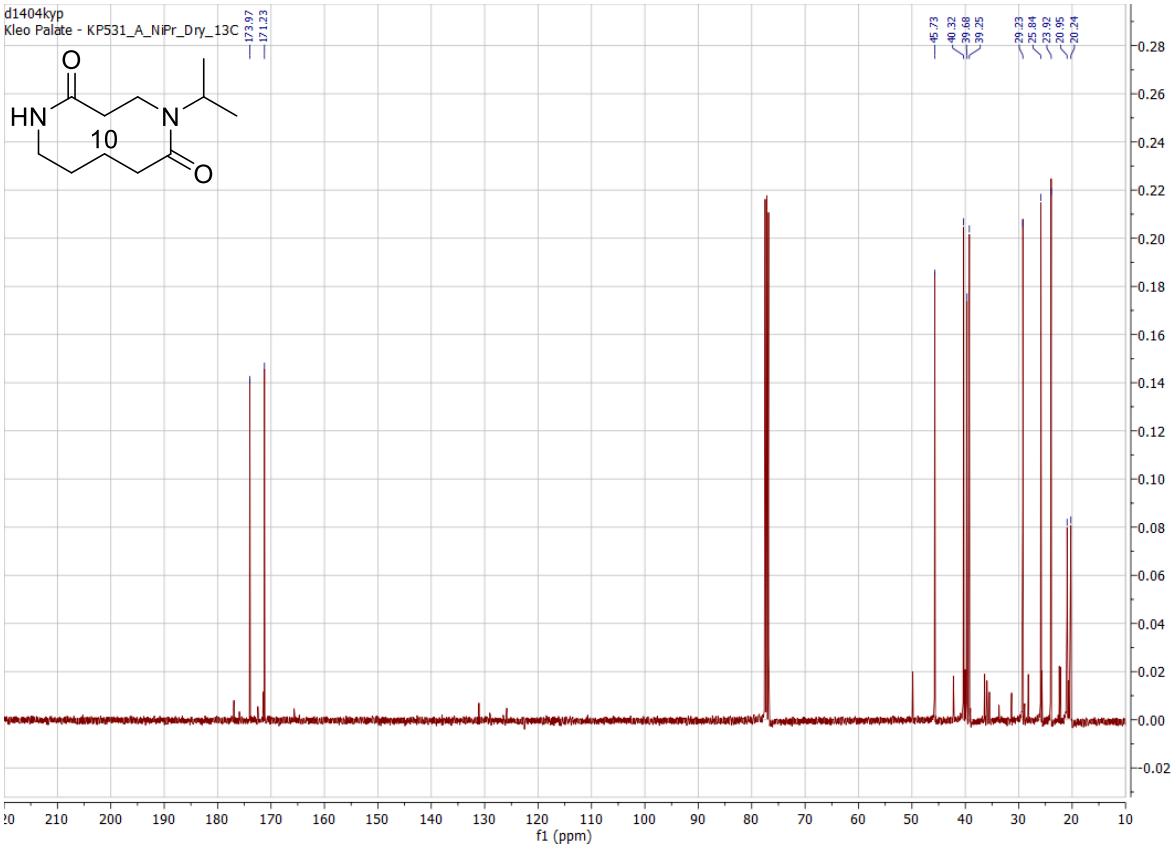
5-Cyclopropyl-1,5-diazecane-2,6-dione (20c) 20:1 mixture of rotamers.



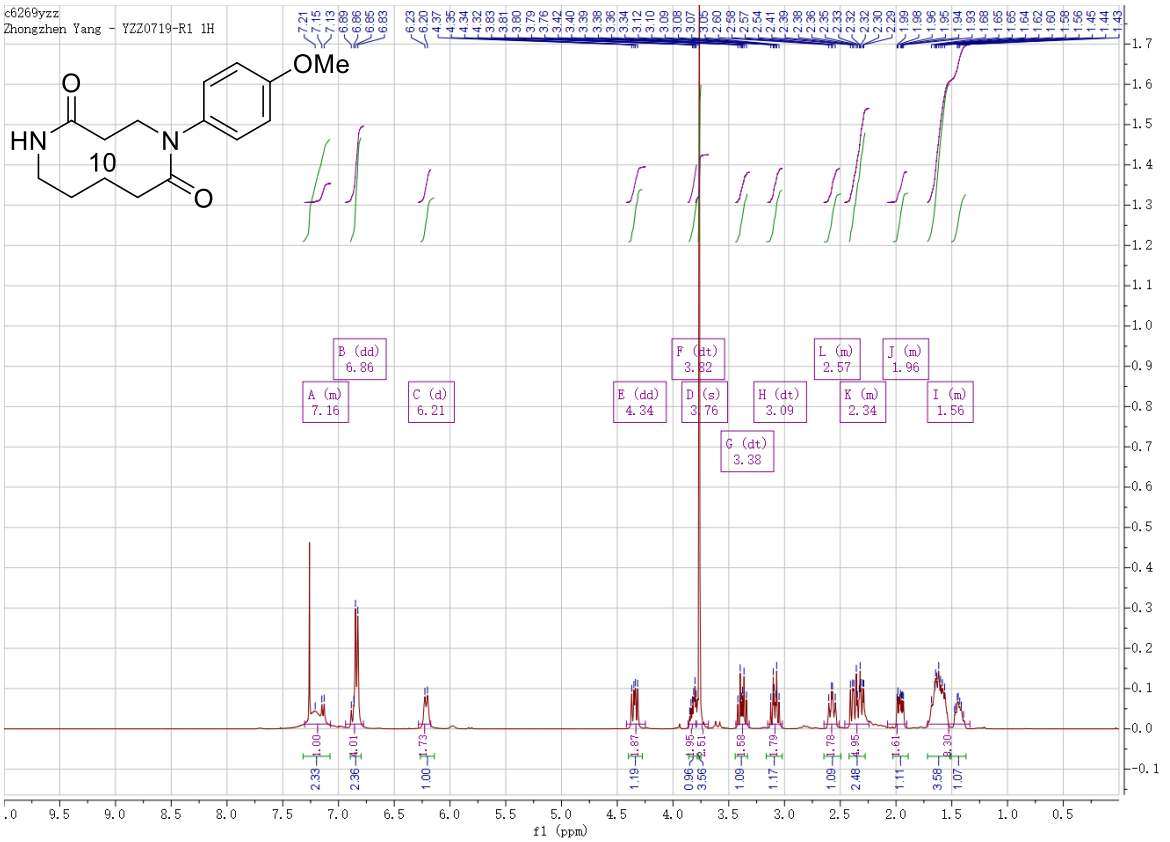


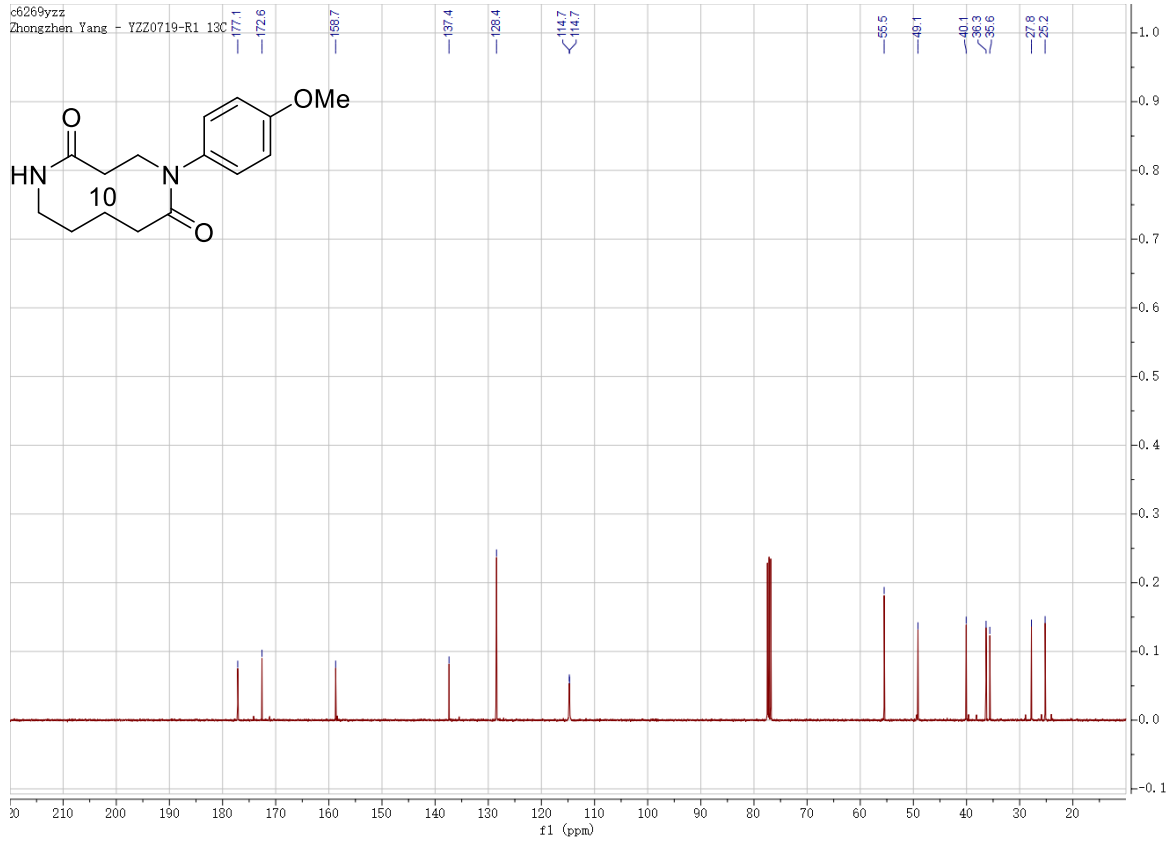
5-Isopropyl-1,5-diazecane-2,6-dione (20d) 1:11 mixture of rotamers.



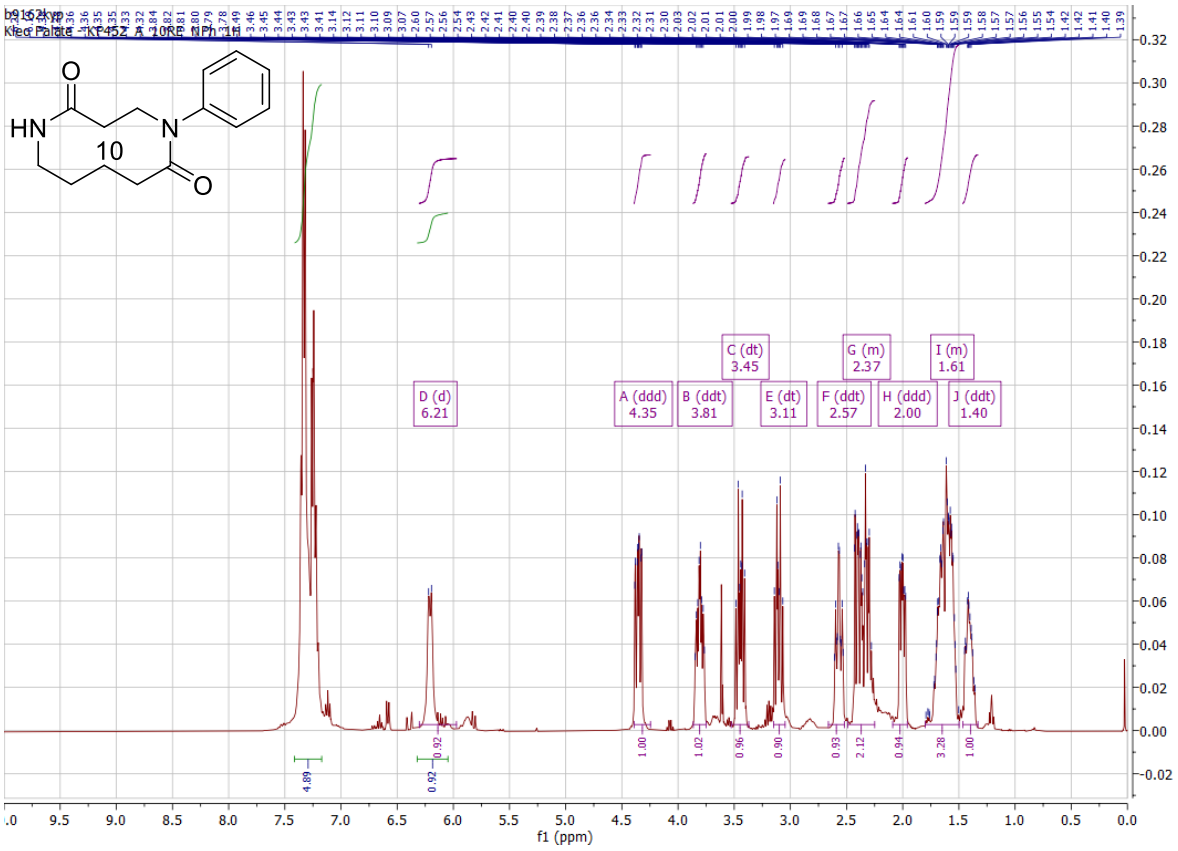


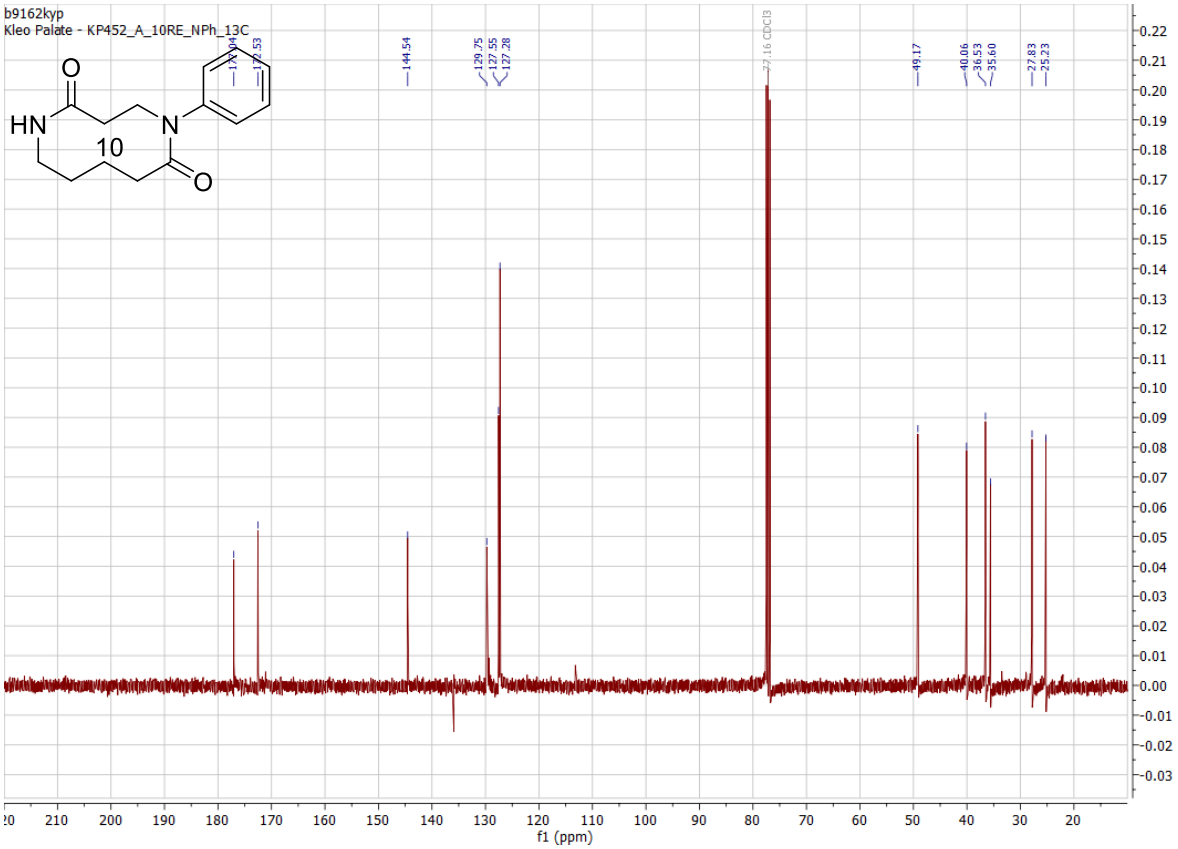
5-(4-Methoxyphenyl)-1,5-diazecane-2,6-dione (20f) In solution in $CDCl_3$, this compound largely a single rotamer, with a trace amount of a minor rotamer visible in the ^{1}H and ^{13}C NMR spectra.



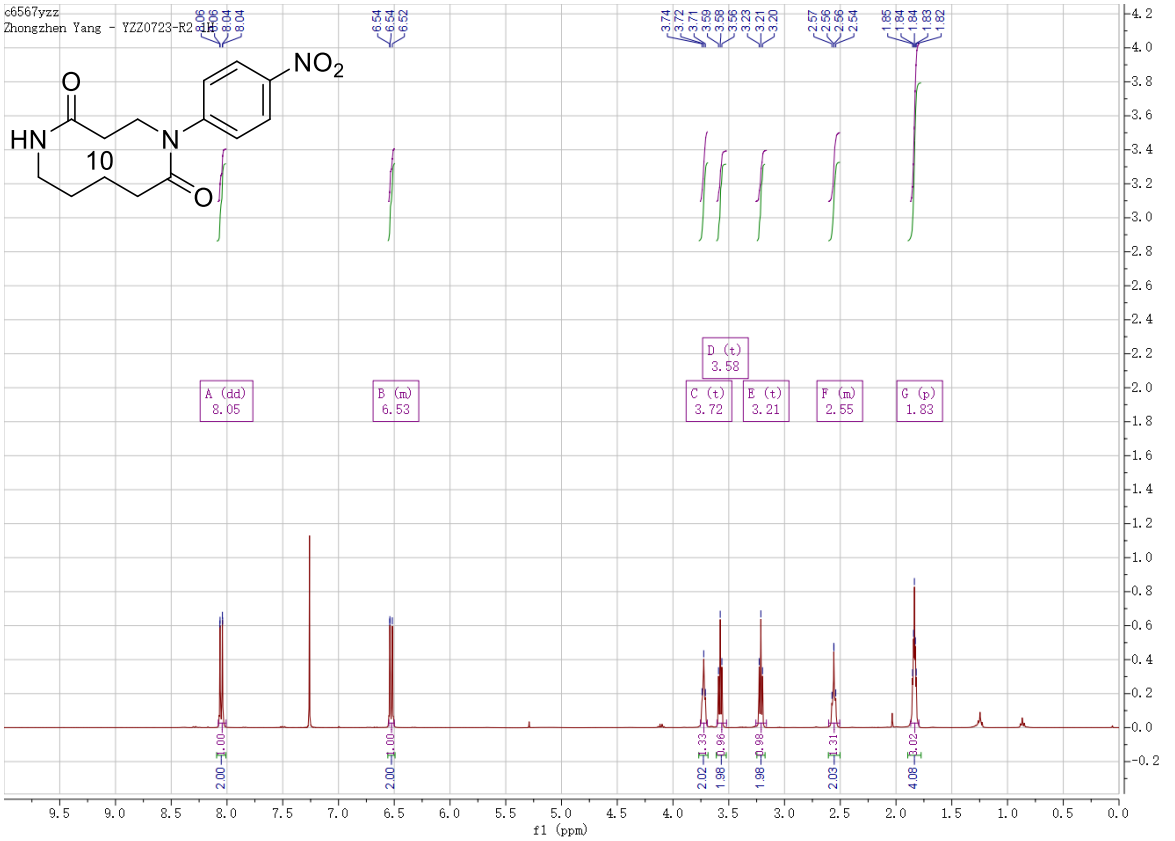


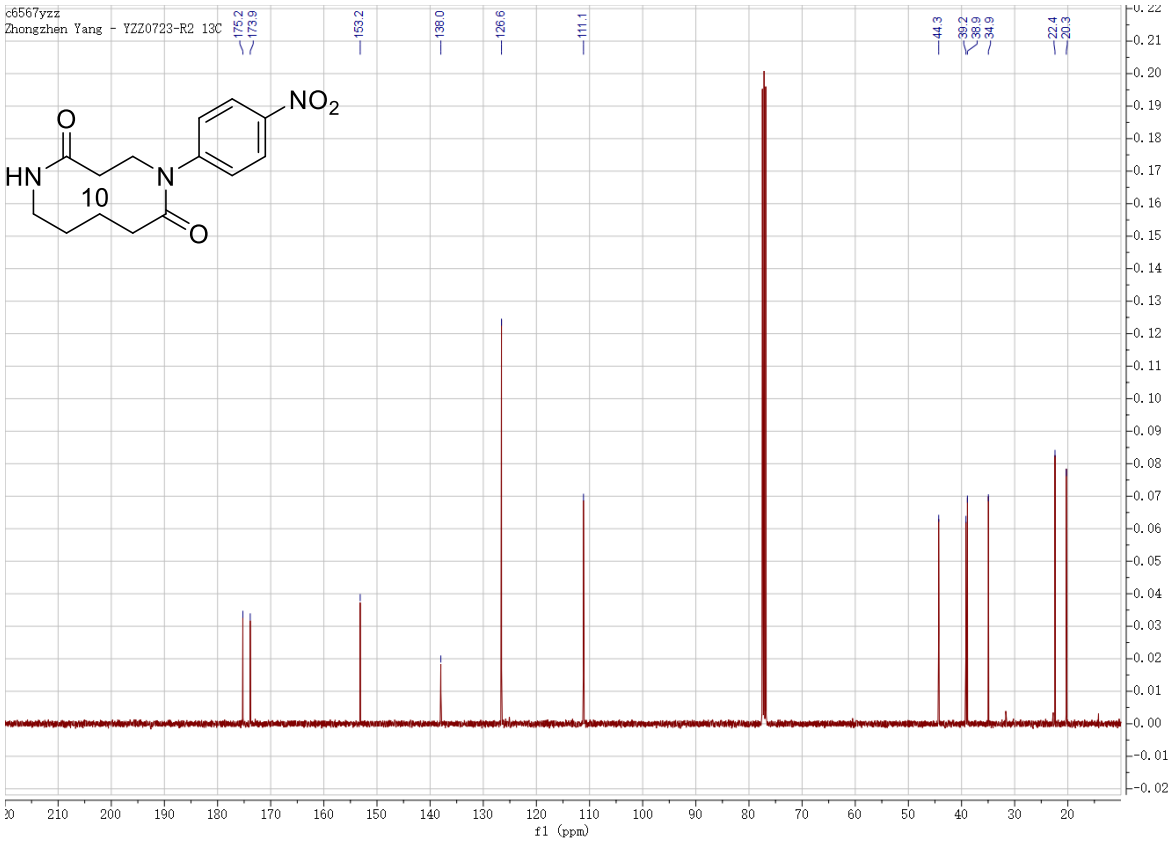
5-Phenyl-1,5-diazecane-2,6-dione (20g)



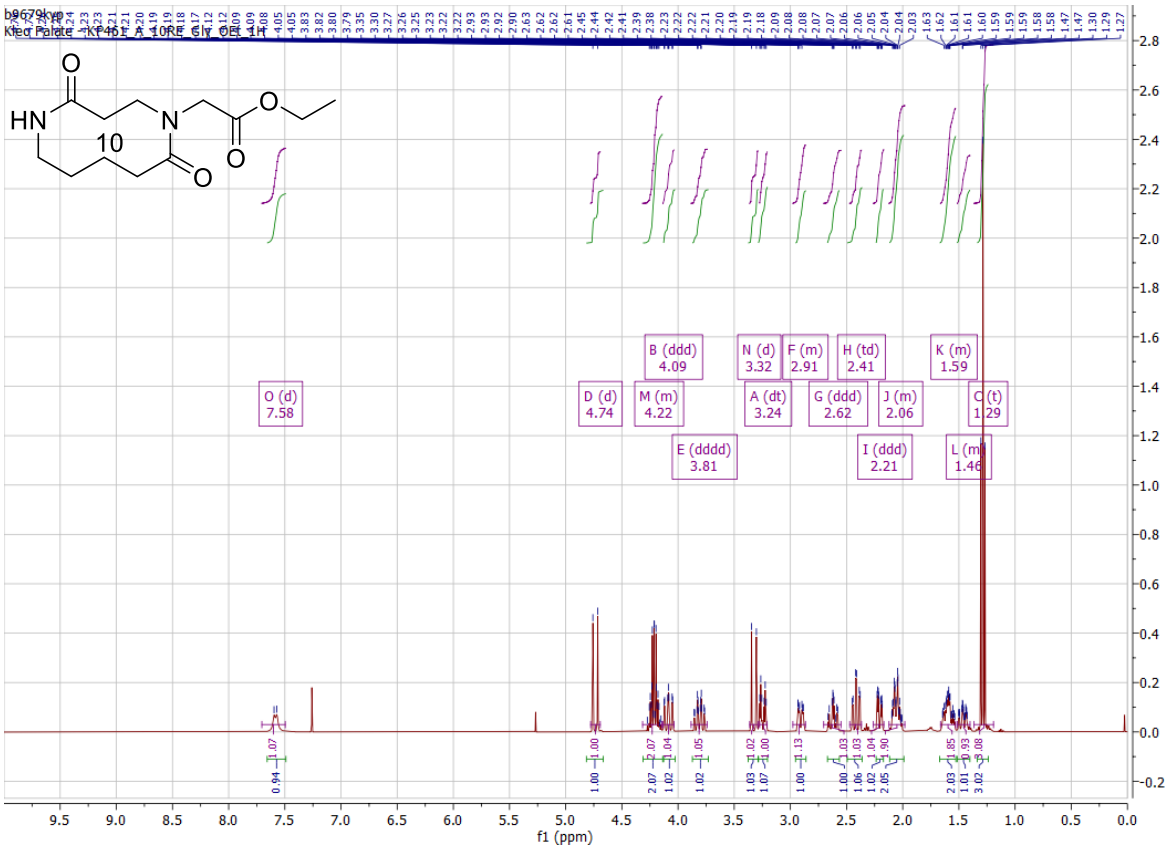


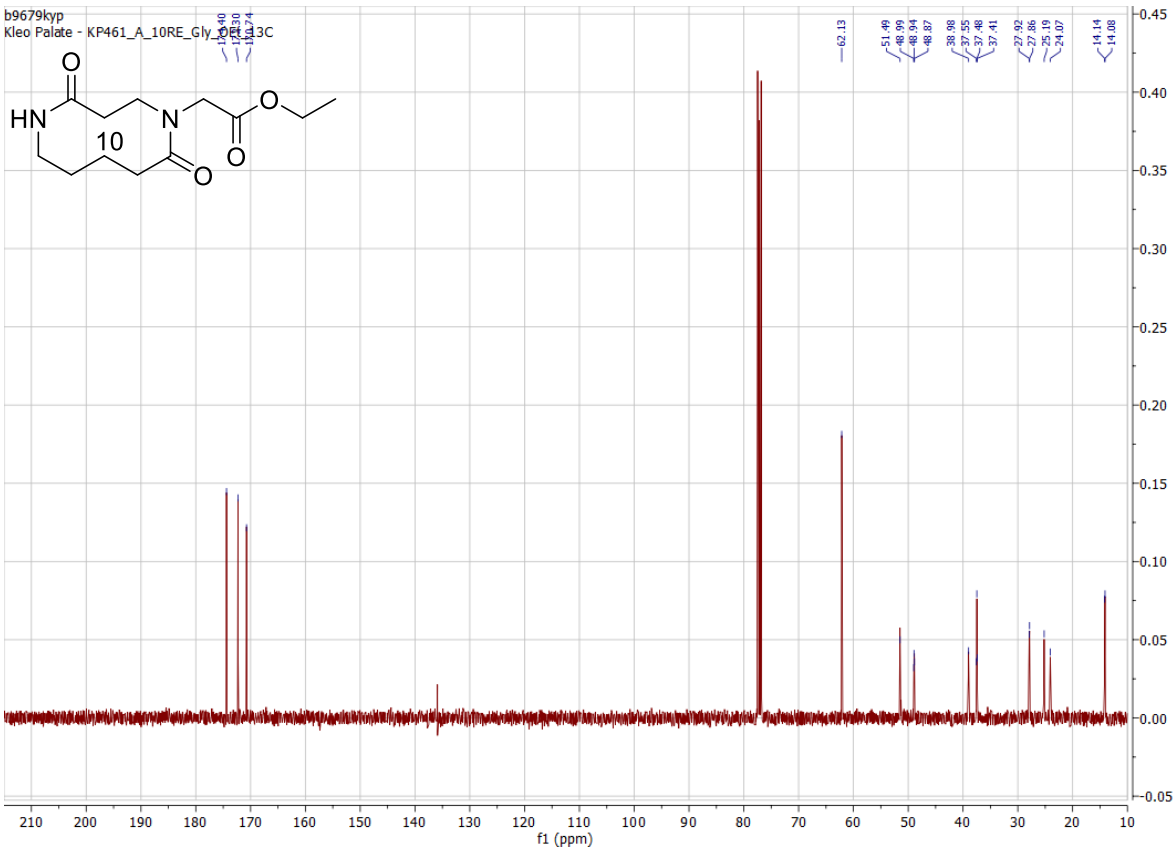
5-(4-Nitrophenyl)-1,5-diazecane-2,6-dione (20h)



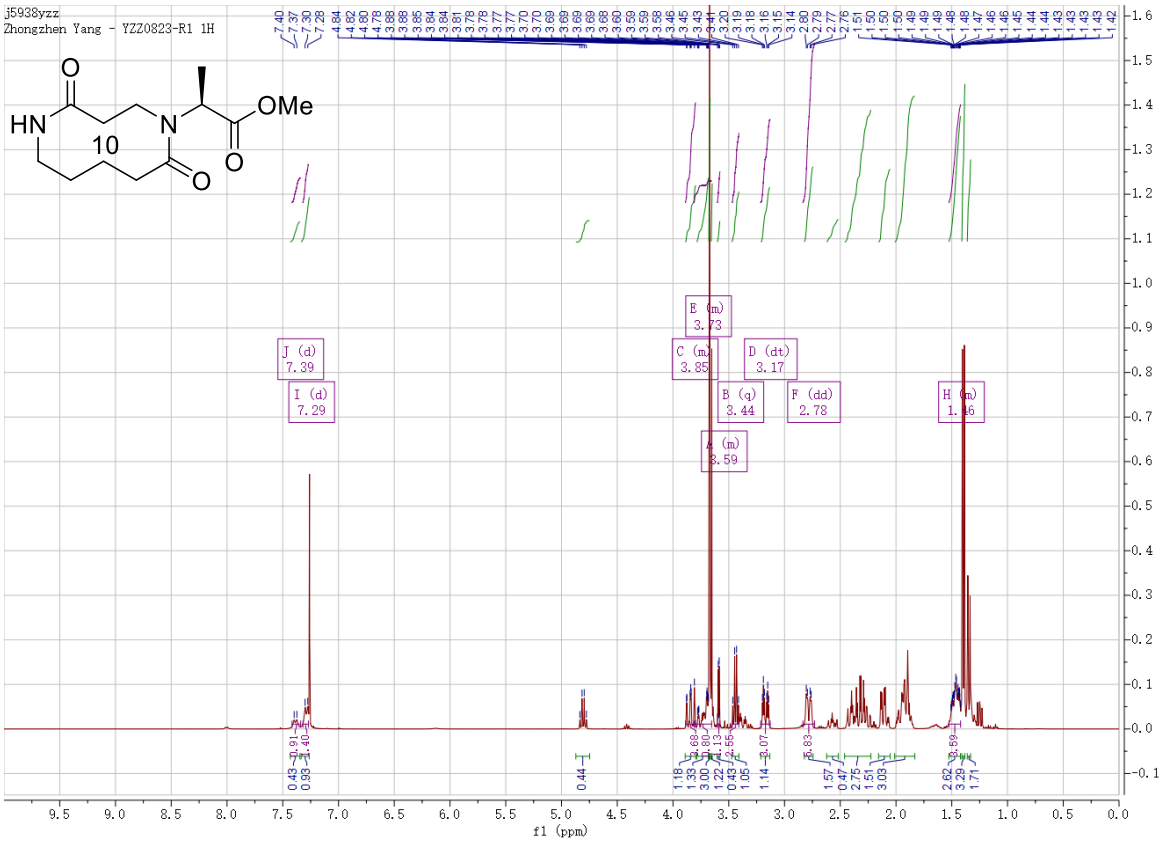


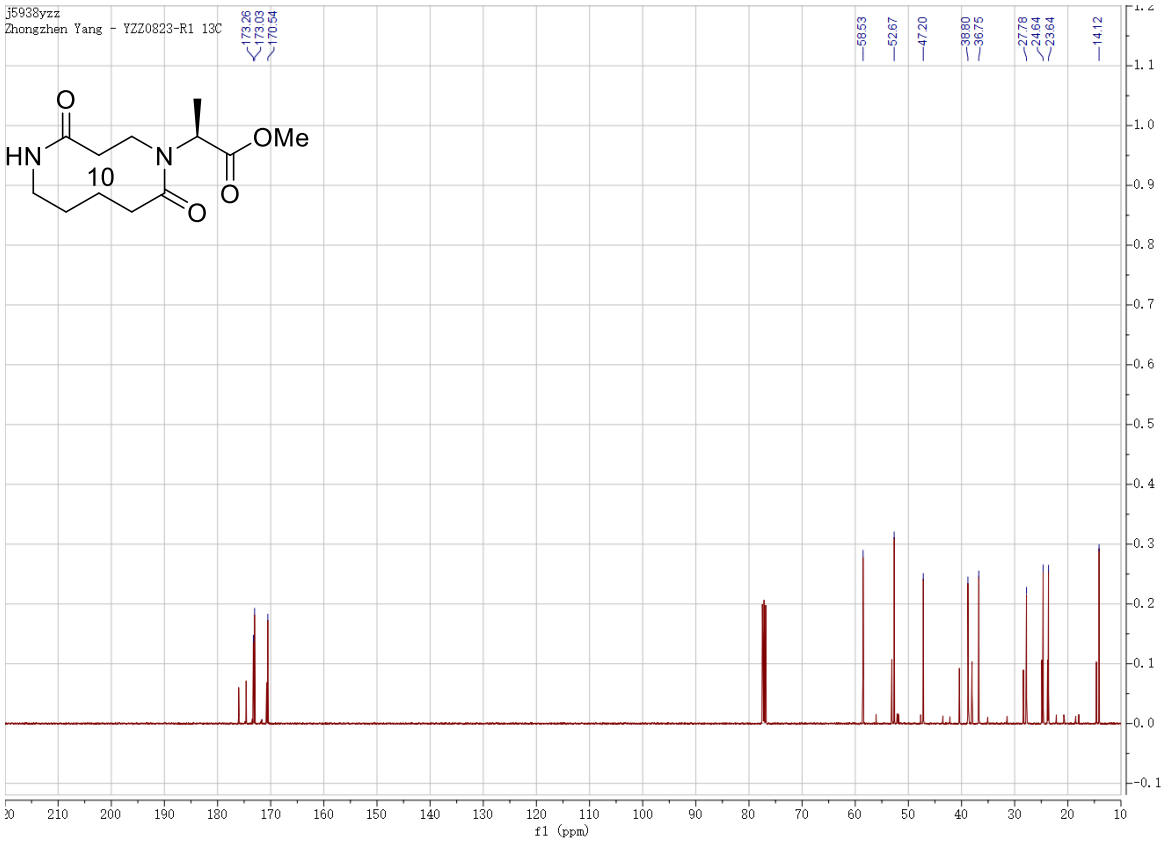
Ethyl 2-(4,10-dioxo-1,5-diazecan-1-yl)acetate (20i)



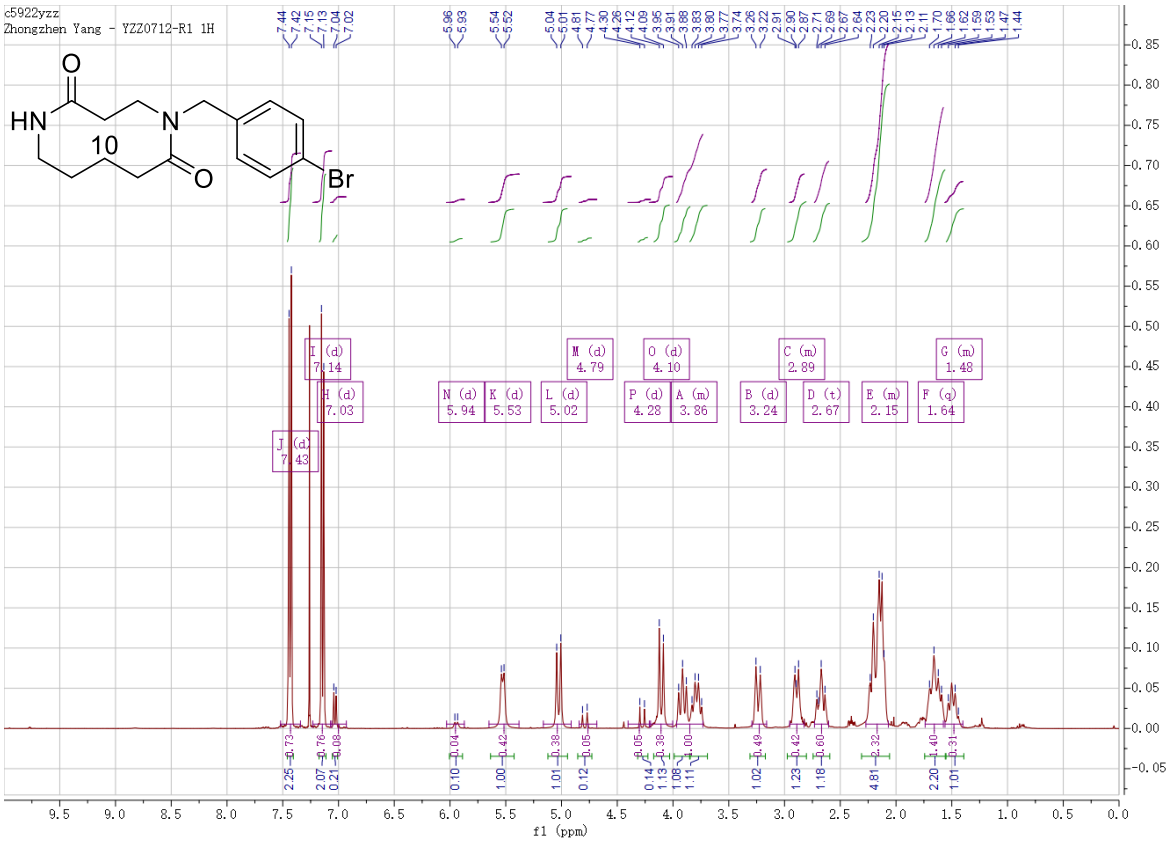


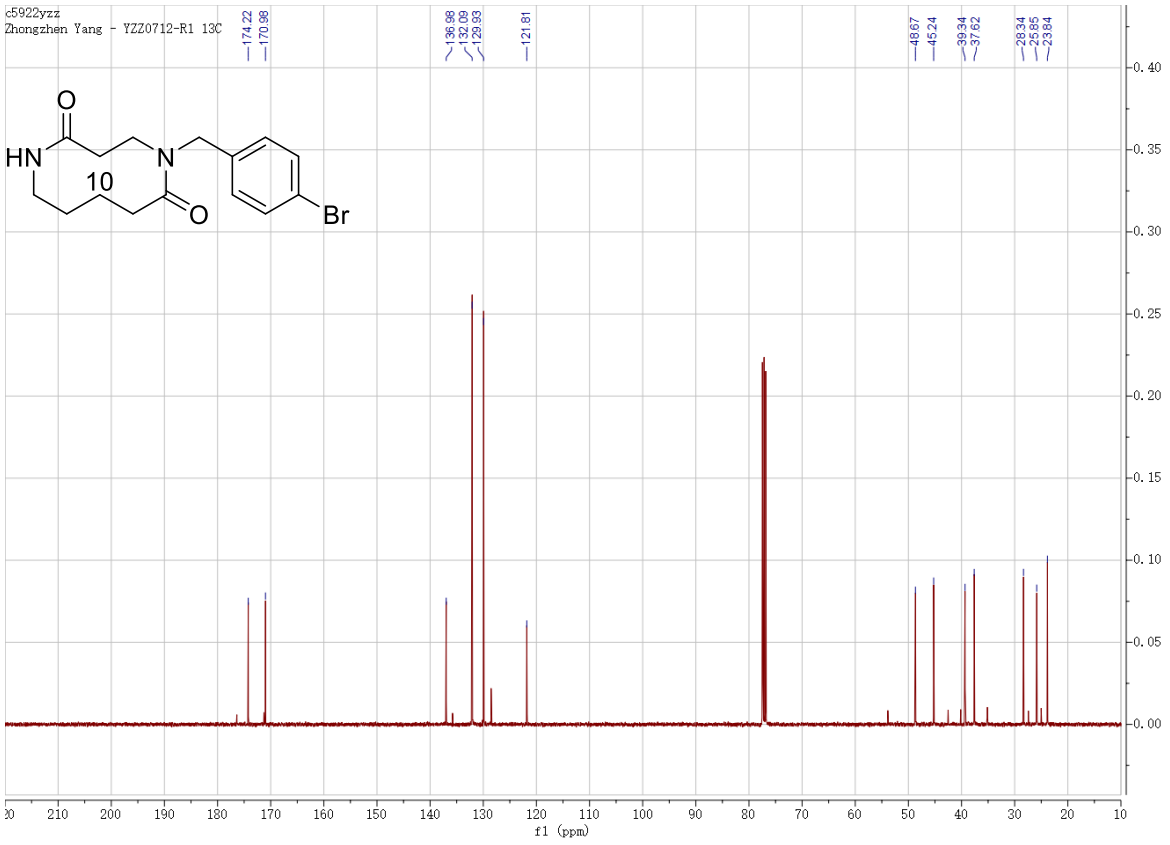
Methyl (*S*)-2-(4,10-dioxo-1,5-diazecan-1-yl)propanoate (20j) 2:1 mixture of rotamers.



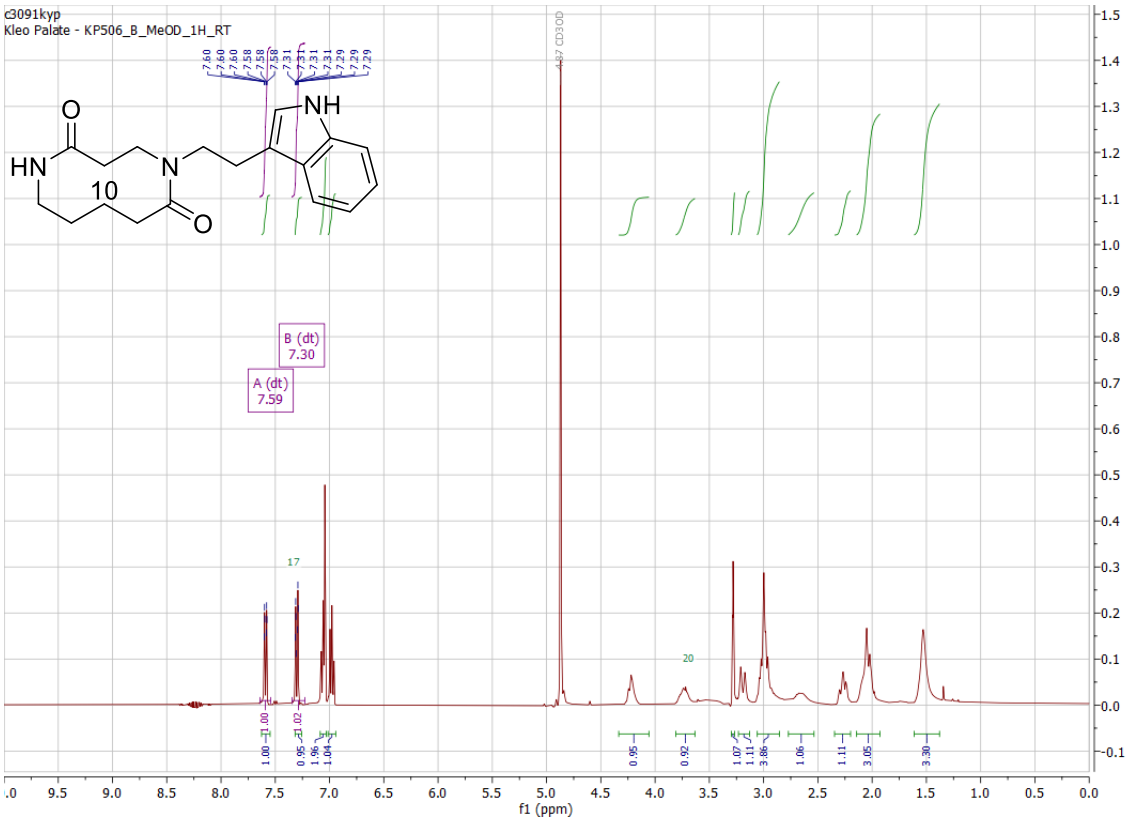


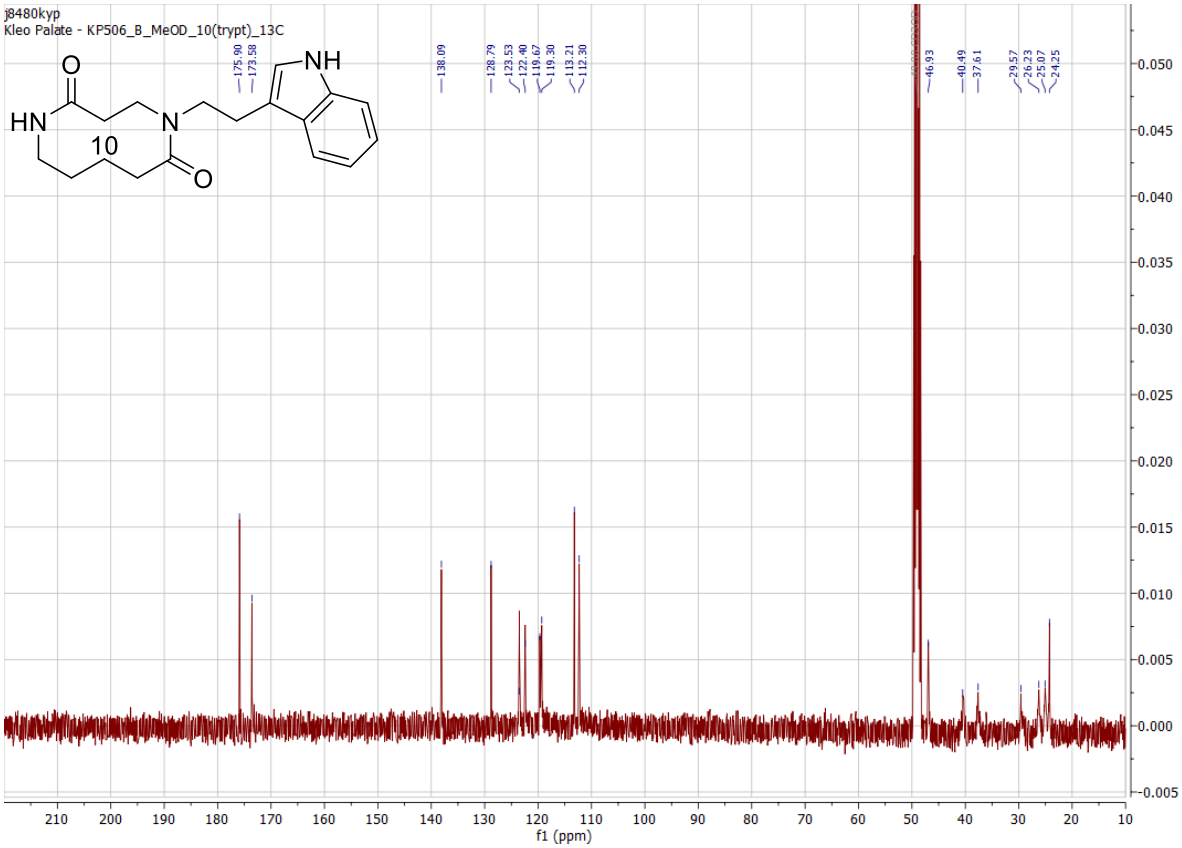
5-(4-Bromobenzyl)-1,5-diazecane-2,6-dione (20k)



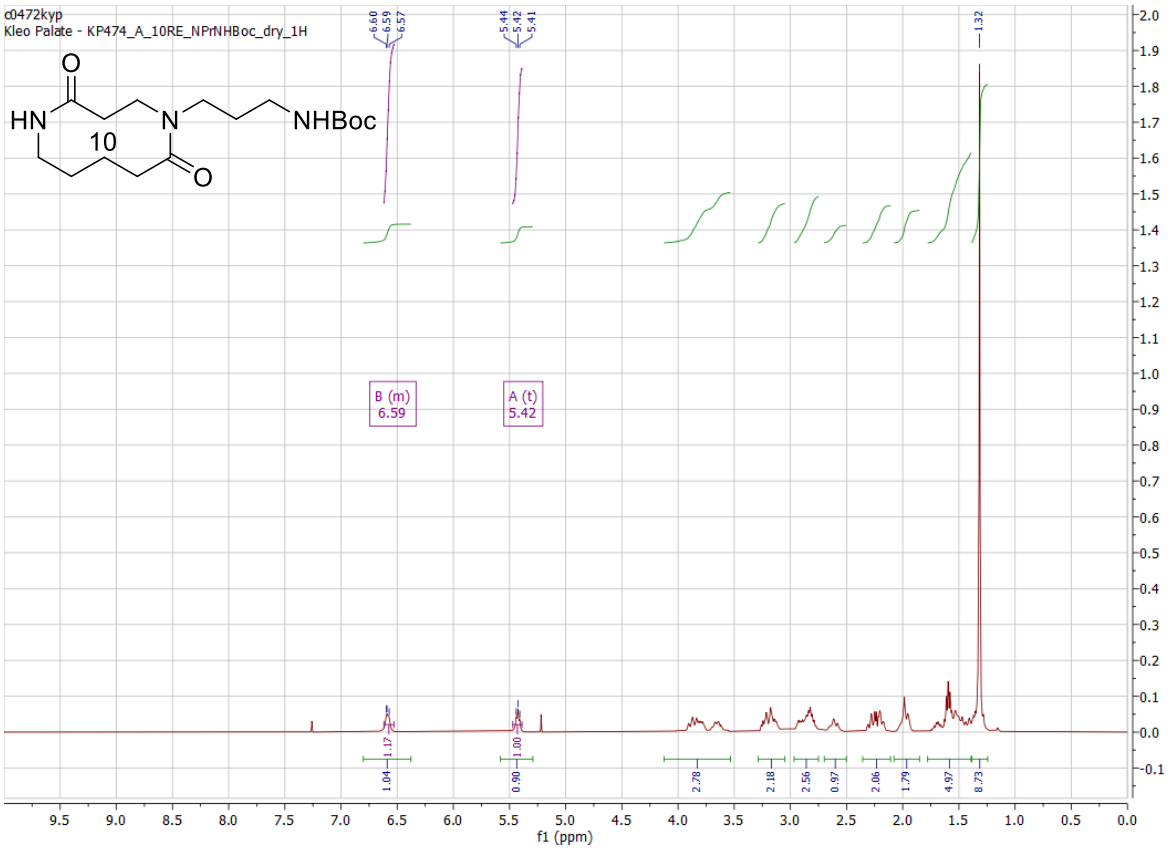


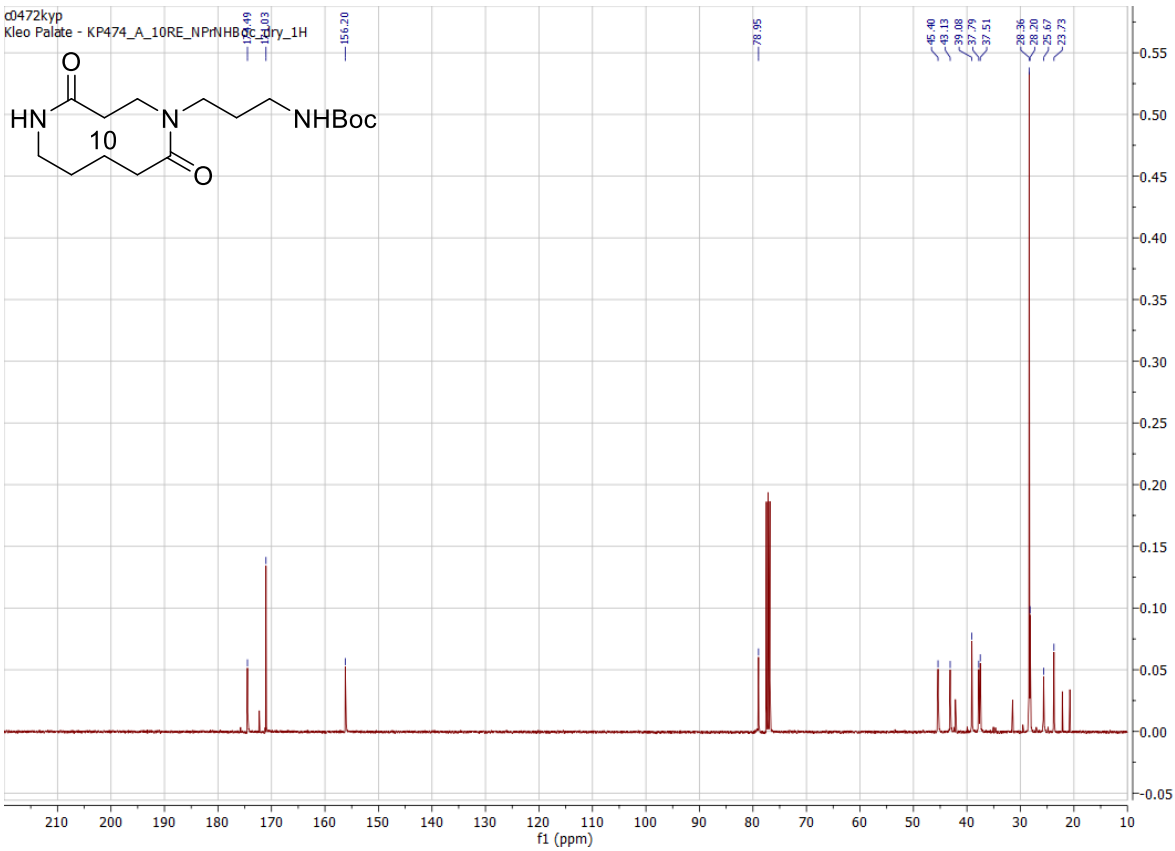
5-(2-(1*H*-Indol-3-yl)ethyl)-1,5-diazecane-2,6-dione (20l). The non-aromatic region of ^{1}H NMR spectrum is significantly affected by rotameric broadening.



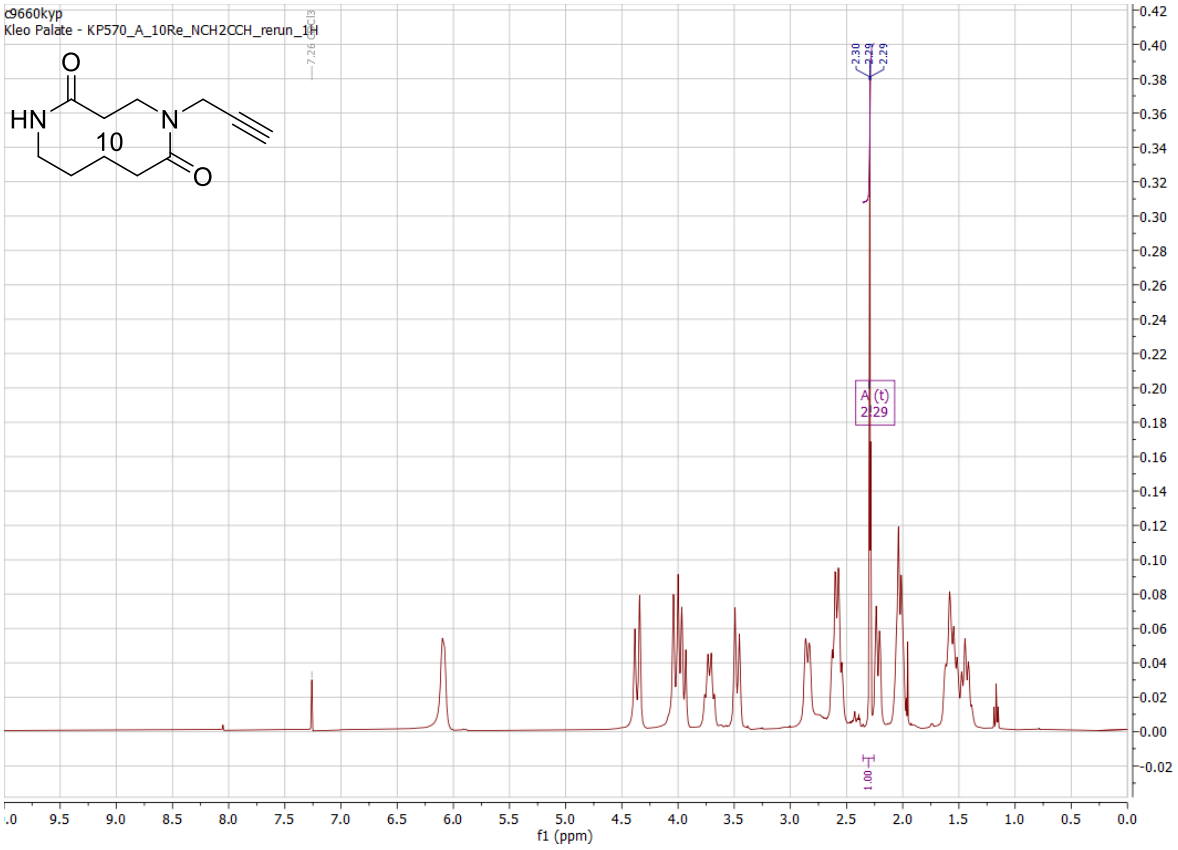


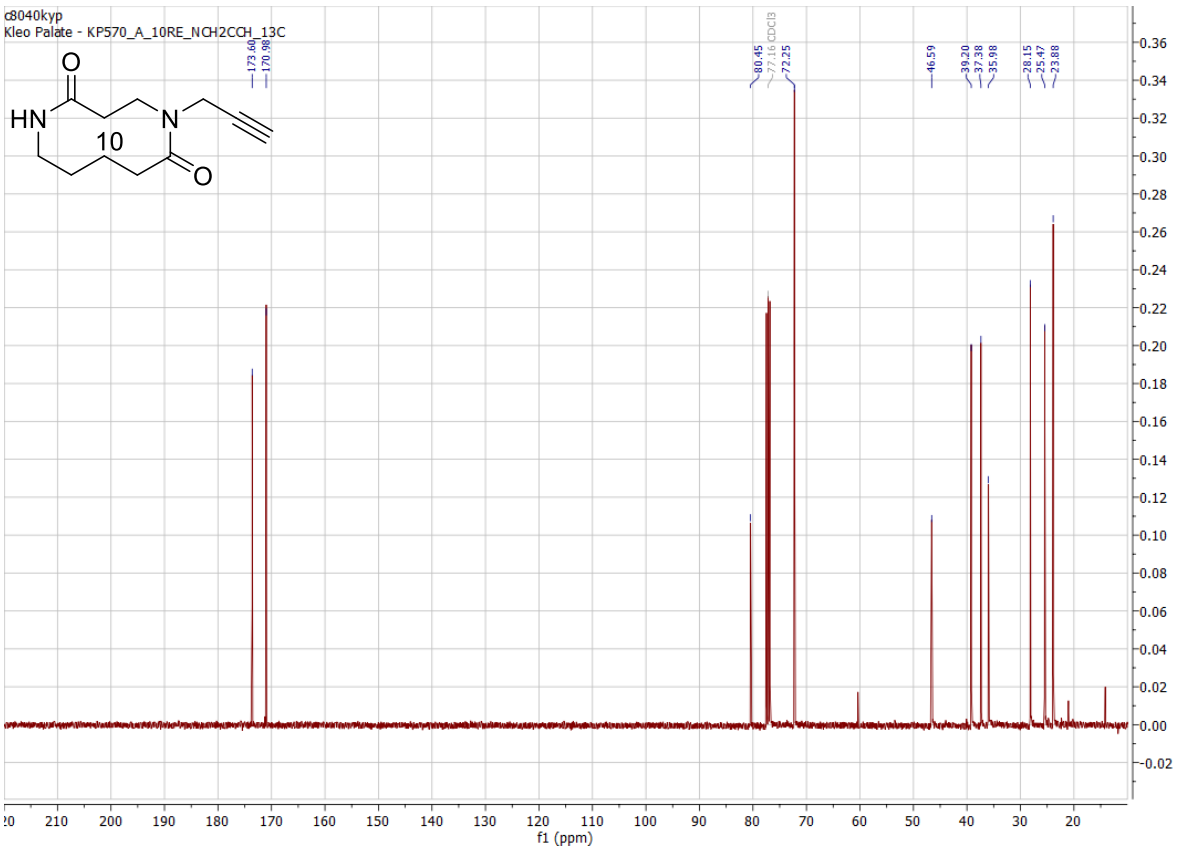
***tert*-Butyl (3-(4,10-dioxo-1,5-diazecan-1-yl)propyl)carbamate (20m)**



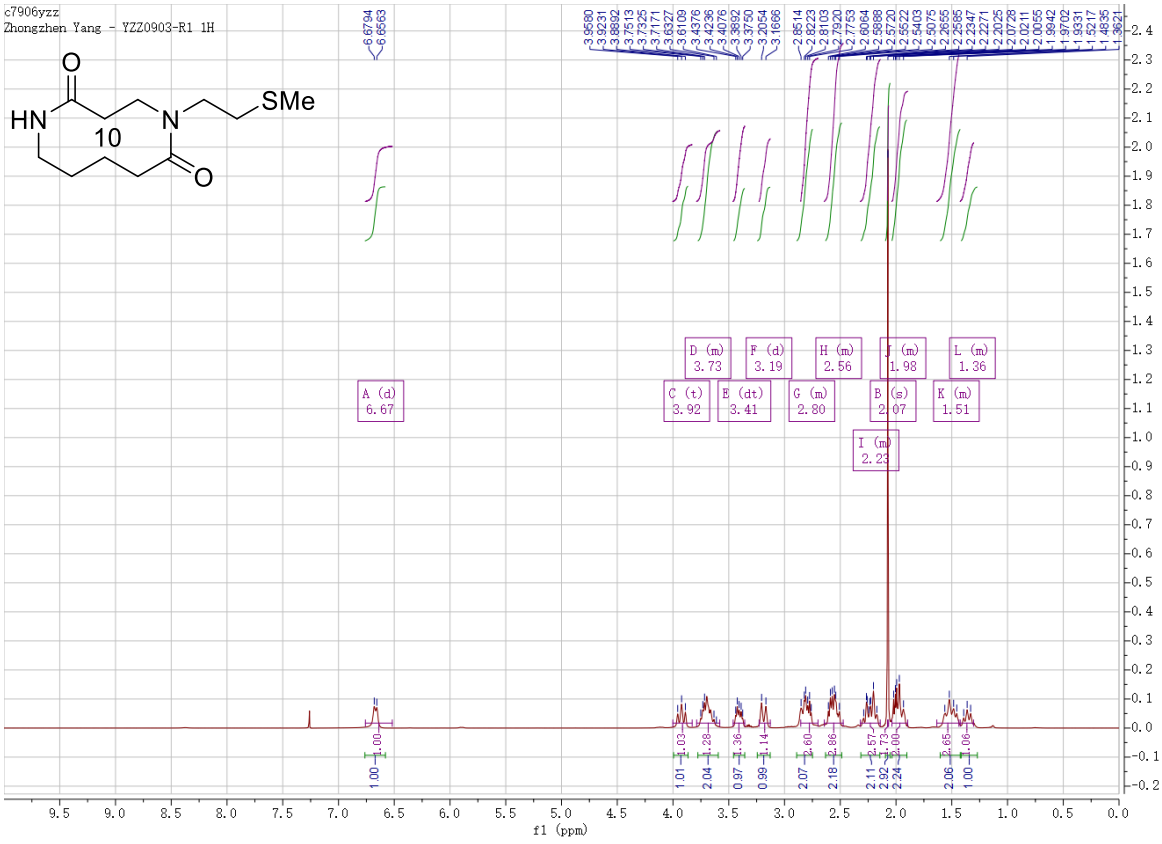


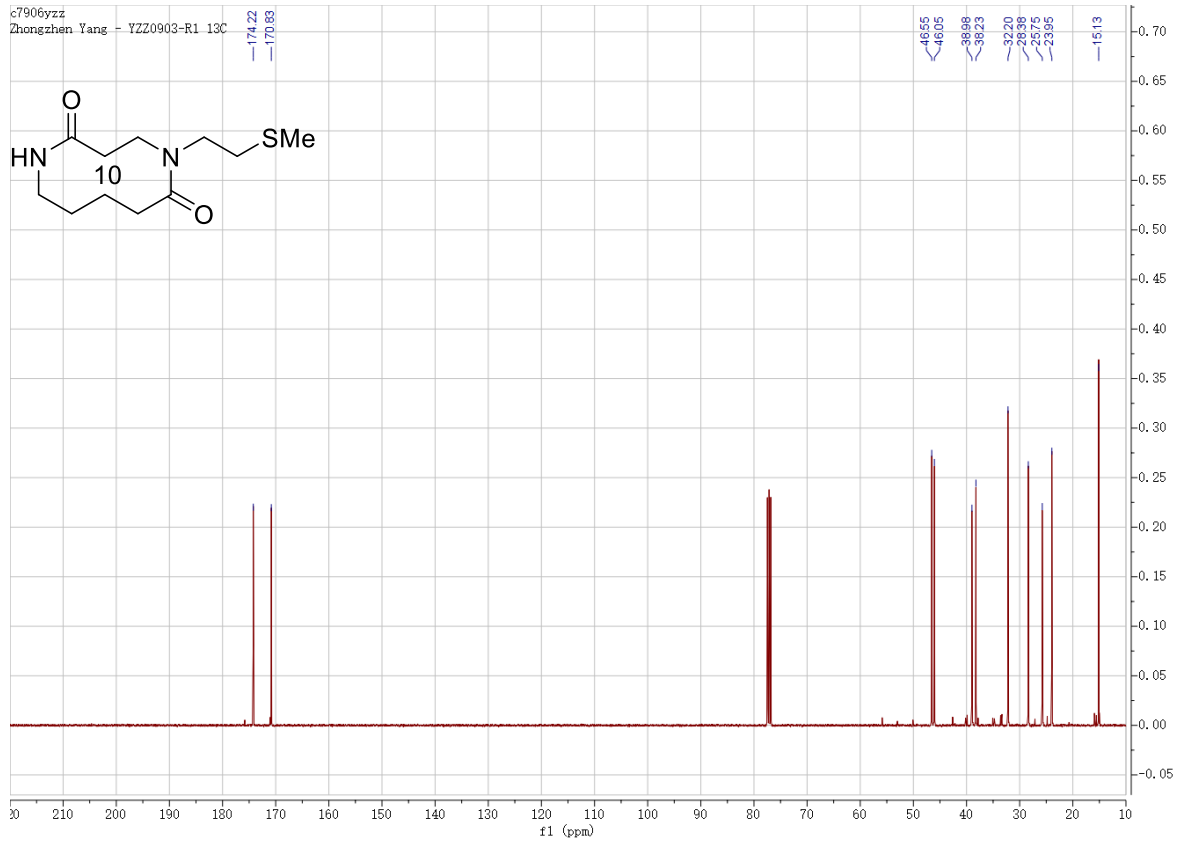
5-(Prop-2-yn-1-yl)-1,5-diazecane-2,6-dione (20n)



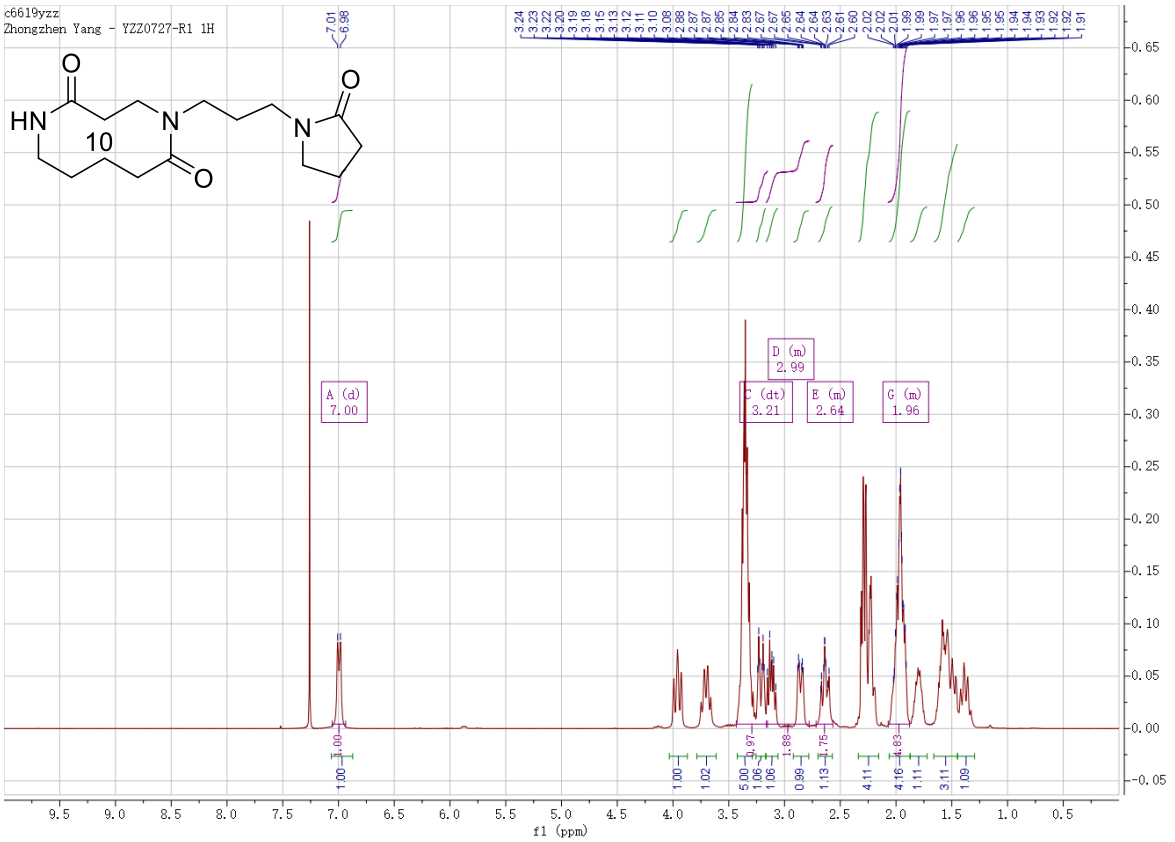


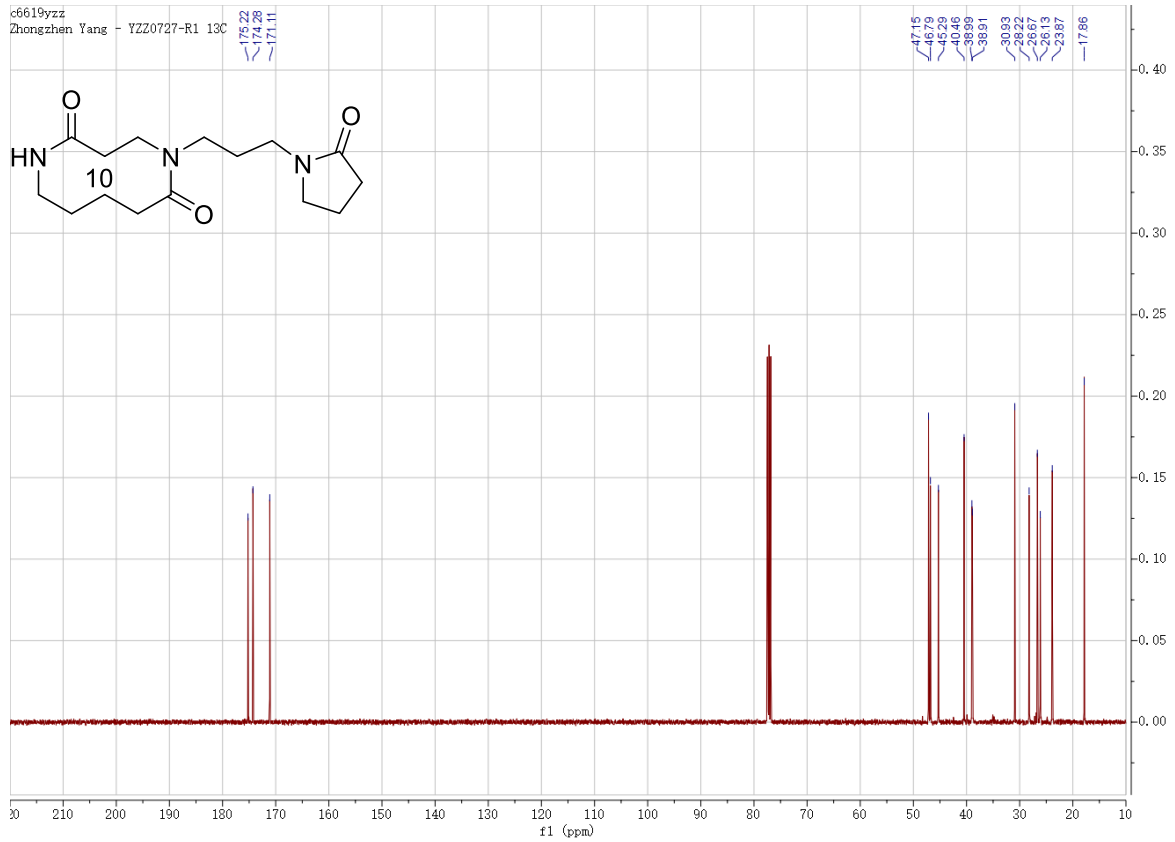
5-(2-(Methylthio)ethyl)-1,5-diazecane-2,6-dione (20o)



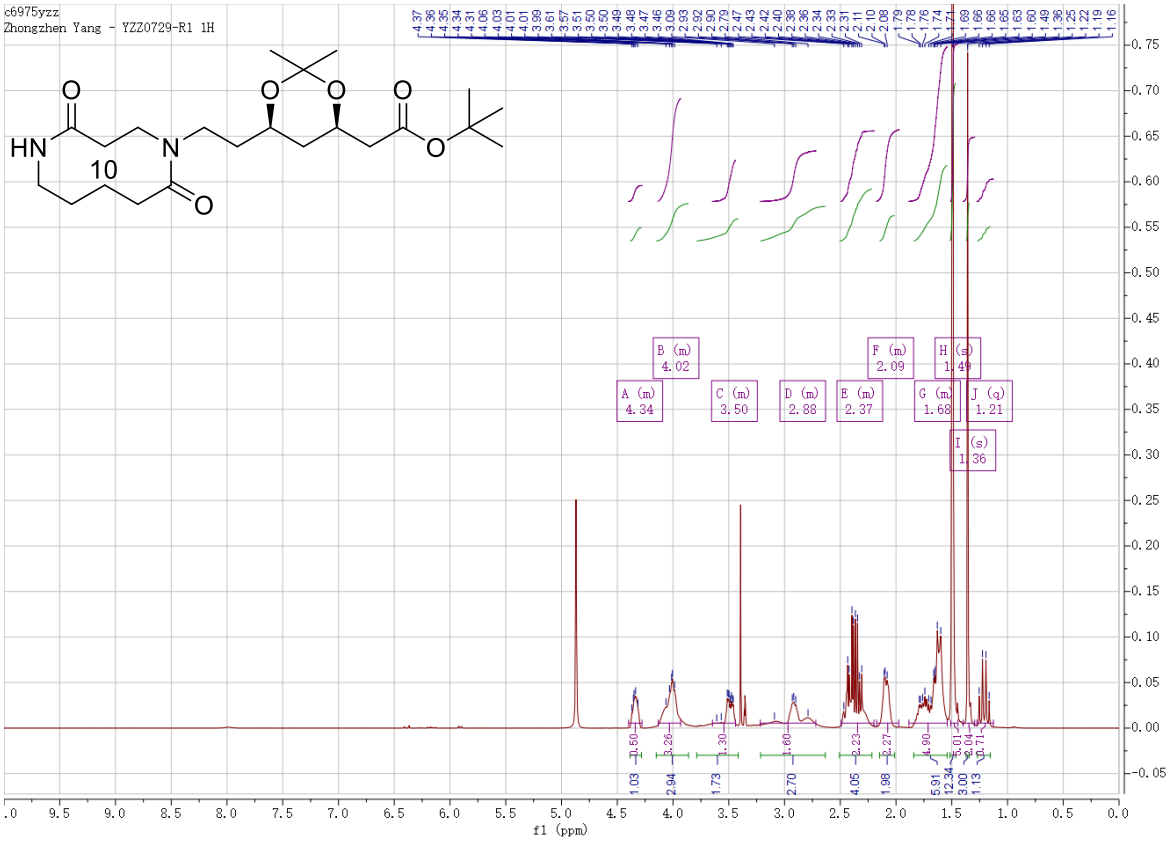


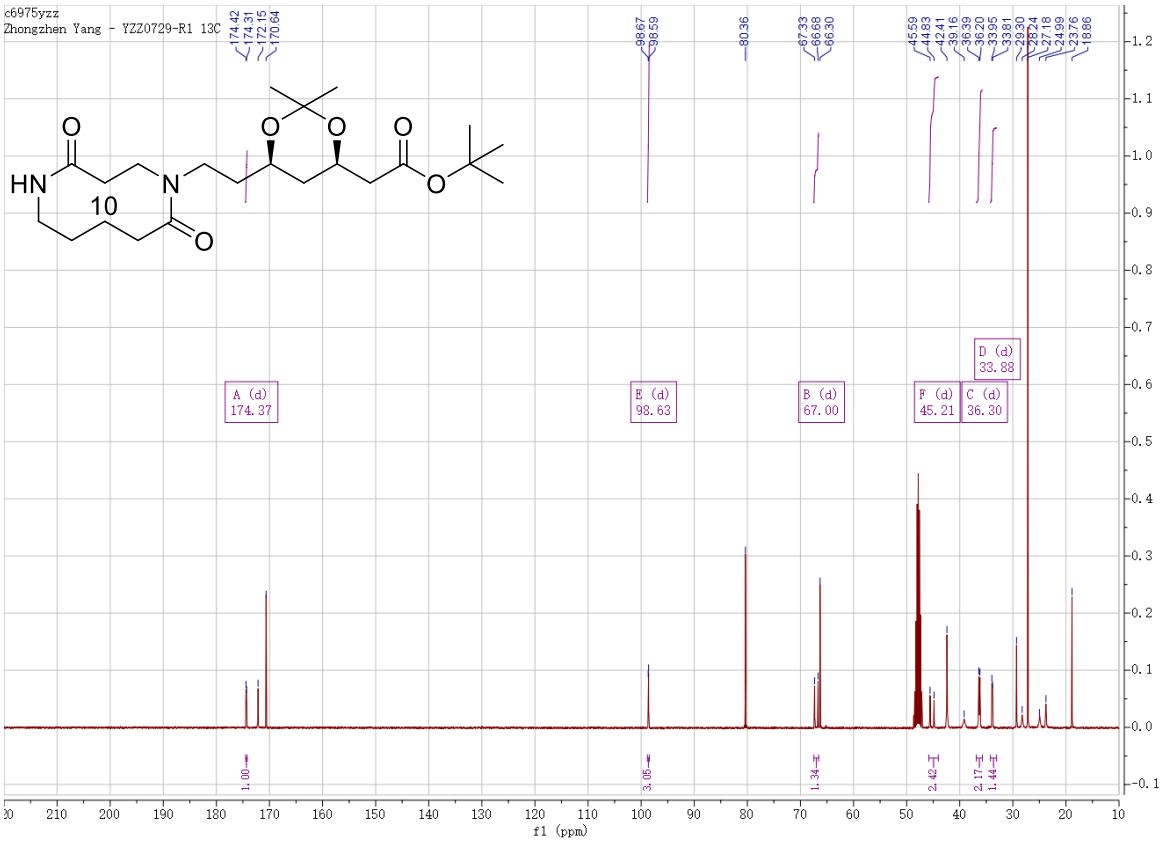
5-(3-(2-Oxopyrrolidin-1-yl)propyl)-1,5-diazecane-2,6-dione (20p)



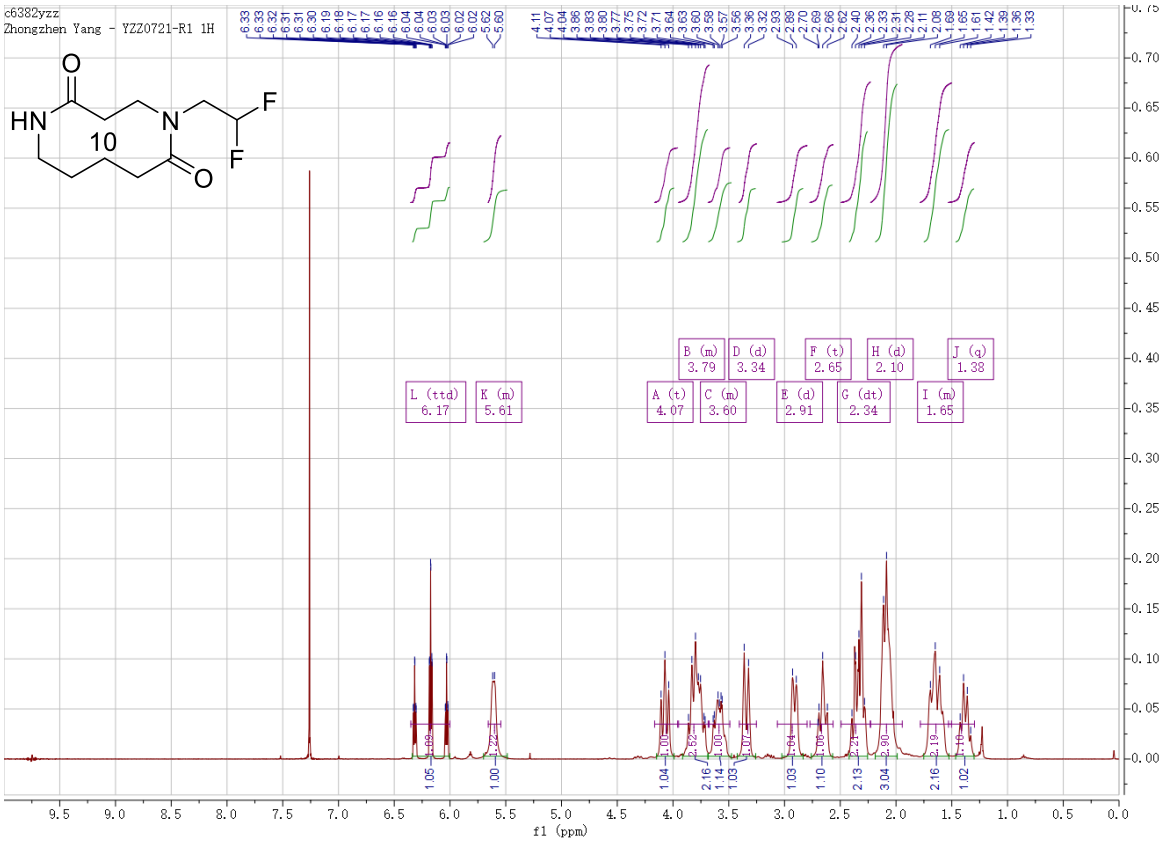


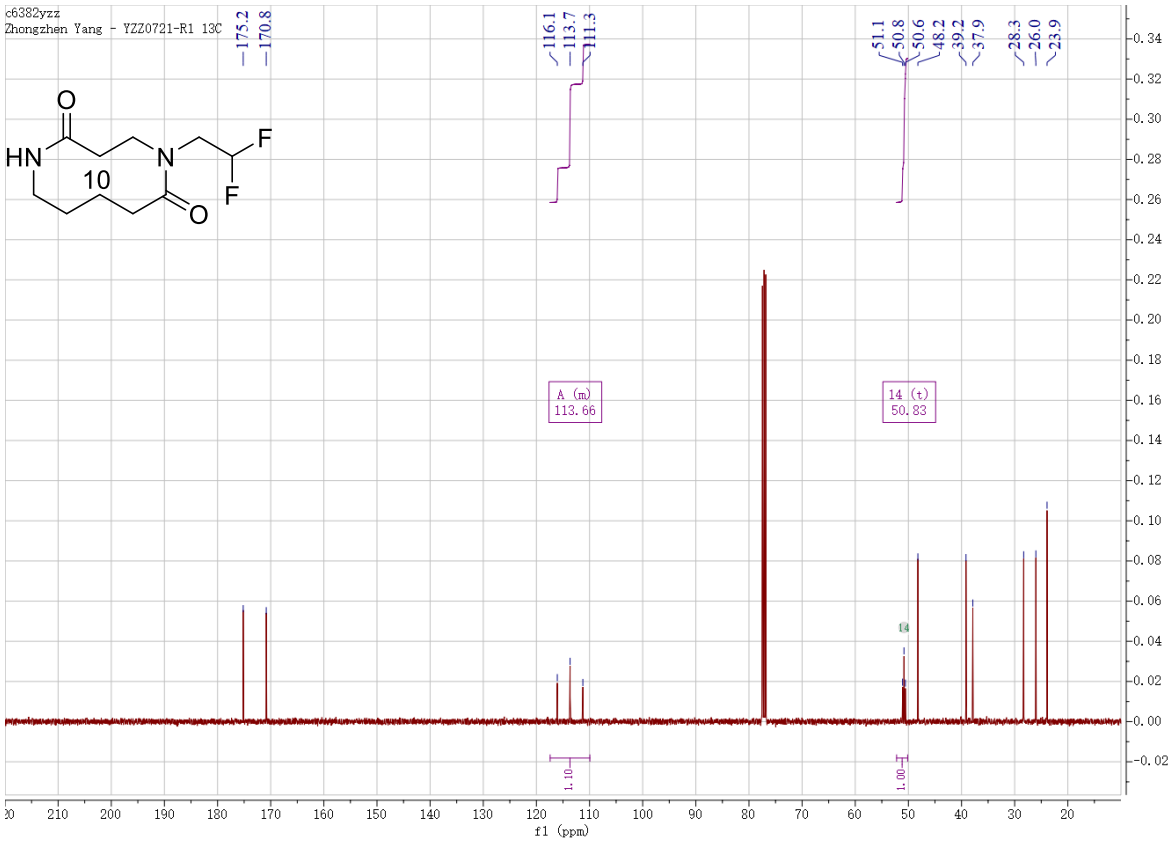
***tert*-Butyl 2-((4*R*,6*R*)-6-(2-(4,10-dioxo-1,5-diazecan-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (20q)**

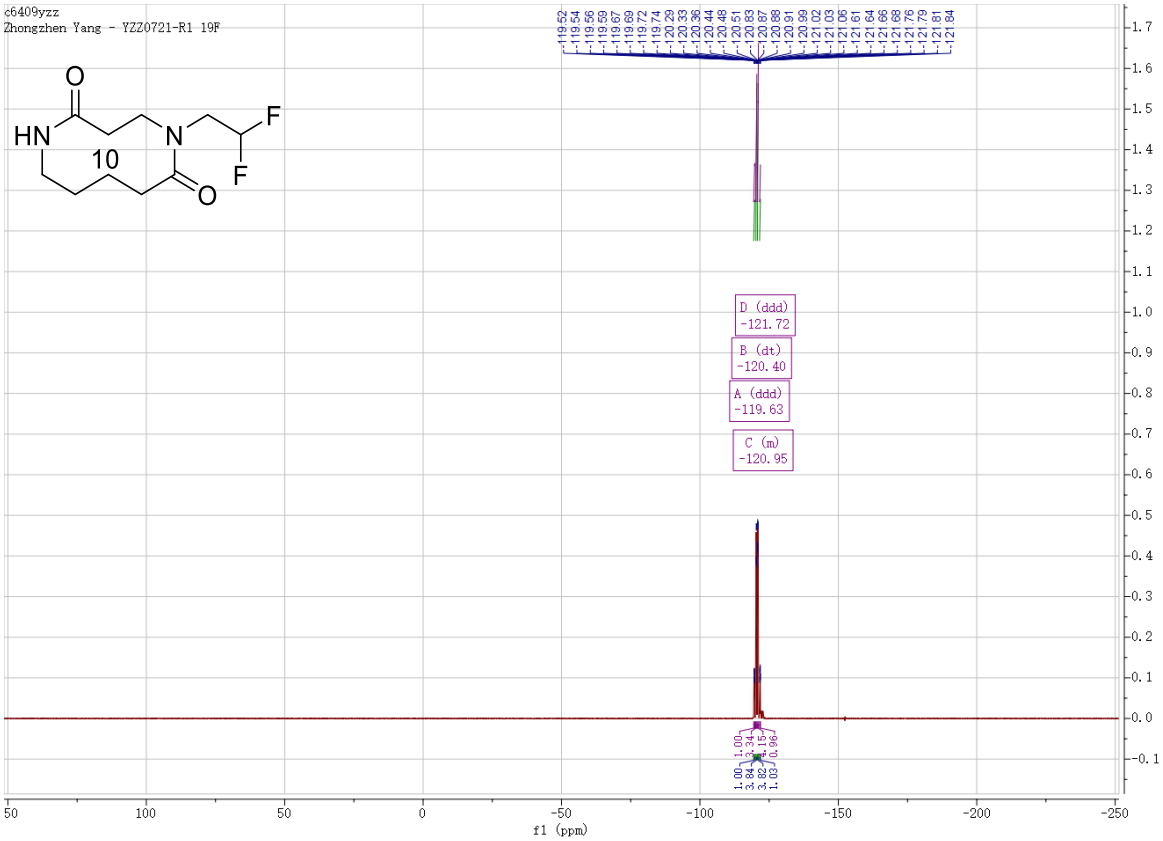


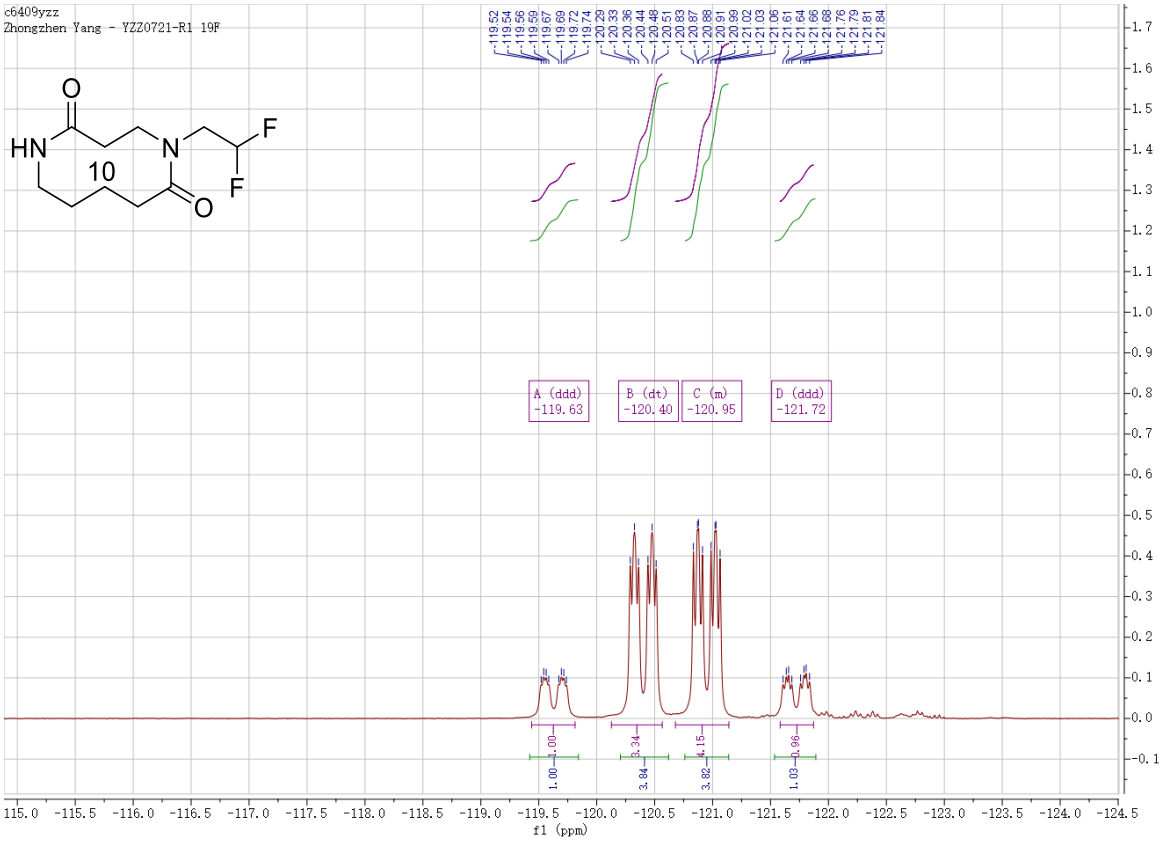


5-(2,2-Difluoroethyl)-1,5-diazecane-2,6-dione (20r)

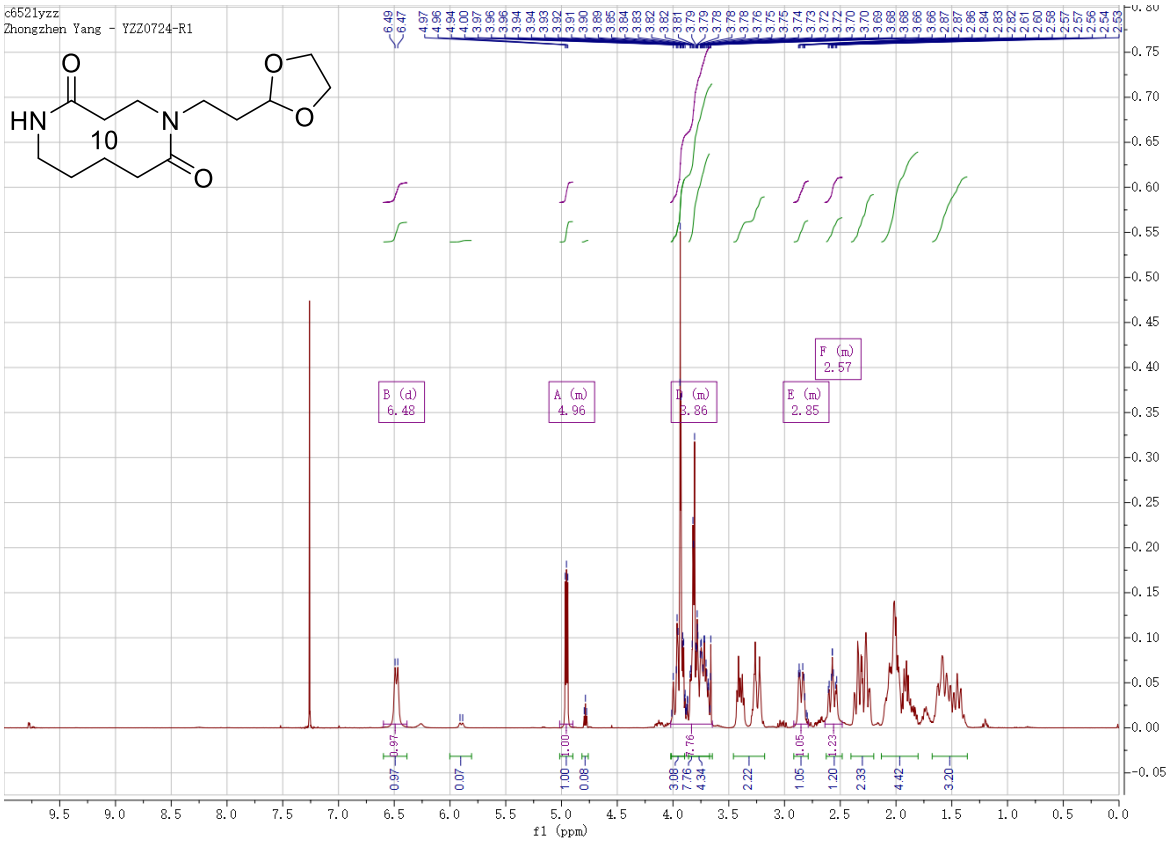


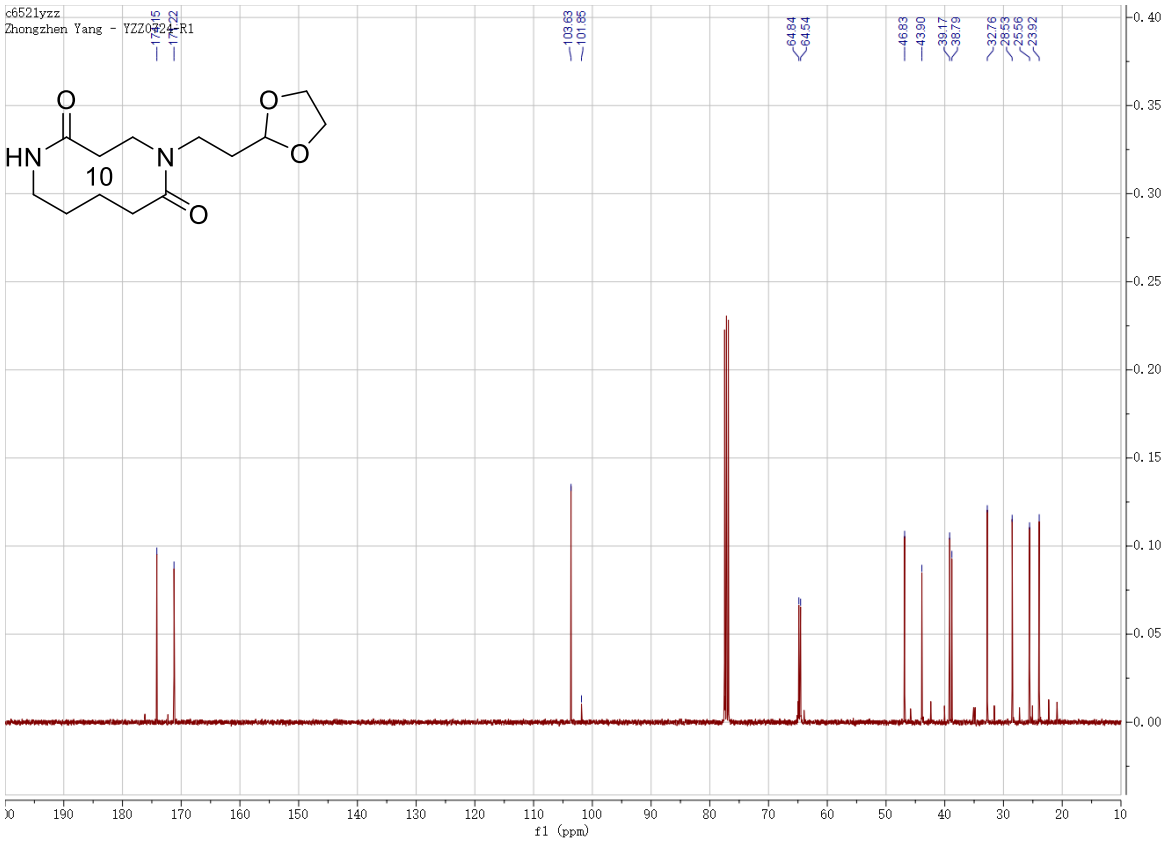



c6409yzz
Zhongzhen Yang - YZZ0721-R1 19F
D (ddd)
-121.72
B (dt)
-120.40
A (ddd)
-119.63
C (m)
-120.95
f1 (ppm)

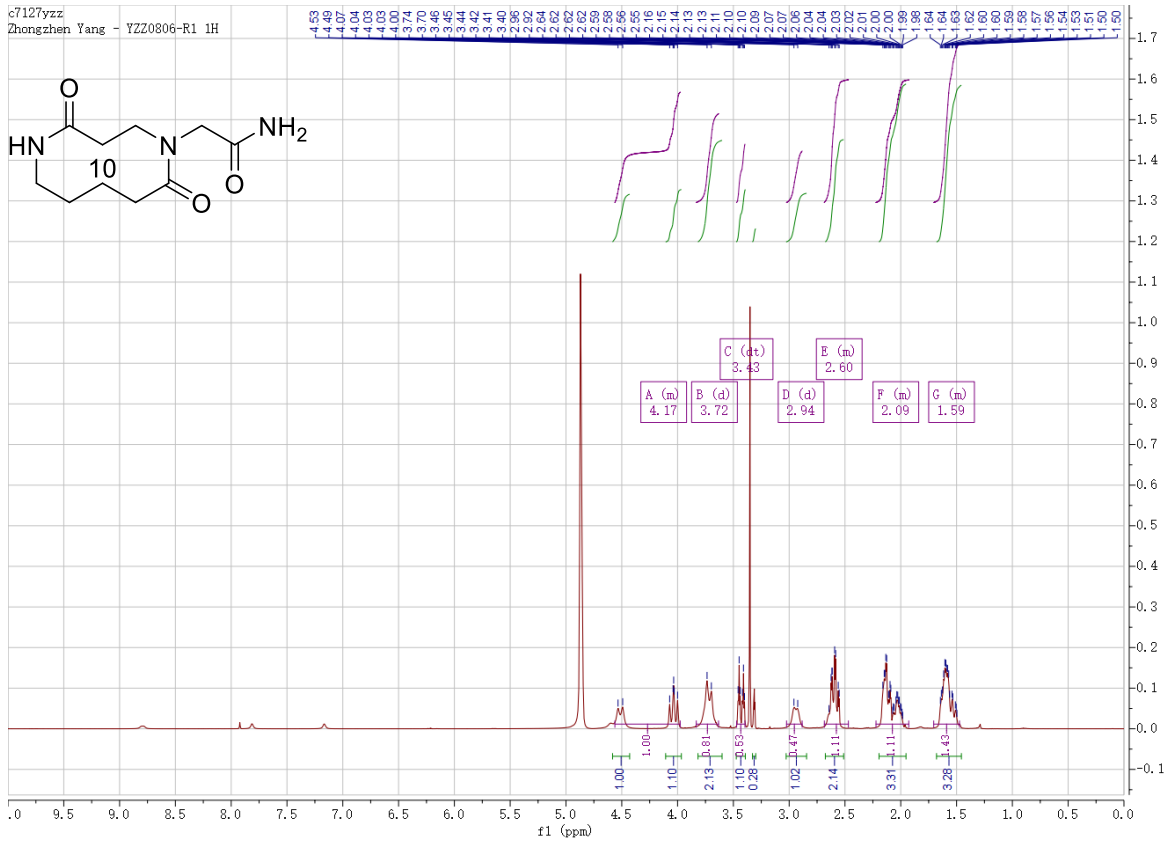

c6409yzz
Zhongzhen Yang - YZZ0721-R1 19F
A (ddd)
-119.63
B (dt)
-120.40
C (m)
-120.95
D (ddd)
-121.72
f1 (ppm)

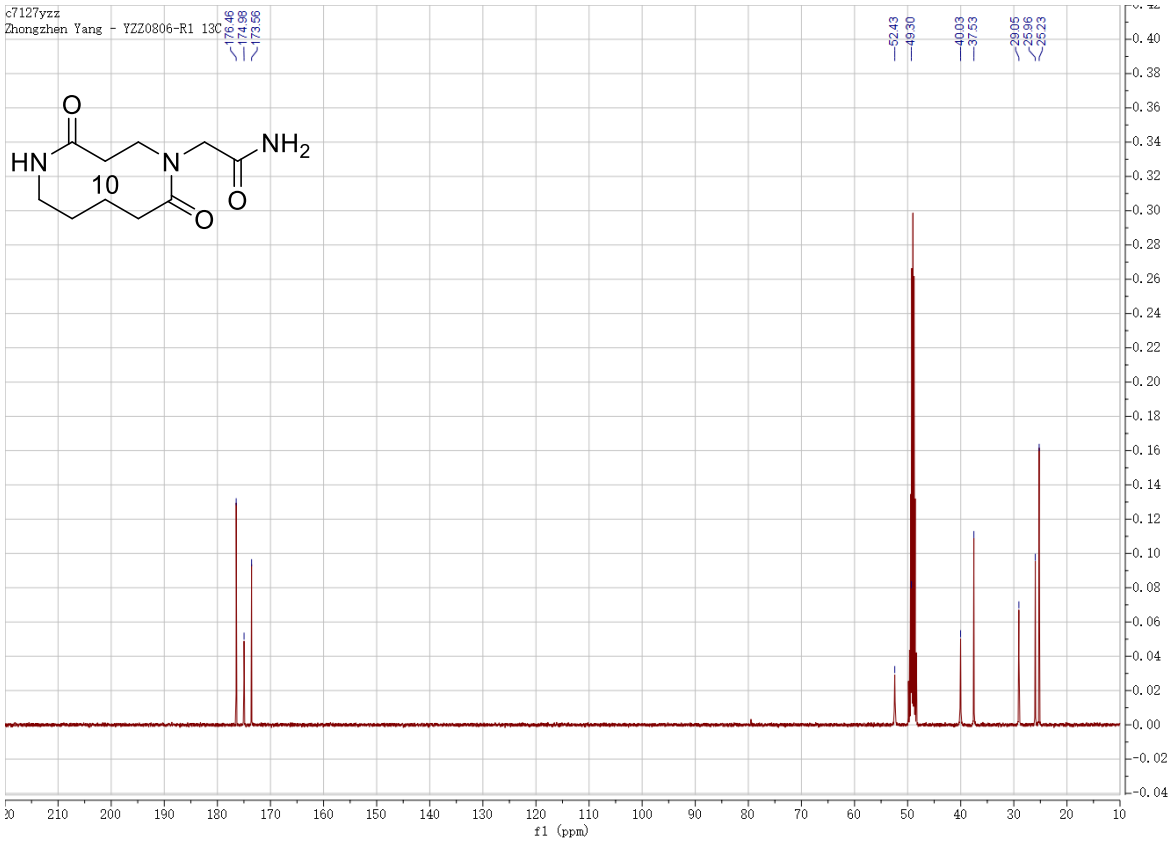
5-(2-(1,3-Dioxolan-2-yl)ethyl)-1,5-diazecane-2,6-dione (20s) 10:1 mixture of rotamers.



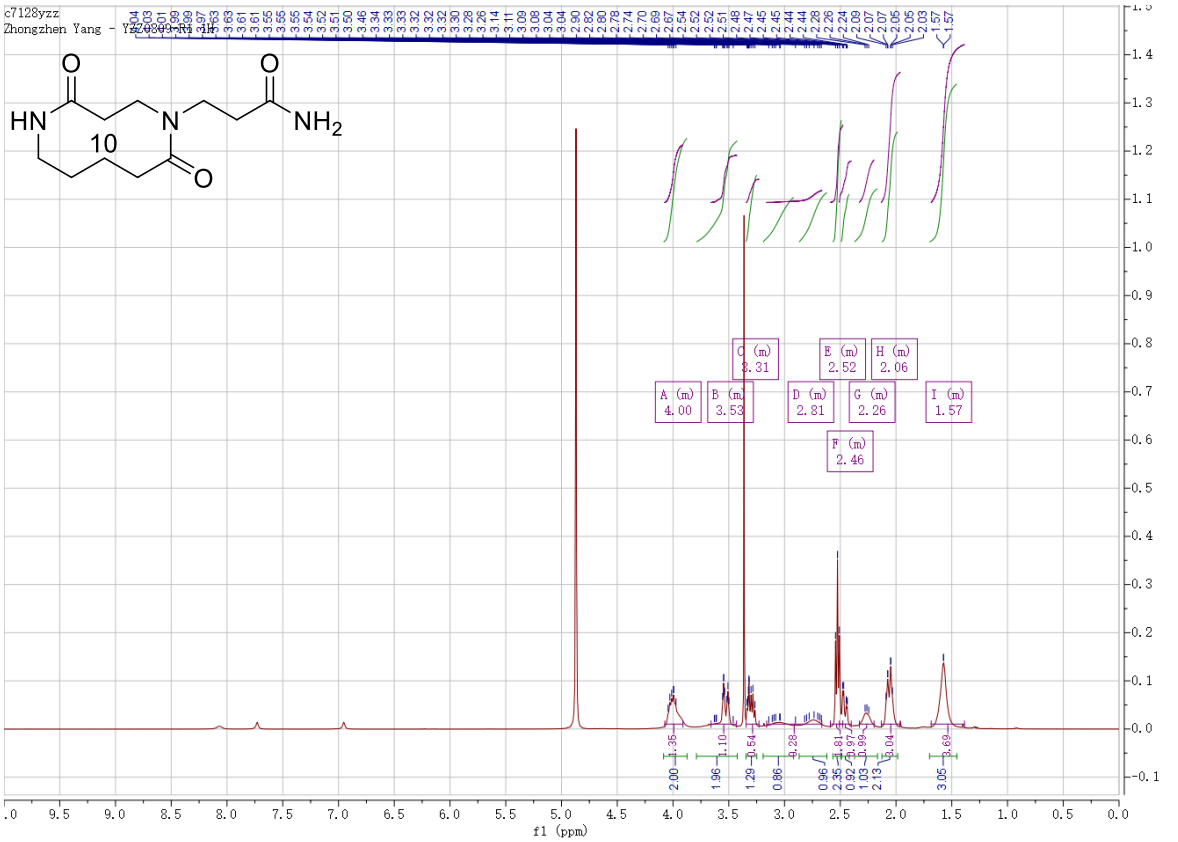


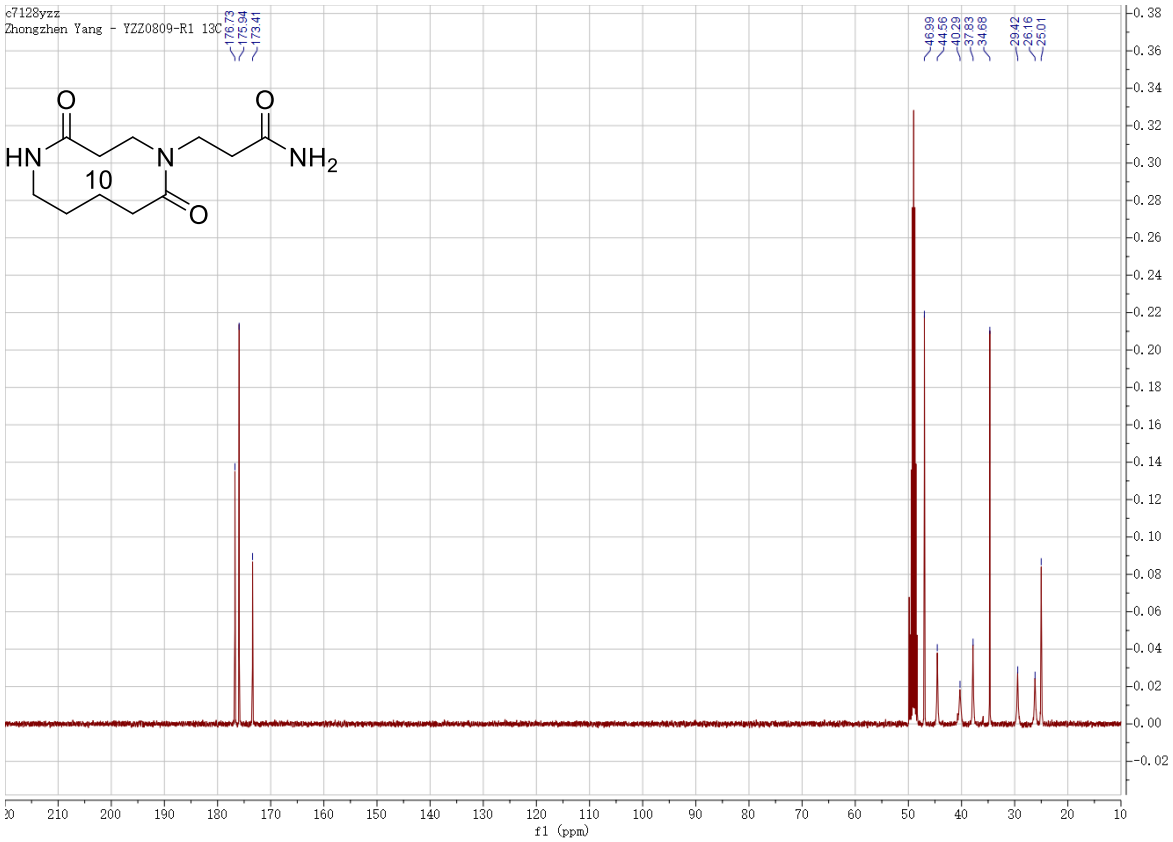
2-(4,10-Dioxo-1,5-diazecan-1-yl)acetamide (20t)



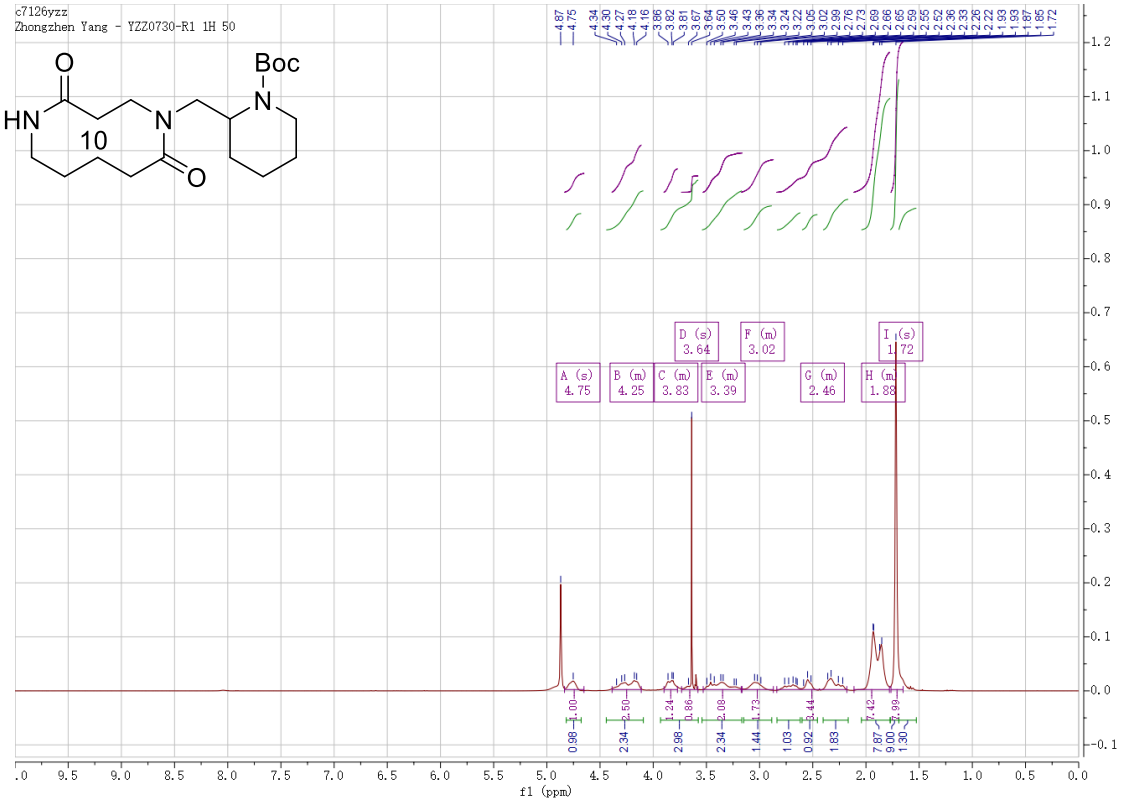


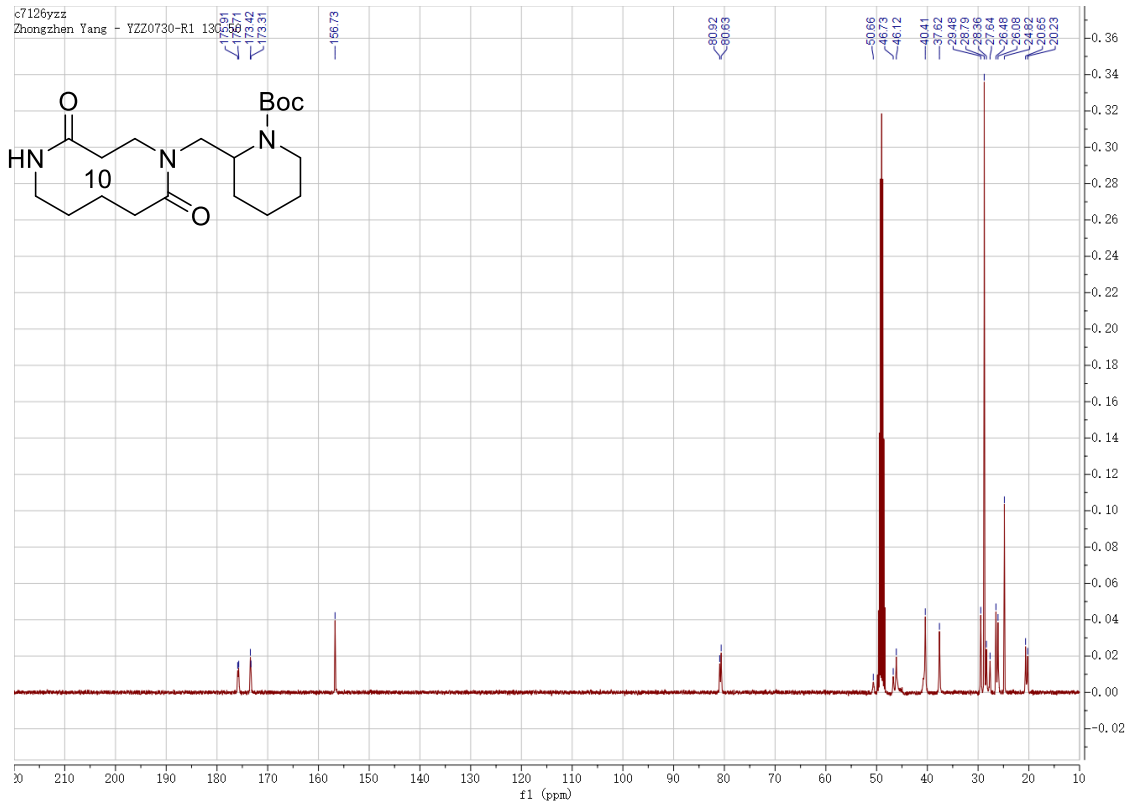
3-(4,10-Dioxo-1,5-diazecan-1-yl)propanamide (20u)



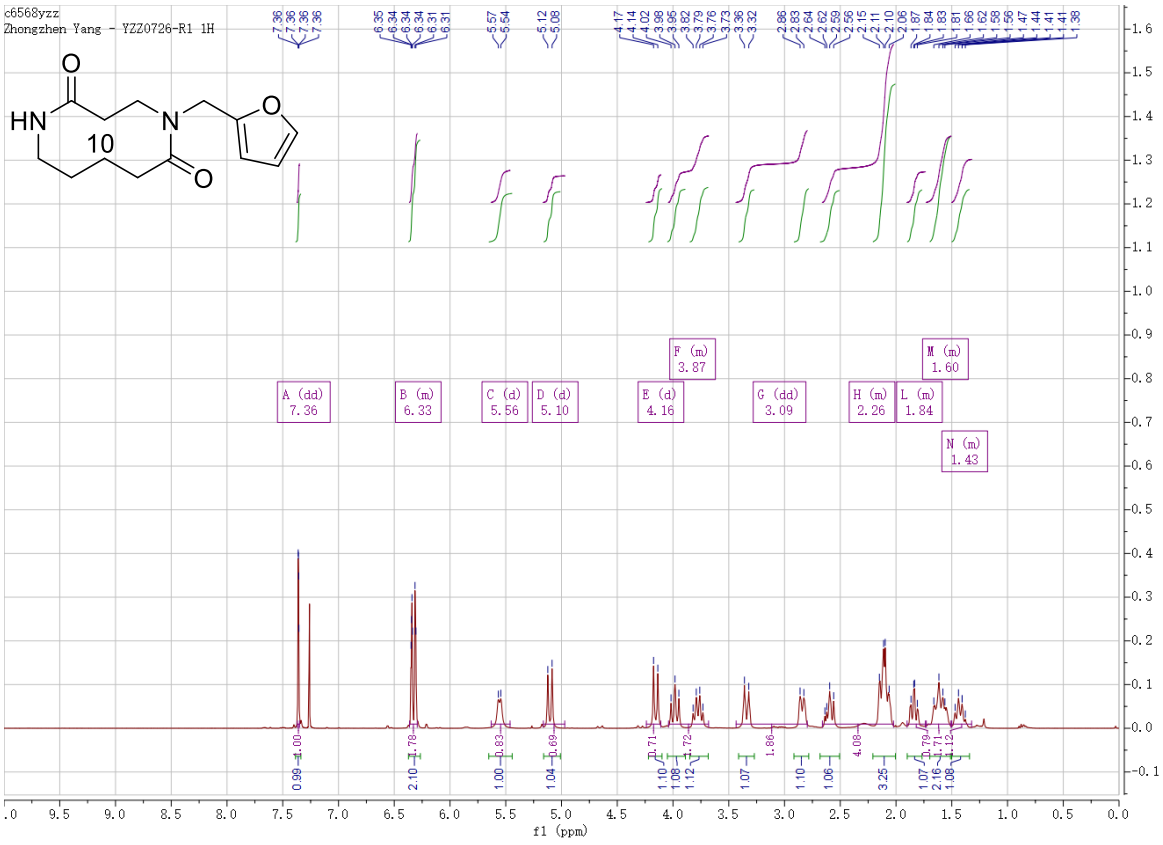


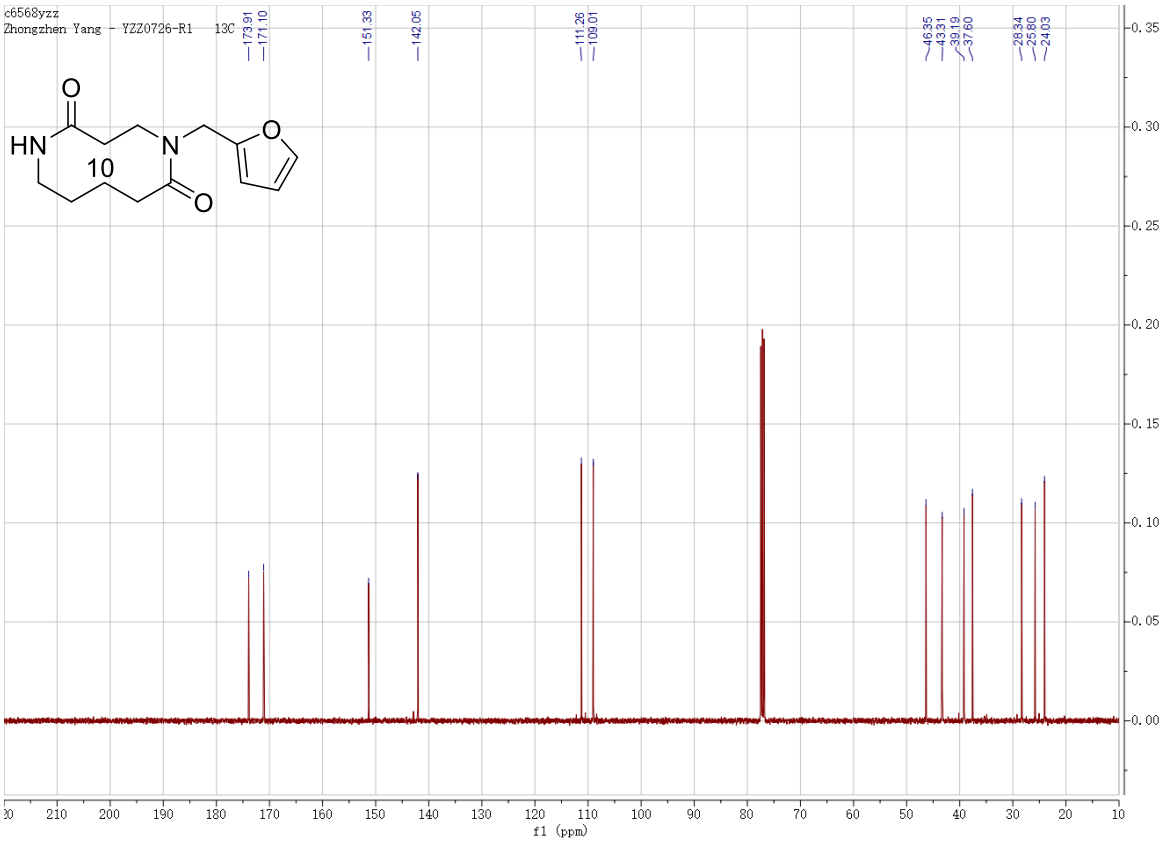
***tert*-Butyl 2-((4,10-dioxo-1,5-diazecan-1-yl)methyl)piperidine-1-carboxylate (20v)** In methanol-d_4 at 50 °C the 1H NMR spectra is severely broadened due to rotamer interconversion, while the ^{13}C NMR spectrum shows it exists as a roughly 1:1 mixture of rotamers under the same conditions.



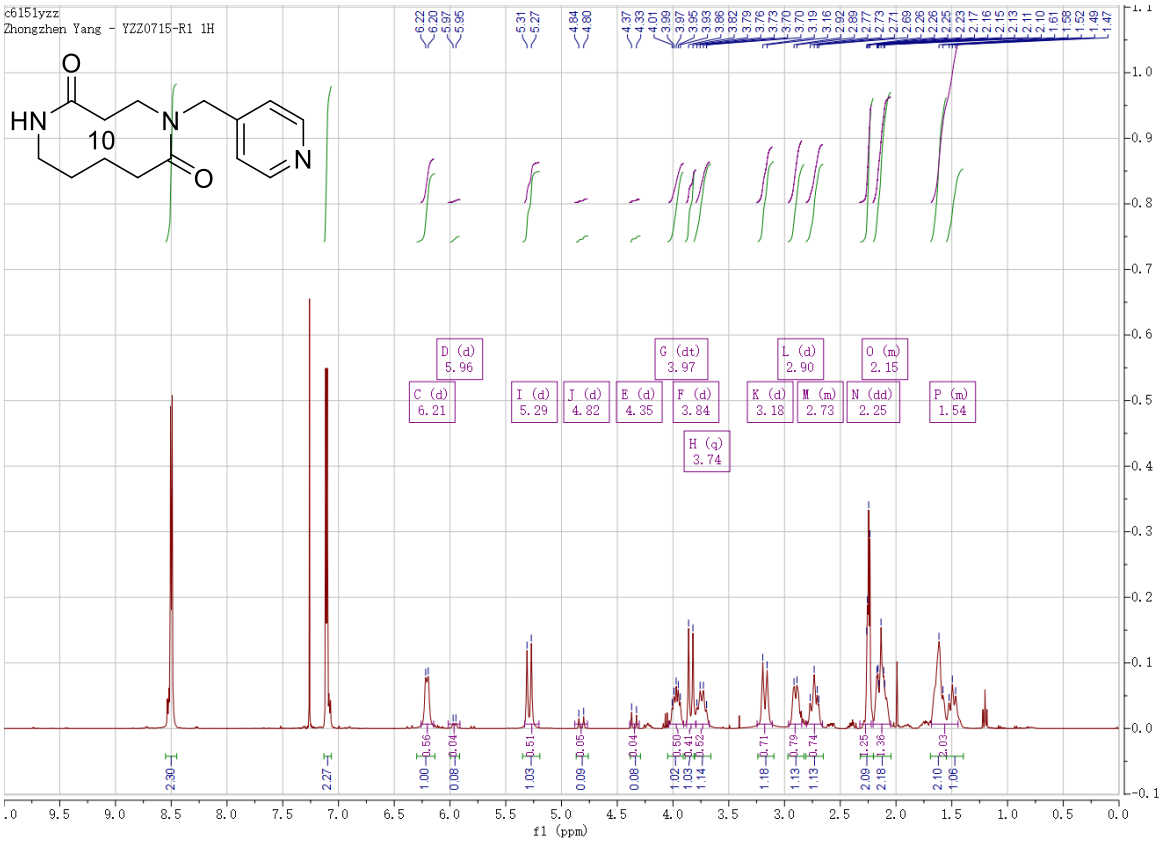


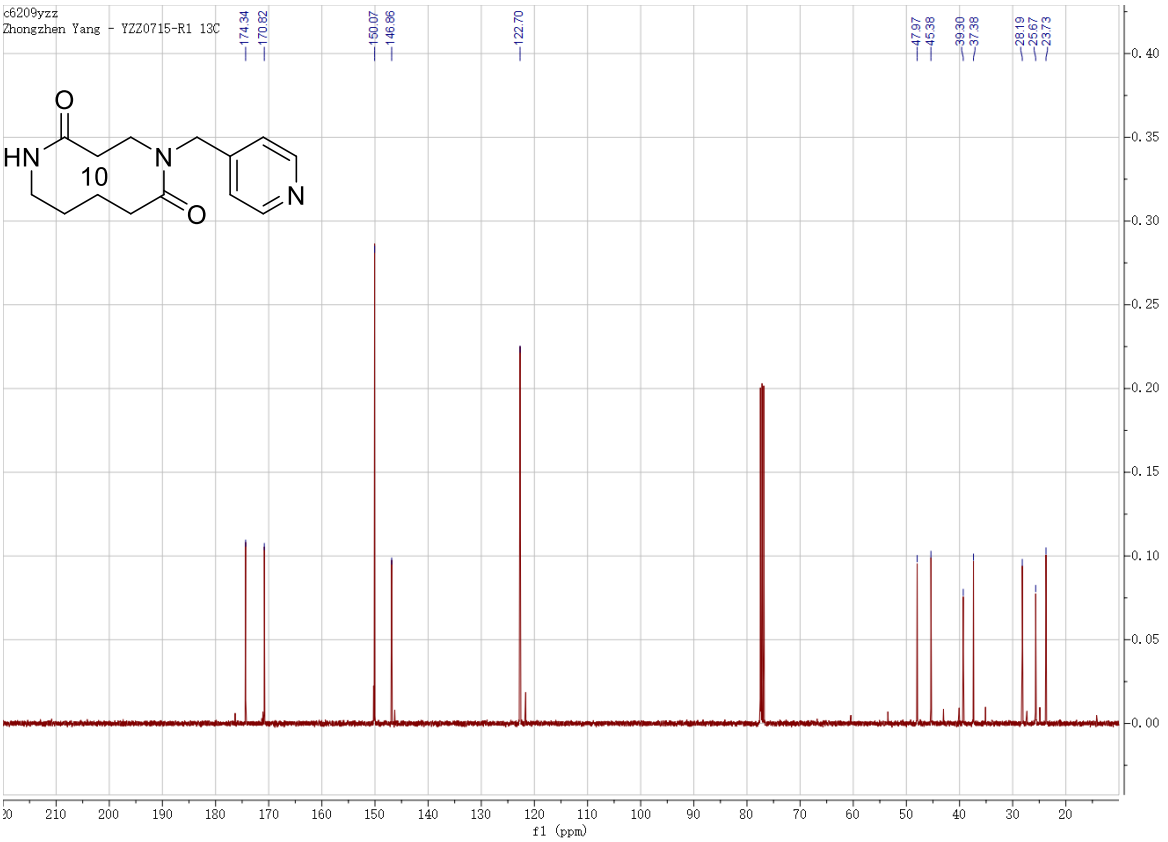
5-(Furan-2-ylmethyl)-1,5-diazecane-2,6-dione (20w)



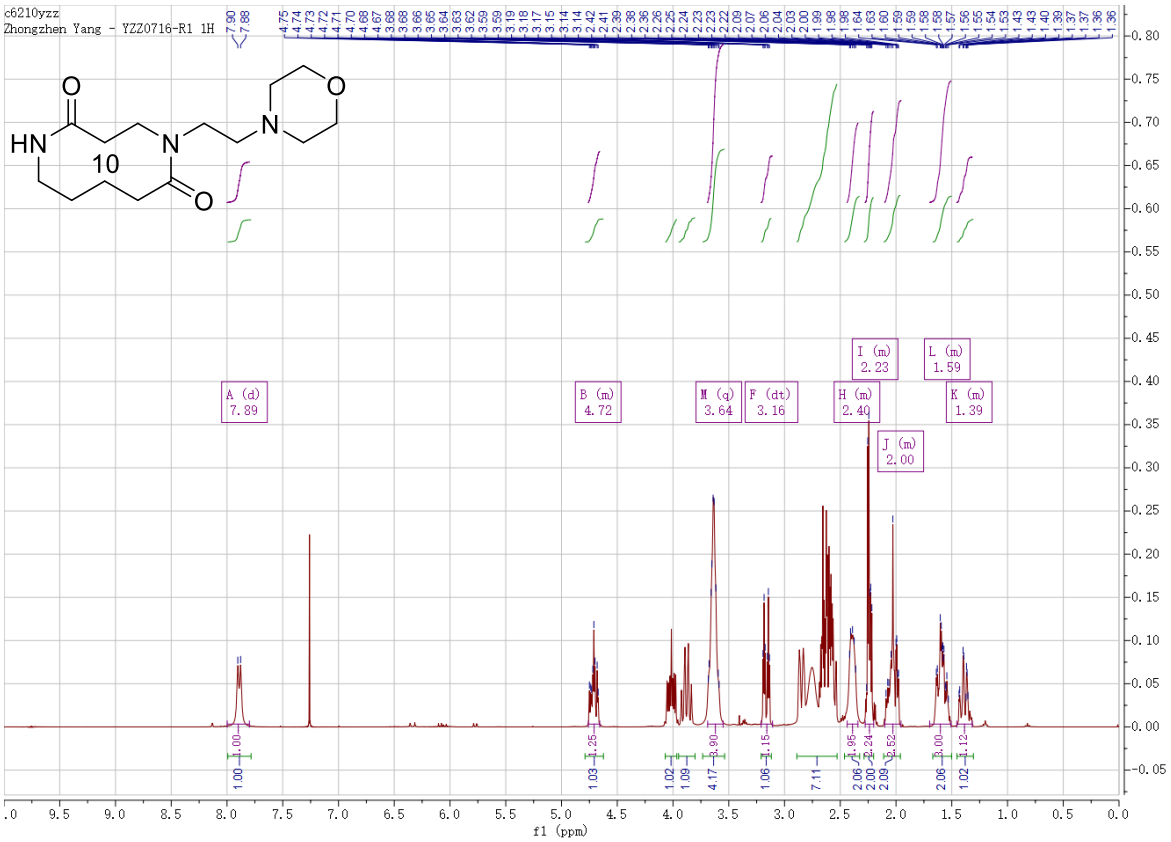


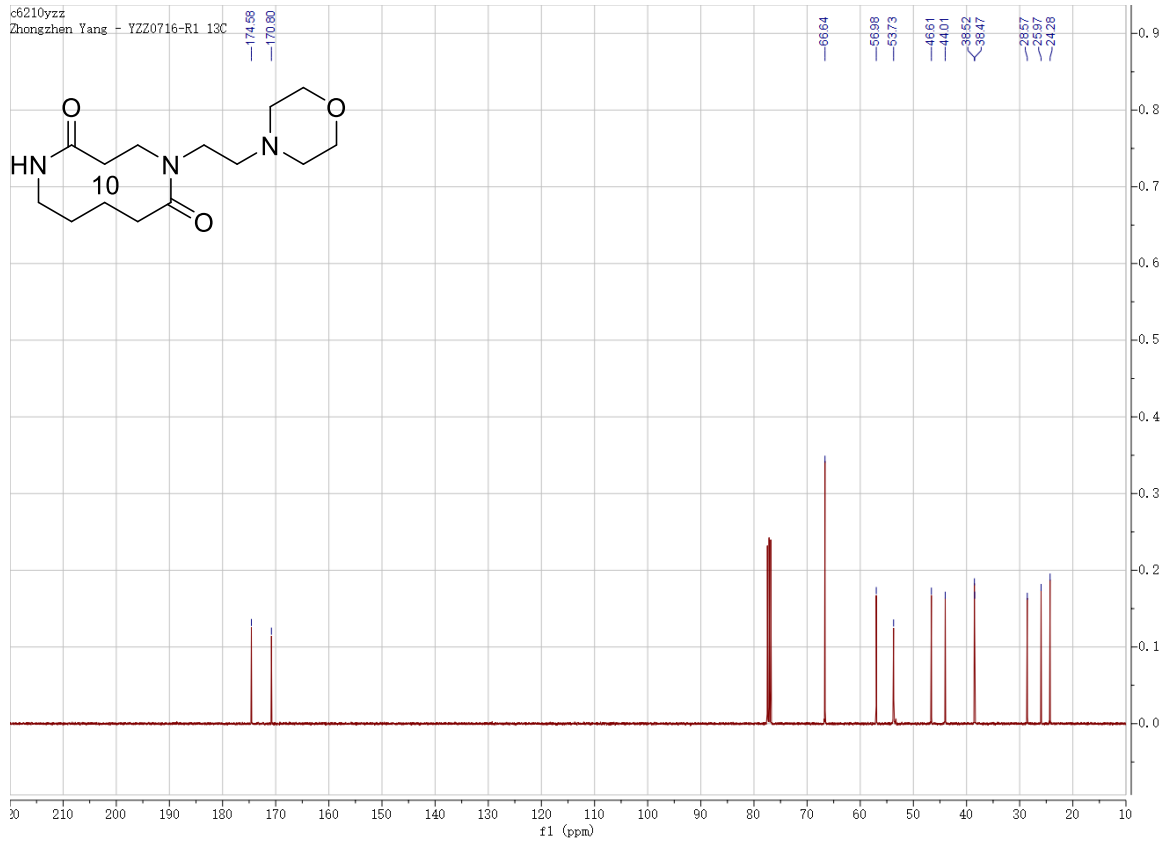
5-(Pyridin-4-ylmethyl)-1,5-diazecane-2,6-dione (20x) 10:1 mixture of rotamers.



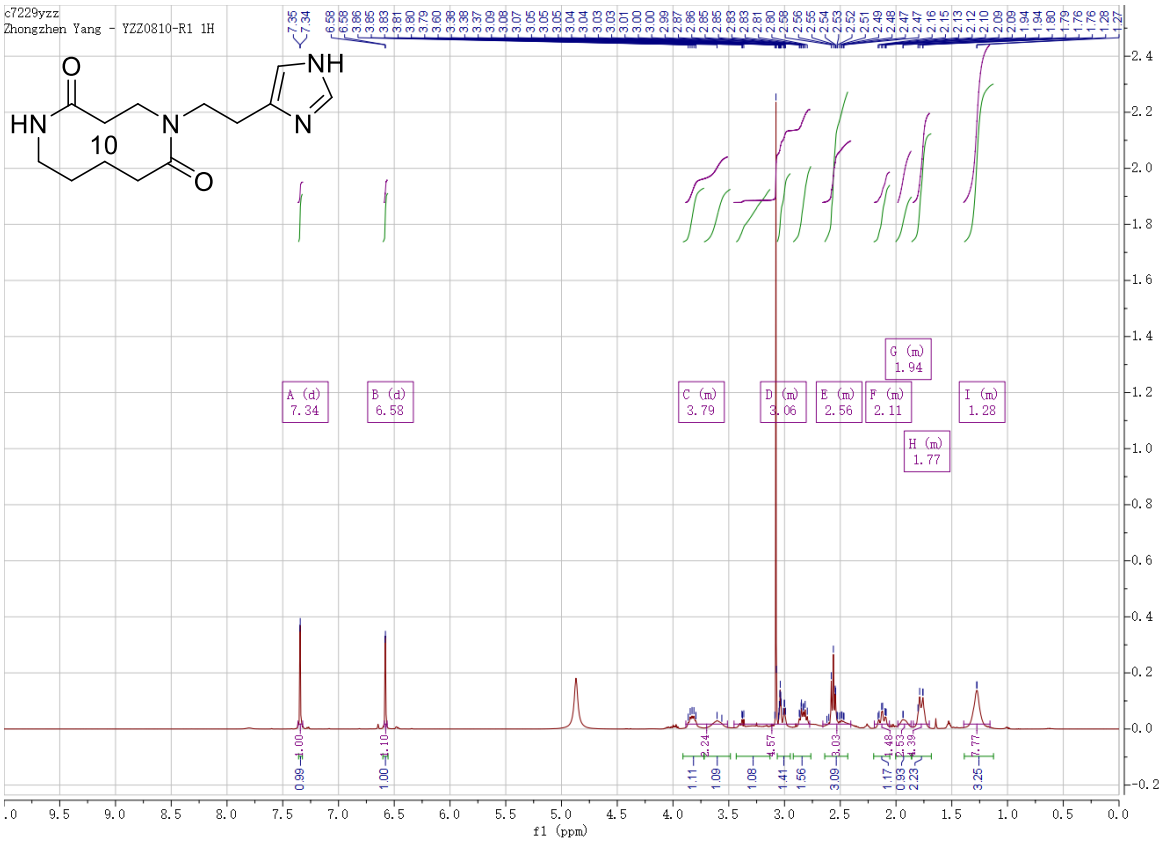


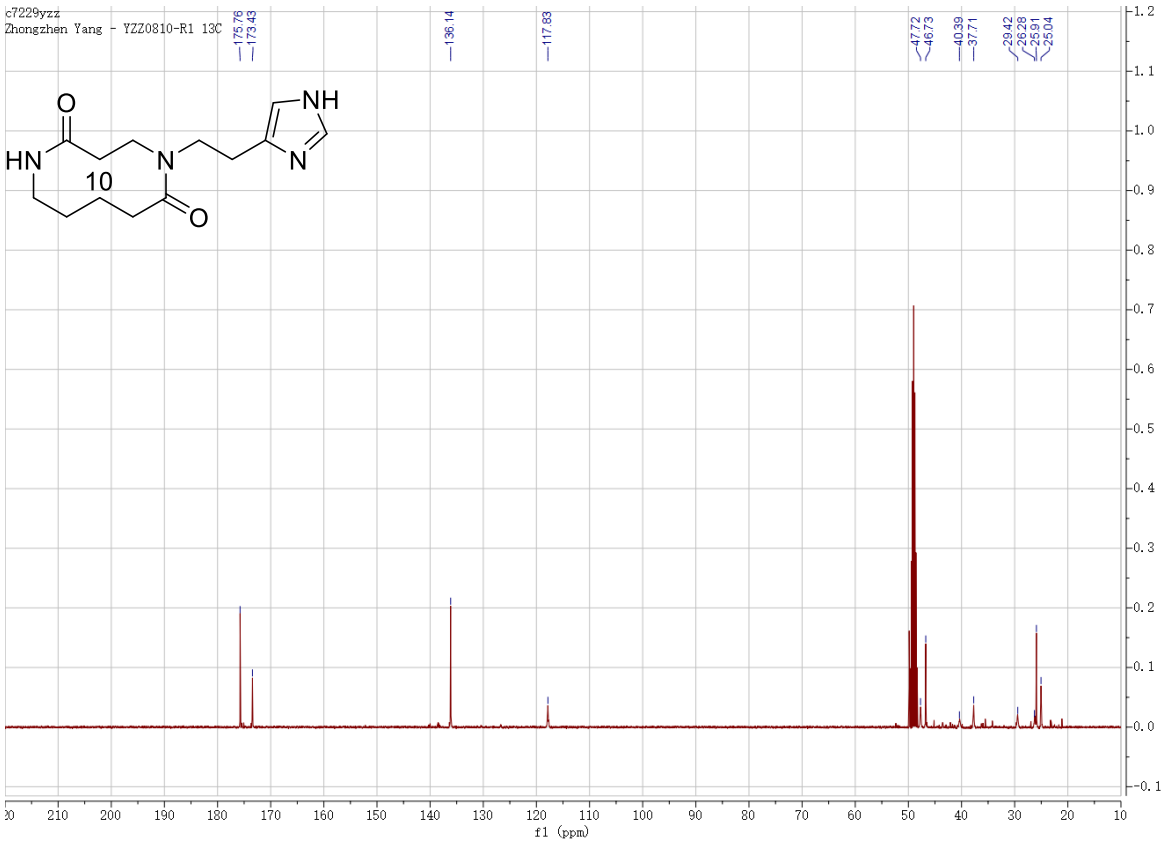
5-(2-Morpholinoethyl)-1,5-diazecane-2,6-dione (20y)



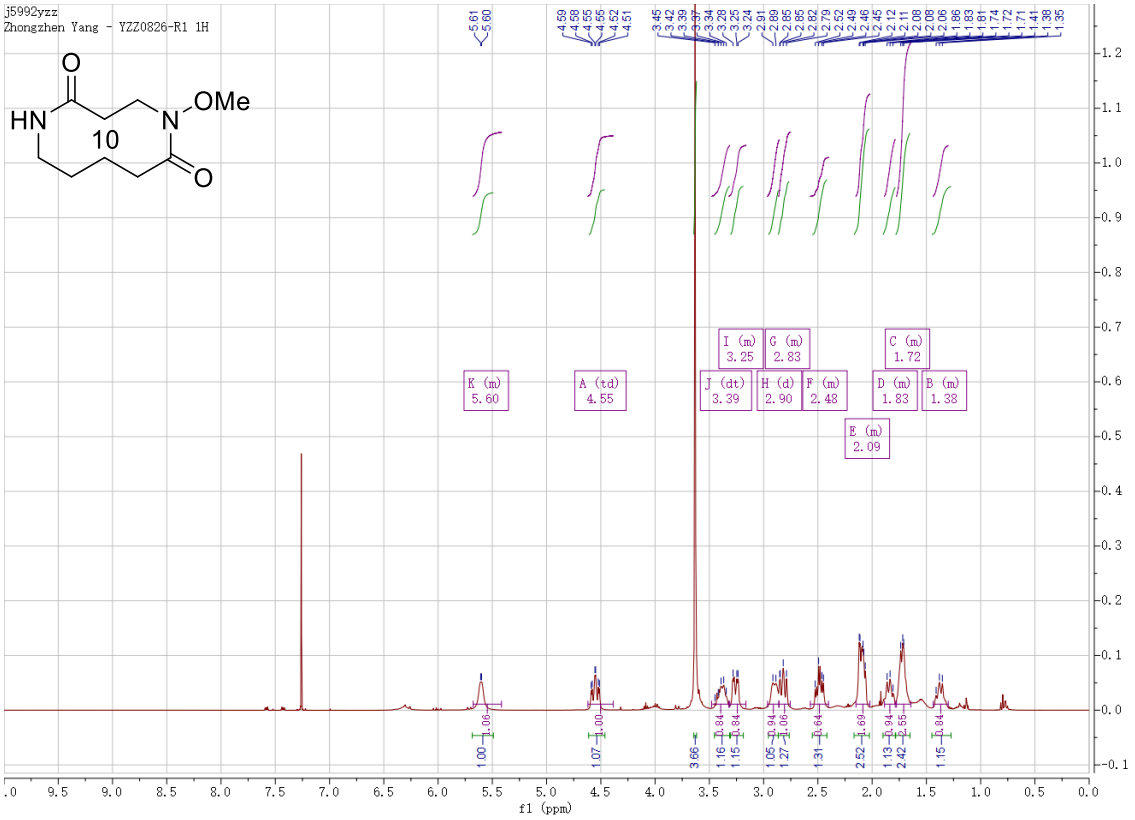


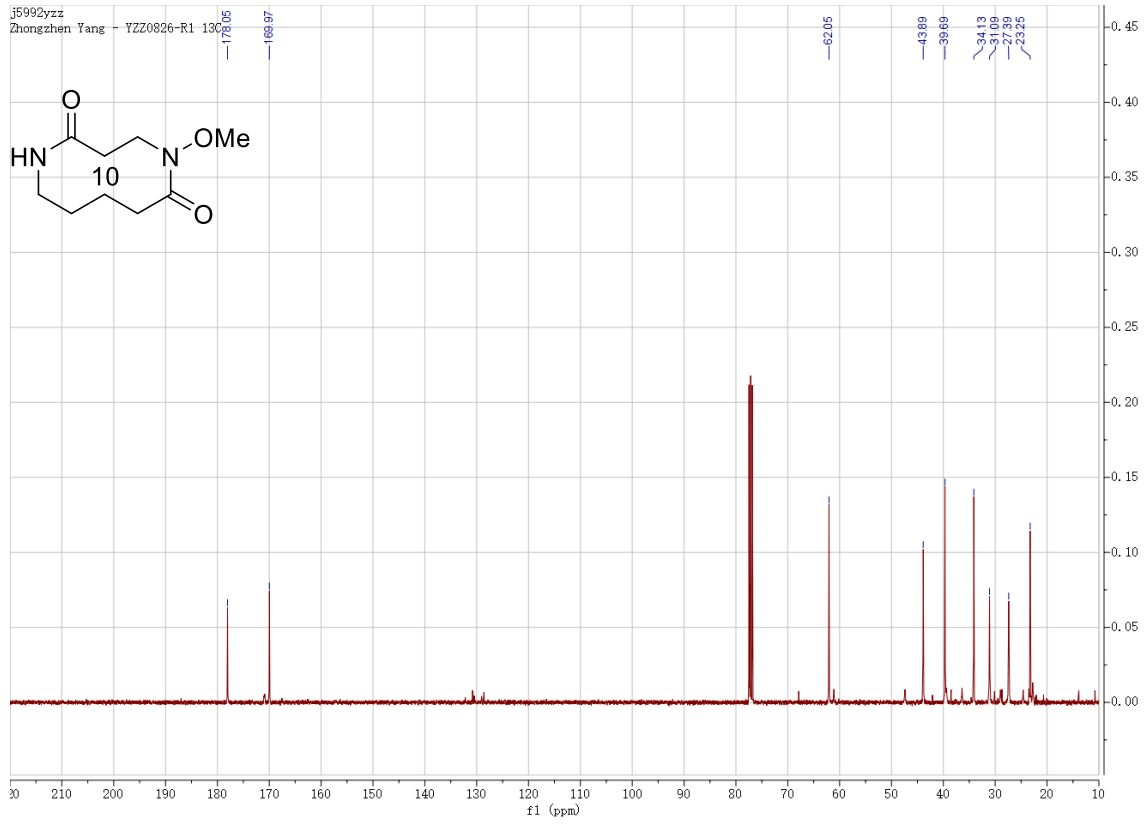
5-(2-(1H-imidazol-4-yl)ethyl)-1,5-diazecane-2,6-dione (20z) In solution in methanol-d4, this compound experiences rotameric broadening.



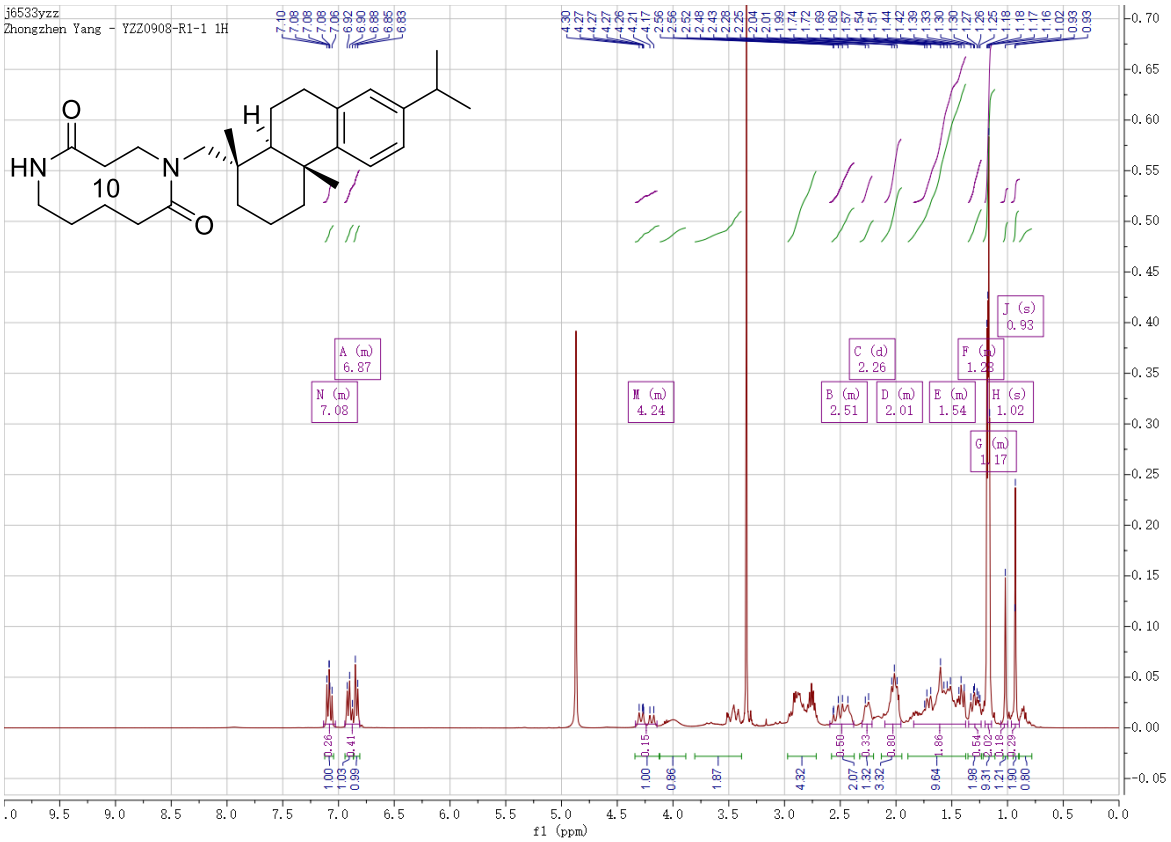


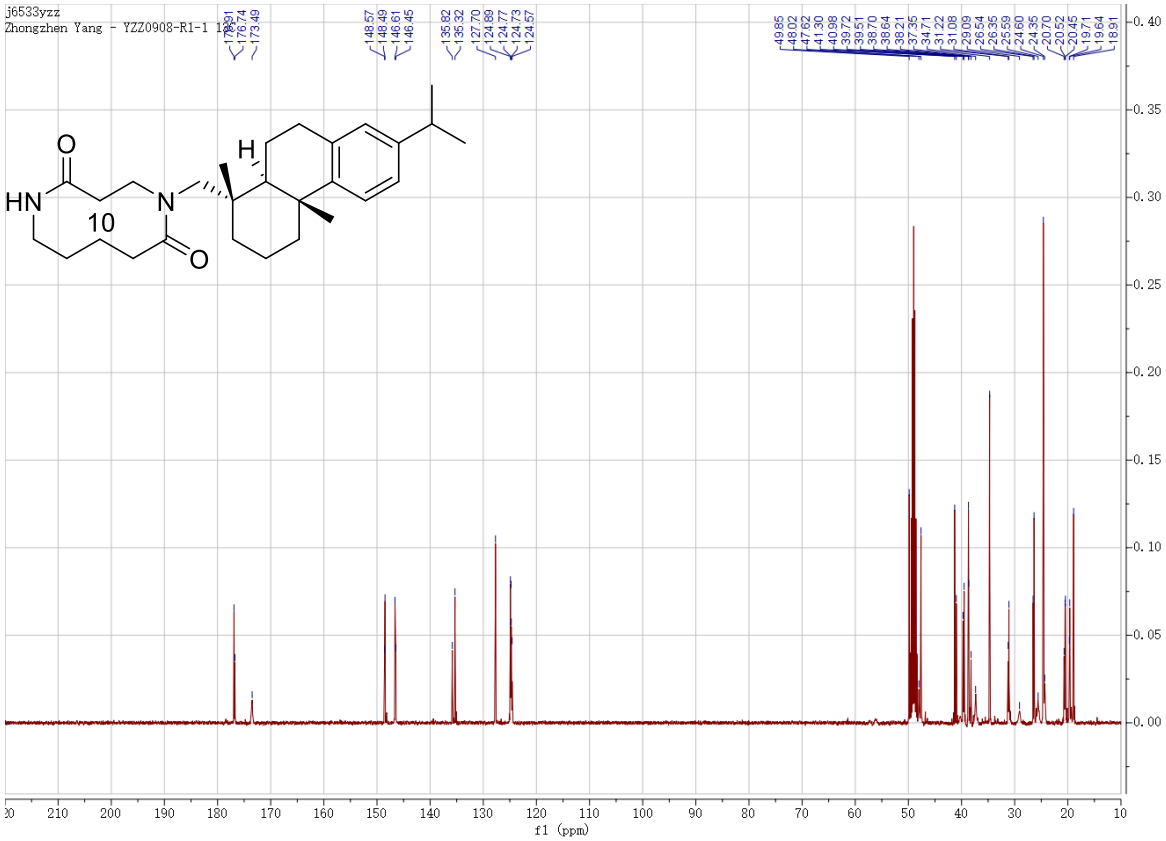
5-Methoxy-1,5-diazecane-2,6-dione (20za) In solution in $CDCl_3$, this compound exists predominantly as a single rotamer, but with rotameric broadening seen in the ^{1}H NMR spectrum and traces of a minor rotamer evident in the ^{13}C NMR spectrum.



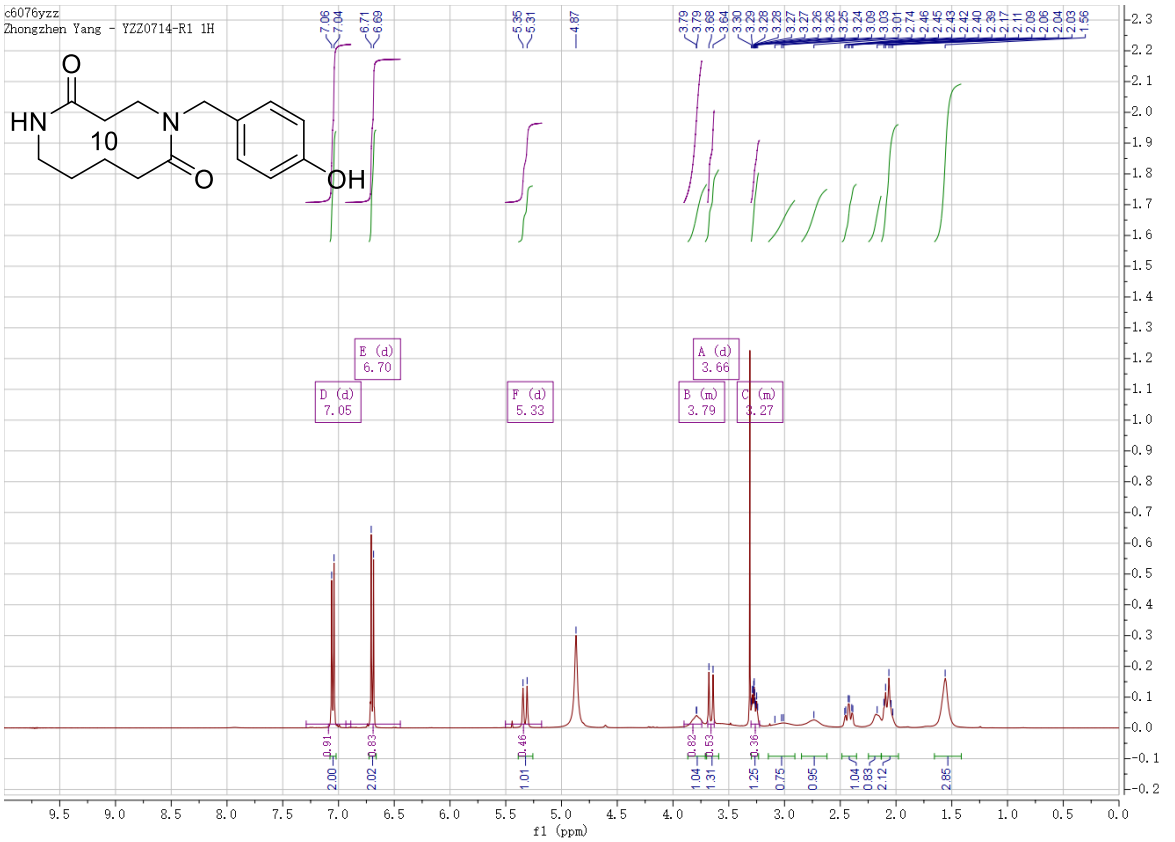


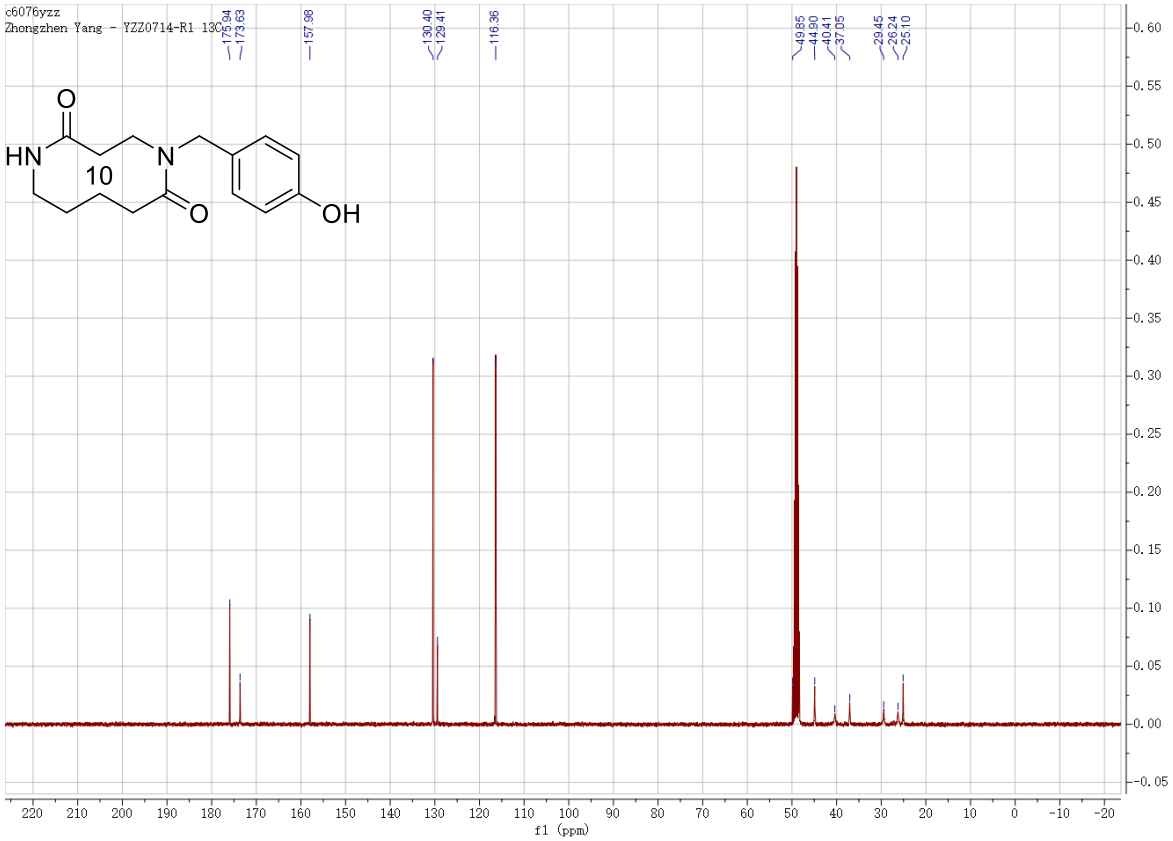
5-(((1S,4aR,10aS)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10aoctahydrophenanthren-1-yl)methyl)-1,5-diazecane-2,6-dione (20zb) 3:2 mixture of rotamers.



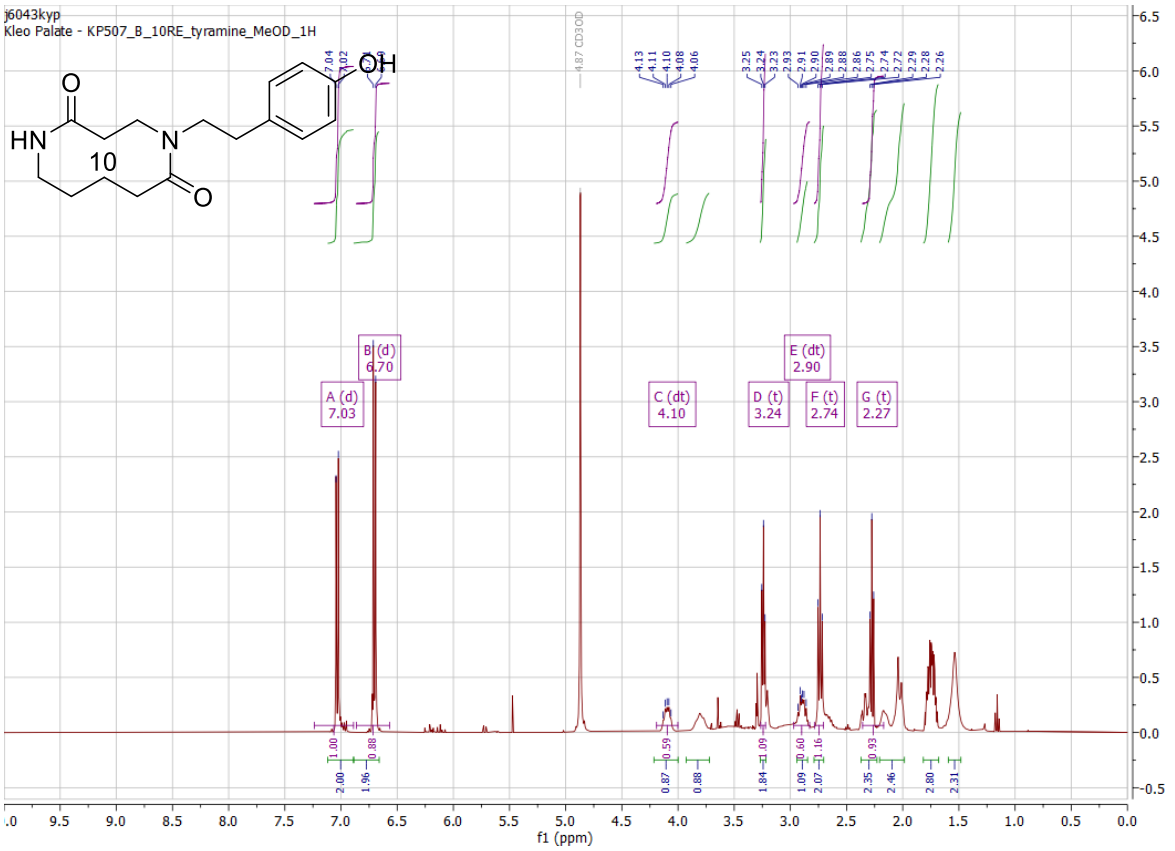


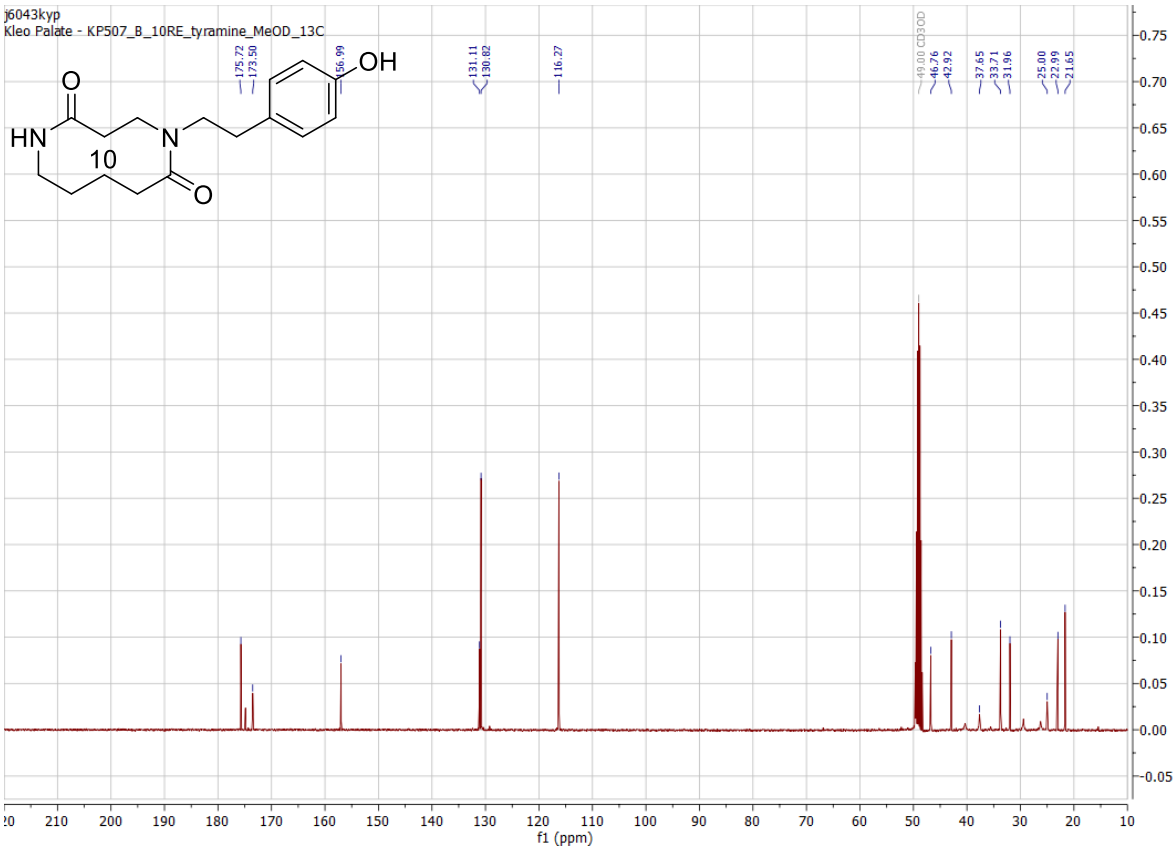
5-(4-Hydroxylbenzyl)-1,5-diazecane-2,6-dione (20zc) Rotameric broadening is evident in both the 1H and 13C NMR spectra.



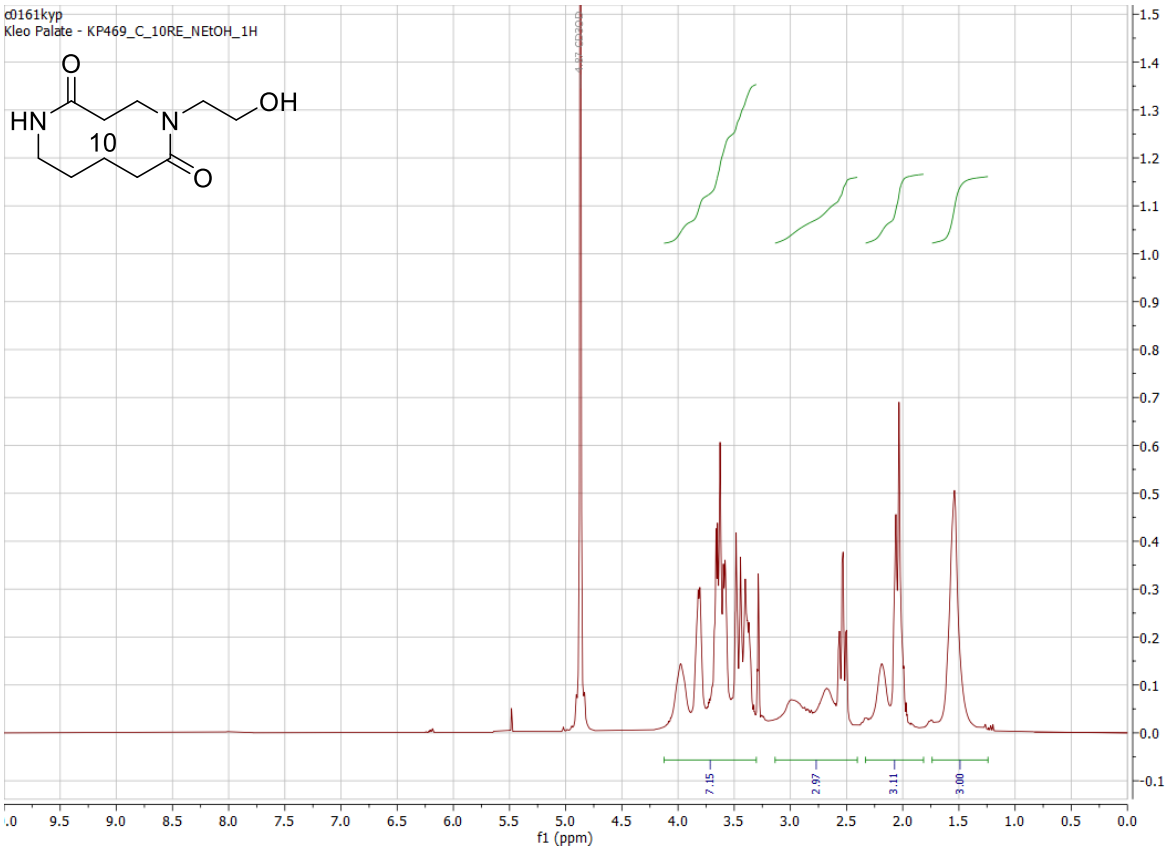


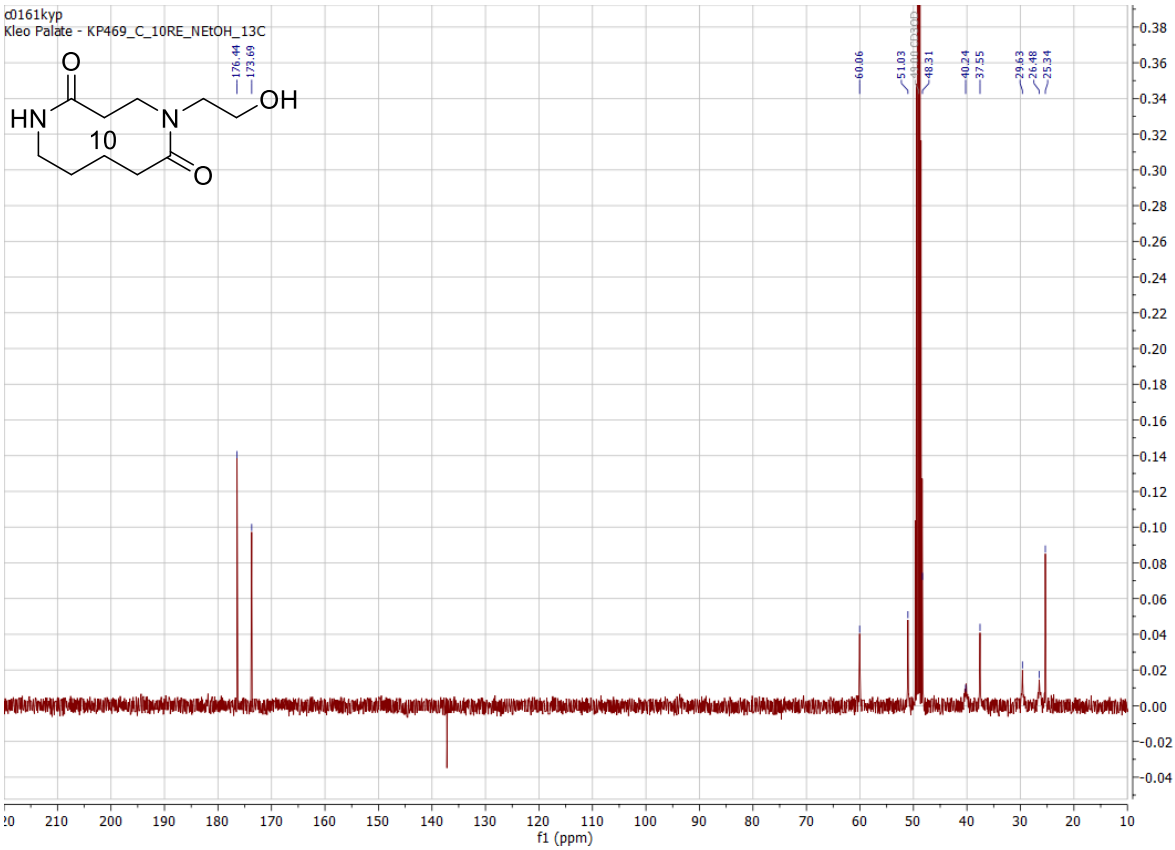
5-(4-Hydroxyphenethyl)-1,5-diazecane-2,6-dione (20zd) Rotameric broadening is evident in both the ^{1}H and ^{13}C NMR spectra.



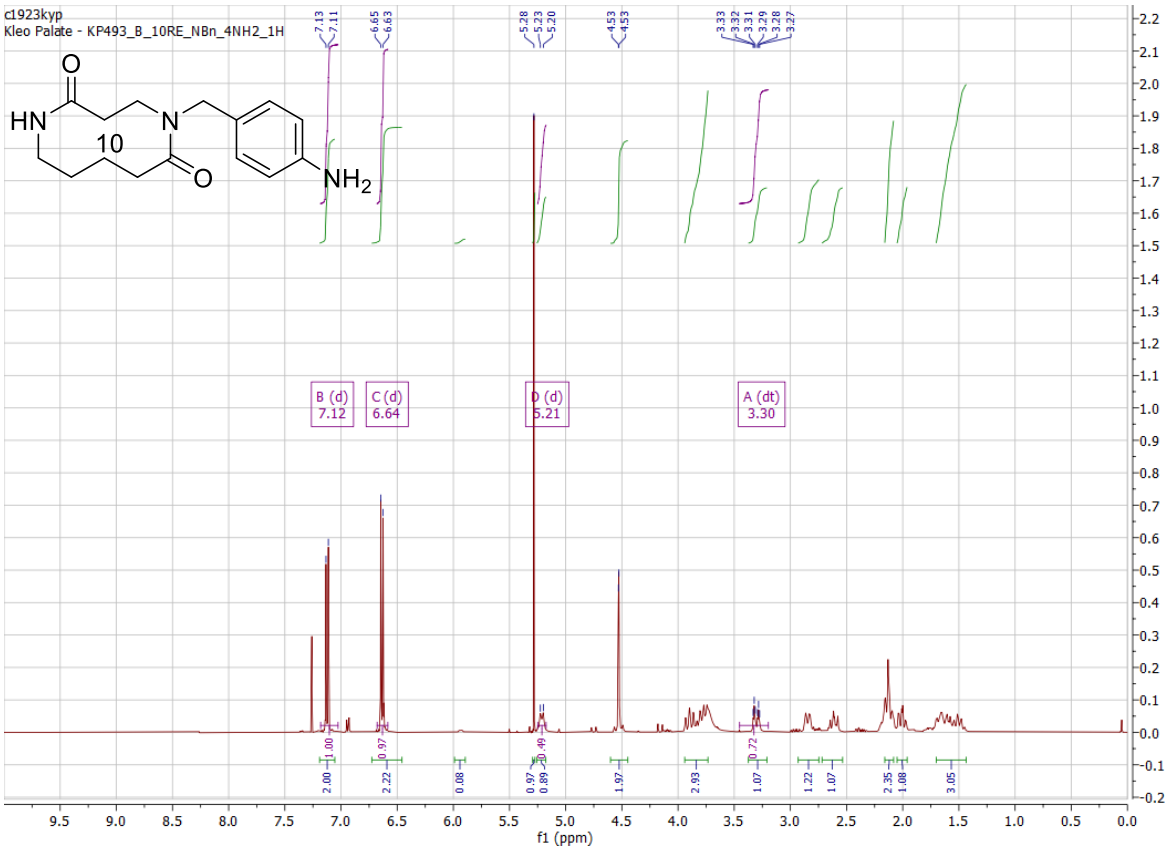


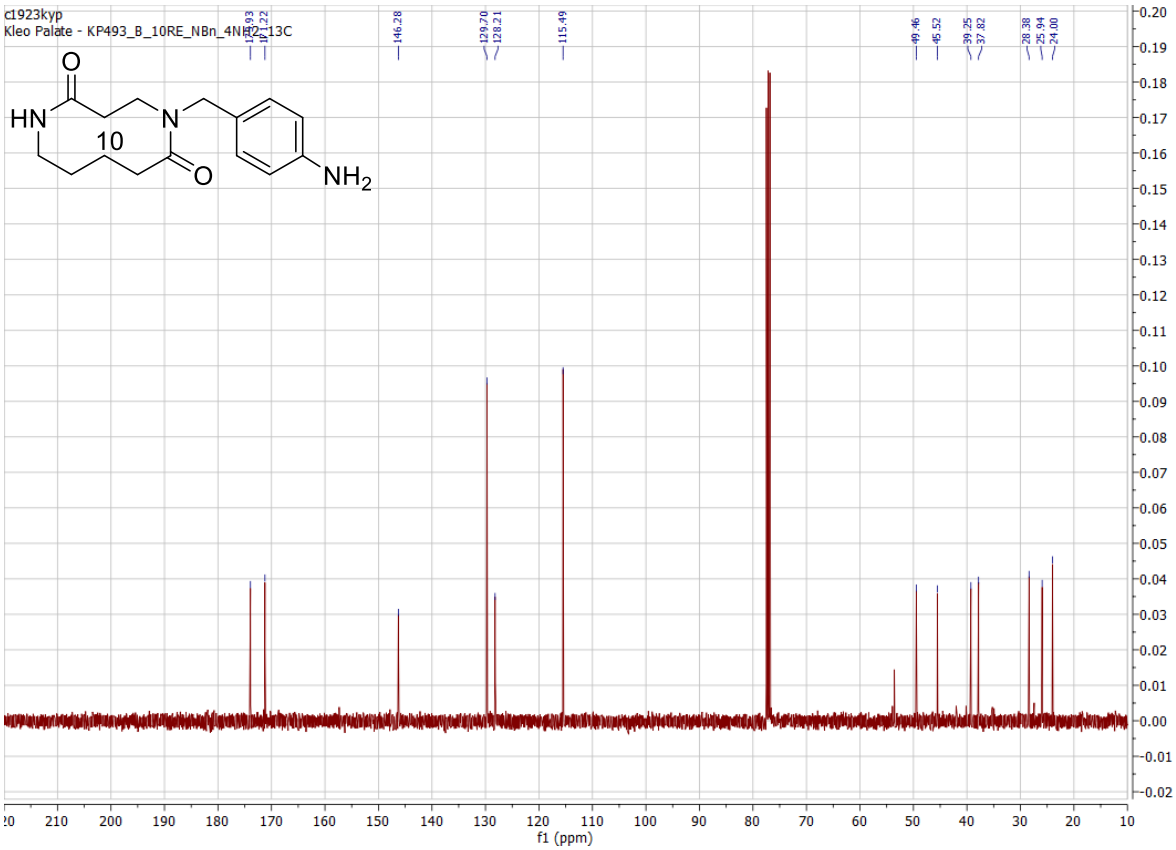
5-(2-Hydroxyethyl)-1,5-diazecane-2,6-dione (20ze) Rotameric broadening is evident in both the ^{1}H and ^{13}C NMR spectra.



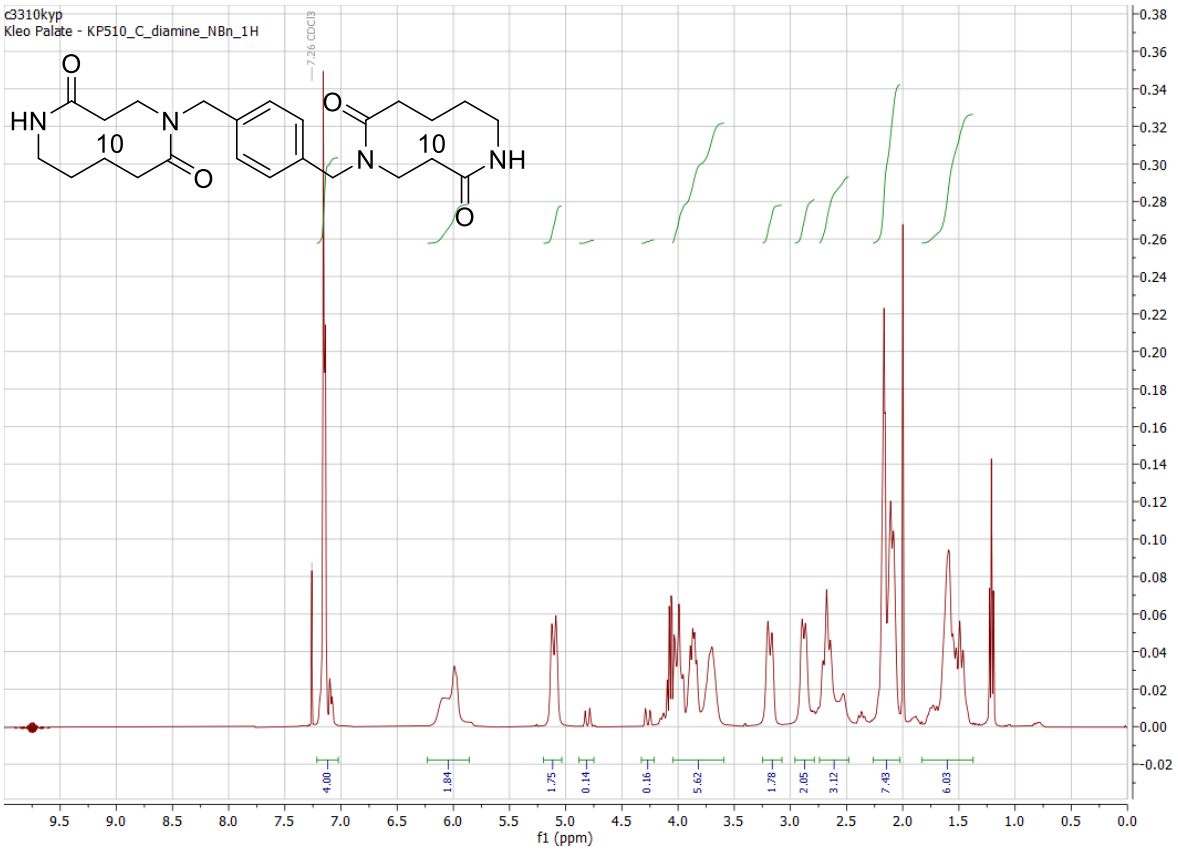


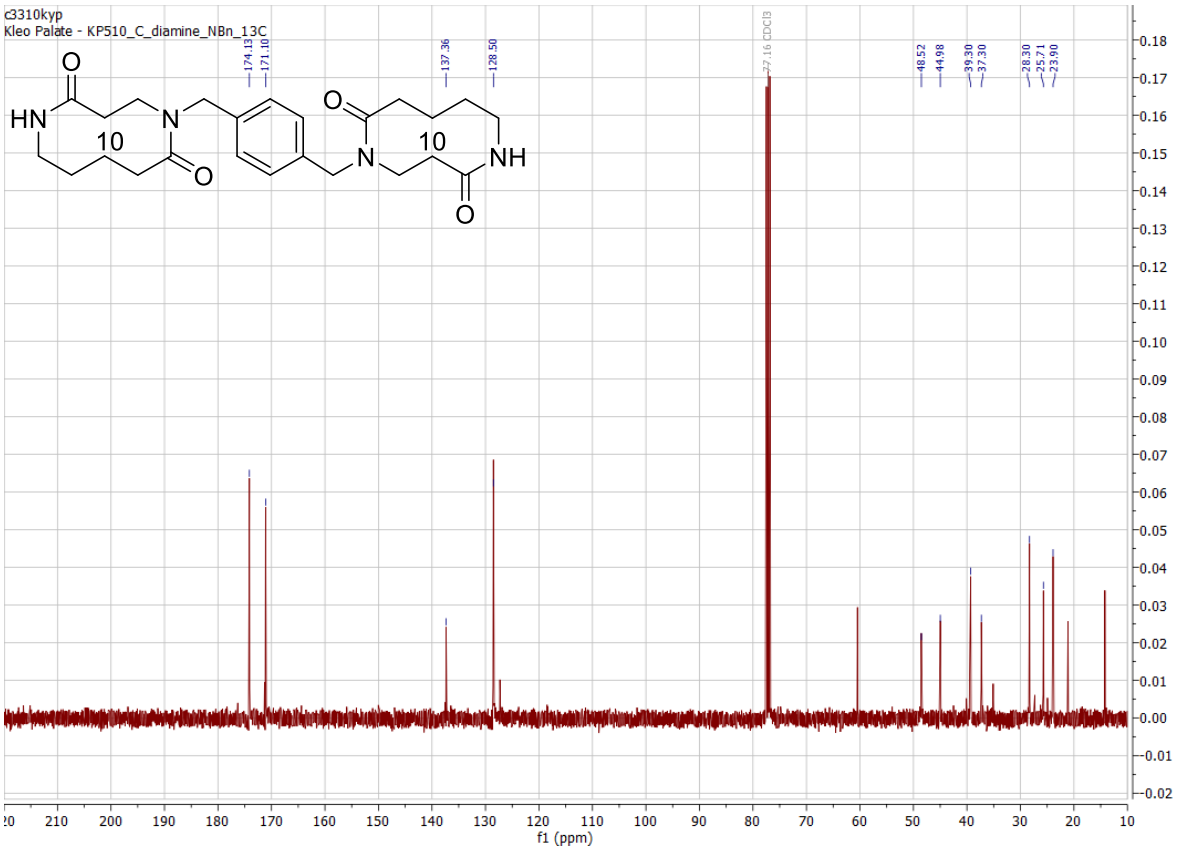
5-(4-Aminobenzyl)-1,5-diazecane-2,6-dione (20zf) Rotameric broadening is evident in the ^{1}H NMR spectrum. Product identity and purity is best seen in the ^{13}C NMR data.



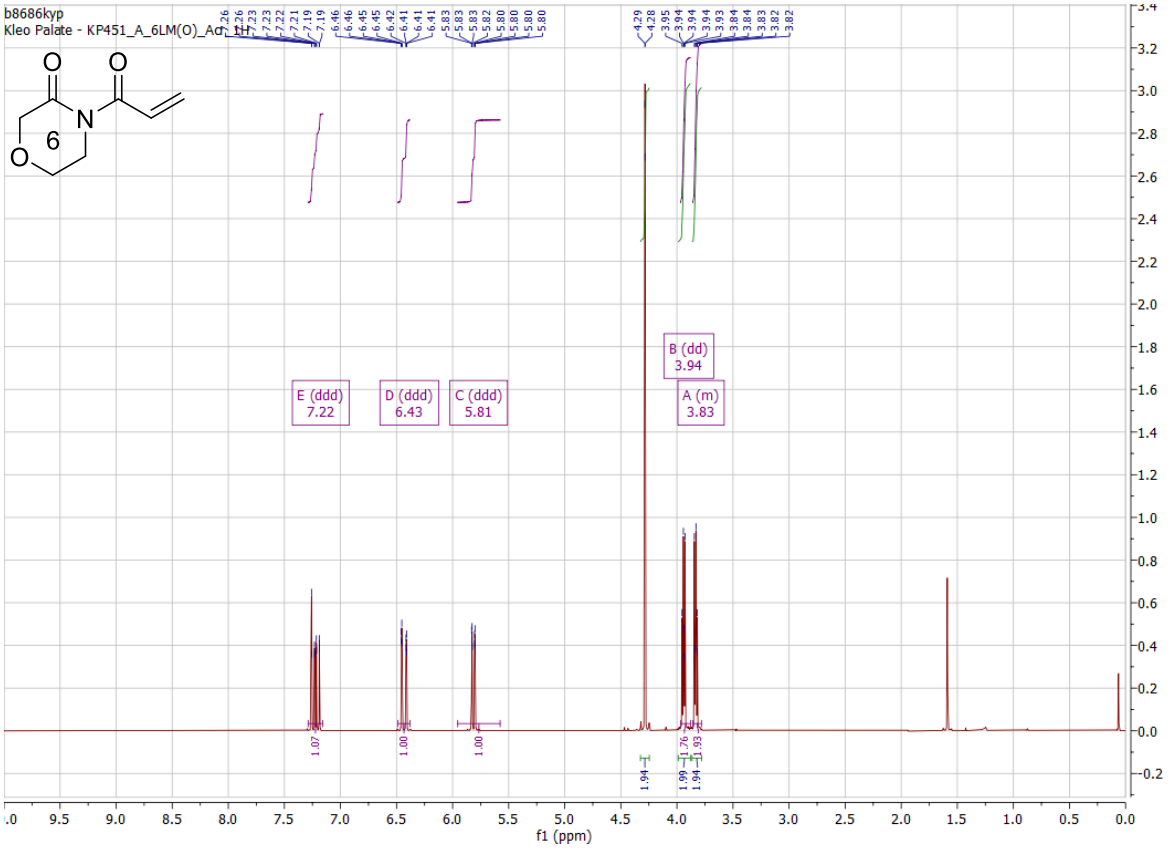


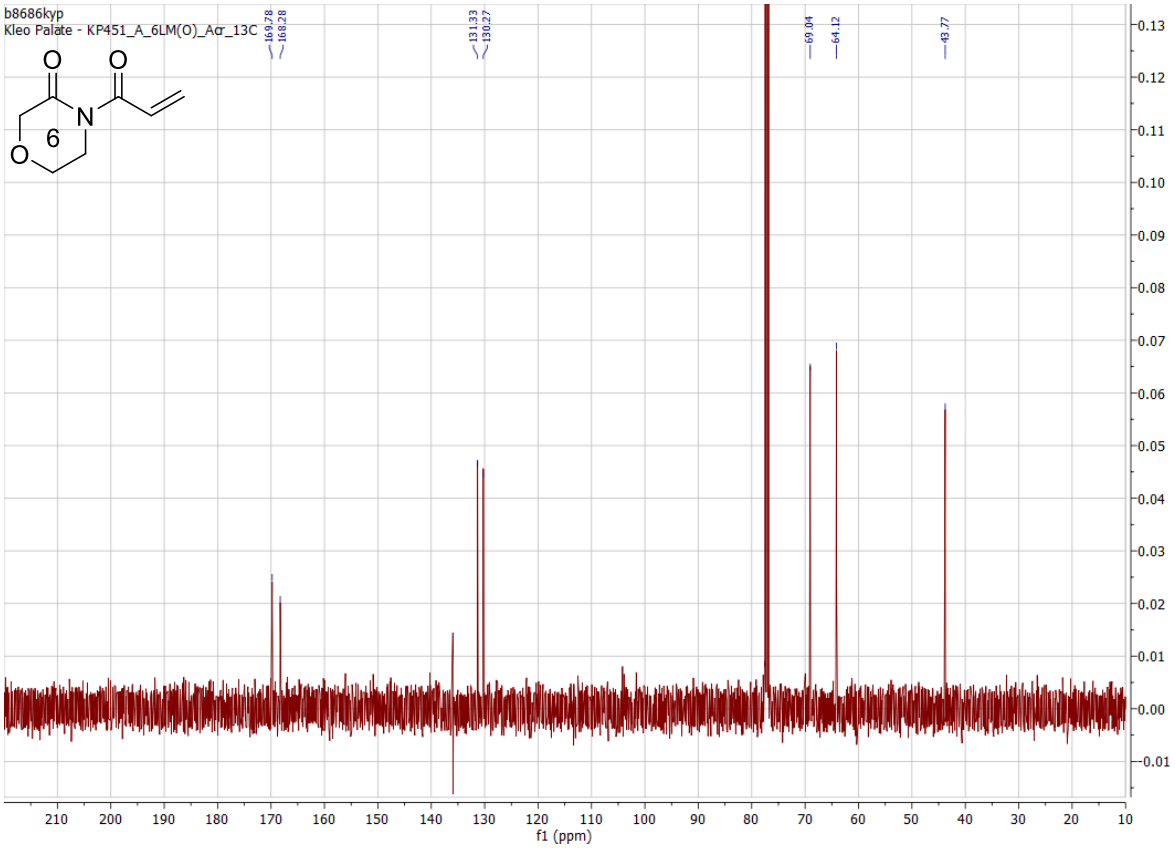
5,5'-(1,4-Phenylenebis(methylene))bis(1,5-diazecane-2,6-dione) (20zg) Severe rotameric broadening is evident in the ^{1}H NMR spectrum. Product identity and purity is best seen in the ^{13}C NMR data.



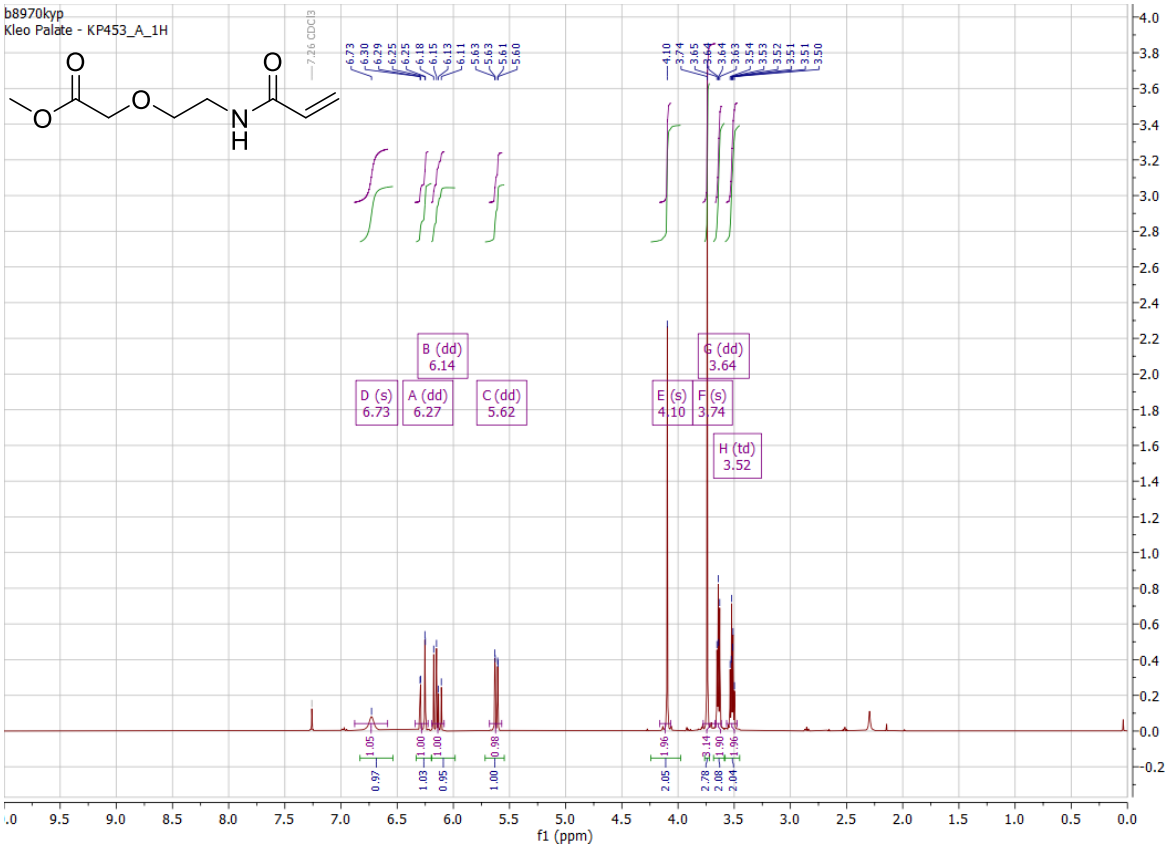


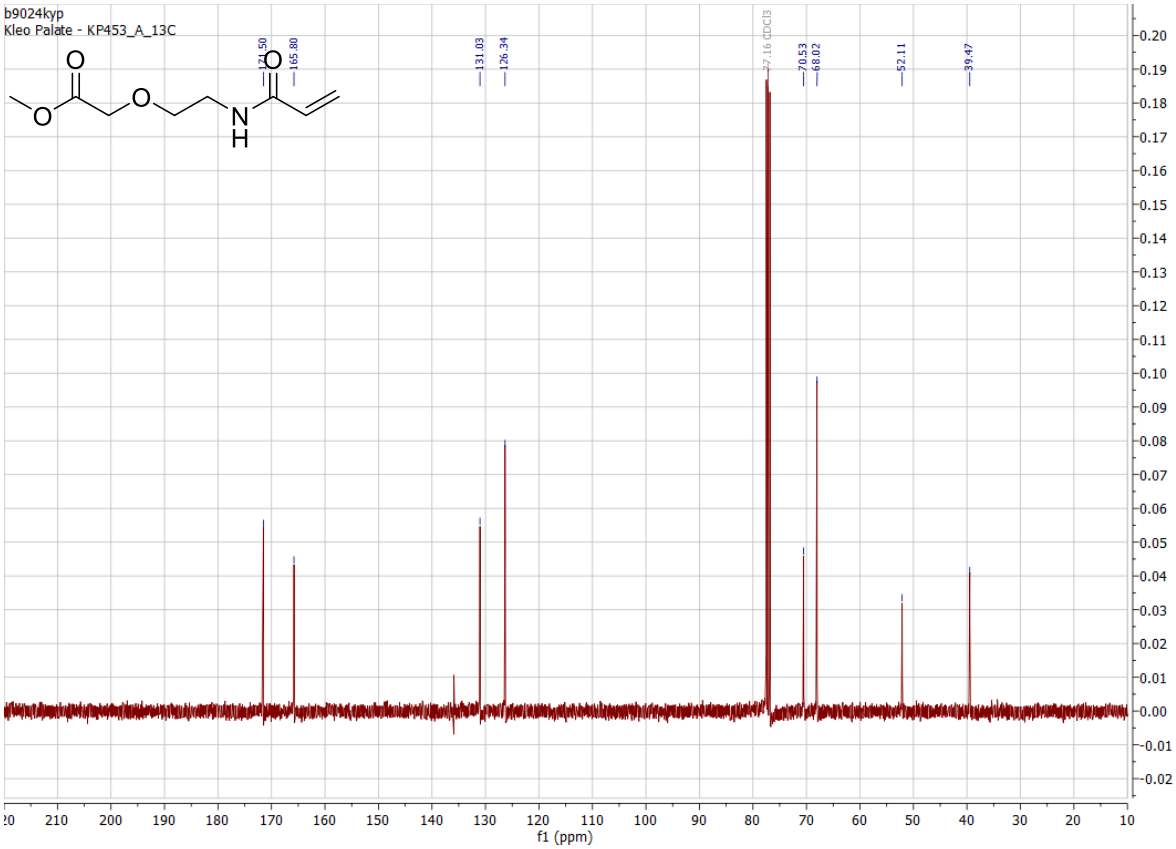
4-Acryloylmorpholin-3-one (21)



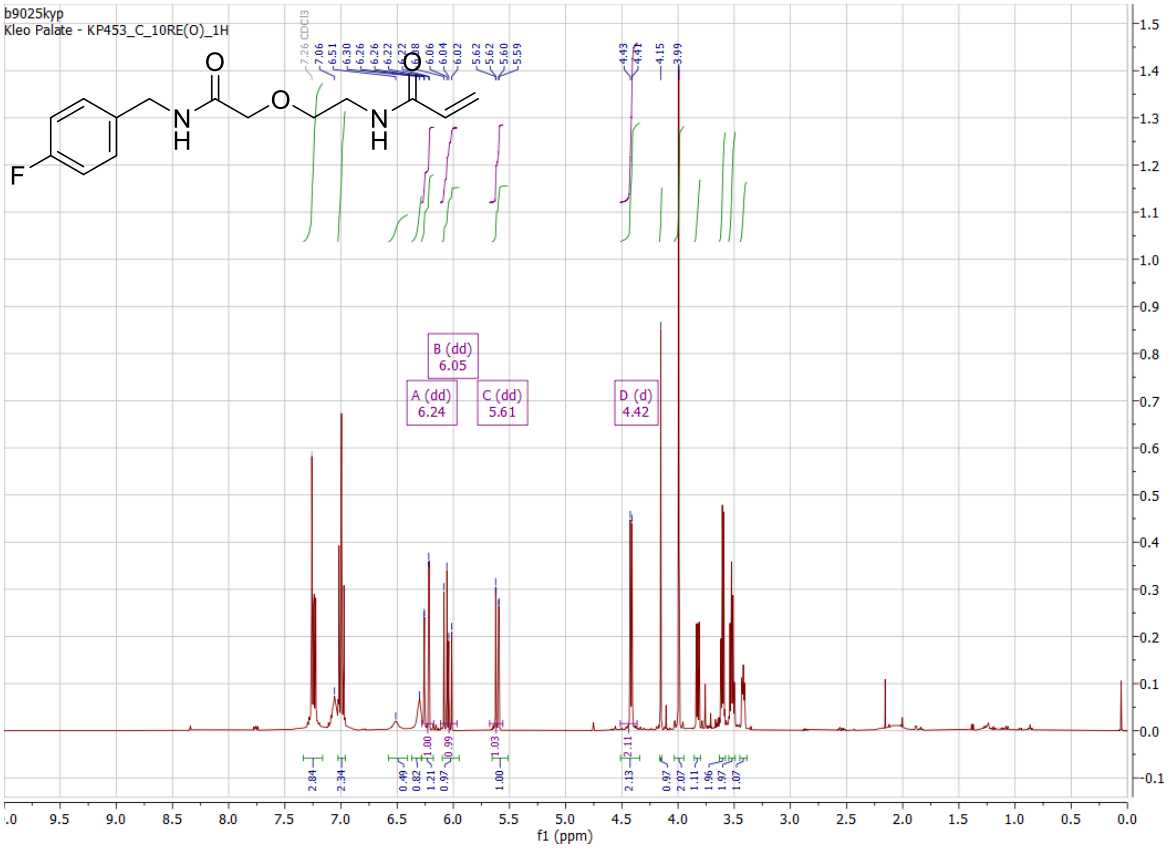


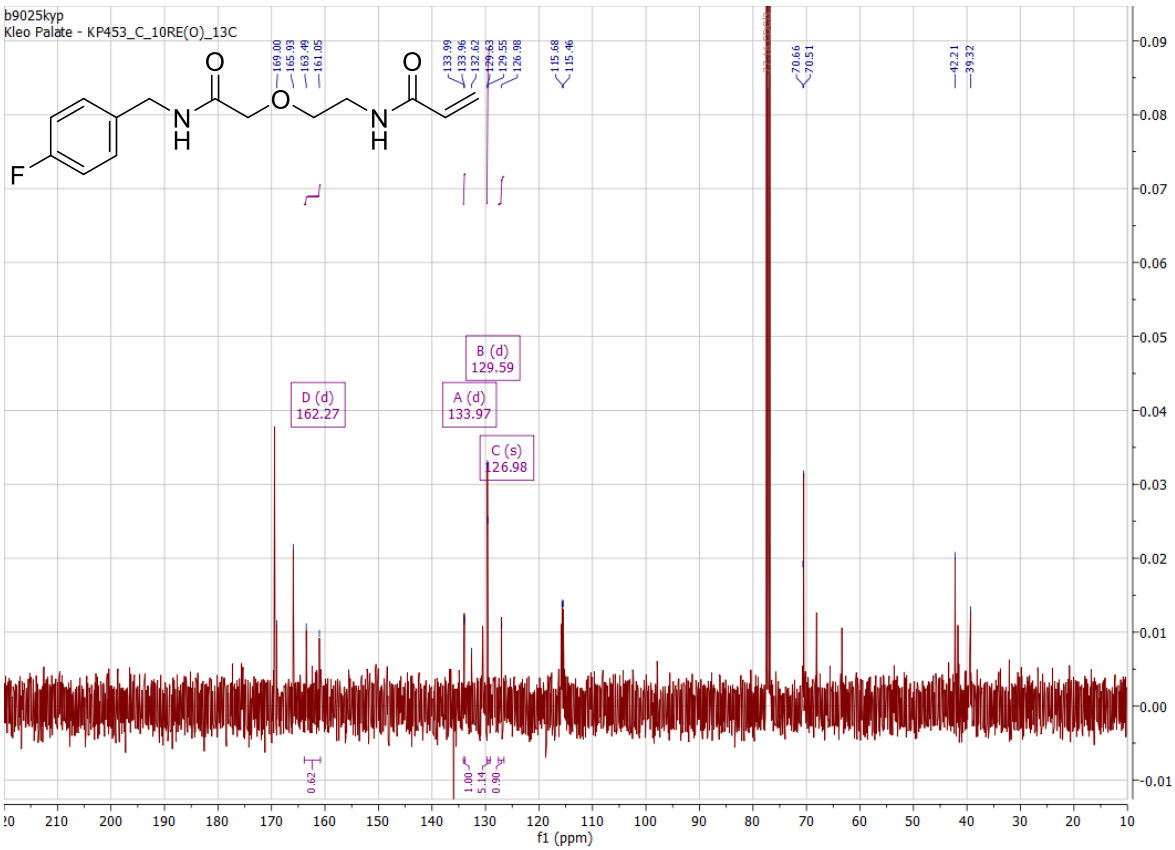
Methyl 2-(2-acrylamidoethoxy)acetate (23)

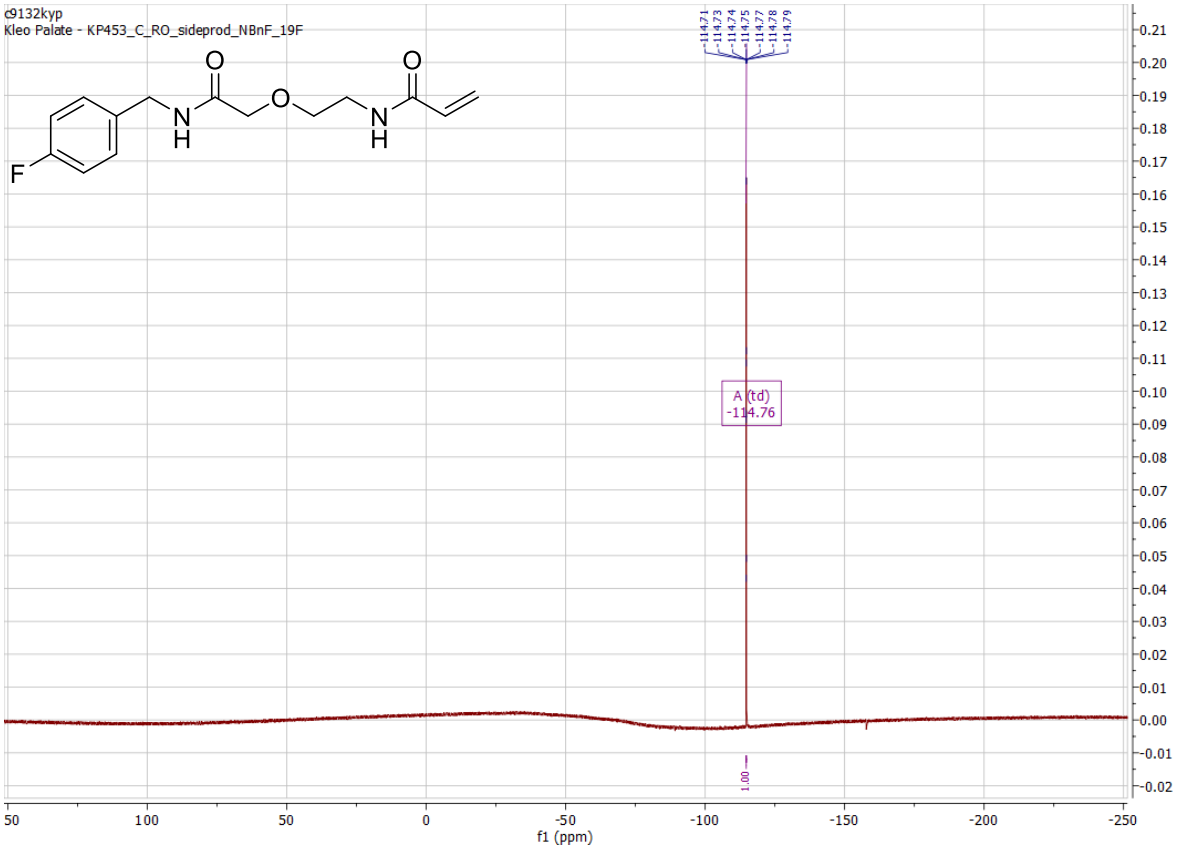


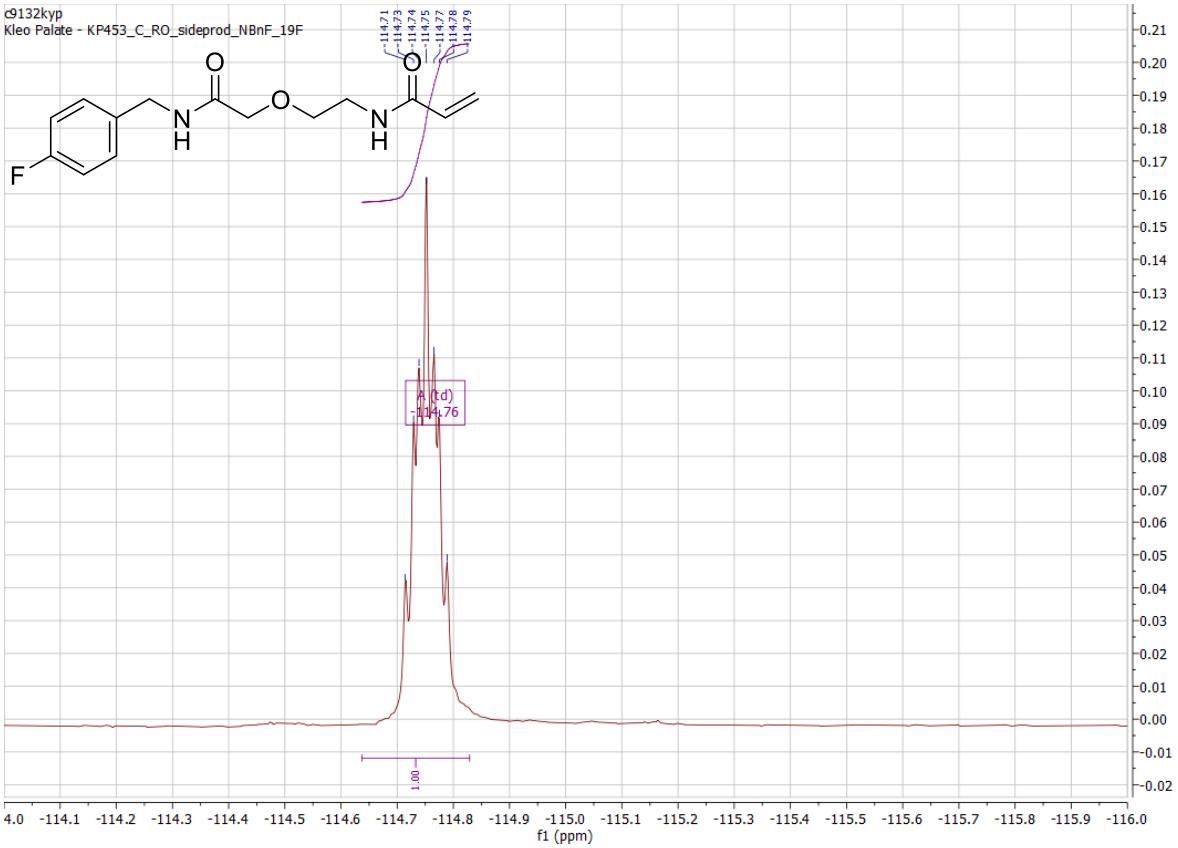


N-(2-(2-((4-fluorobenzyl)amino)-2-oxoethoxy)ethyl)acrylamide (24)

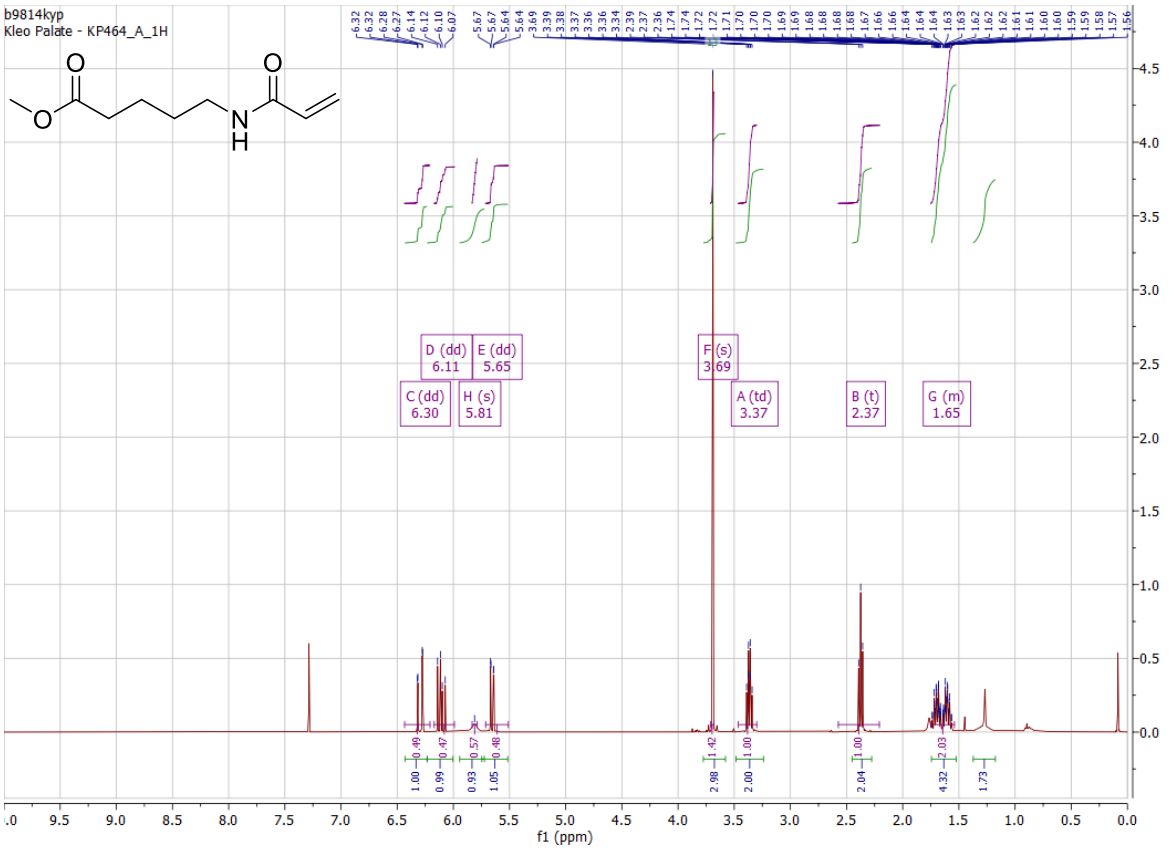


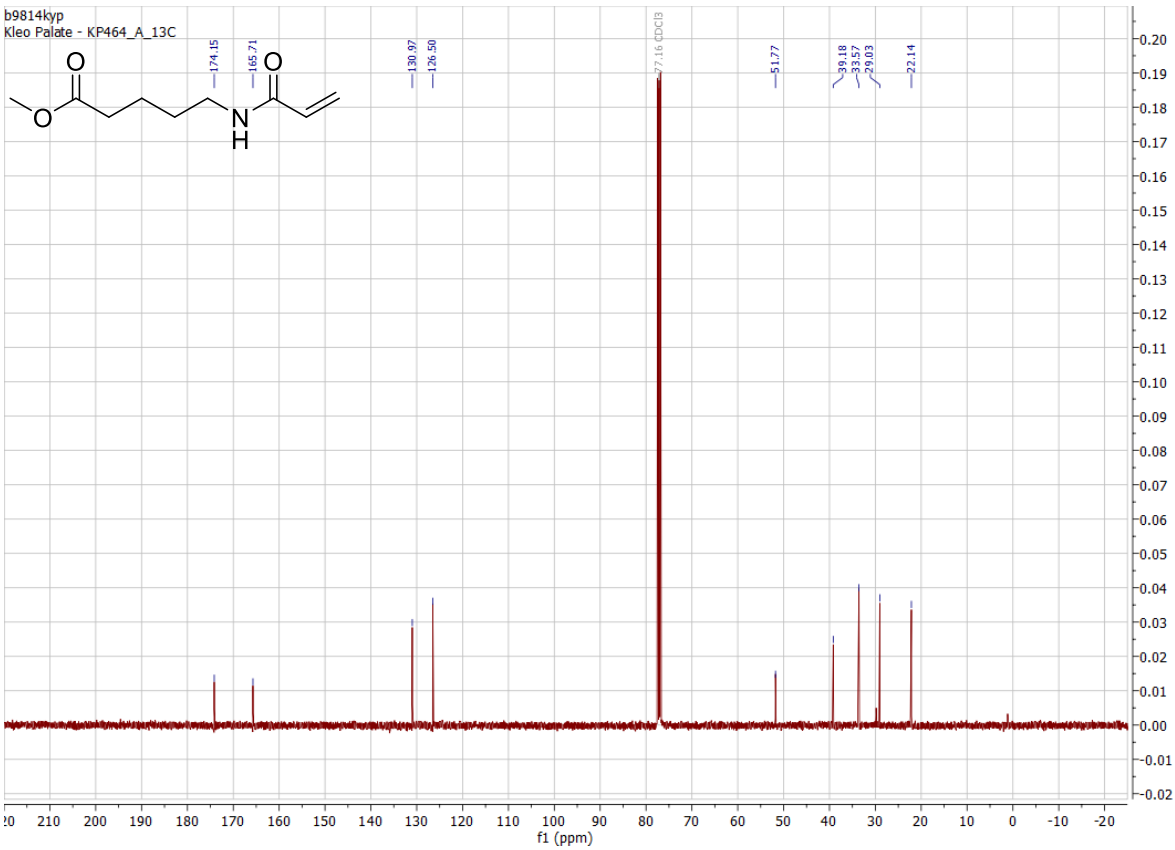



c9132kyp
Kleo Palate - KP453_C_RO_sideprod_NBnF_19F
A (td)
-114.76
f1 (ppm)

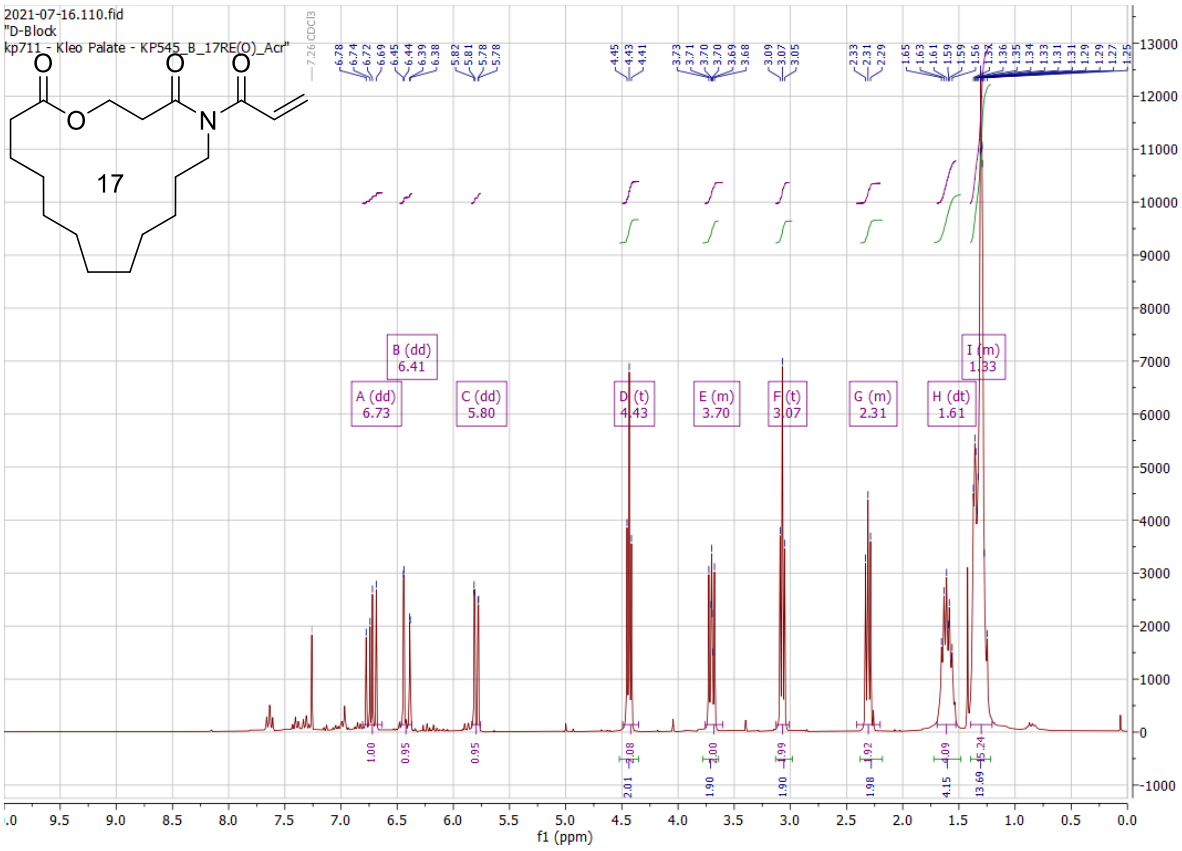

c9132kyp
Kleo Palate - KP453_C_RO_sideprod_NBnF_19F
A (td)
-114.76
f1 (ppm)

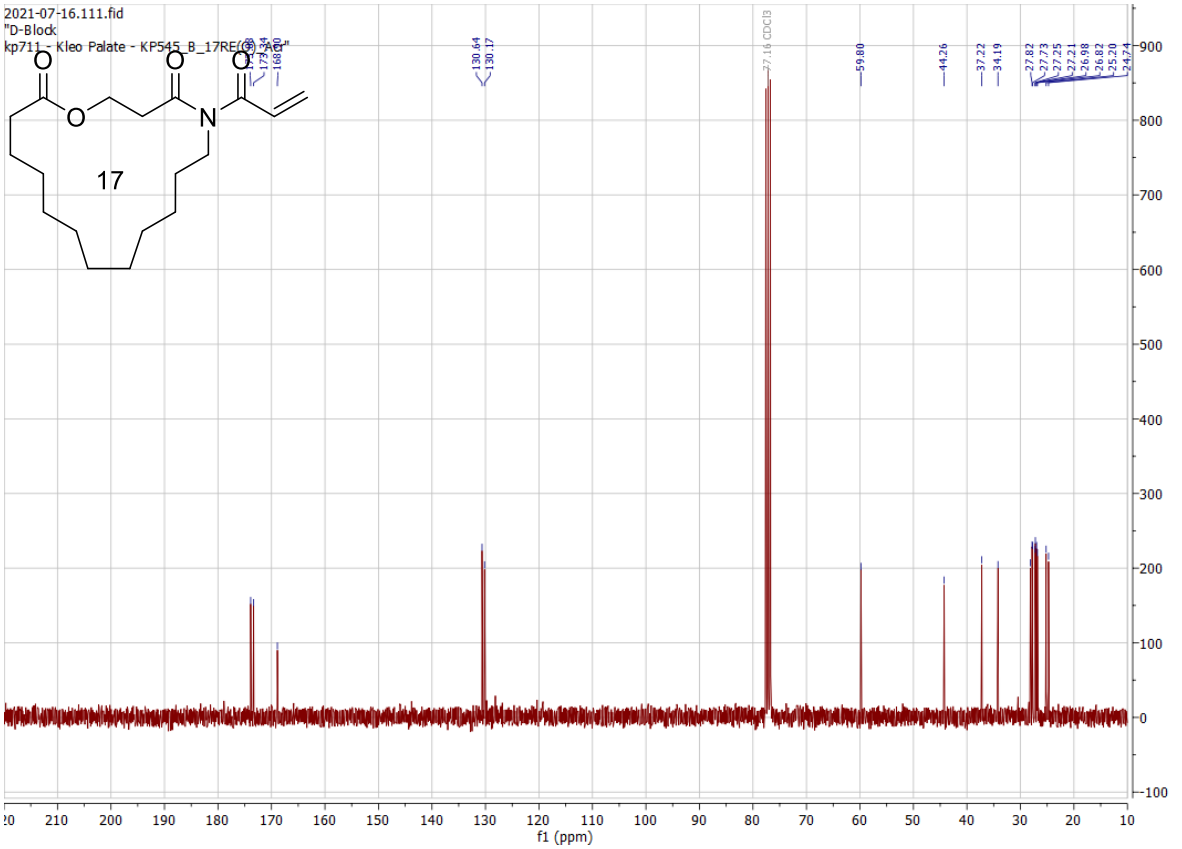
Methyl 5-acrylamidopentanoate (26)



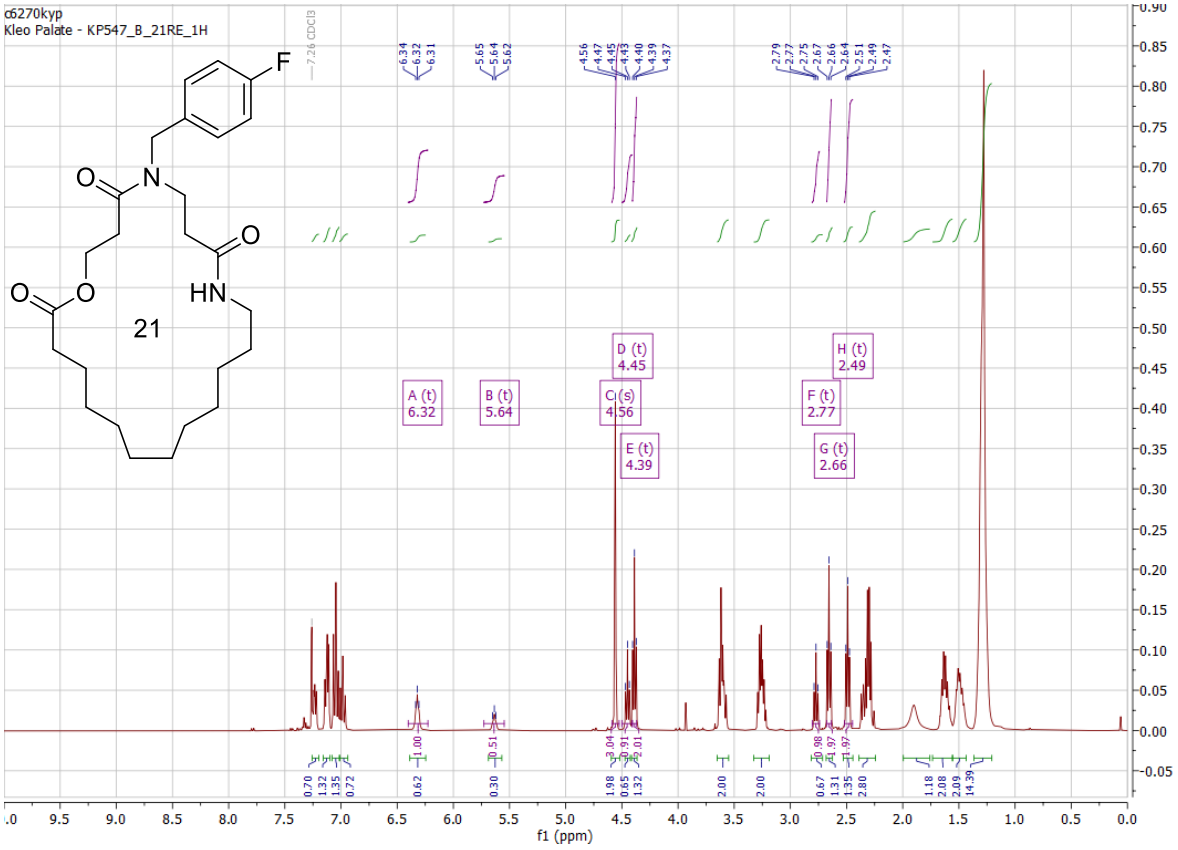


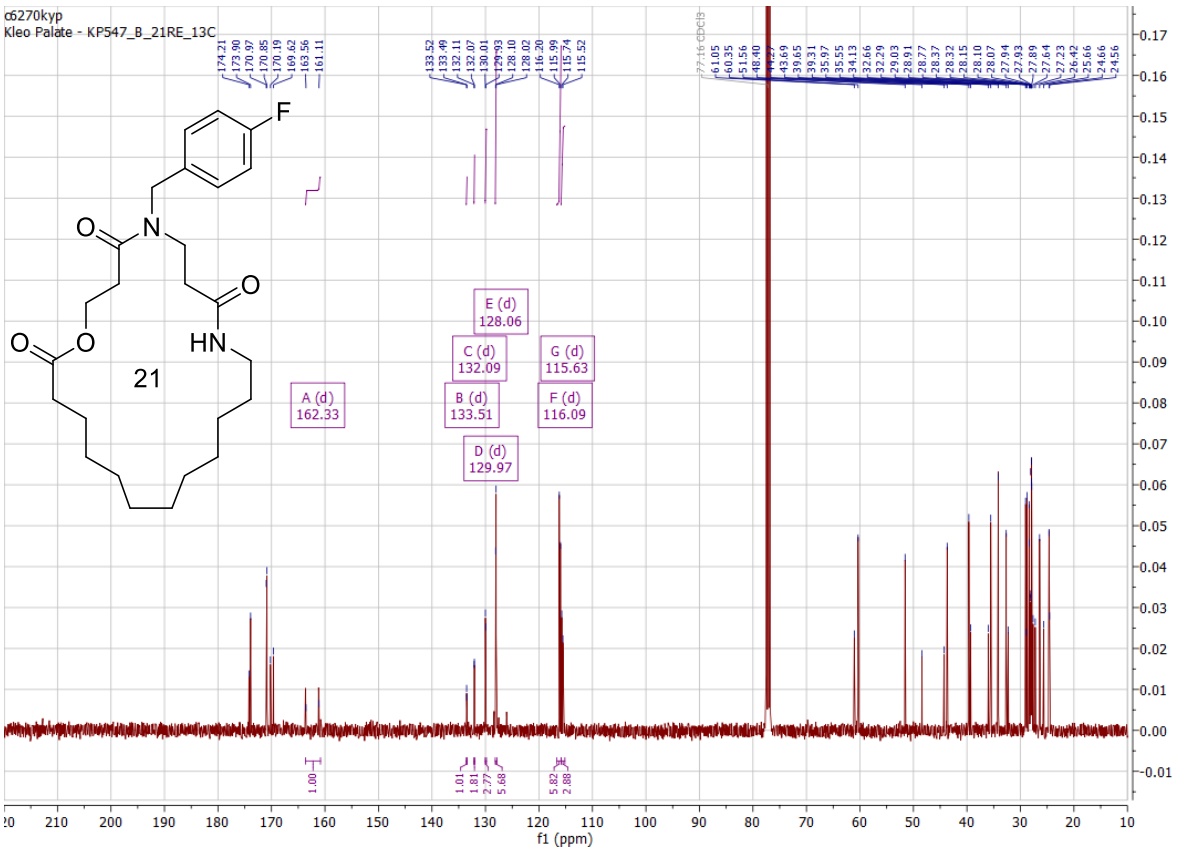
5-Acryloyl-1-oxa-5-azacycloheptadecane-4,17-dione (27)

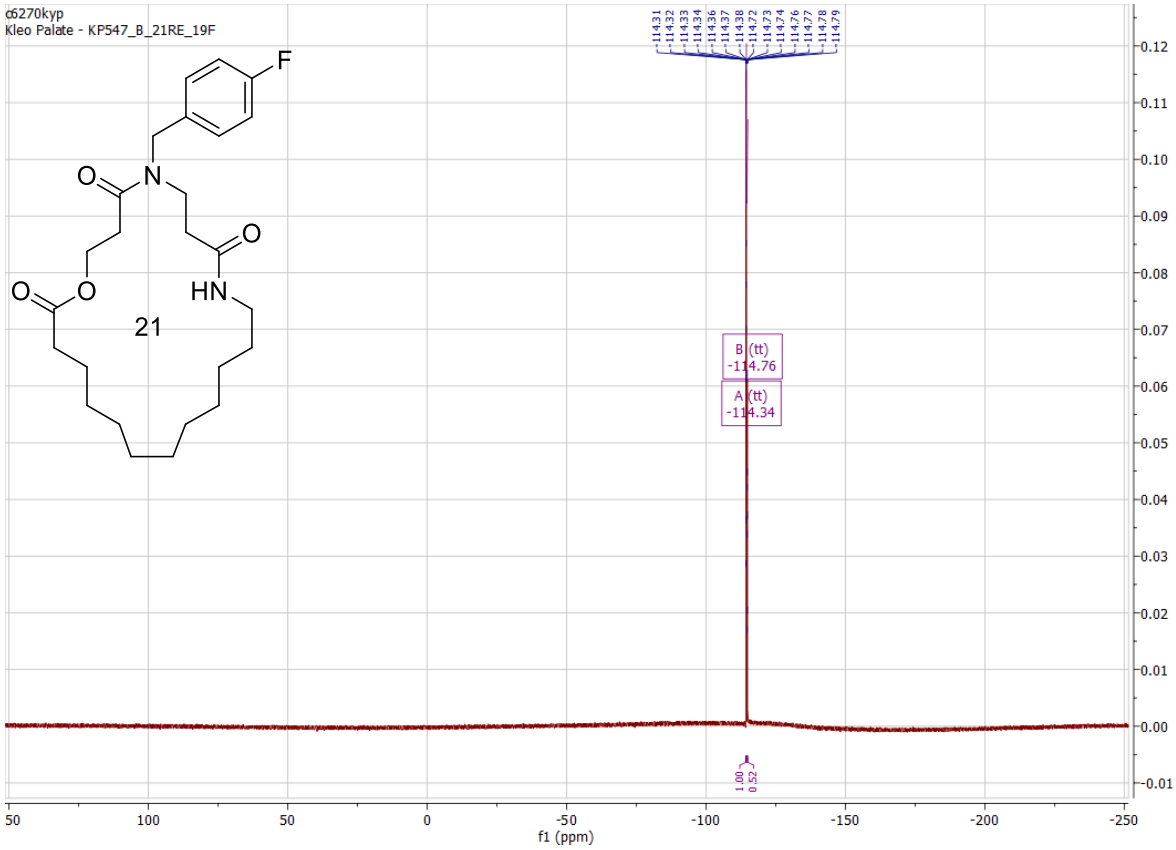


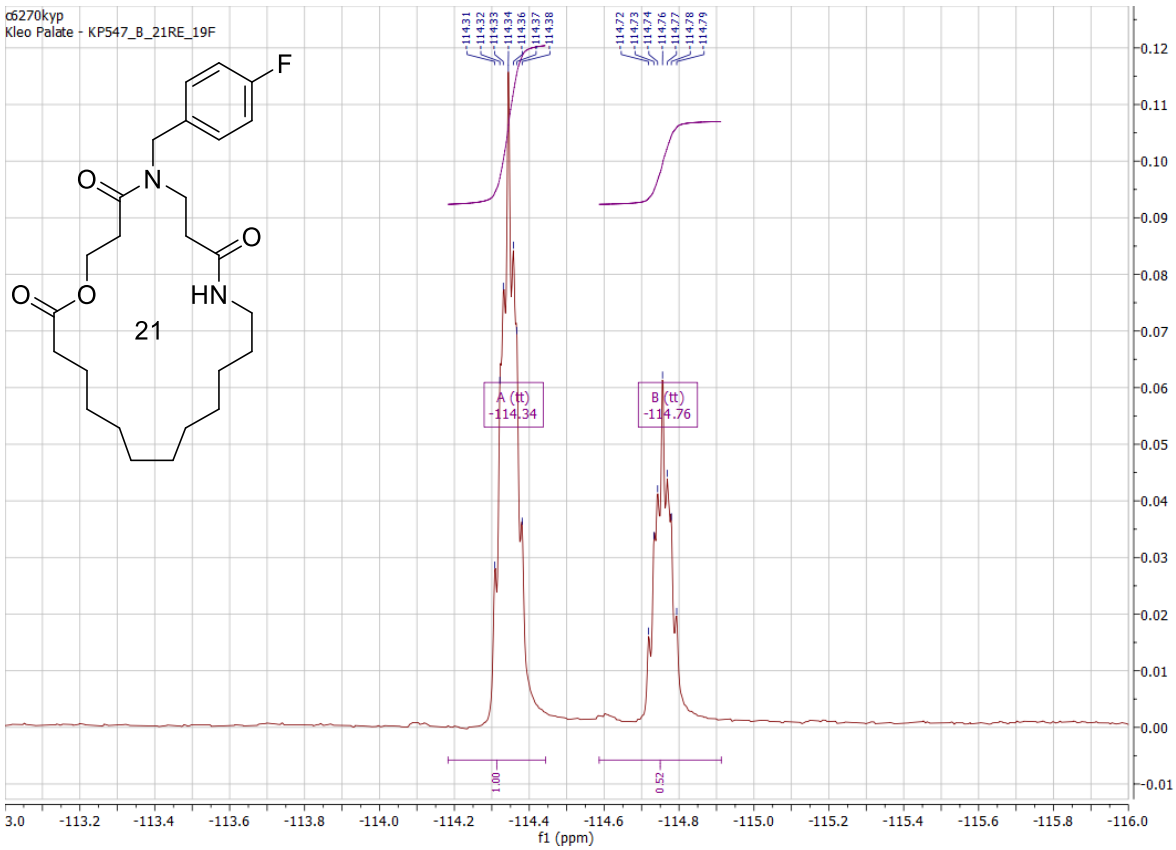


5-(4-Fluorobenzyl)-1-oxa-5,9-diazacyclohenicosane-4,8,21-trione (28) 2:1 mixture of rotamers.

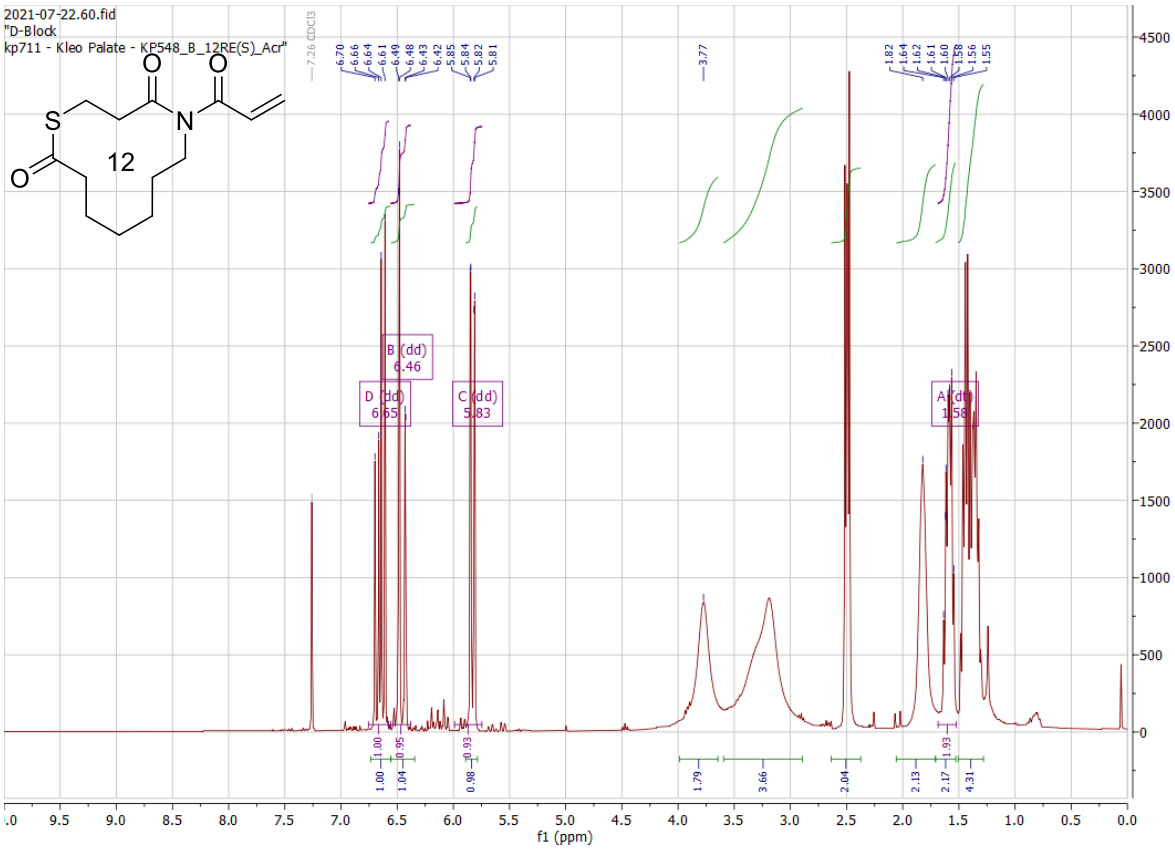


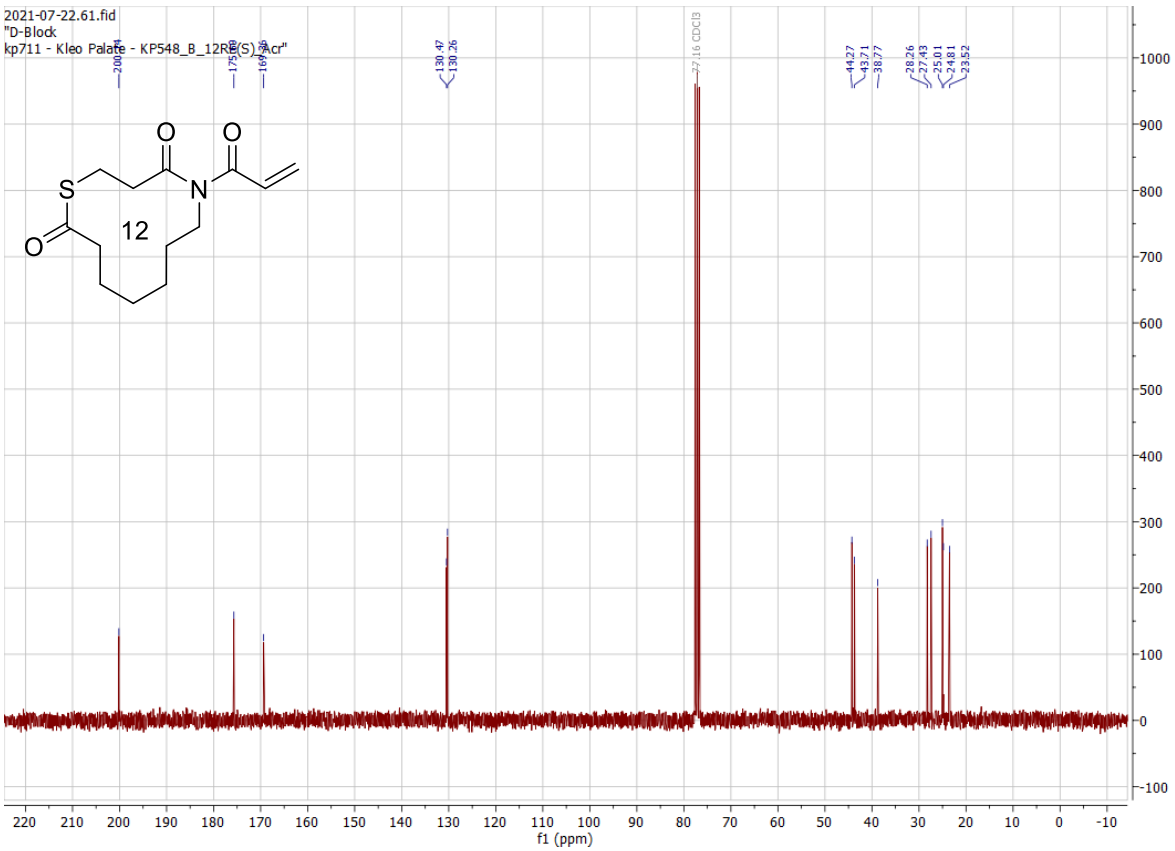



d6270kyp
Kleo Palate - KP547_B_21RE_19F
F
O
N
O
O
O
HN
21
B (tt)
-114.76
A (tt)
-114.34
1.00
0.52
f1 (ppm)

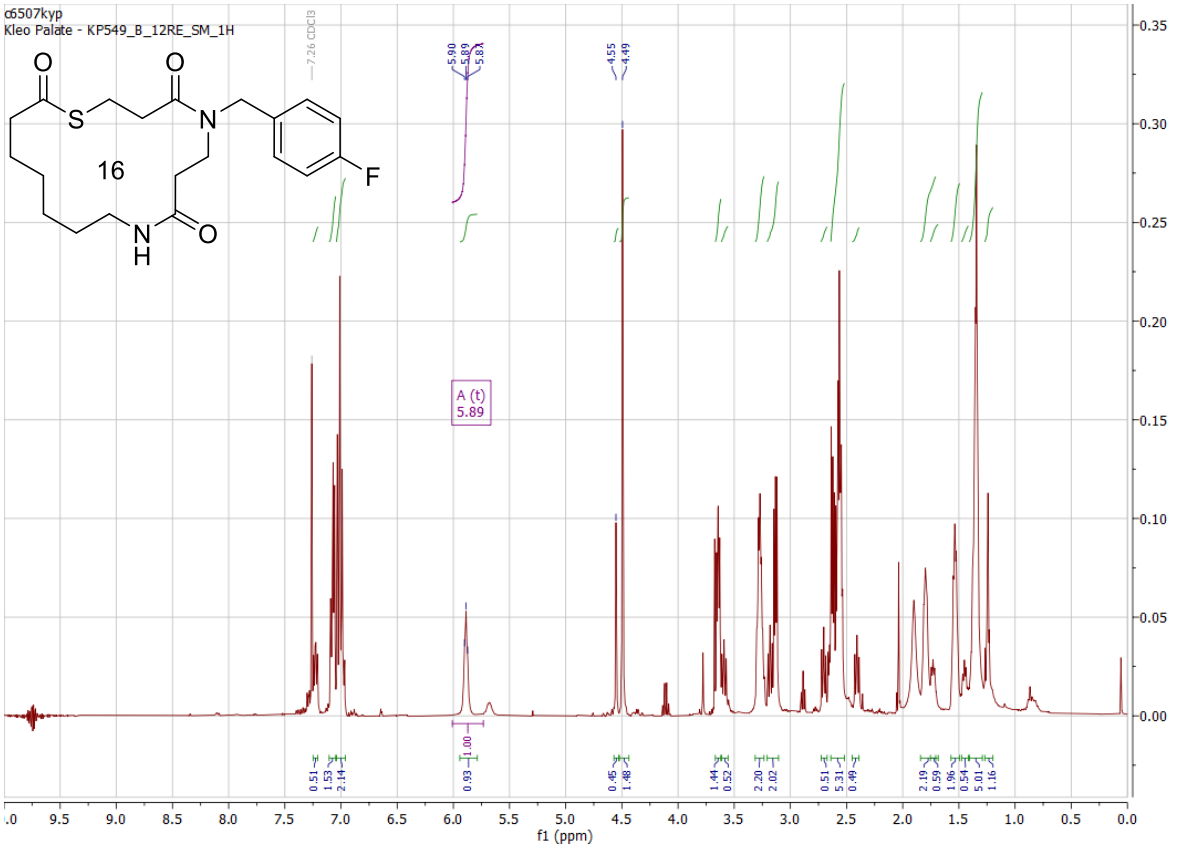

d6270kyp
Kleo Palate - KP547_B_21RE_19F
F
O
N
O
O
O
HN
21
A (tt)
-114.34
B (tt)
-114.76
1.00
0.52
f1 (ppm)

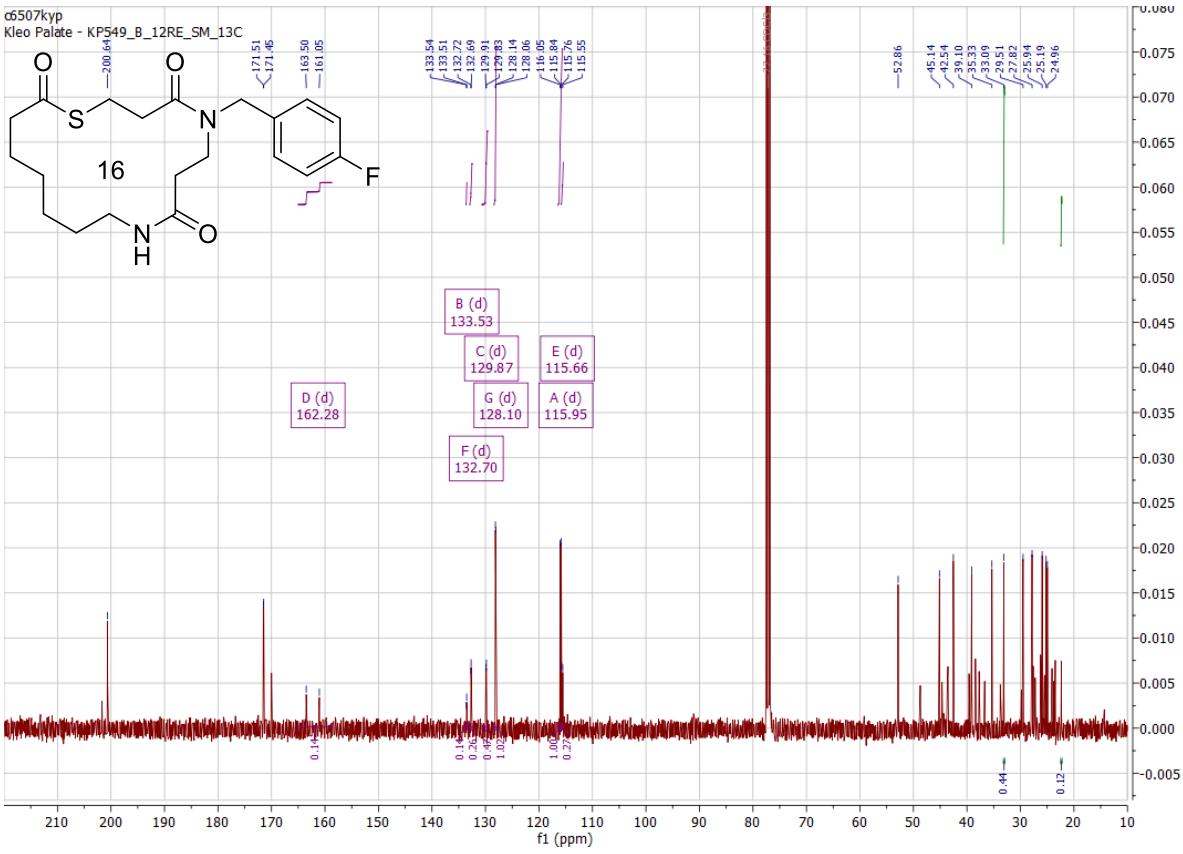
5-Acryloyl-1-thia-5-azacyclododecane-4,12-dione (29)

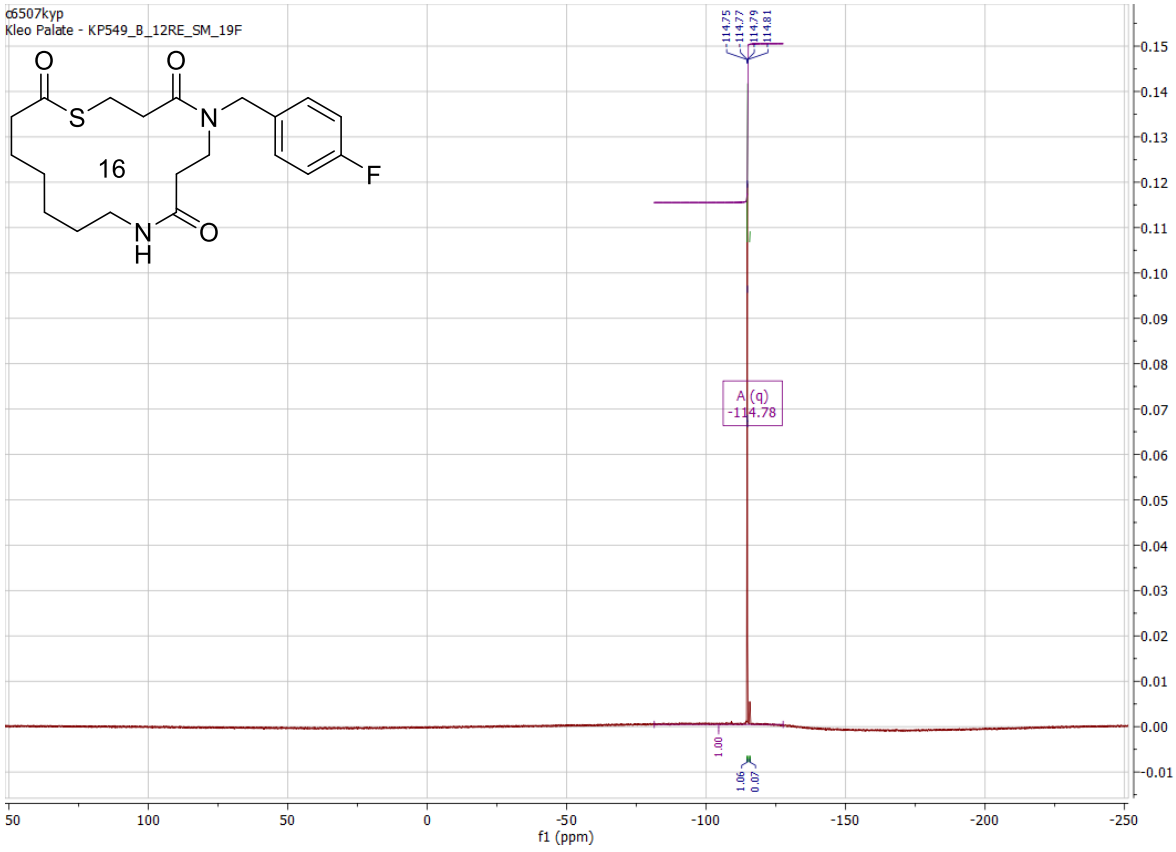


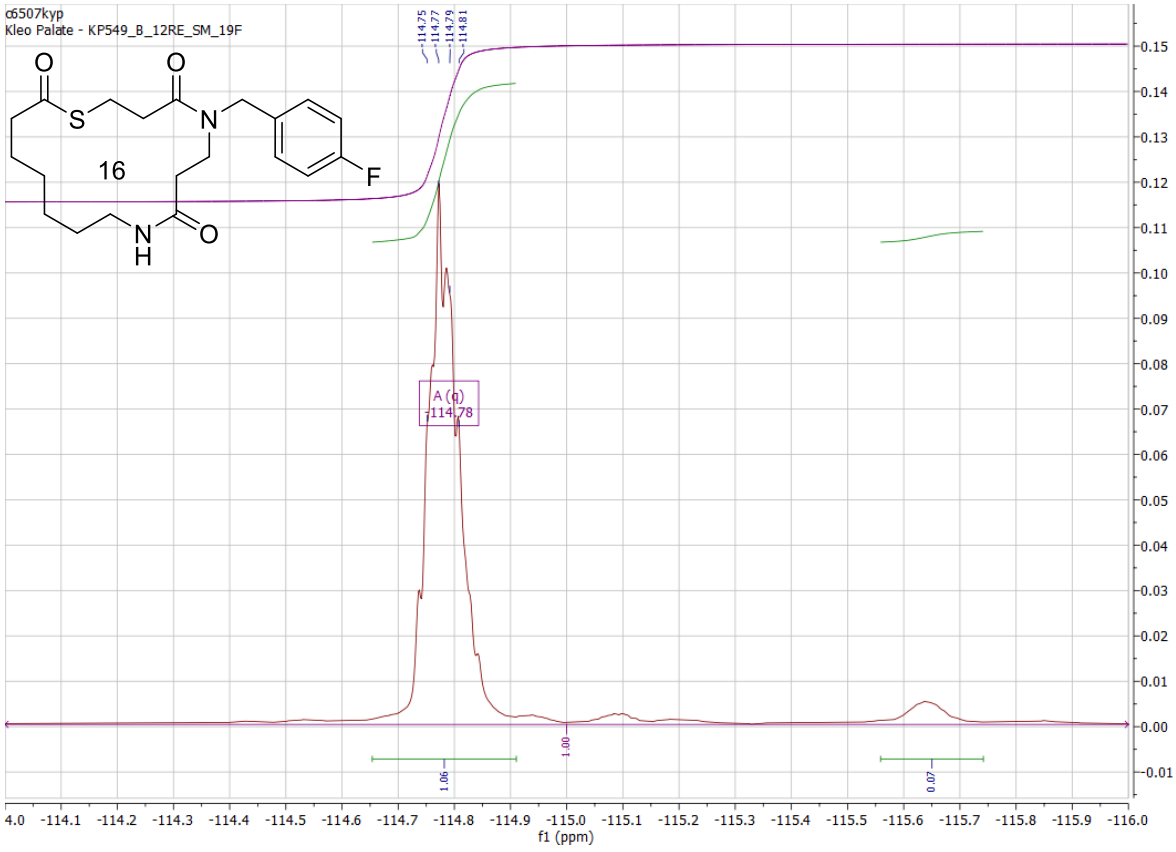


5-(4-Fluorobenzyl)-1-thia-5,9-diazacyclohexadecane-4,8,16-trione (30) 3:1 mixture of rotamers.

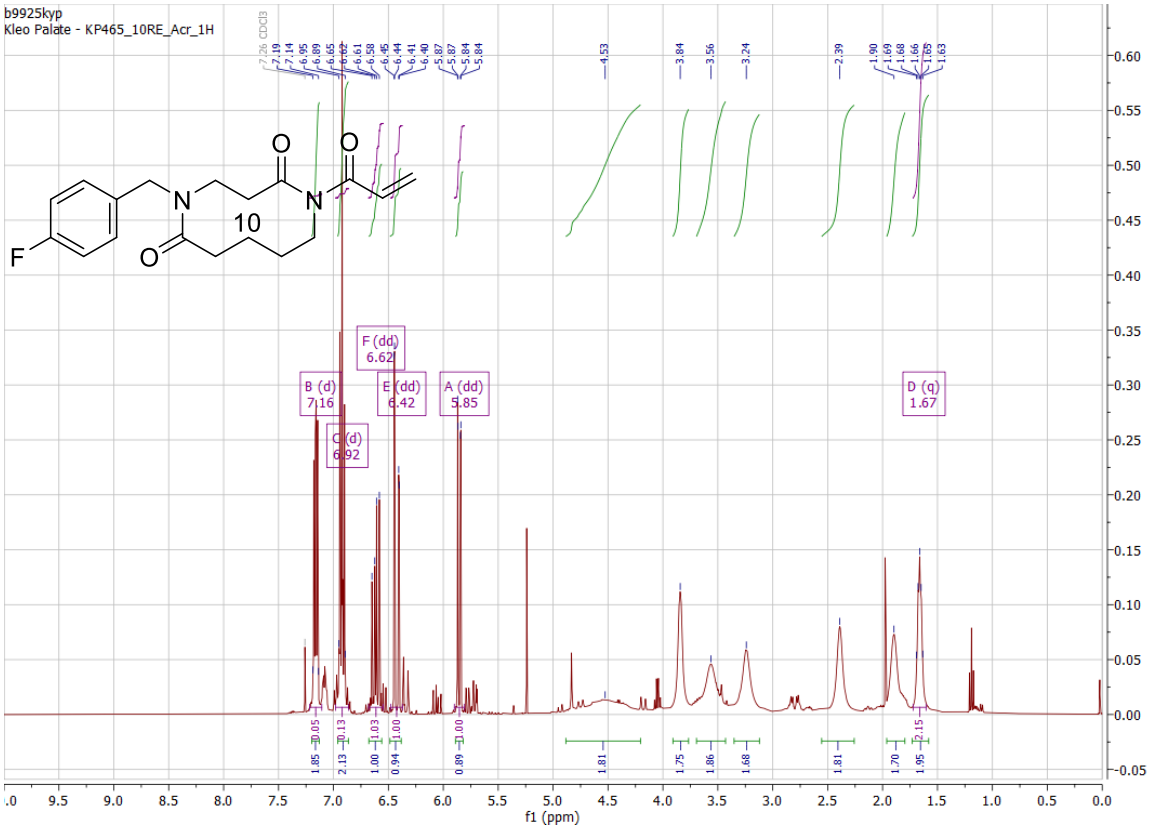


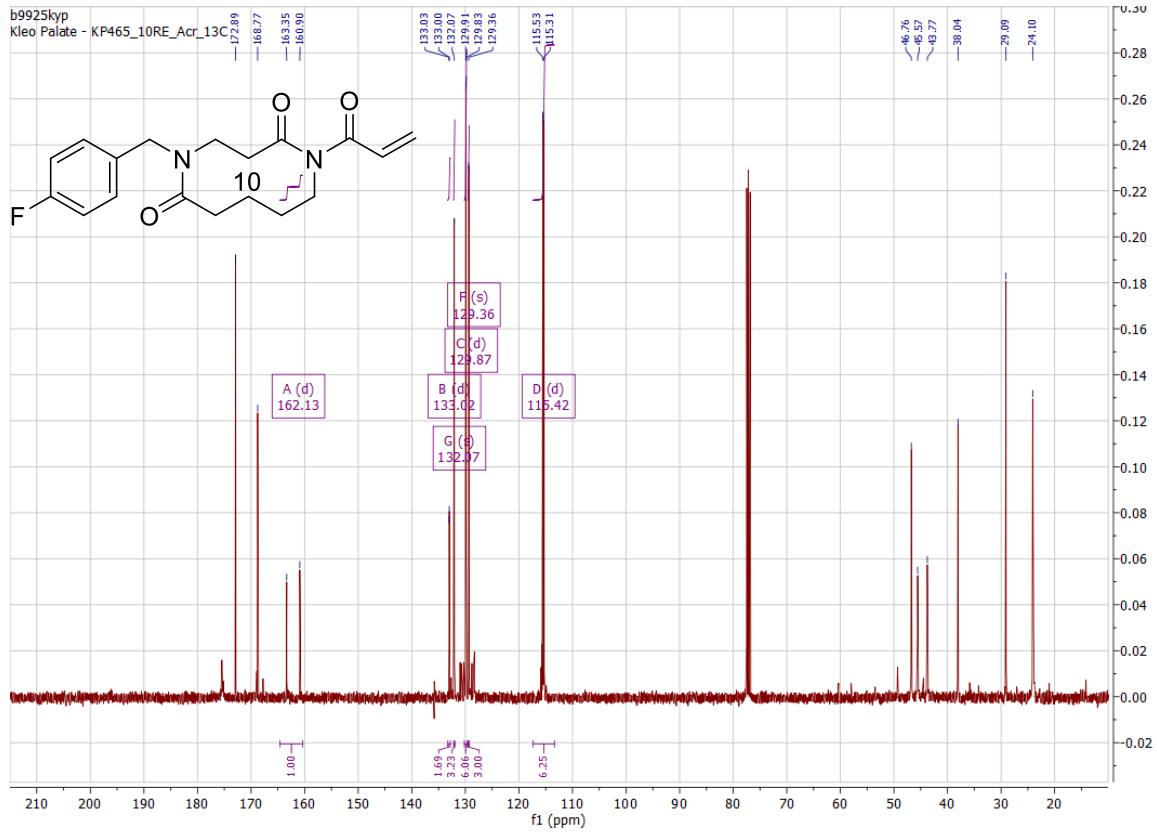


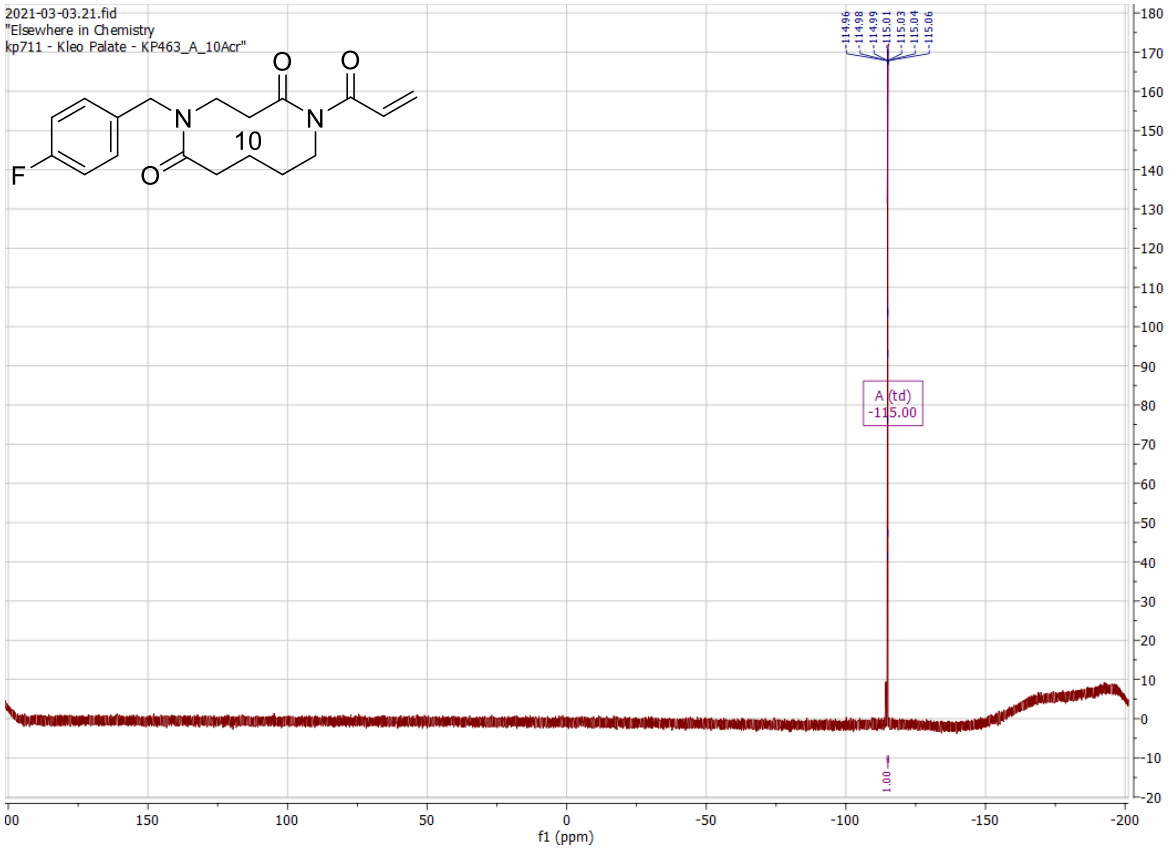

d6507kyp
Kleo Palate - KP549_B_12RE_SM_19F
O
O
S
N
16
F
N
H
O
-114.75
-114.77
-114.79
-114.81
A (q)
-114.78
1.00
1.06
0.07
f1 (ppm)

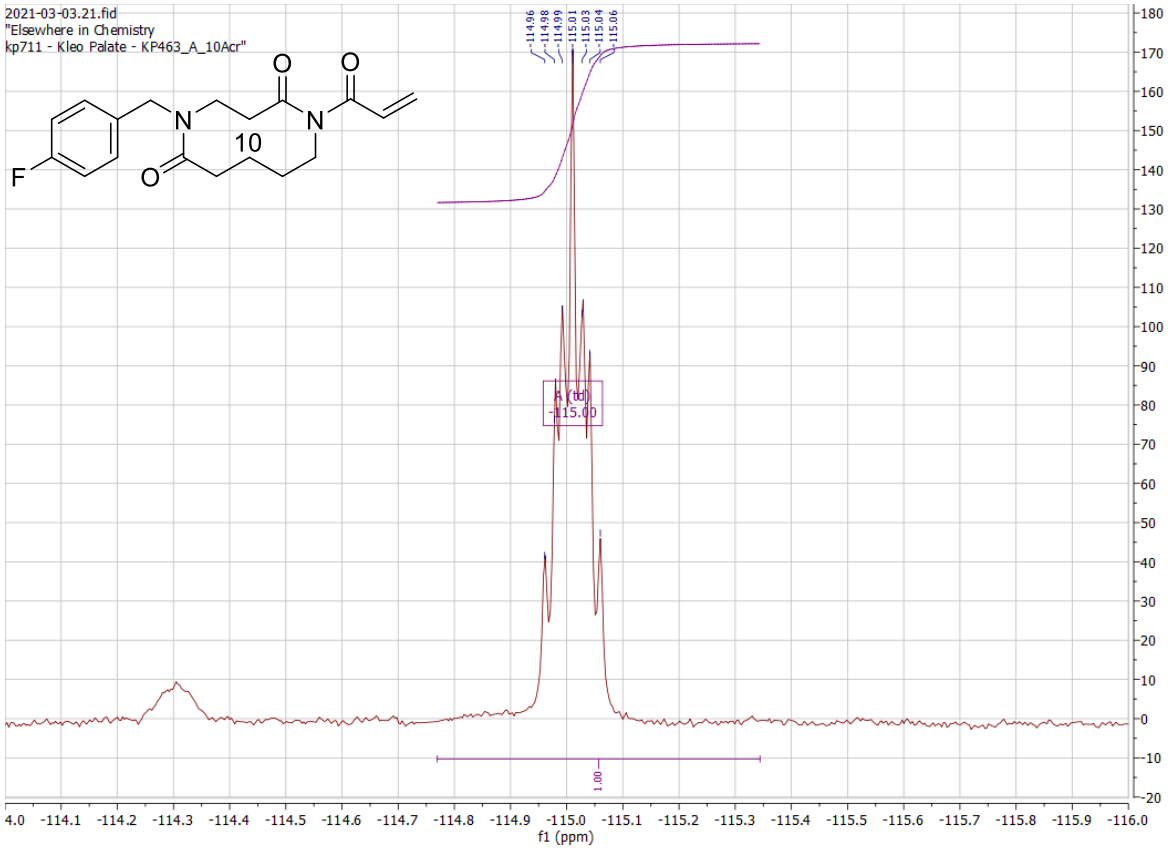

d6507kyp
Kleo Palate - KP549_B_12RE_SM_19F
O
O
S
N
16
F
N
H
O
-114.75
-114.77
-114.79
-114.81
A (q)
-114.78
1.00
1.06
0.07
f1 (ppm)

1-Acryloyl-5-(4-fluorobenzyl)-1,5-diazecane-2,6-dione (S1) In solution in $CDCl_3$, this compound exists largely as a single rotamer, along with a minor rotamer (most clearly seen in the ^{19}F NMR data). The ^{1}H NMR spectrum is significantly affected by rotameric broadening.

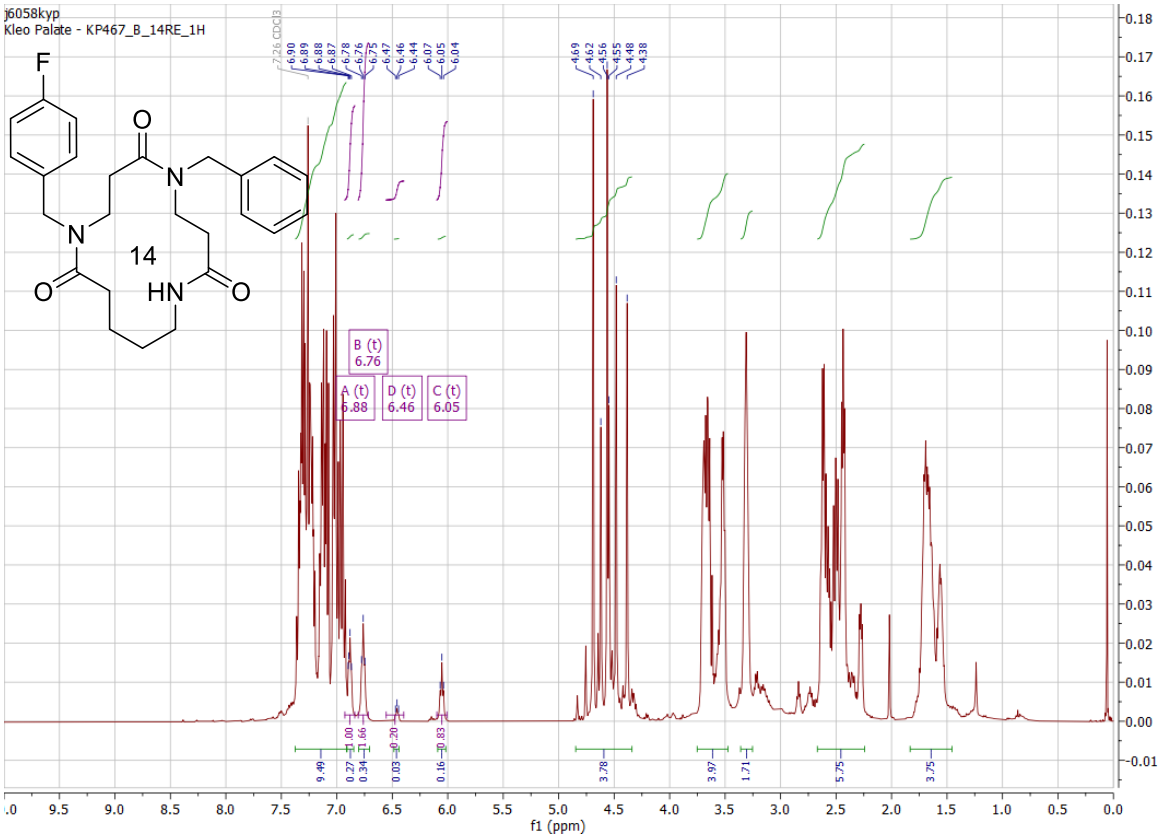


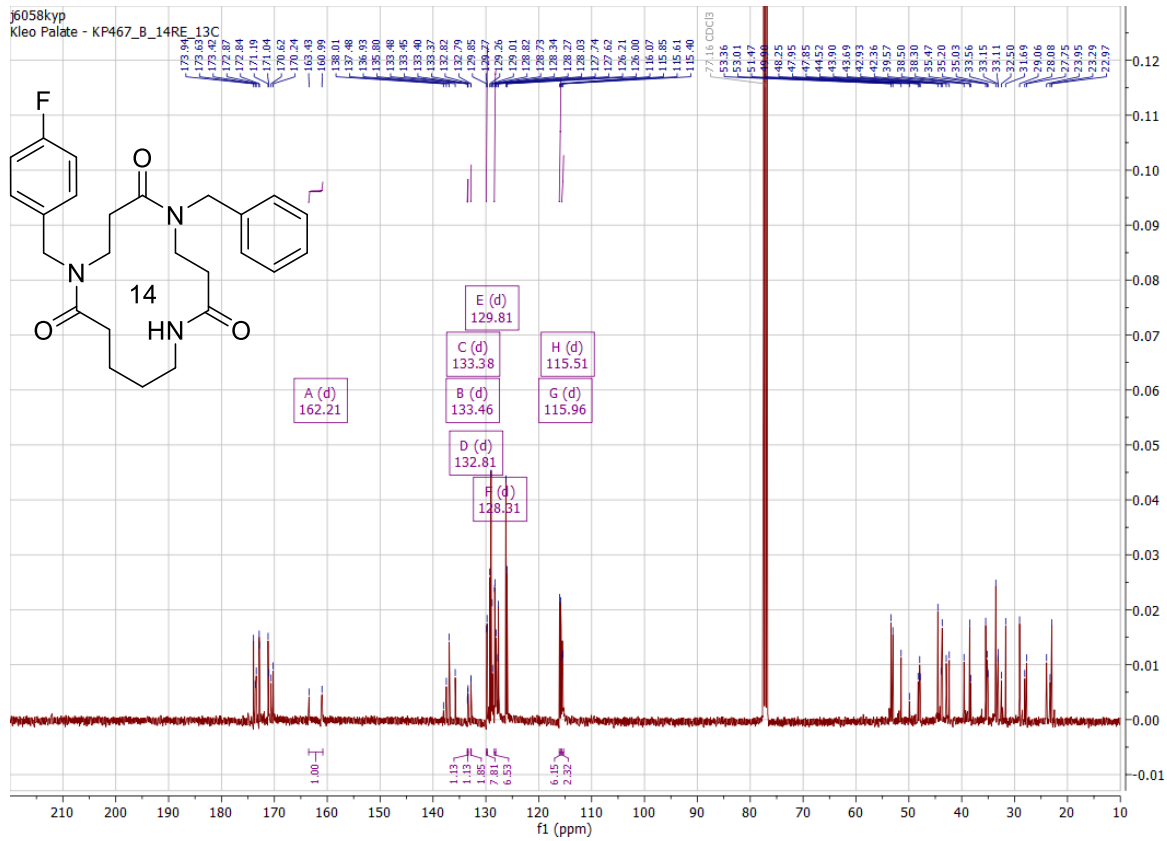


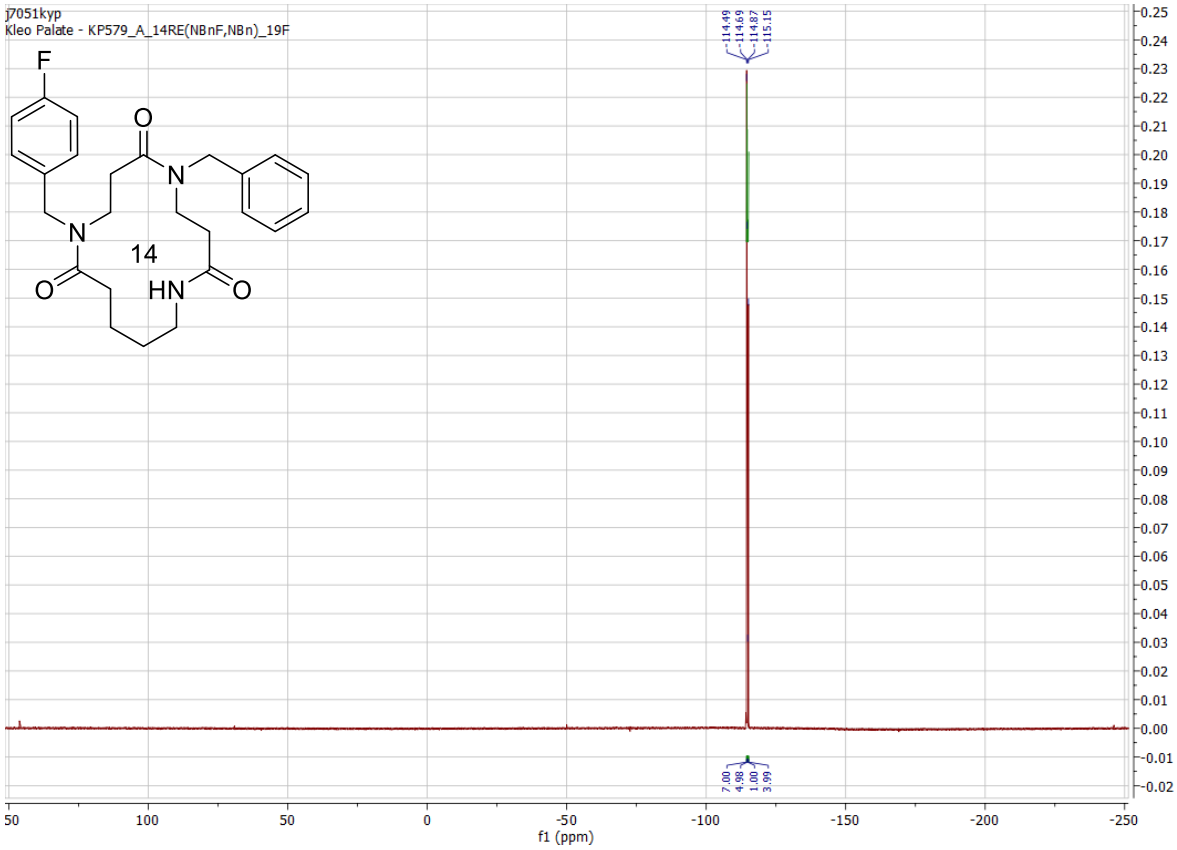

2021-03-03.21.fid
"Elsewhere in Chemistry
kp711 - Kleo Palate - KP463_A_10Acr"
O
O
N
N
10
O
F
-114.96
-114.98
-114.99
-115.01
-115.03
-115.04
-115.06
A (td)
-115.00
1.00
f1 (ppm)

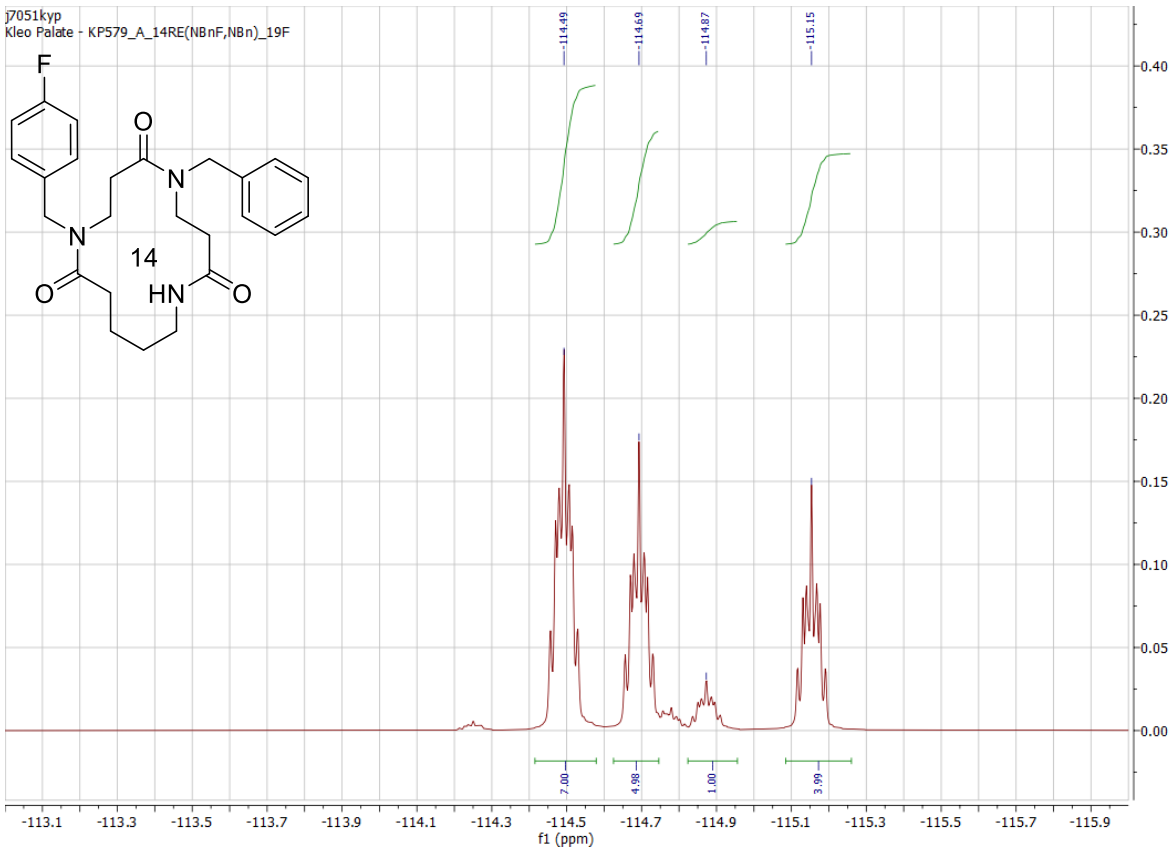

2021-03-03.21.fid
"Elsewhere in Chemistry
kp711 - Kleo Palate - KP463_A_10Acr"
O
O
N
N
10
O
F
-114.96
-114.98
-114.99
-115.01
-115.03
-115.04
-115.06
A (td)
-115.00
1.00
f1 (ppm)

5-Benzyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (31a) This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 4 rotamers visible in a ratio of roughly 7:5:4:1, based on the ^{19}F NMR data and NH signals in the ^{1}H NMR spectrum.

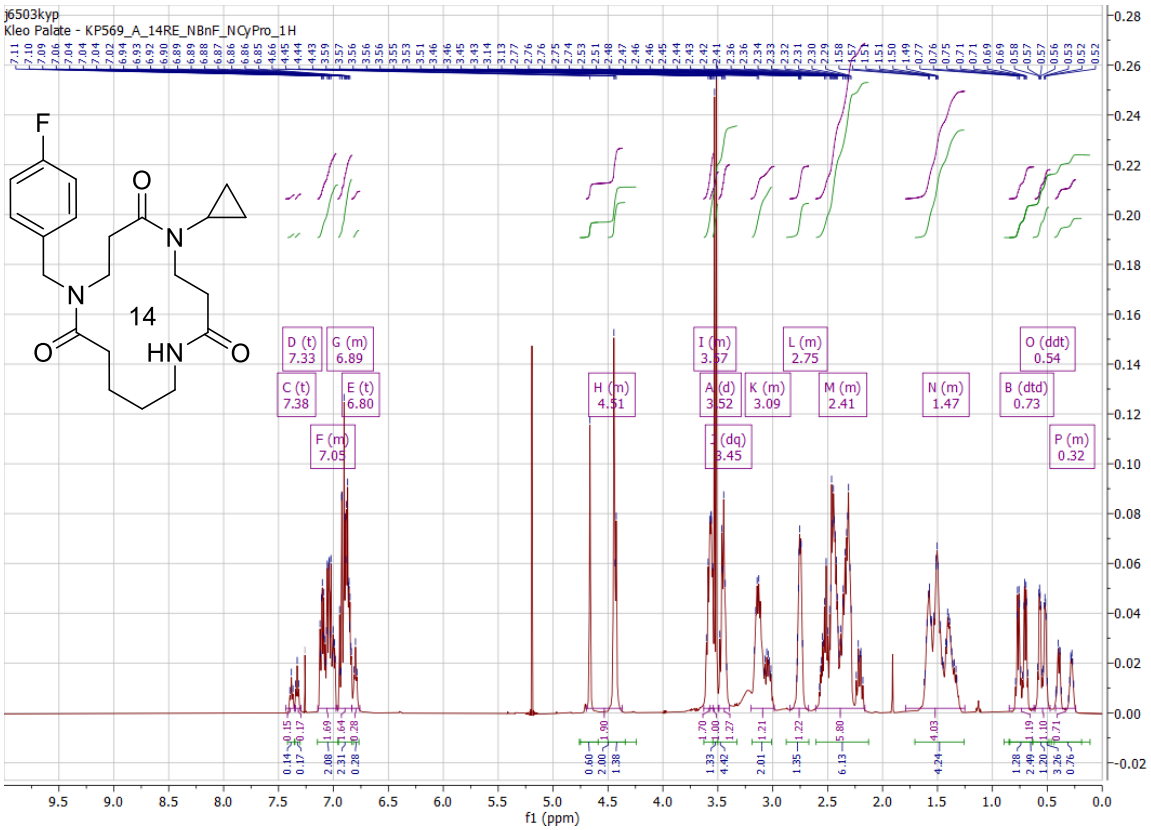


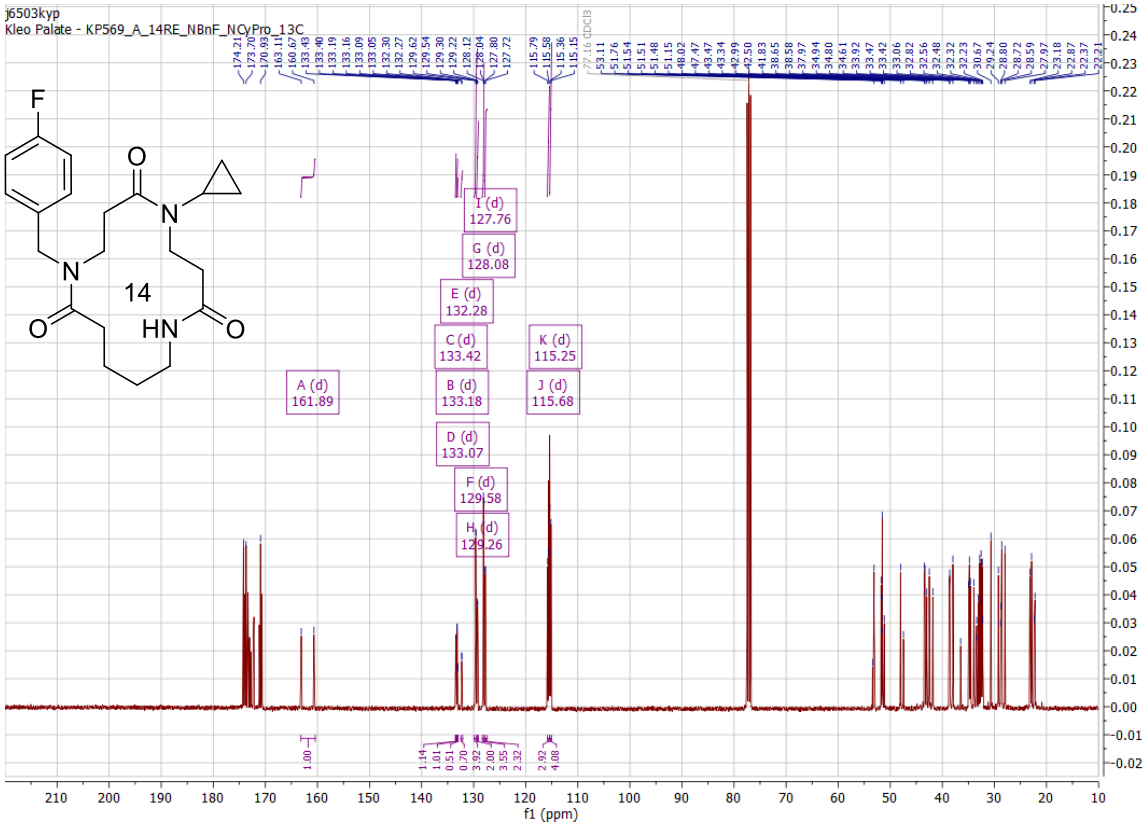


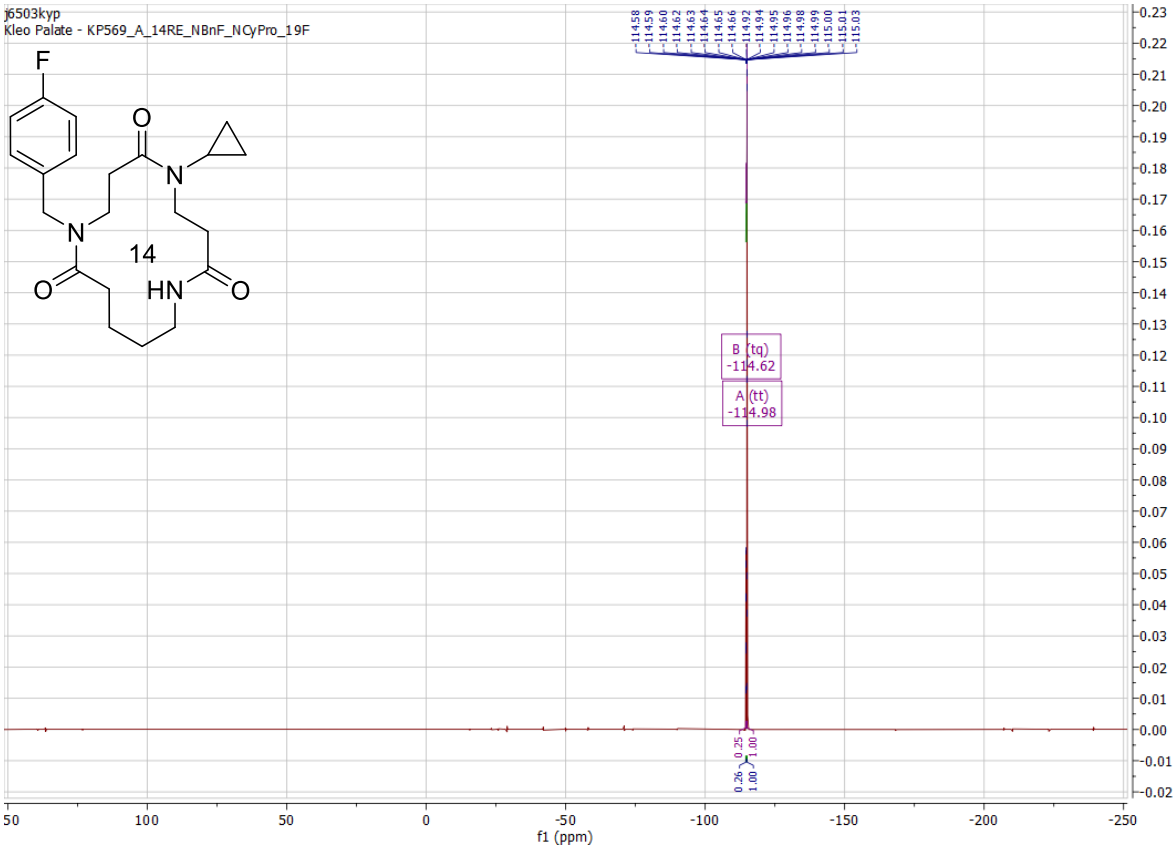

j7051kyp
Kleo Palate - KP579_A_14RE(NBnF,NBn)_19F
F
O
N
N
14
O
HN
O
-114.49
-114.69
-114.87
-115.15
7.00
4.98
1.00
3.99
f1 (ppm)

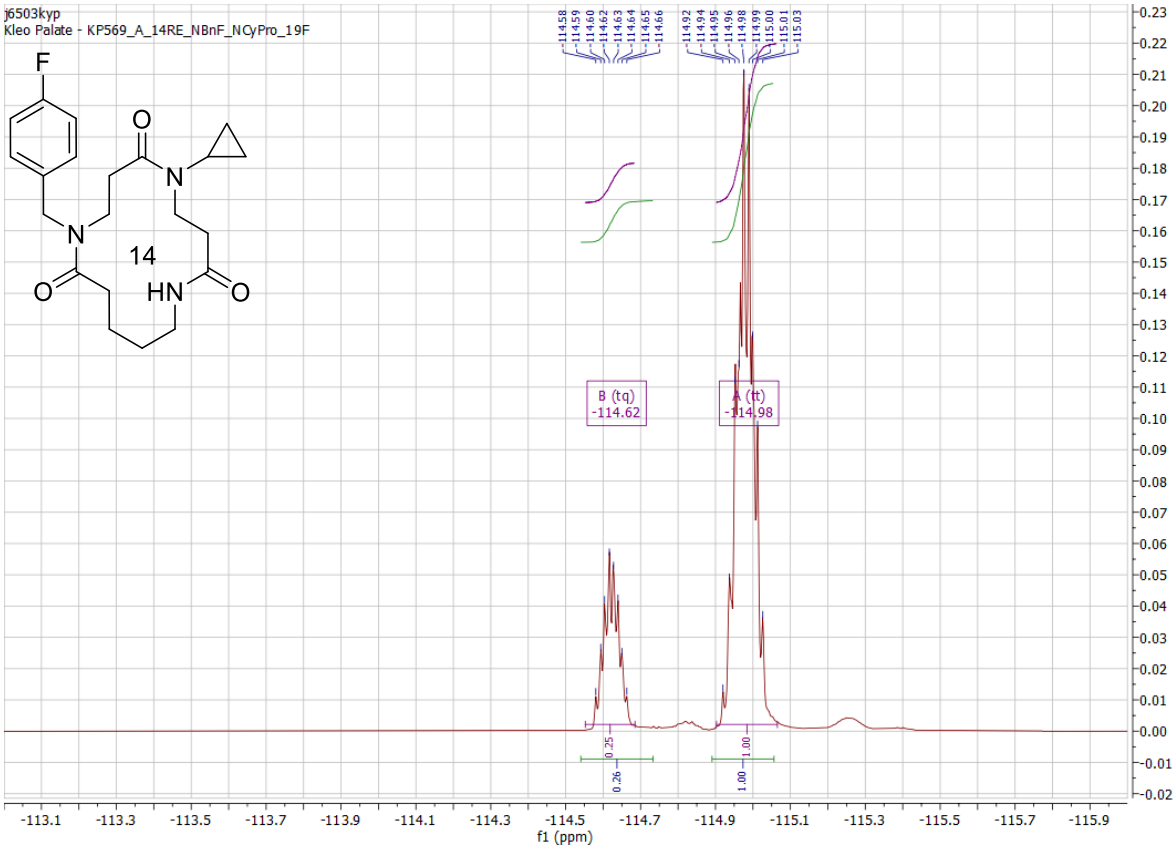

j7051kyp
Kleo Palate - KP579_A_14RE(NBnF,NBn)_19F
F
O
N
N
14
O
HN
O
-114.49
-114.69
-114.87
-115.15
7.00
4.98
1.00
3.99
f1 (ppm)

5-Cyclopropyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (31b) This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 4 main rotamers based on the carbonyl region of the ^{13}C NMR spectrum. Due to overlapping signals in the ^{1}H and ^{19}F NMR, it is difficult to confidently quote a rotamer ratio.

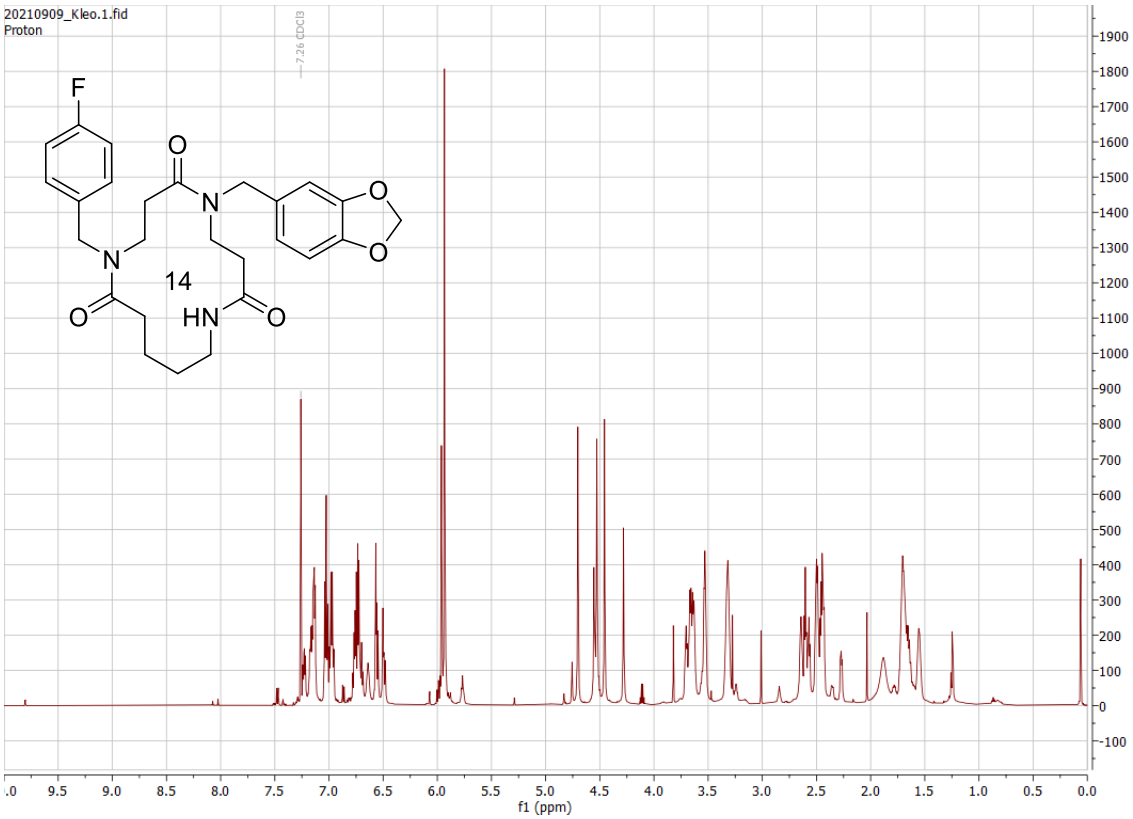


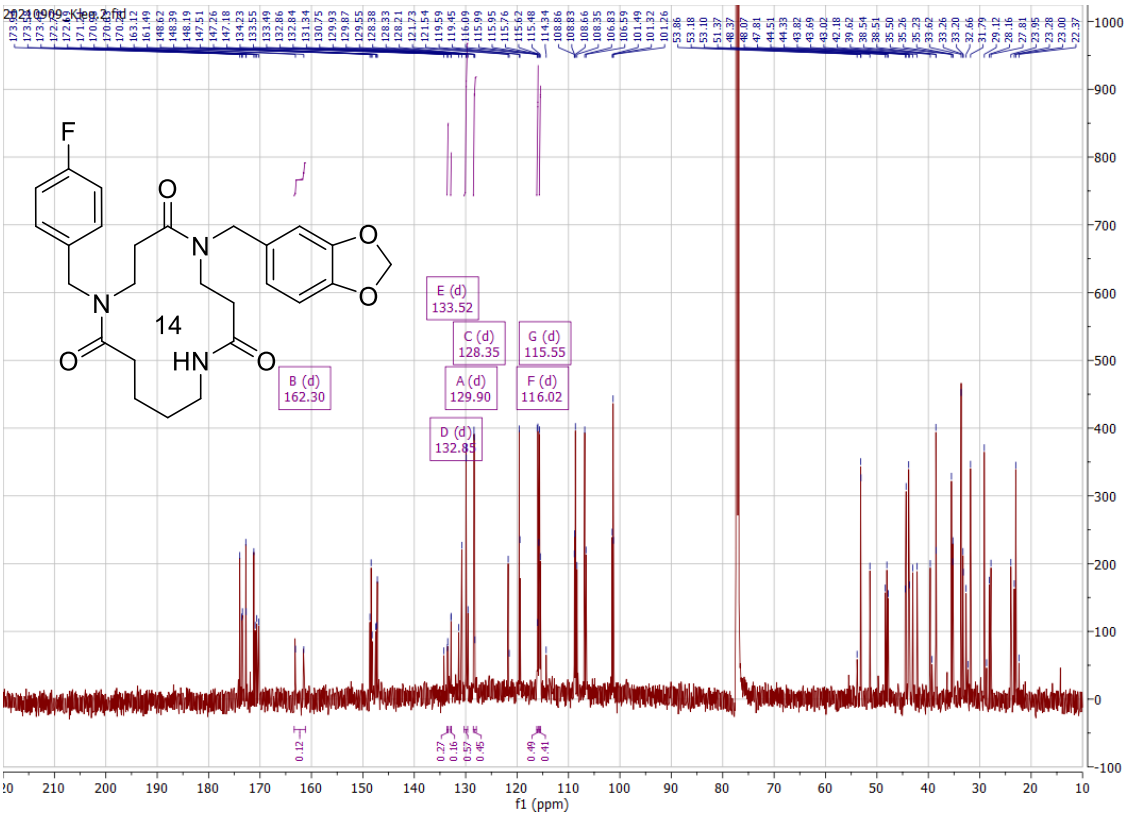


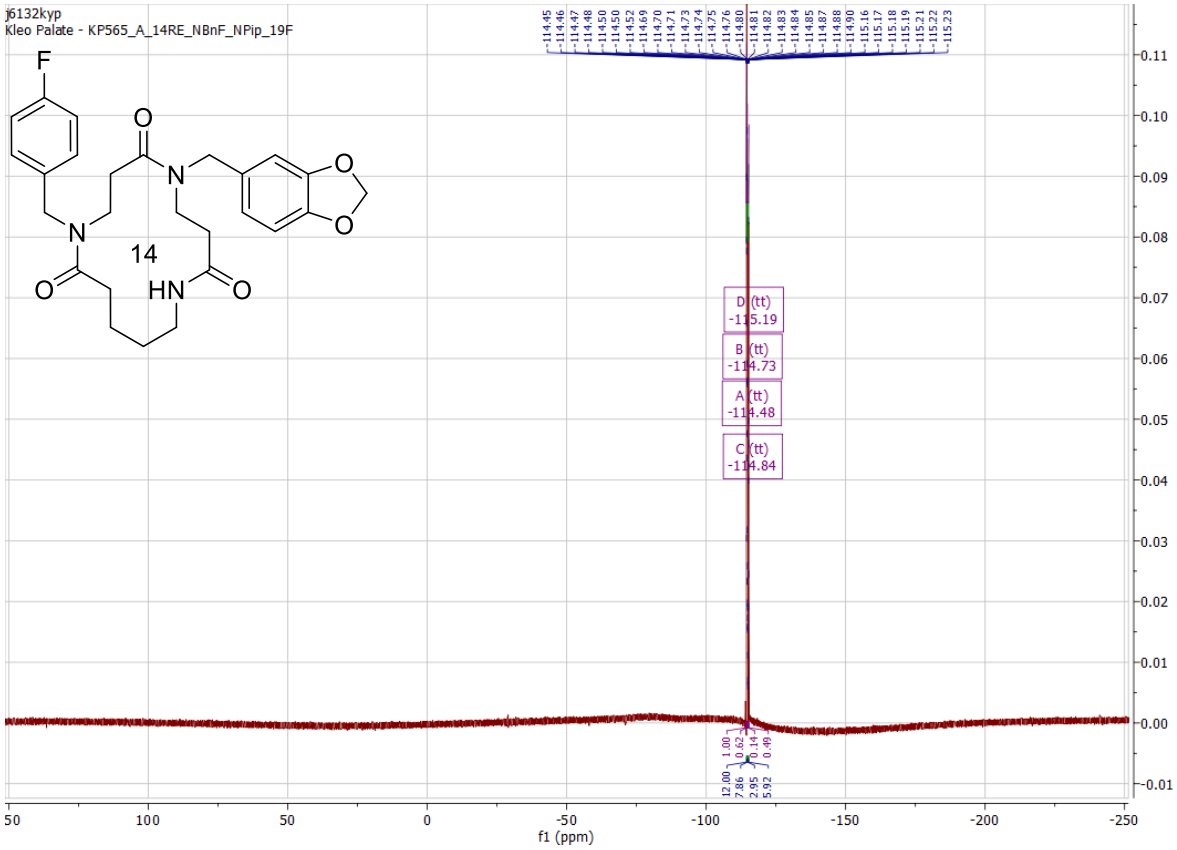

j6503kyp
Kleo Palate - KP569_A_14RE_NBnF_NCyPro_19F
F
O
N
N
14
O
HN
O
B (tq)
-114.62
A (tt)
-114.98
0.26
1.00
f1 (ppm)

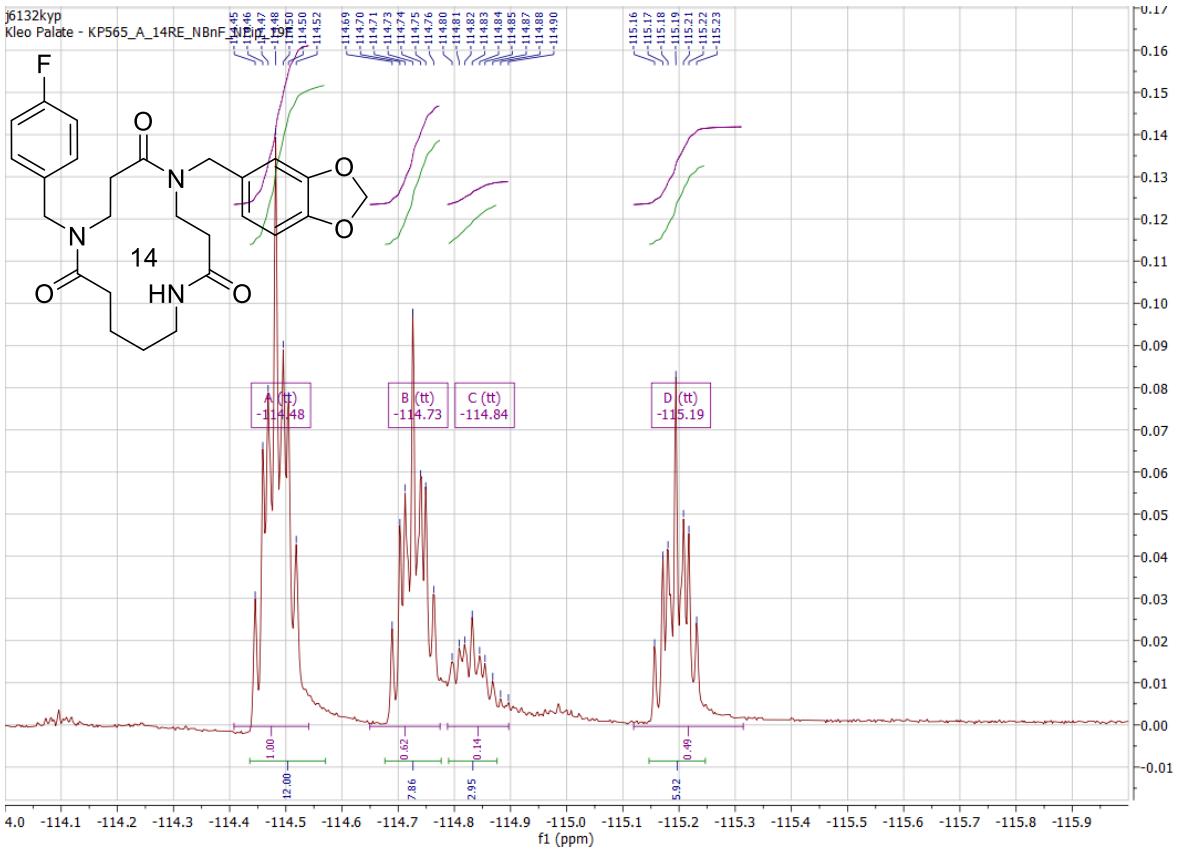

j6503kyp
Kleo Palate - KP569_A_14RE_NBnF_NCyPro_19F
F
O
N
N
14
O
HN
O
B (tq)
-114.62
A (tt)
-114.98
0.26
1.00
f1 (ppm)

5-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (31c) This compounds exists as a complex mixture of rotamers at RT in $CDCl_3$, with 3 main rotamers visible in a ratio of roughly 12:8:6 based on the ^{19}F NMR data and the OC**H**$_2$O signals in the ^{1}H NMR spectrum. A more minor fourth rotamer can also be seen in the ^{19}F NMR spectrum.

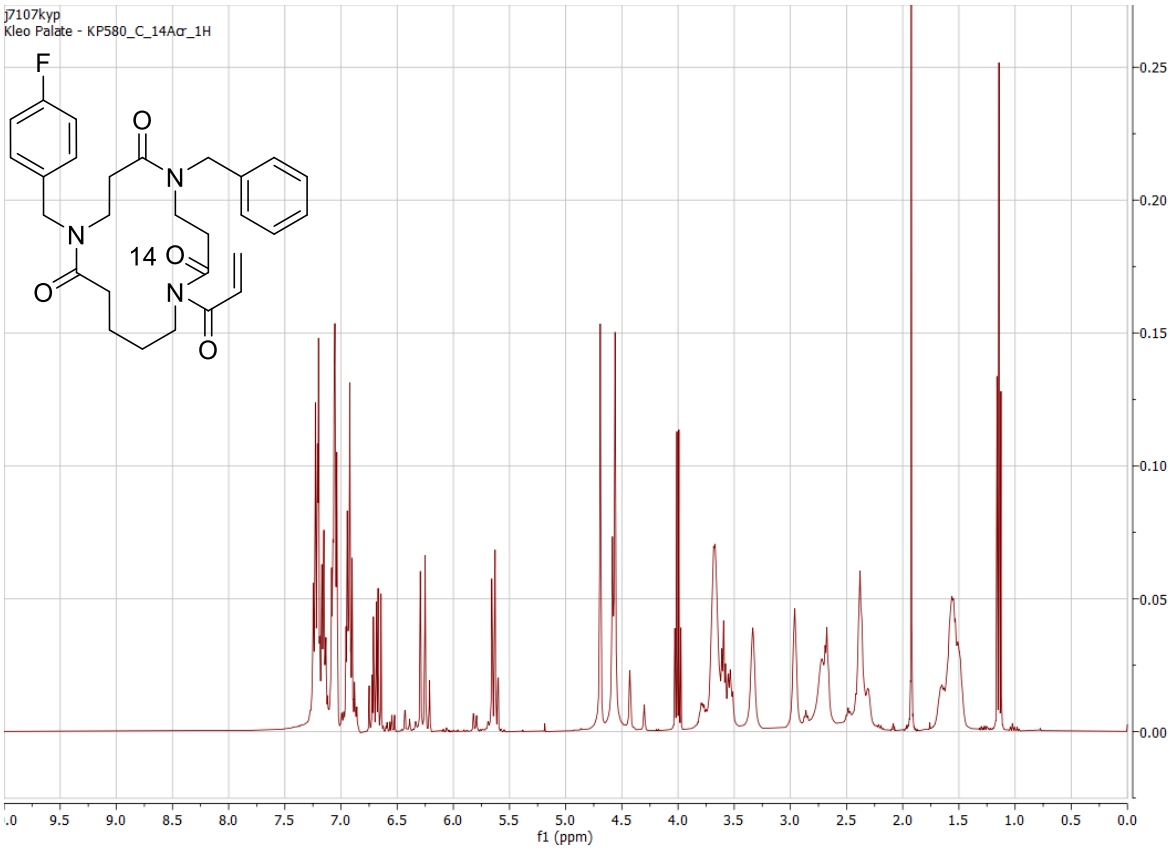


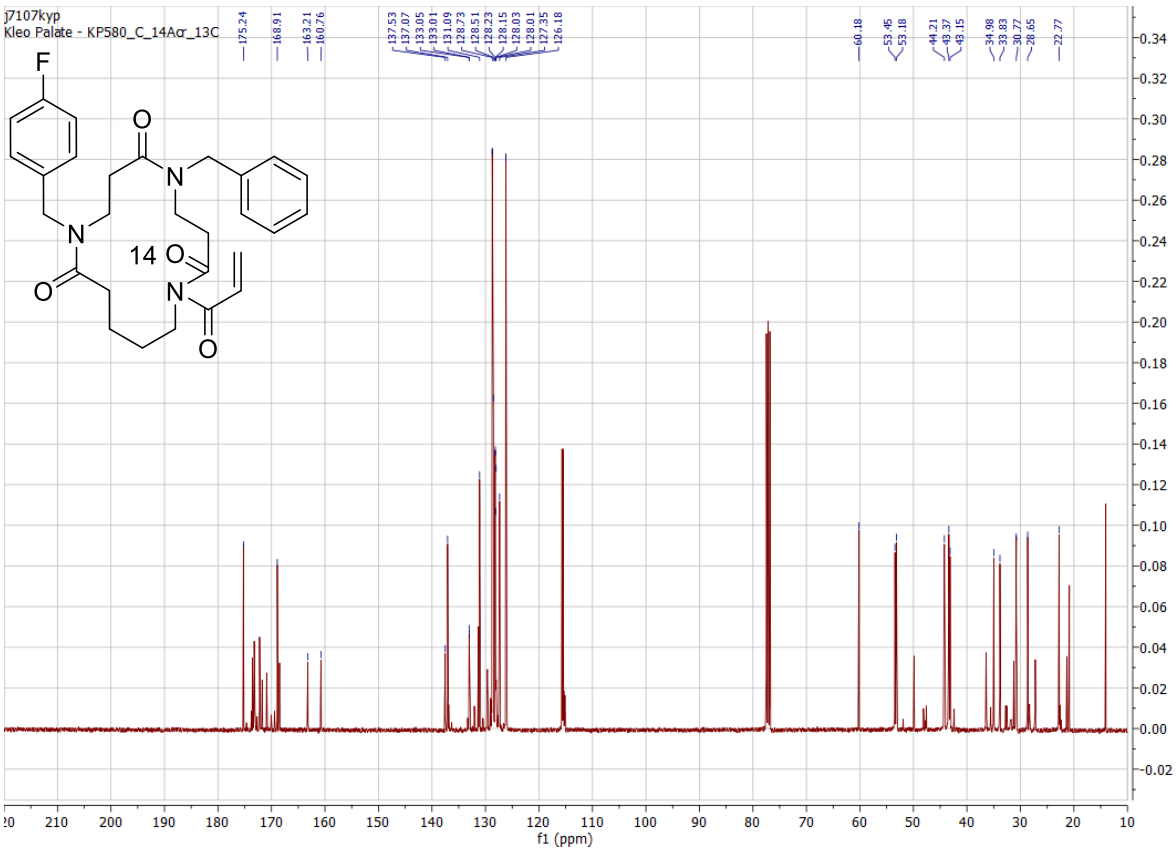


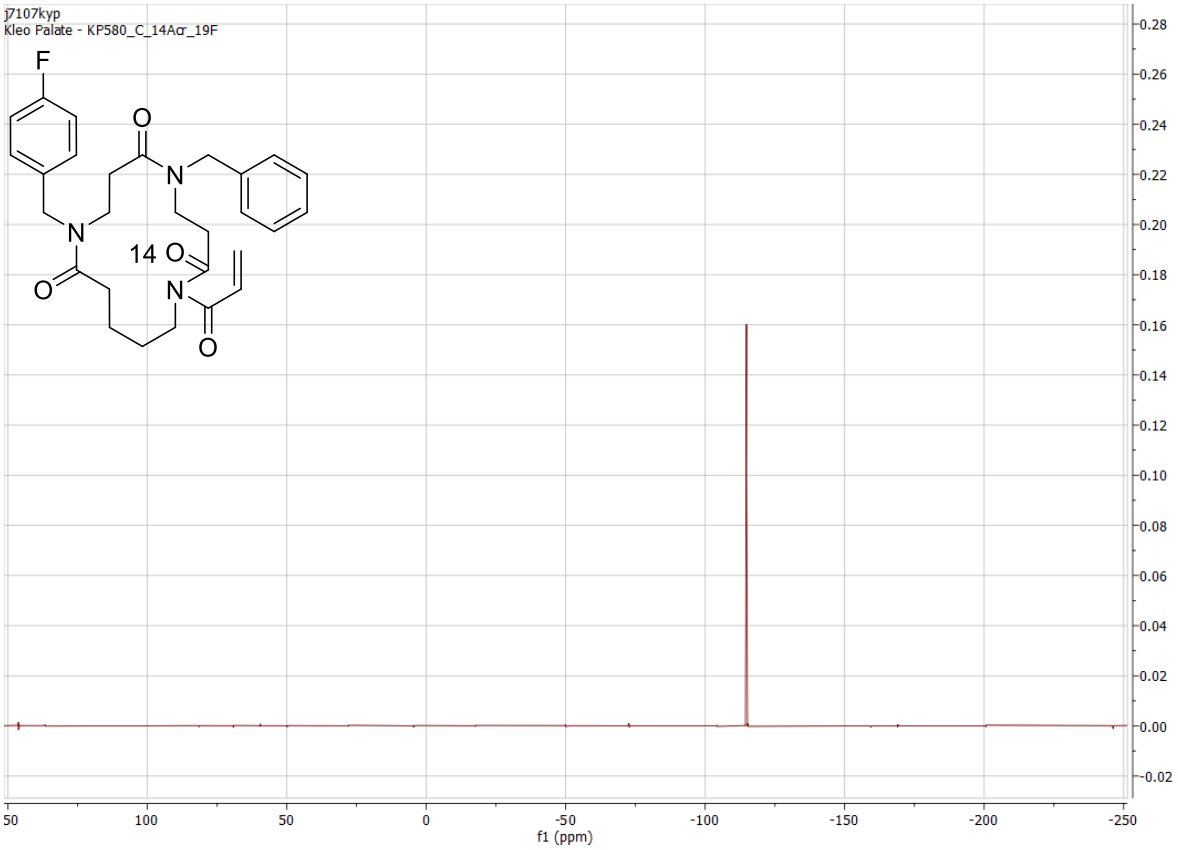

j6132kyp
Kleo Palate - KP565_A_14RE_NBnF_NPip_19F
F
O
N
O
O
N
14
O
HN
O
D (tt)
-115.19
B (tt)
-114.73
A (tt)
-114.48
C (tt)
-114.84
f1 (ppm)

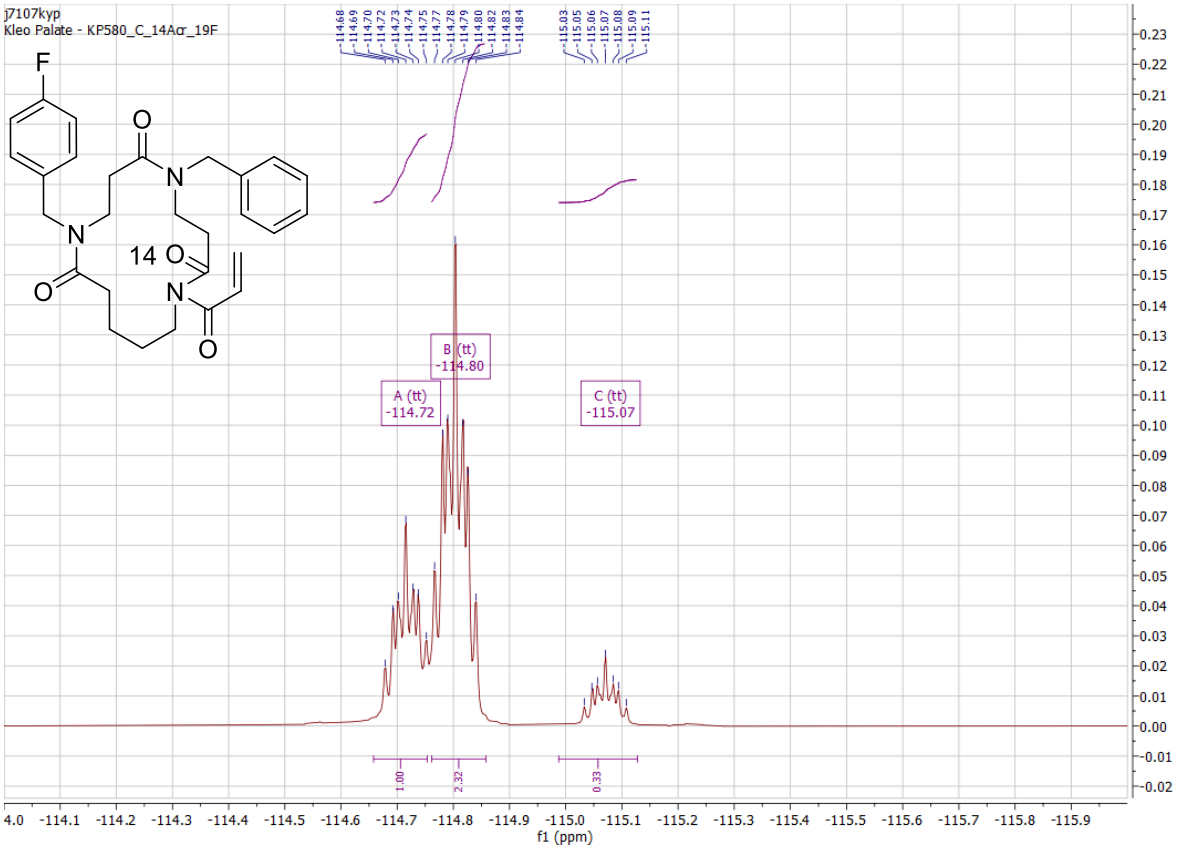

j6132kyp
Kleo Palate - KP565_A_14RE_NBnF_NPip_19F
F
O
N
O
O
N
14
O
HN
O
A (tt)
-114.48
B (tt)
-114.73
C (tt)
-114.84
D (tt)
-115.19
f1 (ppm)

1-Acryloyl-5-benzyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (S2)

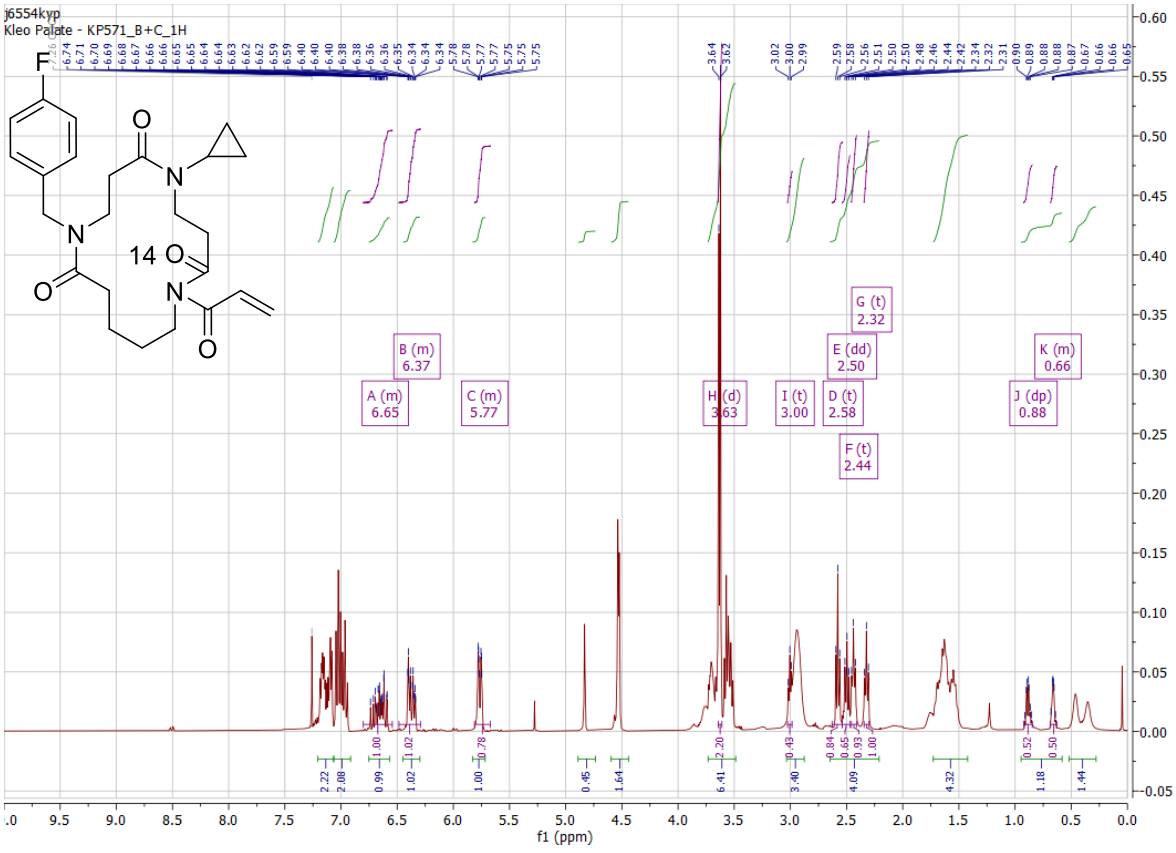


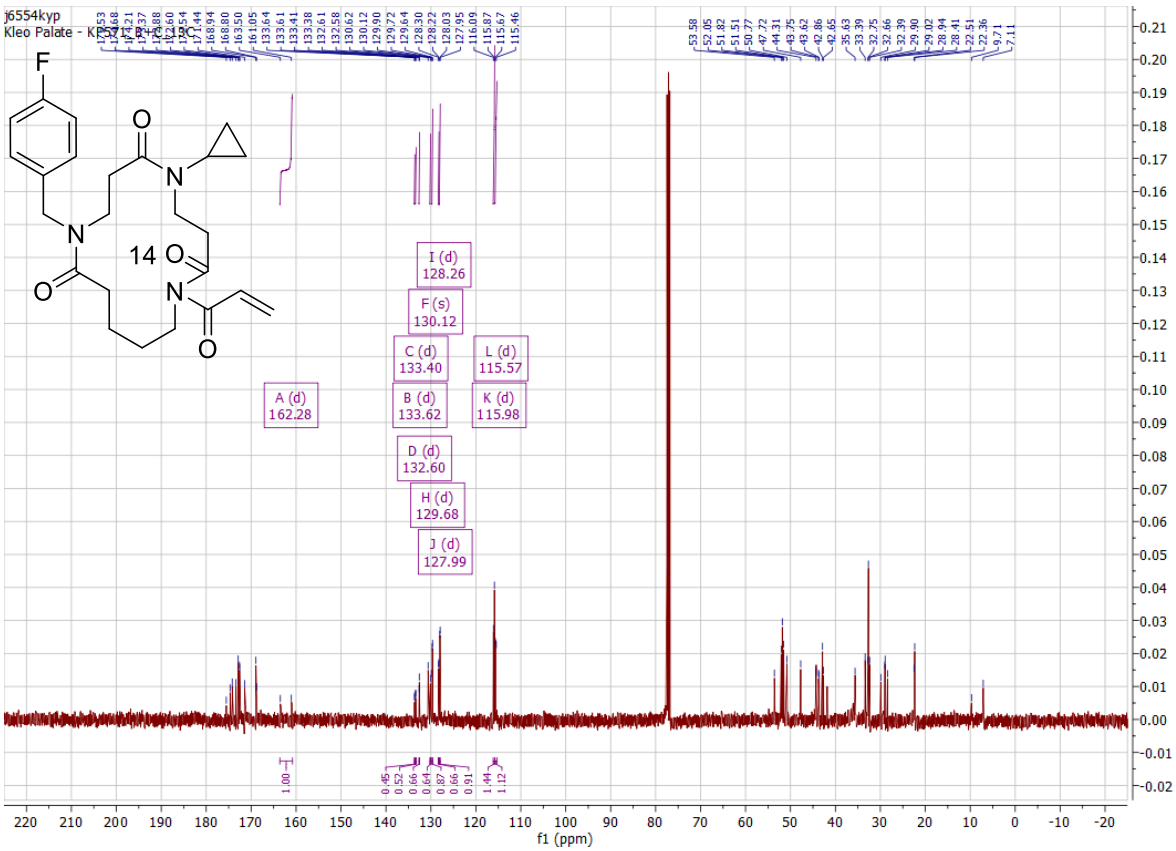


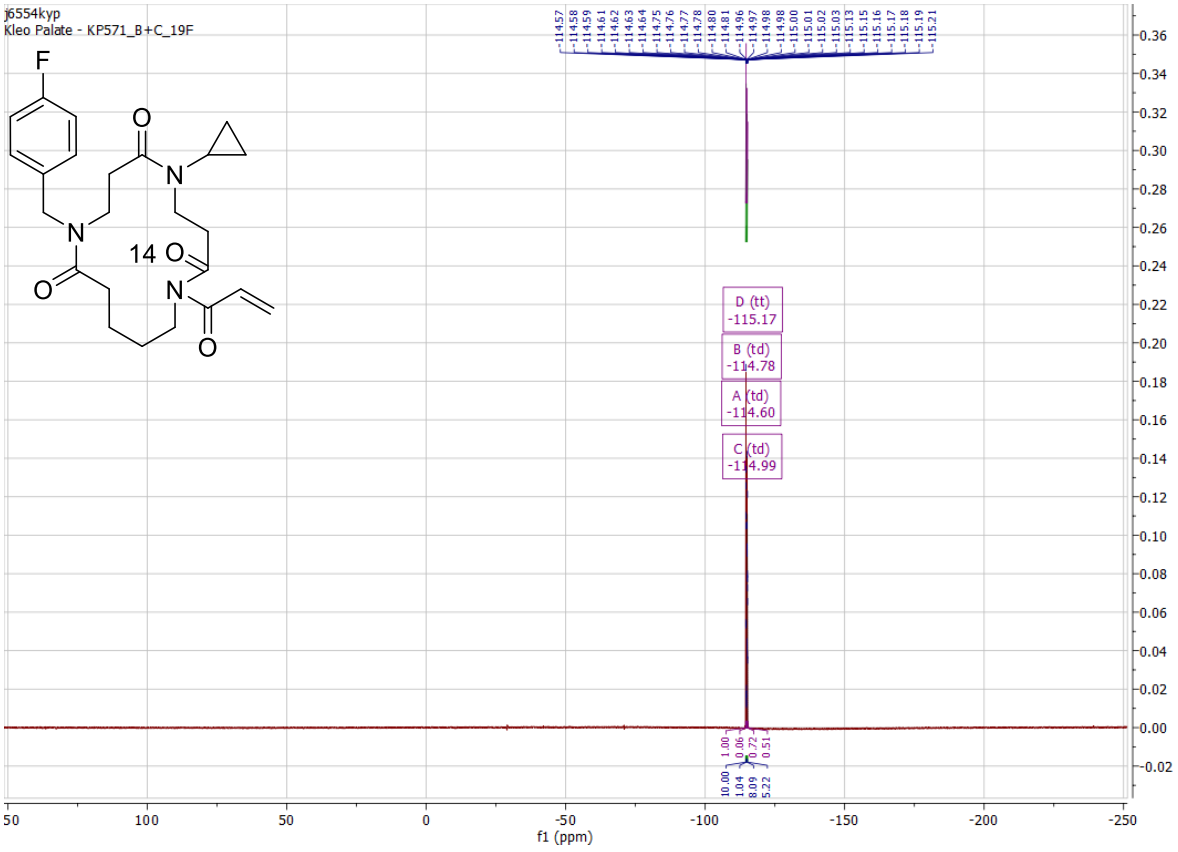

j7107kyp
Kleo Palate - KP580_C_14Acr_19F
F
O
N
N
14 O
O
N
O
O
f1 (ppm)

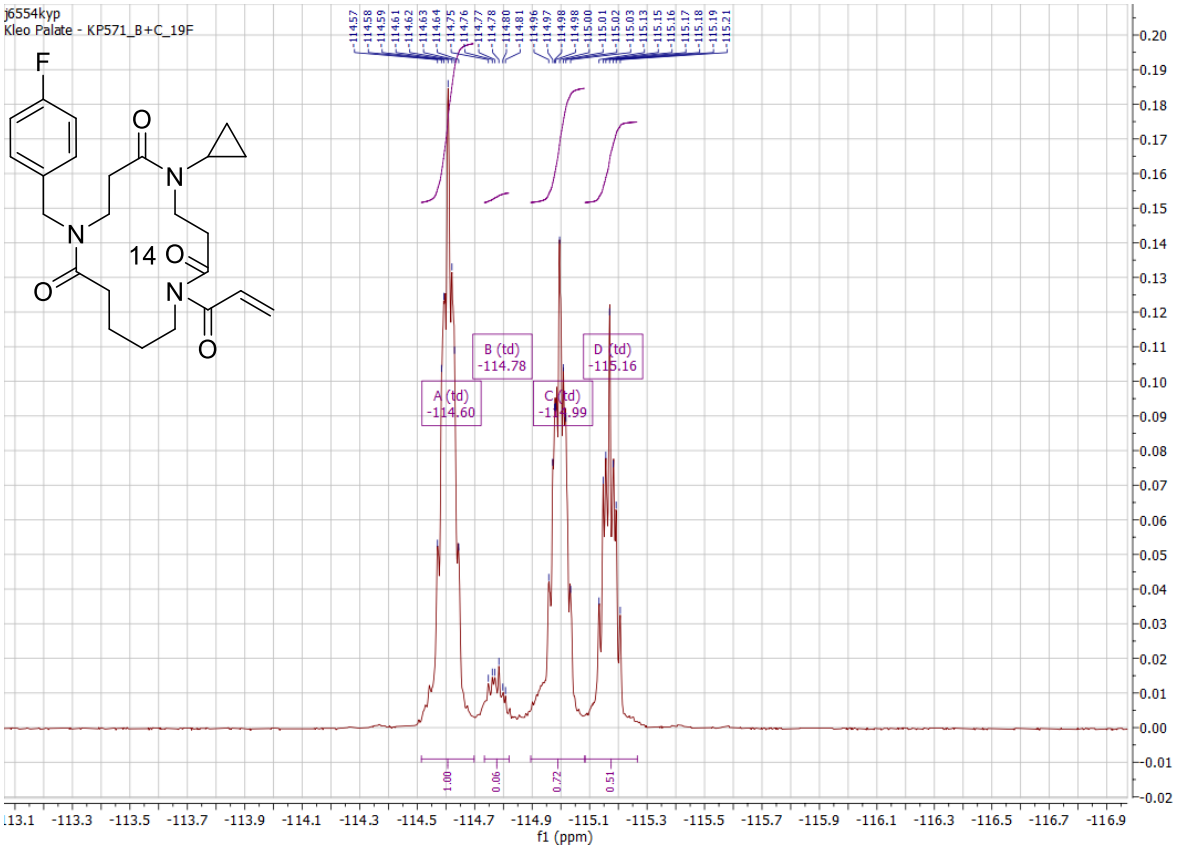

j7107kyp
Kleo Palate - KP580_C_14Acr_19F
F
O
N
N
14 O
O
N
O
B (tt)
-114.80
A (tt)
-114.72
C (tt)
-115.07
1.00
2.32
0.33
f1 (ppm)

1-Acryloyl-5-cyclopropyl-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (S3)

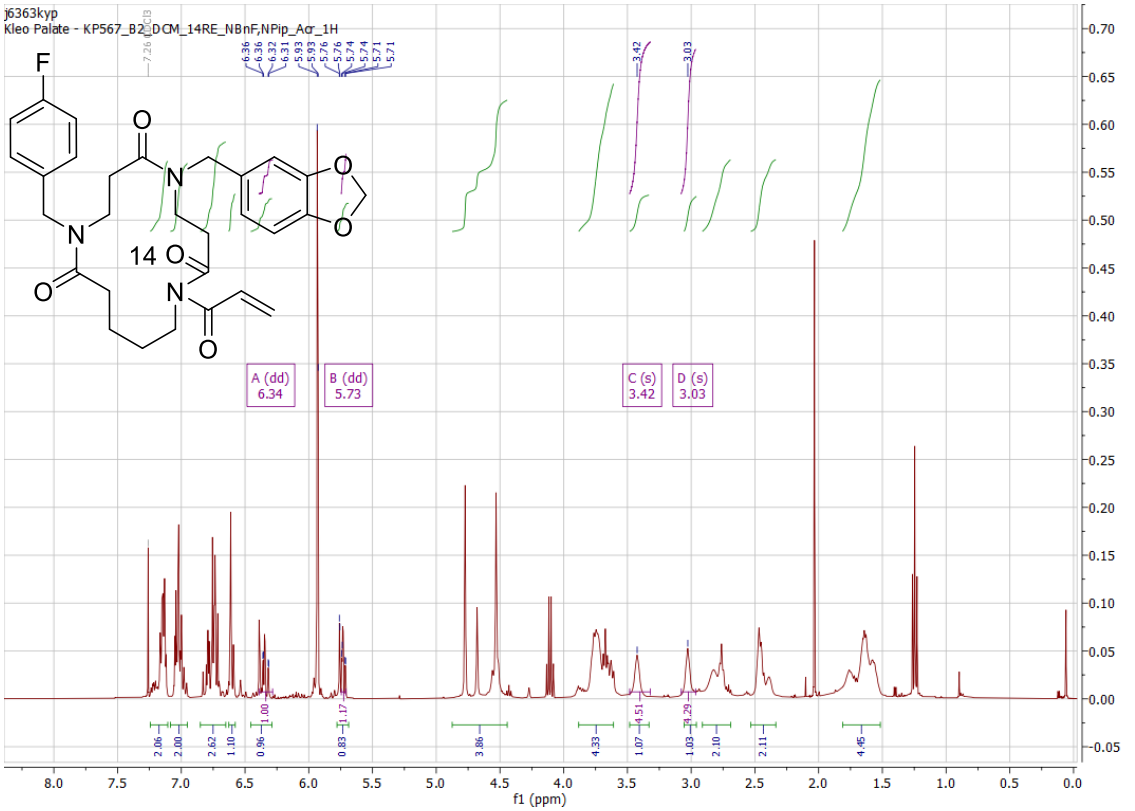


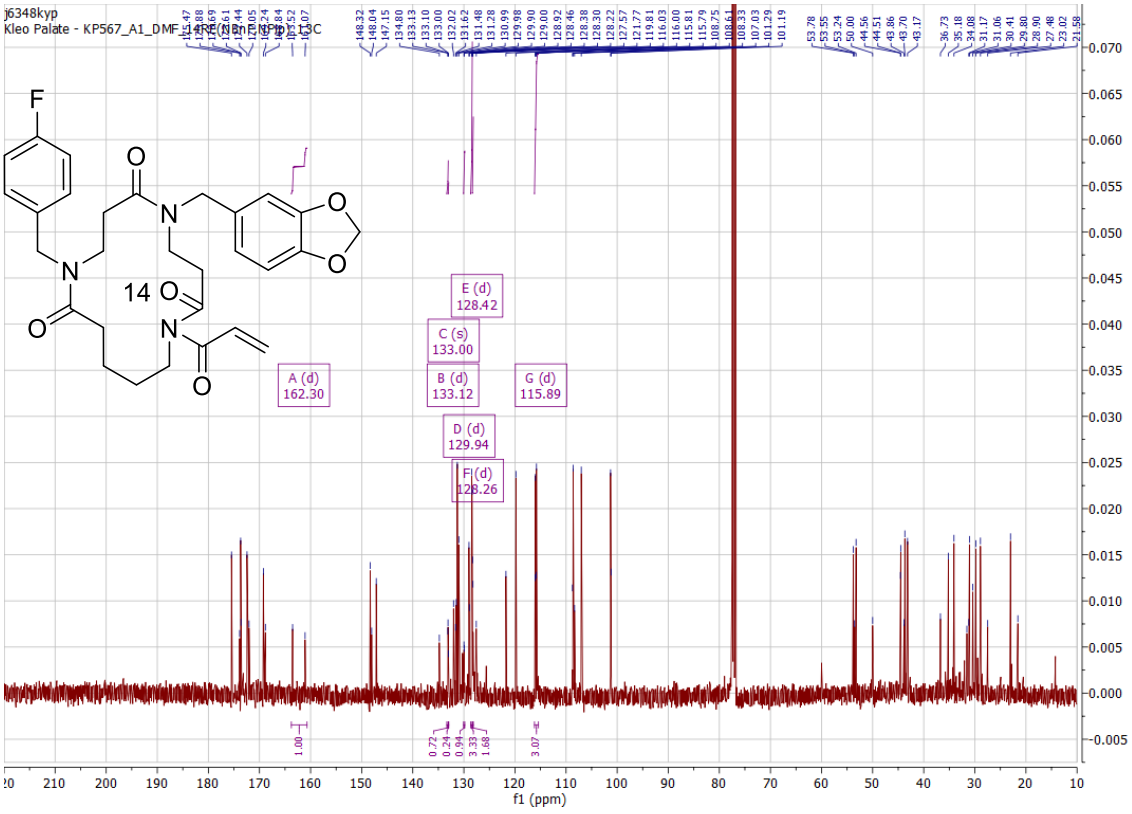


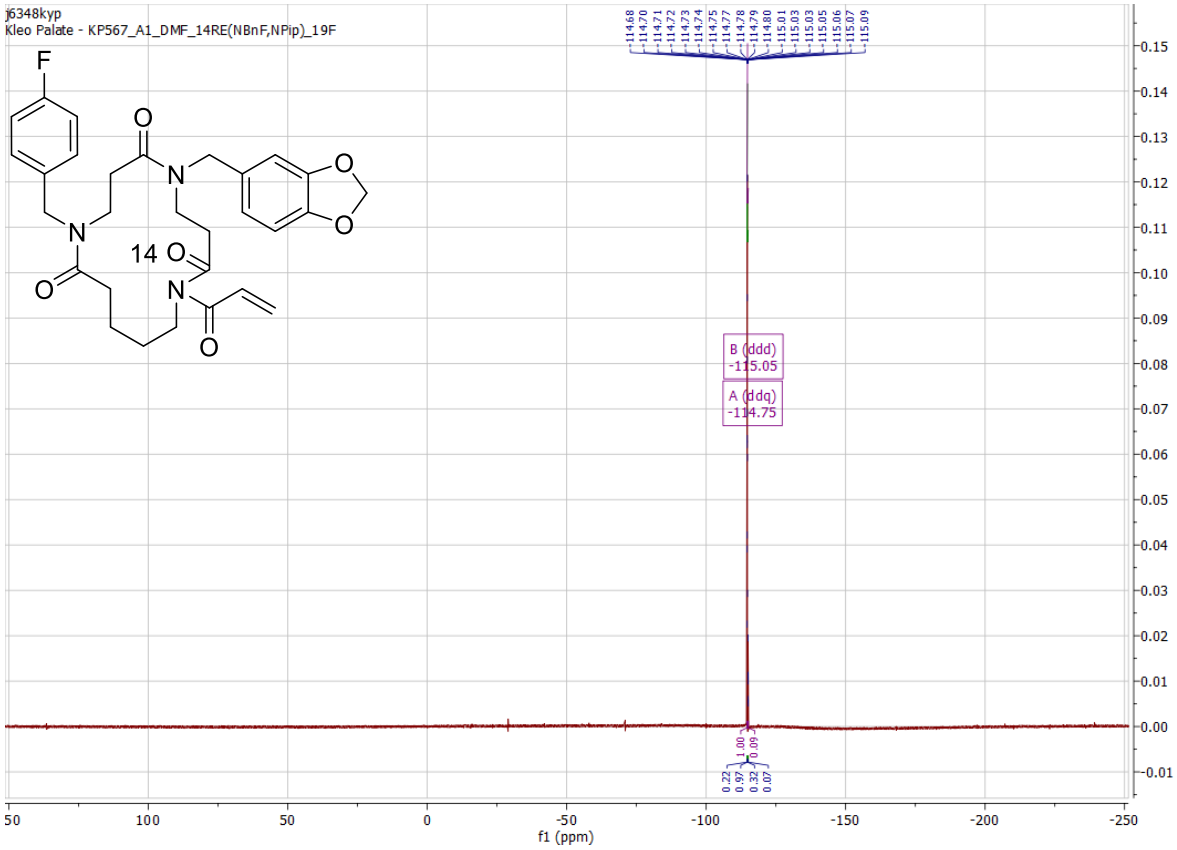

j6554kyp
Kleo Palate - KP571_B+C_19F
D (tt)
-115.17
B (td)
-114.78
A (td)
-114.60
C (td)
-114.99
f1 (ppm)

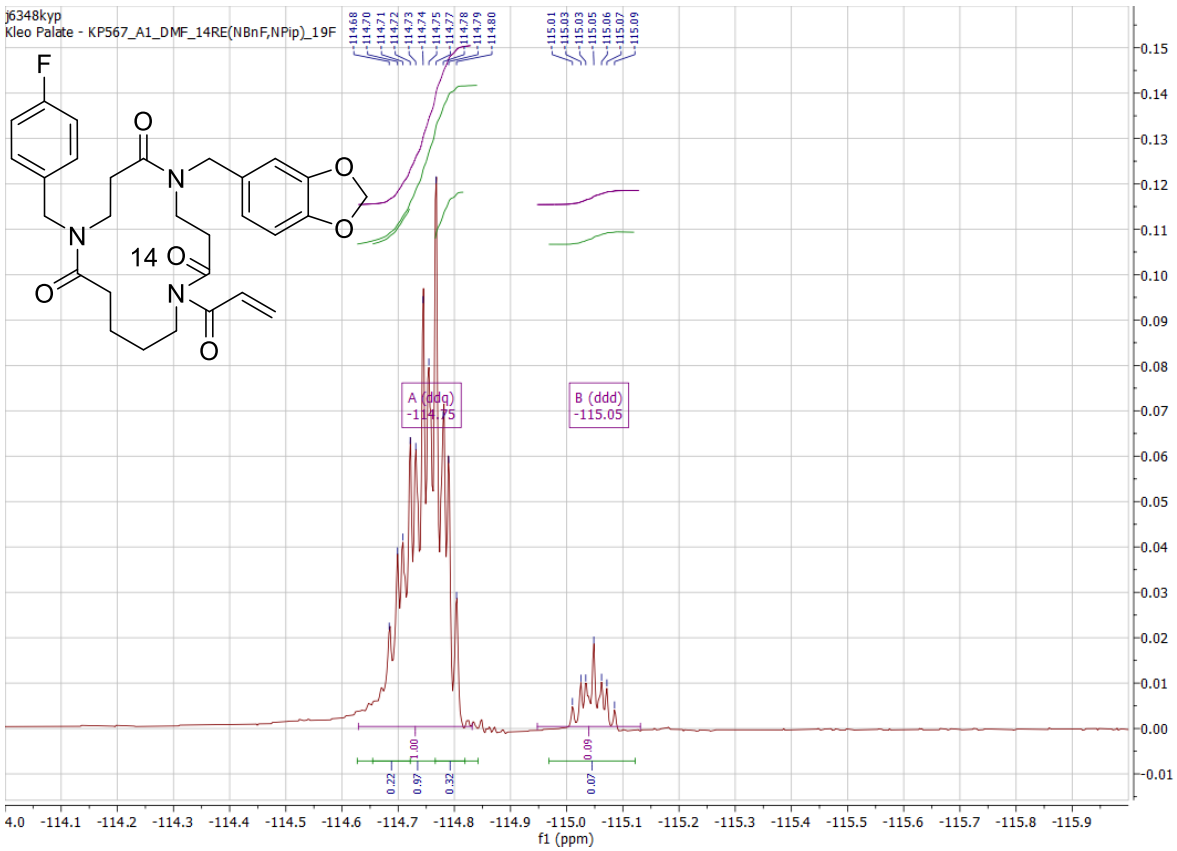

j6554kyp
Kleo Palate - KP571_B+C_19F
B (td)
-114.78
D (td)
-115.16
A (td)
-114.60
f1 (ppm)

1-Acryloyl-5-(benzo[*d*][1,3]dioxol-5-ylmethyl)-9-(4-fluorobenzyl)-1,5,9-triazacyclotetradecane-2,6,10-trione (S4) This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 2 major rotameric forms (≈3:2) based on the carbonyl region of the ^{13}C NMR spectrum, and a third more minor rotamer based on the ^{19}F NMR data. Due to overlapping signals in the ^{1}H and ^{19}F NMR, it is difficult to confidently quote a rotamer ratio.

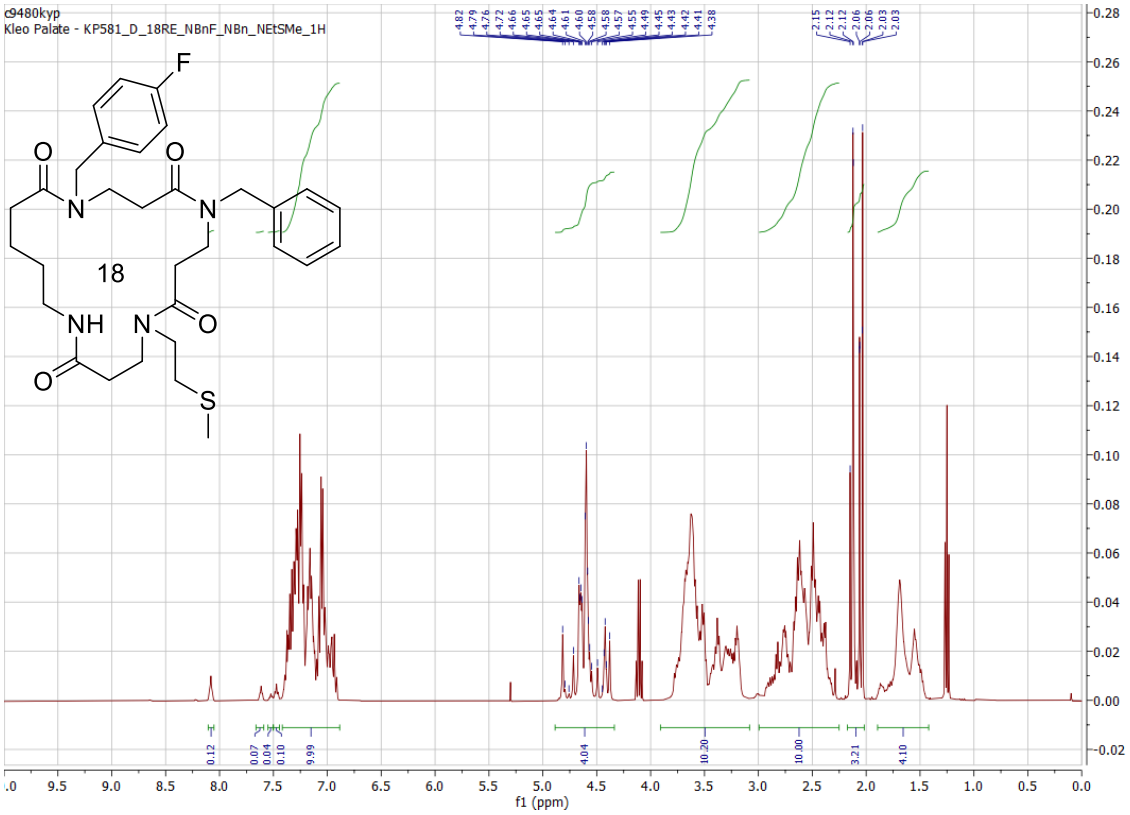


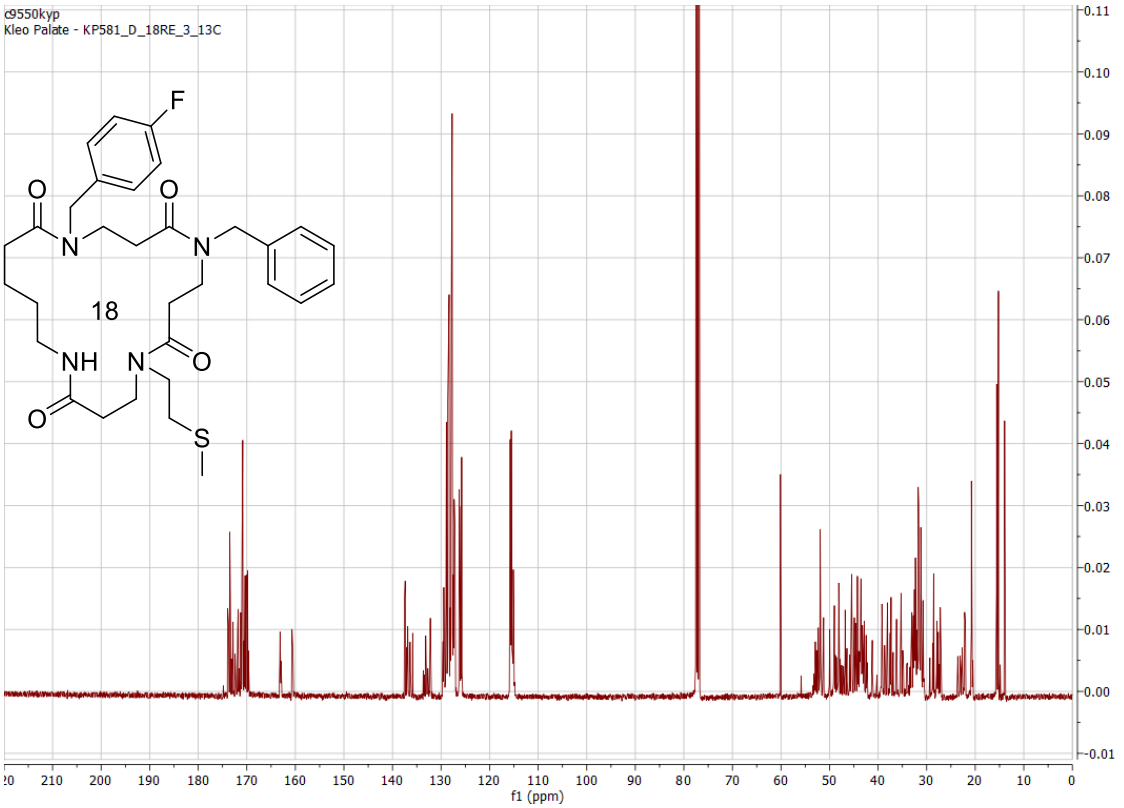


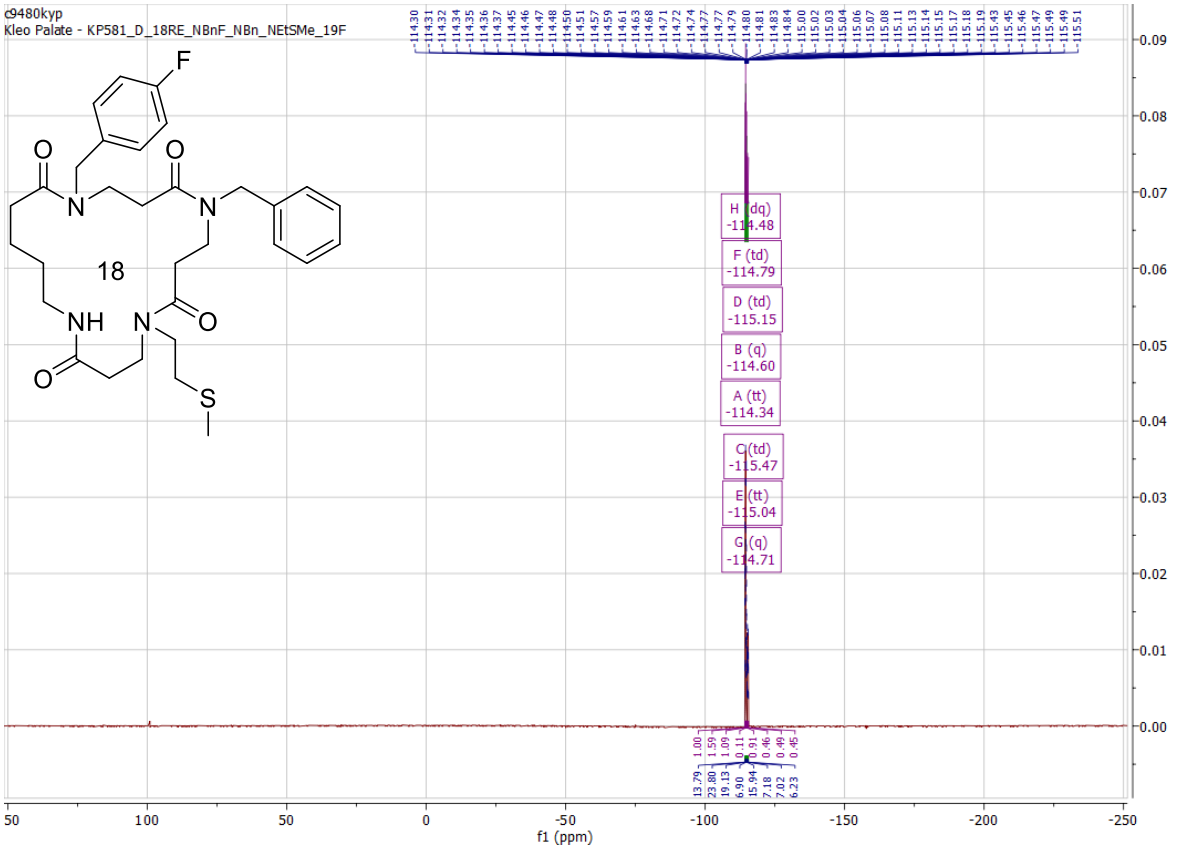

j6348kyp
Kleo Palate - KP567_A1_DMF_14RE(NBnF,NPip)_19F
B (ddd)
-115.05
A (ddq)
-114.75
f1 (ppm)

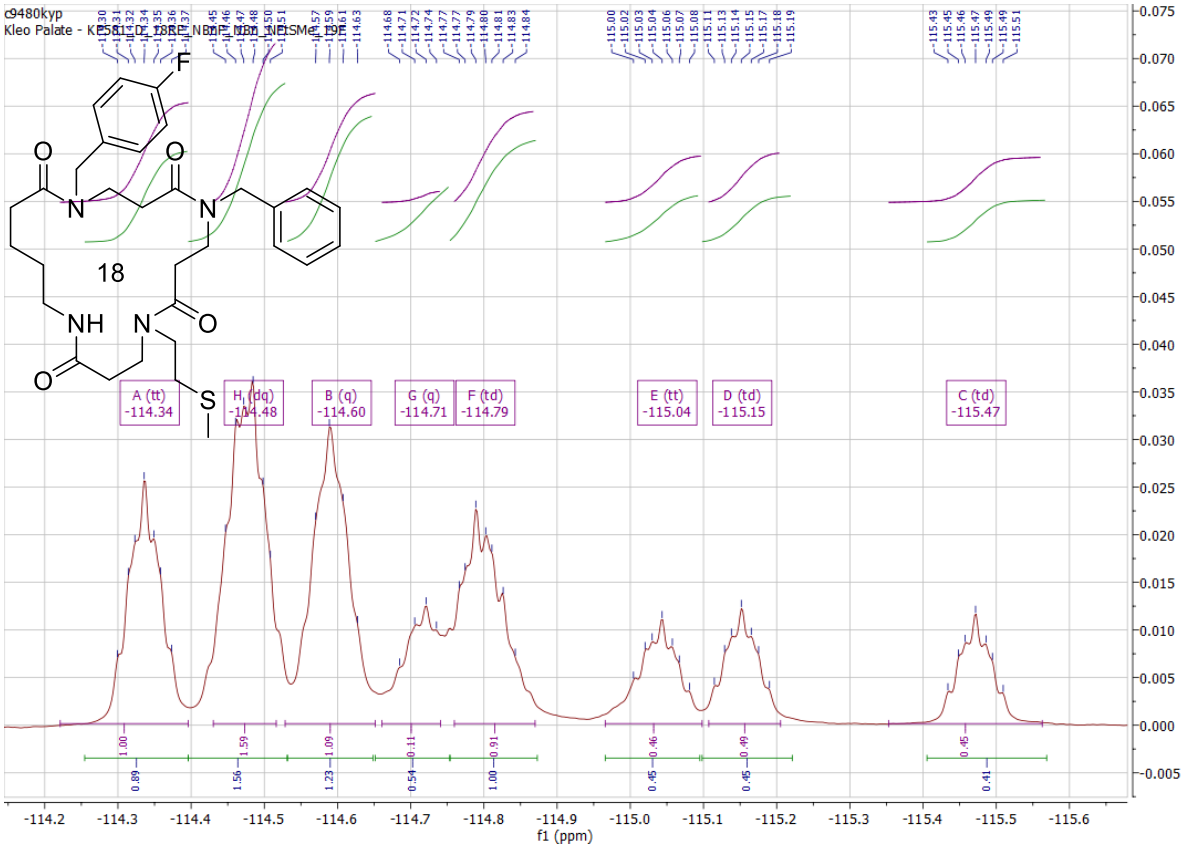

j6348kyp
Kleo Palate - KP567_A1_DMF_14RE(NBnF,NPip)_19F
A (ddq)
-114.75
B (ddd)
-115.05
f1 (ppm)

9-Benzyl-13-(4-fluorobenzyl)-5-(2-(methylthio)ethyl)-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (32a) This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 8 rotameric forms observable in the ^{19}F NMR data, and 32 (i.e. 4 × 8) signals consistent with CO groups in the ^{13}C NMR. Due to overlapping signals in the NMR data, it is not possible to confidently quote a rotamer ratio.

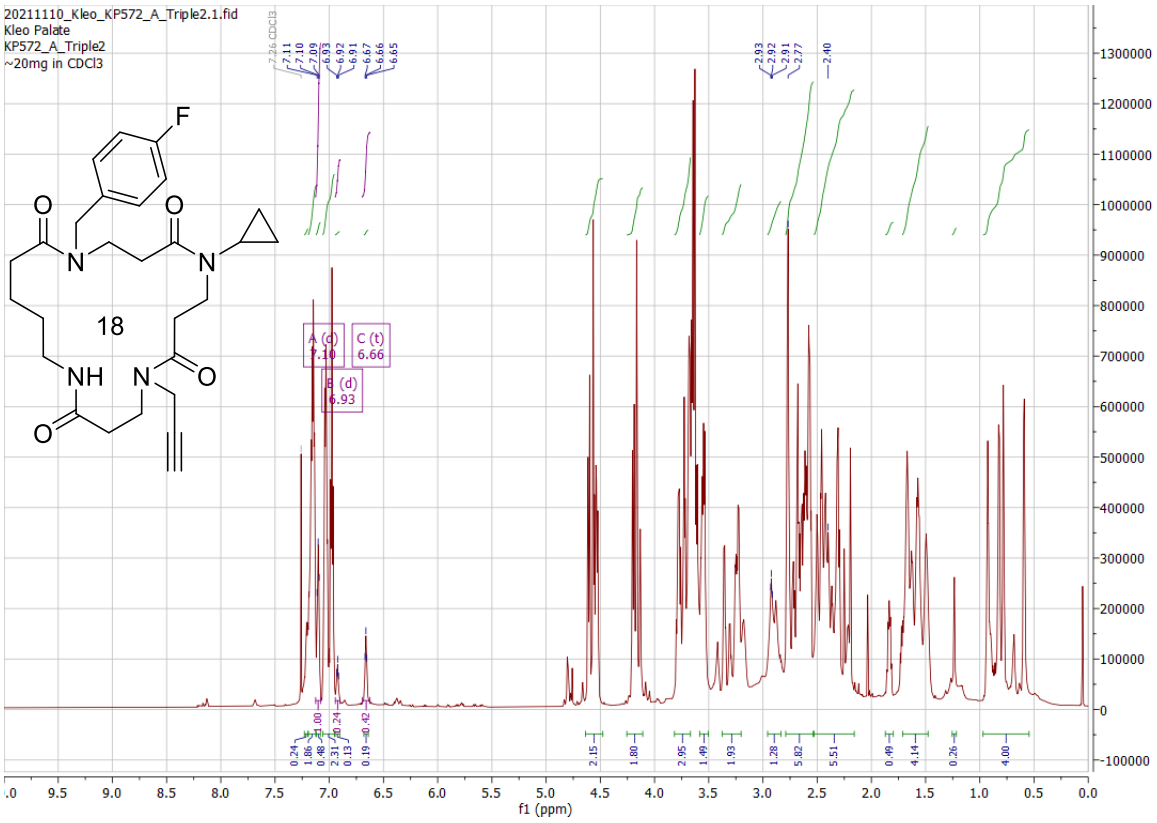


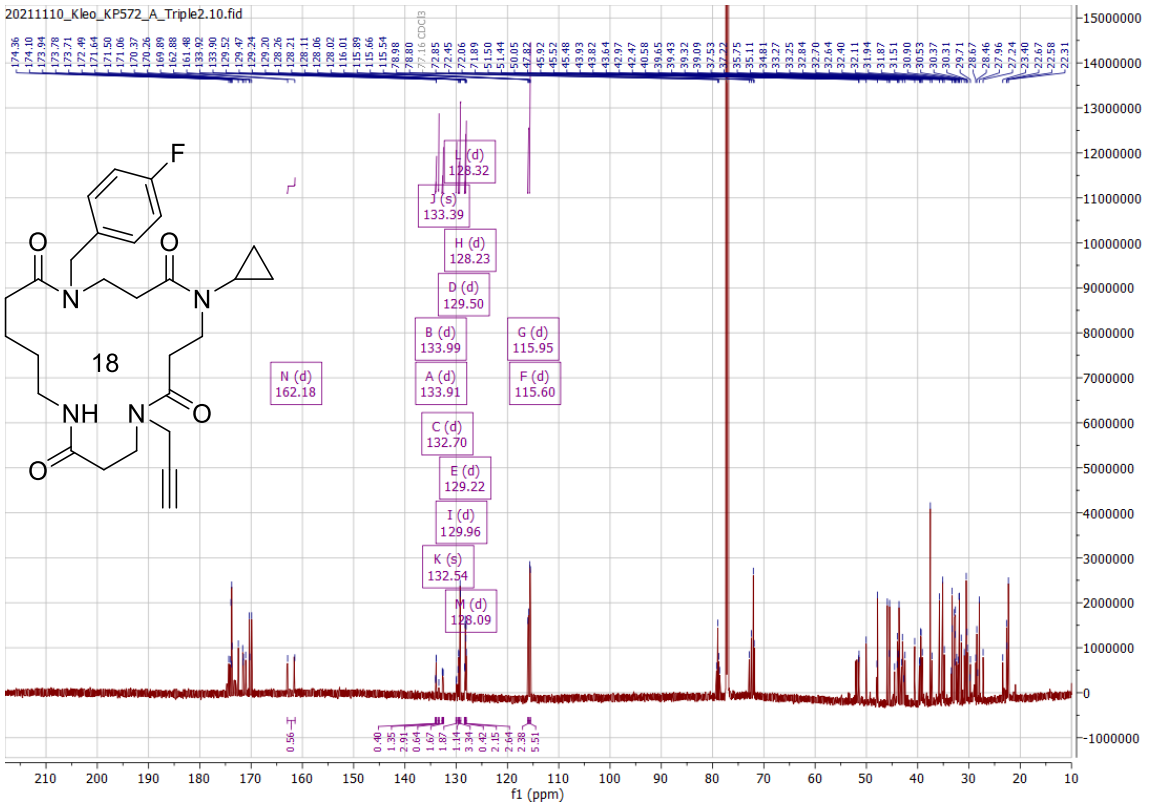


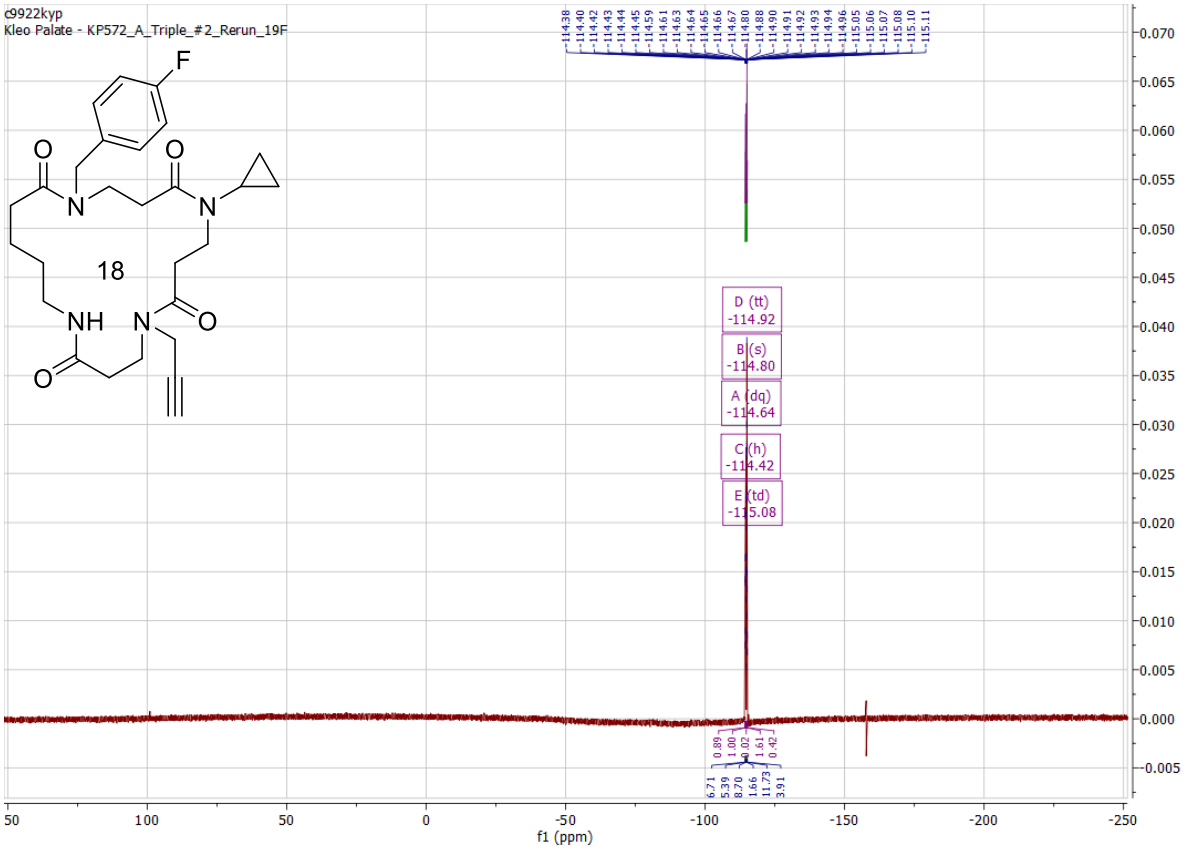

c9480kyp
Kleo Palate - KP581_D_18RE_NBnF_NBn_NEtSMe_19F
F
O
O
N
N
18
NH
N
O
O
O
S
H (dq)
-114.48
F (td)
-114.79
D (td)
-115.15
B (q)
-114.60
A (tt)
-114.34
C (td)
-115.47
E (tt)
-115.04
G (q)
-114.71
f1 (ppm)

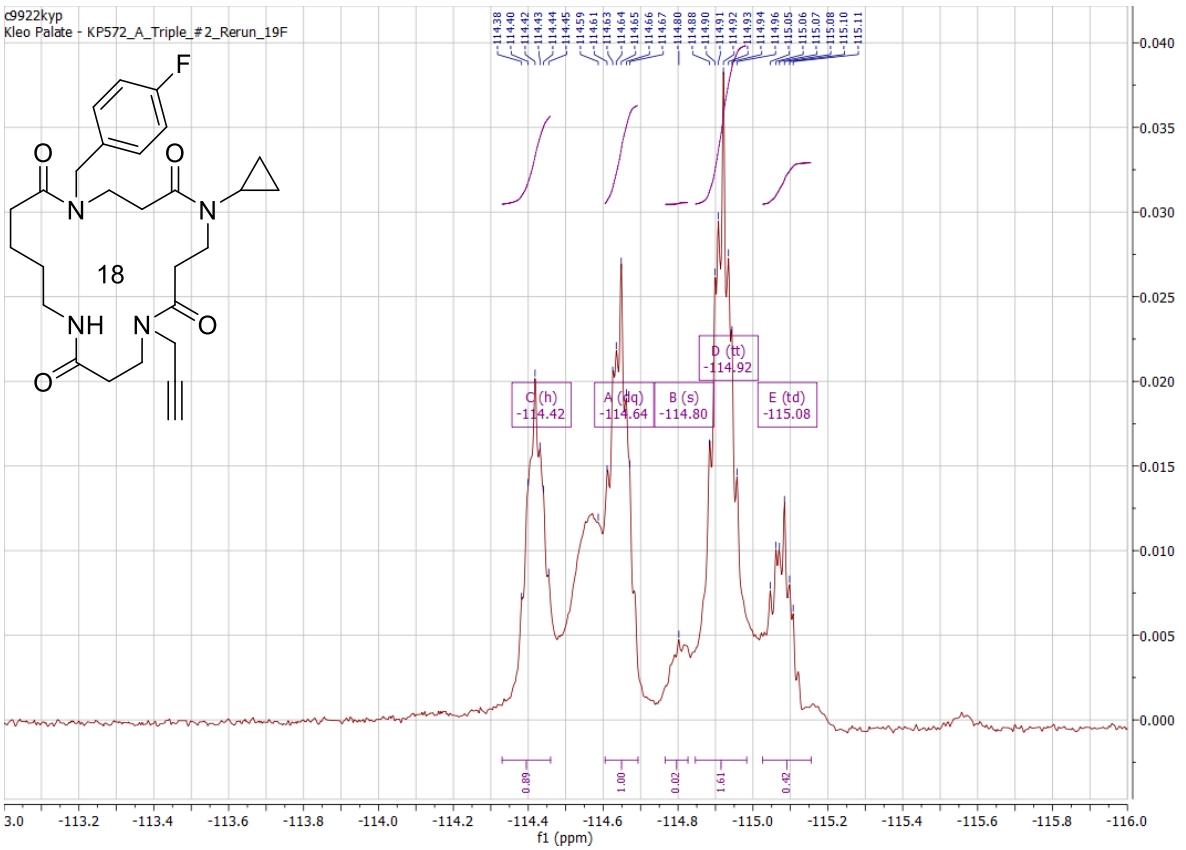

c9480kyp
Kleo Palate - KP581_D_18RE_NBnF_NBn_NEtSMe_19F
A (tt)
-114.34
H (dq)
-114.48
B (q)
-114.60
G (q)
-114.71
F (td)
-114.79
E (tt)
-115.04
D (td)
-115.15
C (td)
-115.47
f1 (ppm)

9-Cyclopropyl-13-(4-fluorobenzyl)-5-(prop-2-yn-1-yl)-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (32b) This compound exists as a complex mixture of rotamers at RT in $CDCl_3$, with 6 rotameric forms observable in the ^{19}F NMR data. Due to overlapping signals in the NMR data, it is not possible to confidently quote a rotamer ratio.

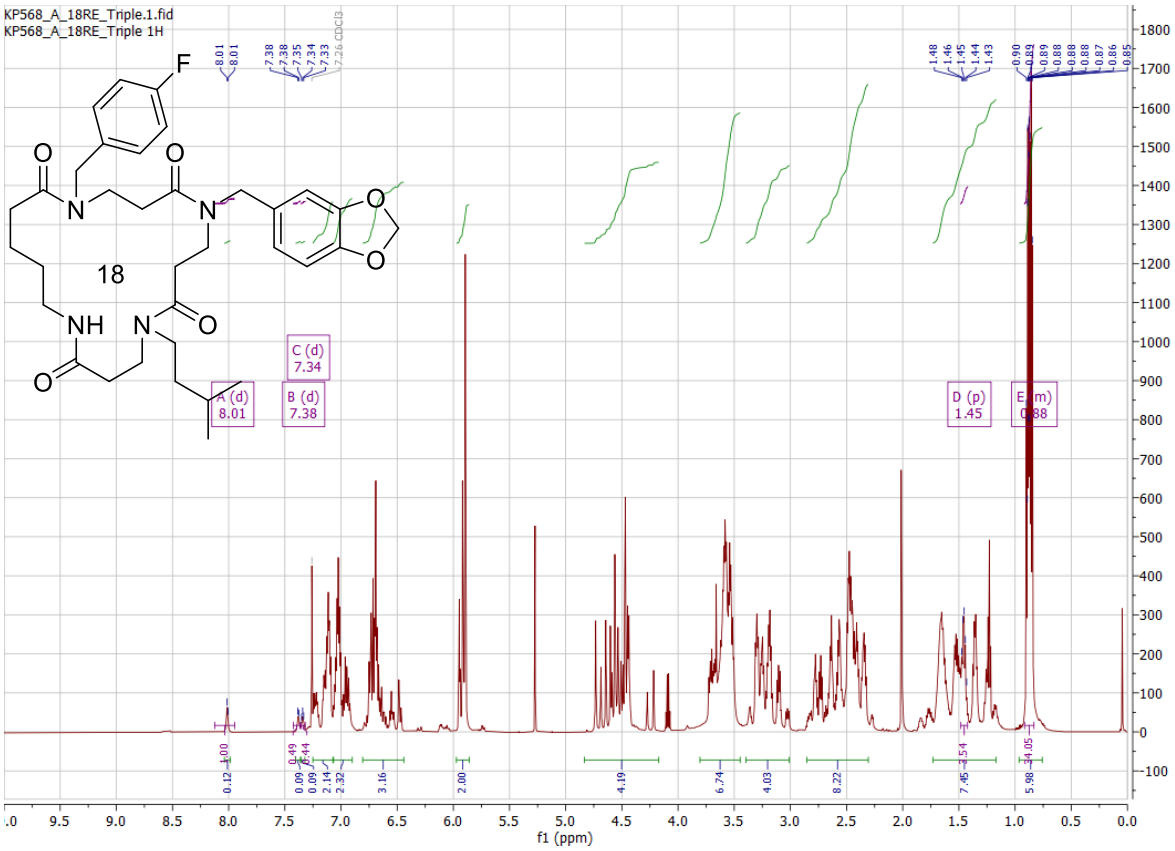


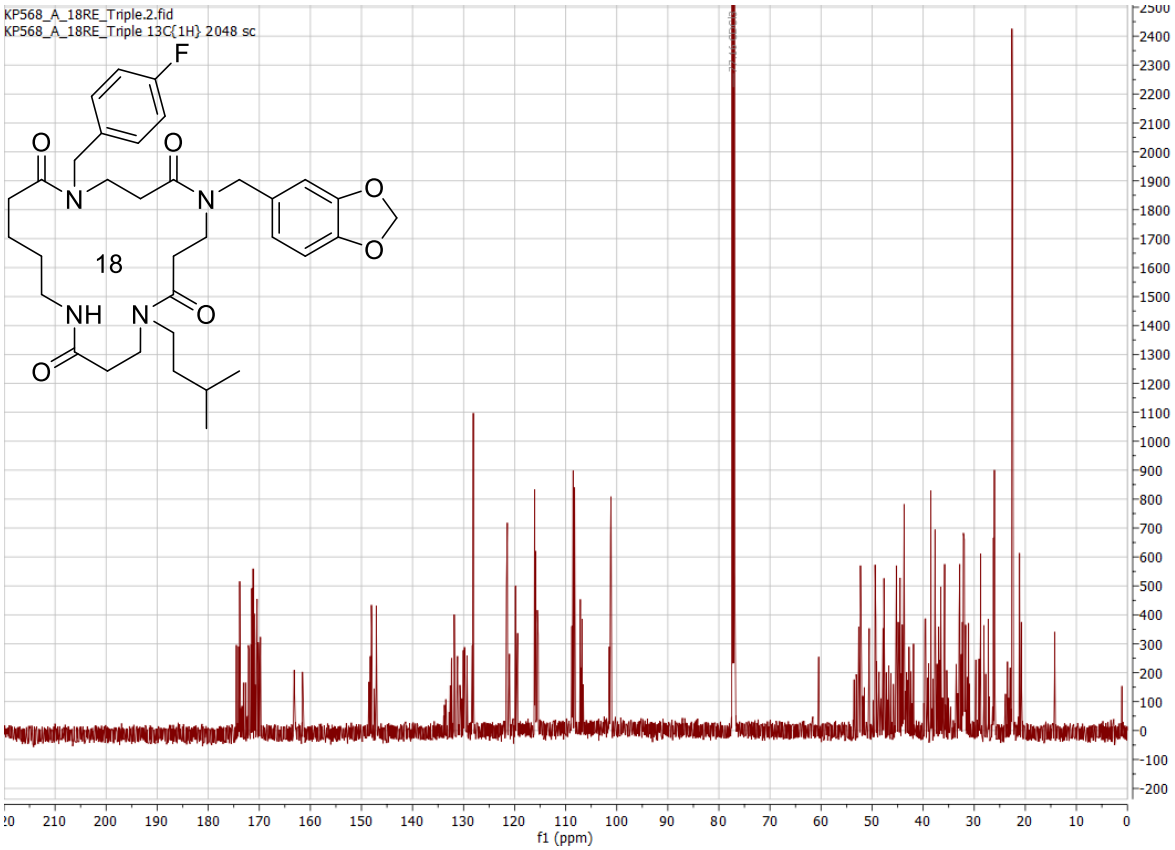


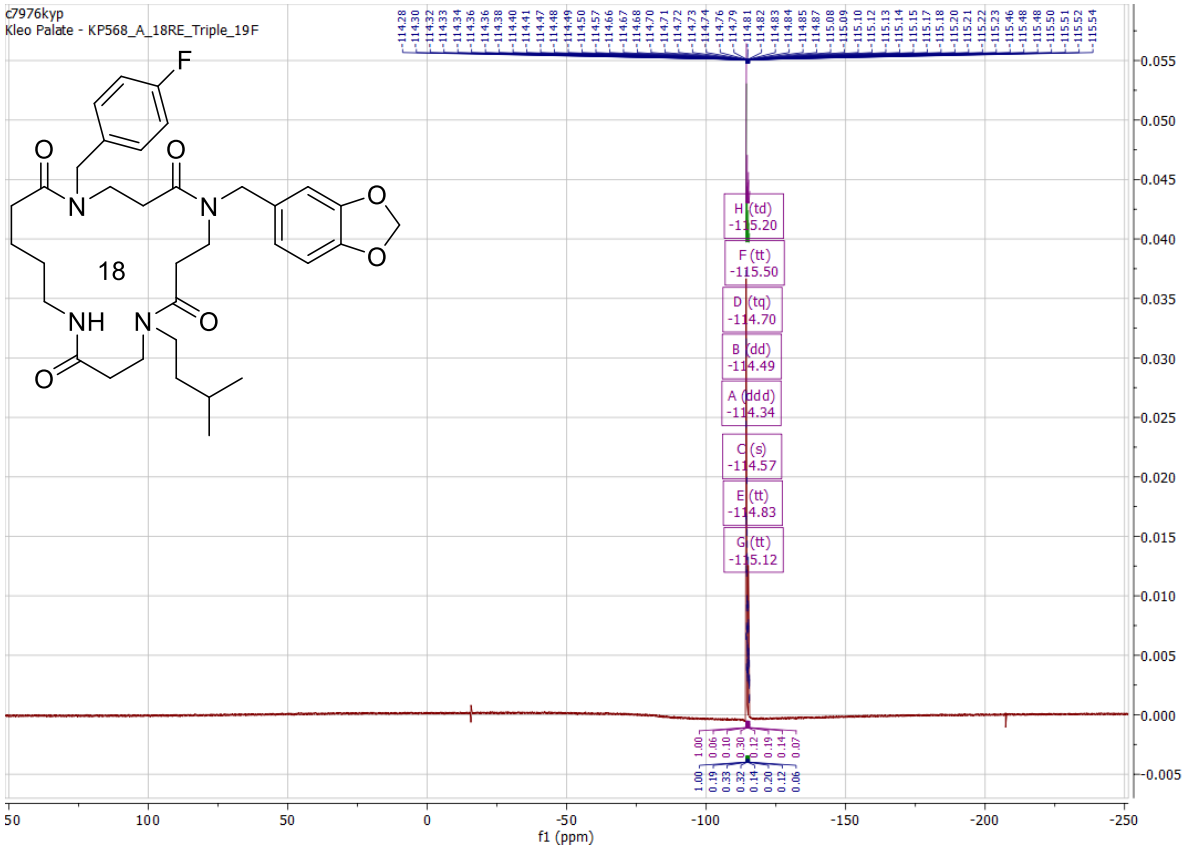

c9922kyp
Kleo Palate - KP572_A_Triple_#2_Rerun_19F
F
O
O
N
N
18
NH
N
O
O
O
D (tt)
-114.92
B (s)
-114.80
A (dq)
-114.64
C (h)
-114.42
E (td)
-115.08
f1 (ppm)

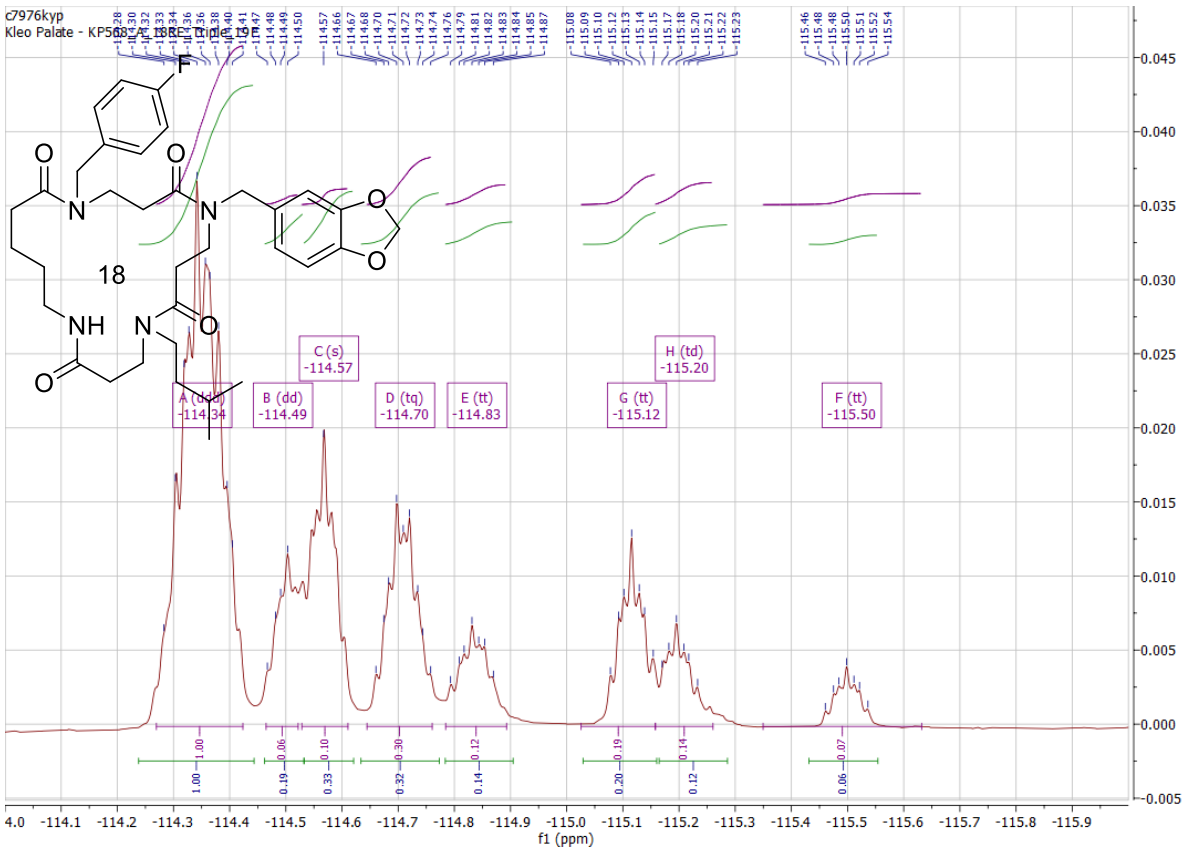

c9922kyp
Kleo Palate - KP572_A_Triple_#2_Rerun_19F
F
O
O
N
N
18
NH
N
O
O
O
D (tt)
-114.92
C (h)
-114.42
A (dq)
-114.64
B (s)
-114.80
E (td)
-115.08
f1 (ppm)

9-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-13-(4-fluorobenzyl)-5-isopentyl-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (32c) ($CDCl_3$ at 298 K)

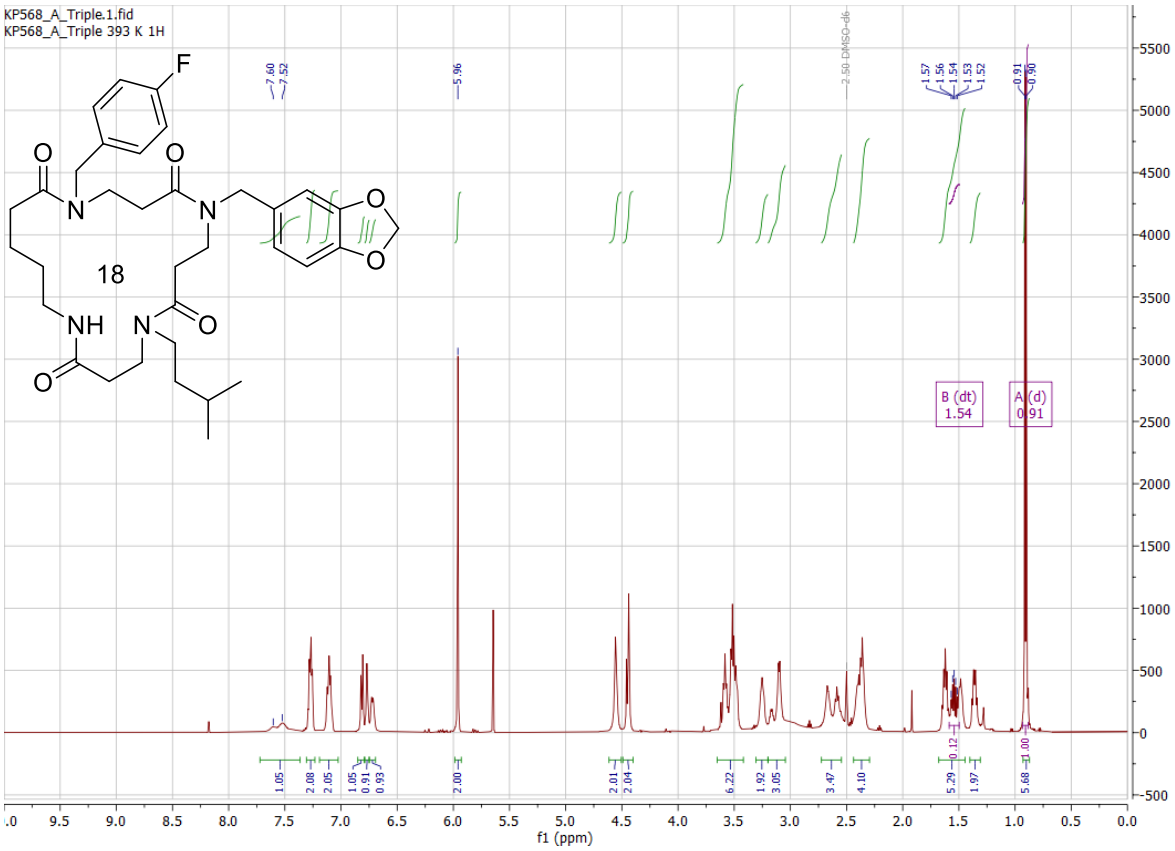


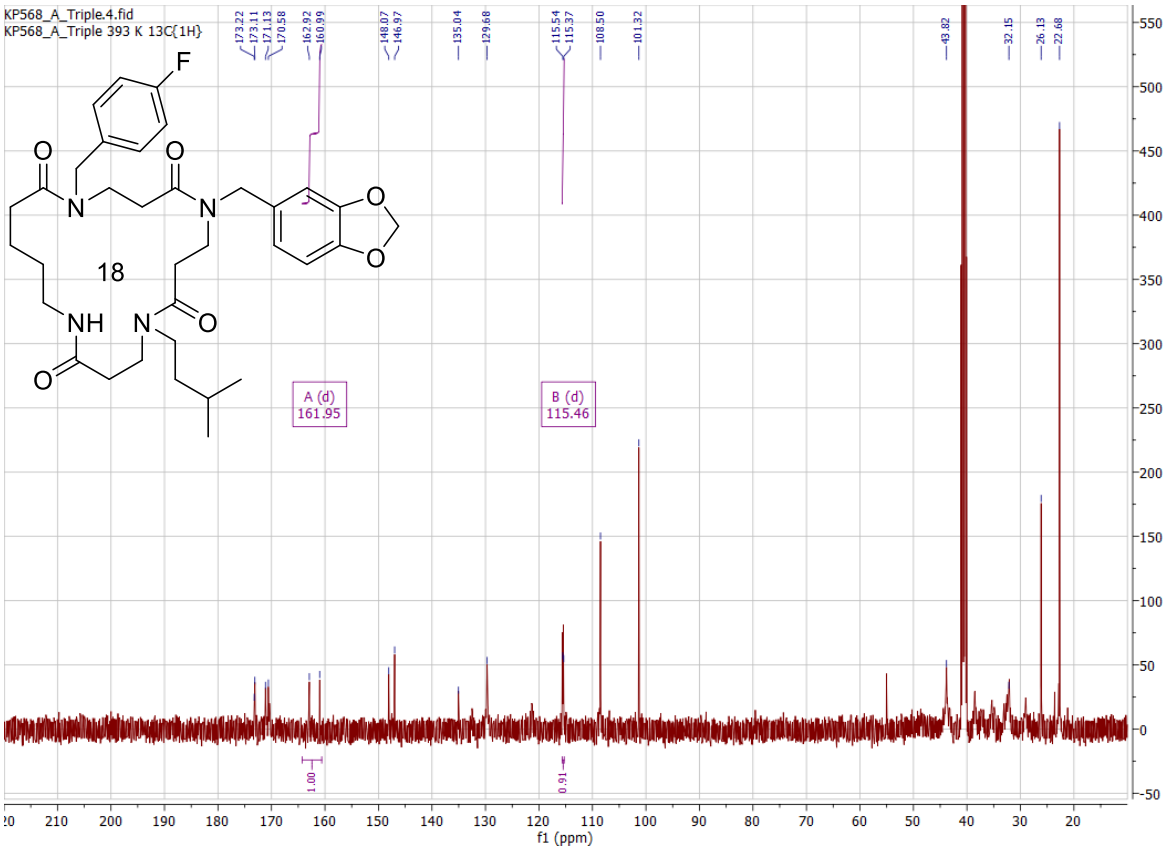


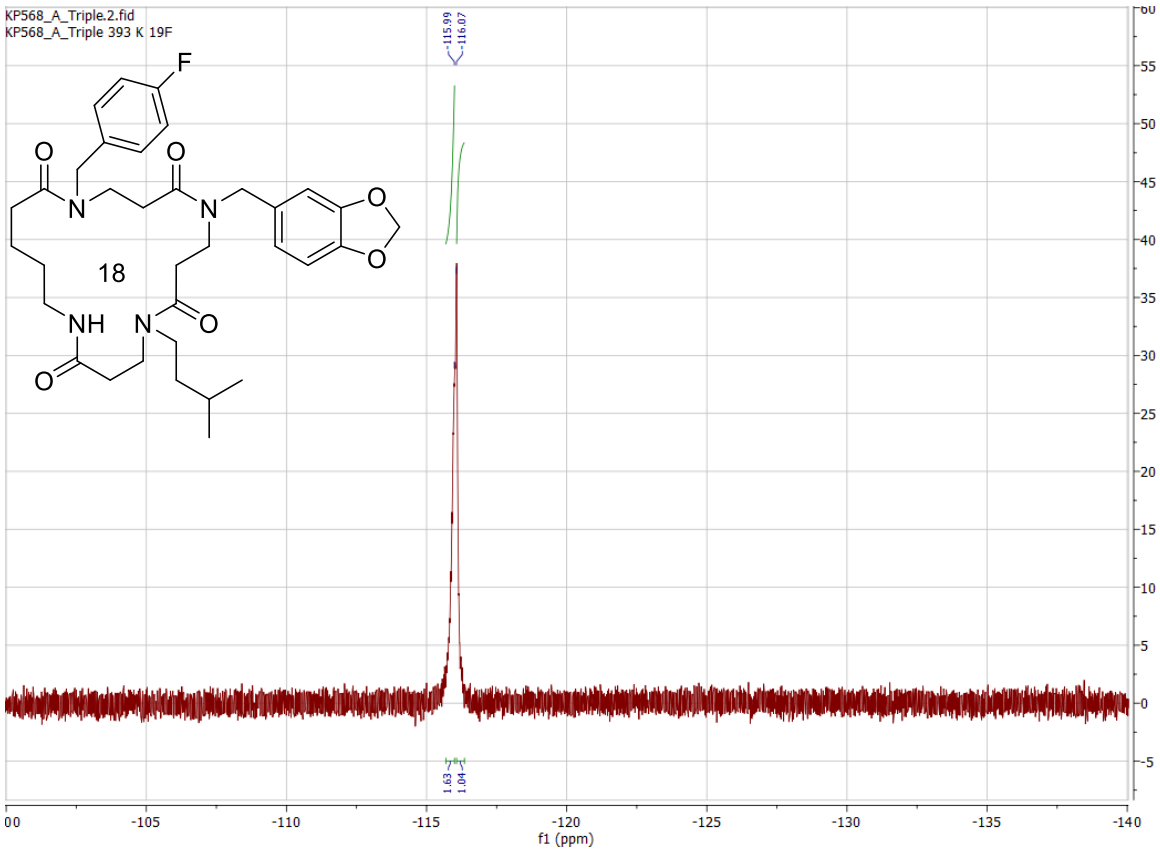

c7976kyp
Kleo Palate - KP568_A_18RE_Triple_19F
F
O
O
N
N
O
O
18
NH
N
O
O
H (td)
-115.20
F (tt)
-115.50
D (tq)
-114.70
B (dd)
-114.49
A (ddd)
-114.34
C (s)
-114.57
E (tt)
-114.83
G (tt)
-115.12
f1 (ppm)

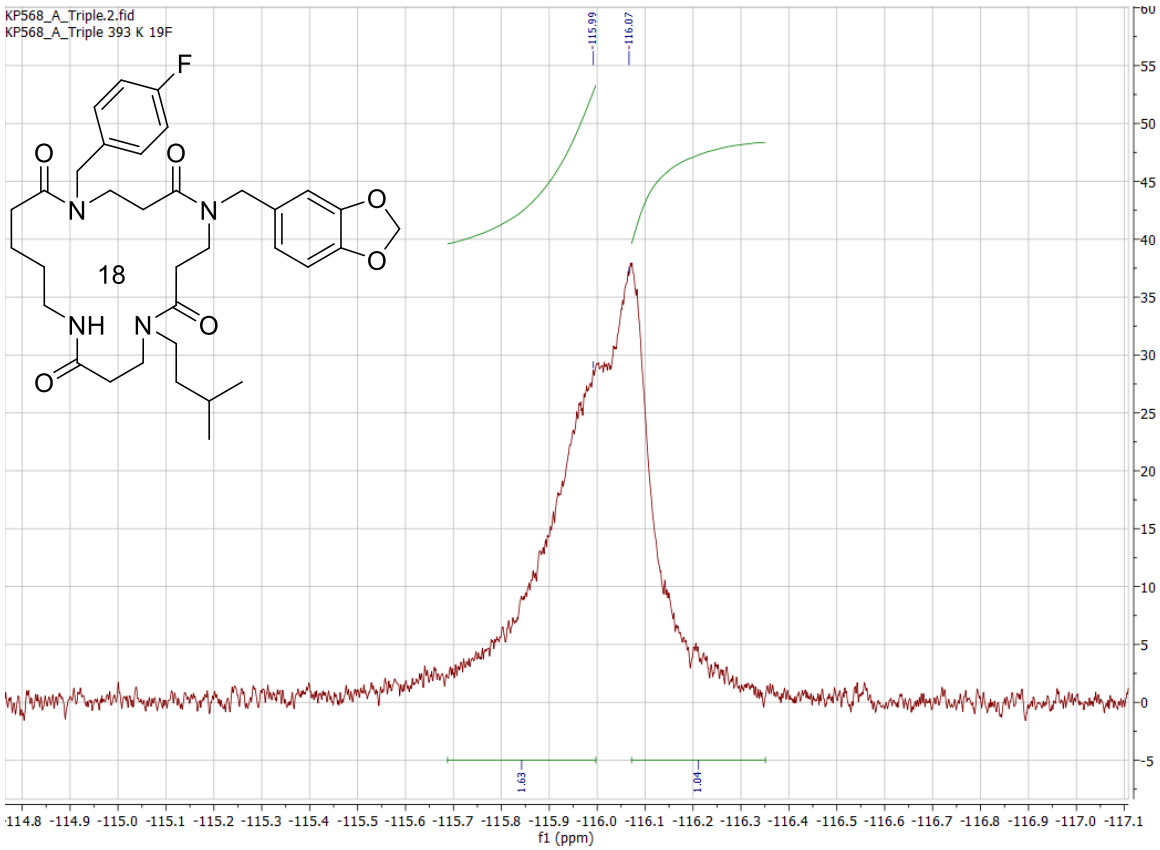

c7976kyp
Kleo Palate - KP568_A_18RE_Triple_19F
F
O
O
N
N
O
O
18
NH
N
O
O
C (s)
-114.57
A (ddd)
-114.34
B (dd)
-114.49
D (tq)
-114.70
E (tt)
-114.83
H (td)
-115.20
G (tt)
-115.12
F (tt)
-115.50
f1 (ppm)

9-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-13-(4-fluorobenzyl)-5-isopentyl-1,5,9,13-tetraazacyclooctadecane-2,6,10,14-tetraone (32c) – (d_6-DMSO at 393 K)






KP568_A_Triple.2.fid
KP568_A_Triple 393 K 19F
F
O
O
N
N
O
O
18
NH
N
O
O
-115.99
-116.07
1.63
1.04
f1 (ppm)


KP568_A_Triple.2.fid
KP568_A_Triple 393 K 19F
F
O
O
N
N
O
O
18
NH
N
O
O
-115.99
-116.07
1.63
1.04
f1 (ppm)

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