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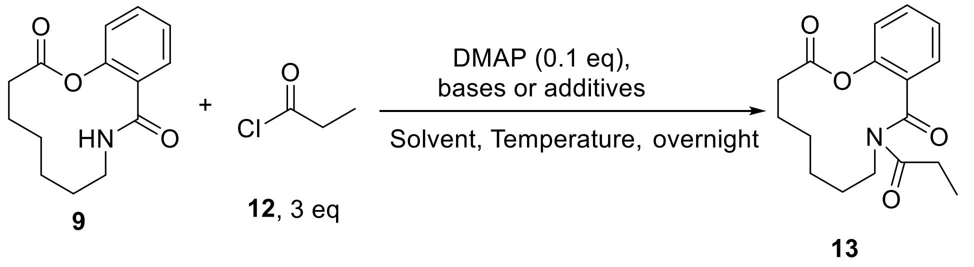
1) General Information

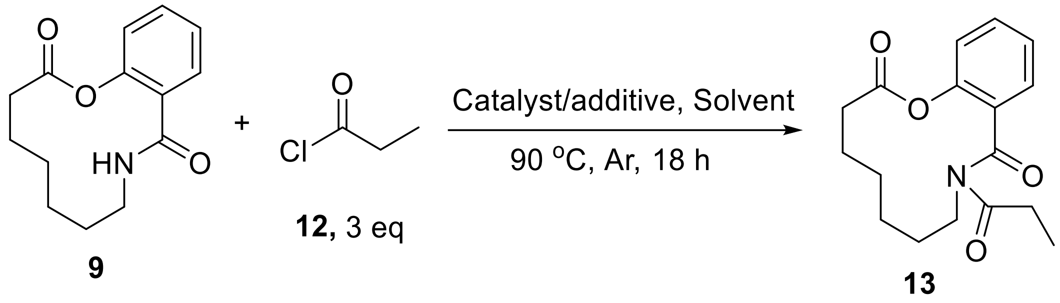
Except where stated, all reagents were purchased from commercial sources and used without further purification. Anhydrous CH_2Cl_2 and THF were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. ^{1}H NMR, ^{13}C NMR, and ^{31}P spectra were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer (operating at 400 MHz and 100 MHz). All Spectroscopic 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. In cases where products were formed as a mixture of rotamers, their ratio was determined by integration of signals in the ^{1}H NMR spectrum. 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. 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.

2) *N*-Acylation Optimisation Tables



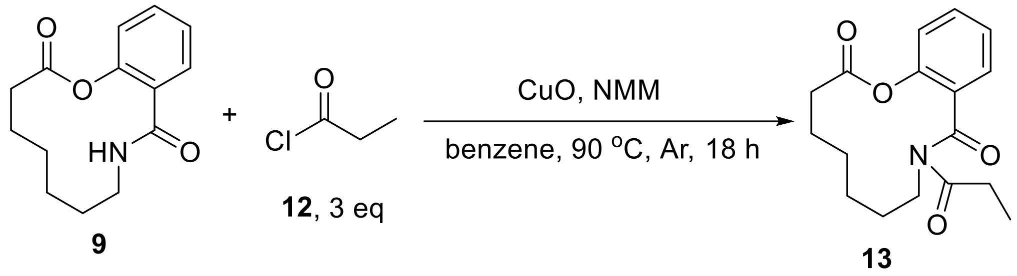
Entry	Solvent and Temperature (°C)	Bases and additives	Isolated yield of **13** (%)
1	DCE, 90	pyridine (6 eq)	28
2	DCE, 90	4-picoline (6 eq)	0
3	DCE, 90	NEt_3 (6 eq)	0
4	DCE, 90	imidazole (6 eq)	0
5	DCE, 90	CuO (2 eq)	27
6	DCE, 90	$Zn(OAc)_2$ (2 eq)	0
7	toluene, 90	CuO (2 eq)	10
8	benzene, 90	CuO (2 eq)	30
9	1,4-dioxane, 90	CuO (2 eq)	0

Table S1: Initial optimization of the *N*-acylation of lactam **9**. Yield refers to isolated yield of product following purification by column chromatography.



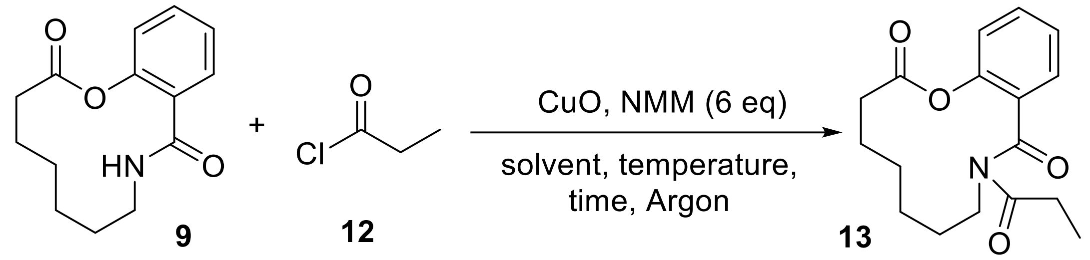
Entry	Catalyst	additive	solvent	Ratio of **9:13**
1	CuO (0.4 eq)	DMAP (0.4 eq)	DCE	69: 31
2	CuO (0.4 eq)	DMAP (0.4 eq)	benzene	51: 49
3	CuO (0.4 eq)		DCE	80: 20
4	CuO (0.4 eq)		benzene	48: 52
5	CuO (0.4 eq)	Imidazole	benzene	93:7
6	CuO (0.4 eq)	Pyridine	benzene	51:49
7	CuO (0.4 eq)	NEt_3	benzene	100:0
8	CuO (0.4 eq)	NMM	benzene	30:70

Table S2 Optimization of different conditions using CuO as a catalyst. Ratio of **9:13** was measured by integration of signals in the ^{1}H NMR spectrum of the unpurified reaction mixtures.



Entry	CuO (eq)	NMM (eq)	Other bases (eq)	Ratio of 9:13
1	2	4.0		42: 58
2	2	1.0		12: 88
3	0.2	6.0		**5:95**
4	0.2	6.0	DMAP (0.1)	9:91
5	**0.2**	**4.0**	**Pyridine (2.0)**	**11:89**

Table S3: Optimization of different equivalents of CuO and NMM in benzene. Ratio of **9:13** was measured by integration of signals in the ^{1}H NMR spectrum of the unpurified reaction mixtures.

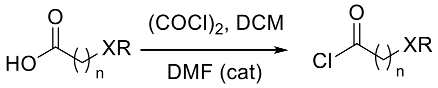


Entry	**CuO (eq)**	**12 (eq)**	**Solvent**	**Temperature (°C)**	**Time (hour)**	**Yield of 13 (%)** [a]
1	0.2	3.0	benzene	90	18	92
2	0.1	3.0	benzene	90	18	93 (84[b])
3	0.1	3.0	cyclohexane	90	18	78
4	0.1	3.0	benzene	50	18	82
5	0.1	3.0	benzene	65	18	88
6	0.1	3.0	benzene	80	18	97 (92)[b]
7	0.1	2.0	benzene	80	18	60
8	0.1	1.5	benzene	80	18	45
9	0.1	3.0	benzene	80	6	84
10	0.1	3.0	benzene	80	1	82
11	0.1	3.0	benzene	80	18	96[c]

Table S4: Final optimisation reactions. [a] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield; [c] Reaction without argon.

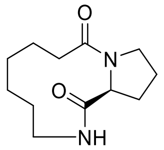
3) Synthetic procedures and characterisation data

General procedure for acid chloride formation



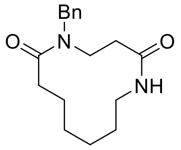
Oxalyl chloride (3 mmol) was added to a suspension of carboxylic acid (1 mmol) in DCM (5 mL), followed by a catalytic amount of DMF (1 drop/mmol of carboxylic acid). The resulting mixture was stirred at RT for 1 h and concentrated *in vacuo* to remove all solvent and excess oxalyl chloride, affording the acid chloride, which was dried with a high vacuum for 1 h at RT before use.

(*S*)-Decahydro-1*H*-pyrrolo[1,2-a][1,4]diazacycloundecine-1,9(2*H*)-dione (7)



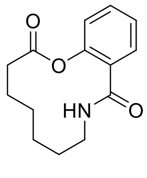
A mixture of azocan-2-one (635 mg, 5 mmol), DMAP (61 mg, 0.5 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (35 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of Fmoc-Pro-Cl (7.5 mmol, 1.50 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in DCM (18 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (150 mL) and washed with 10% aq. HCl (150 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (60 mL) and DBU (7.6 mL, 50 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a white solid (430 mg, 52%); $R_f = 0.18$ (19:1 ethyl acetate: methanol); $[\alpha]_D^{21} = -4.3$ (1.1 mg/mL in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 5.97 (d, *J* = 10.3 Hz, 1H, N**H**), 4.35 (dd, *J* = 9.0 Hz, 3.7 Hz, 1H, NC**H**), 3.95 – 3.85 (m, 1H, NC**H**$_2$), 3.70 – 3.42 (m, 2H, NC**H**$_2$), 3.00 – 2.92 (m, 1H, NC**H**$_2$), 2.47 – 1.25 (m, 10H, 5 × C**H**$_2$), 1.06 – 0.82 (m, 2H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 174.1 (**C**O), 173.3 (**C**O), 62.5 (N**C**H), 47.2 (N**C**H$_2$), 39.4 (NH**C**H$_2$), 32.0 (**C**H$_2$), 31.8 (**C**H$_2$), 29.1 (**C**H$_2$), 26.0 (**C**H$_2$), 24.3 (**C**H$_2$), 23.2 (**C**H$_2$), 22.5 (**C**H$_2$). HRMS (ESI): calcd. for $C_{12}H_{20}N_2NaO_2$, 247.1417. Found: $[MNa]^+$, 247.1418 (–0.3 ppm error). Spectroscopic data are consistent with those previously reported.[1]

5-Benzyl-1,5-diazacyclododecane-2,6-dione (8)



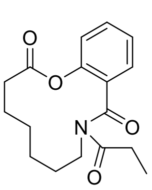
A mixture of azocan-2-one (500 mg, 3.93 mmol), DMAP (50 mg, 0.393 mmol) and pyridine (1.90 mL, 23.6 mmol) in DCM (30 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (5.89 mmol, 1.50 equiv., freshly prepared from *N*-benzyl β-alanine using the general procedure) in DCM (15 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (150 mL) and washed with 10% aq. HCl (150 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (40 mL) and DBU (6 mL, 39.3 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a colorless oil (780 mg, 69%); R_f = 0.42 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.37 – 7.27 (m, 3H, Ar-C**H**), 7.18 – 7.10 (m, 2H, Ar-C**H**), 6.46 (d, *J* = 9.4 Hz, 1H, N**H**), 4.90 (d, *J* = 16.9 Hz, 1H, NCH_2), 4.41 (d, *J* = 16.9 Hz, 1H, NC**H**$_2$), 4.55 (dddd, *J* = 14.5, 9.4, 5.1, 1.3 Hz, 1H, C**H**$_2$) , 3.75 (dddd, *J* = 13.4, 9.5, 7.5, 6.2 Hz, 1H, C**H**$_2$), 2.92 – 2.83 (m, 1H, C**H**$_2$), 2.77 (dt, *J* = 15.7, 5.2 Hz, 1H, C**H**$_2$), 2.59 (ddd, *J* = 15.6, 9.5, 5.7 Hz, 1H, C**H**$_2$), 2.49 (ddd, *J* = 14.8, 10.4, 2.0 Hz, 1H, C**H**$_2$), 2.13 (ddd, *J* = 14.8, 8.2, 2.0 Hz, 1H, C**H**$_2$), 1.63 – 1.39 (m, 8H, 4 × C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 176.0 (**C**O), 170.3 (**C**O), 136.5 (Ar-**C**), 129.1 (Ar-**C**H), 127.8 (Ar-**C**H), 126.5 (Ar-**C**H), 51.7 (N**C**H$_2$Ph), 40.8 (N**C**H$_2$), 39.1 (**C**H$_2$), 35.2 (**C**H$_2$), 32.4 (**C**H$_2$), 27.5 (**C**H$_2$), 25.7 (**C**H$_2$), 23.8 (**C**H$_2$), 22.1 (**C**H$_2$). HRMS (ESI): calcd. for $C_{17}H_{25}N_2O_2$, 289.1911. Found: $[MH]^+$, 289.1907 (1.2 ppm error). Spectroscopic data are consistent with those previously reported. [2]

4,5,6,7,8,9-Hexahydro-2H-benzo[b][1]oxa[5]azacyclododecine-2,10(3*H*)-dione (9)



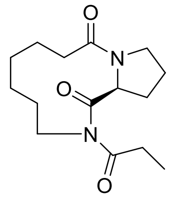
A mixture of azacyclooctan-2-one (500 mg, 3.93 mmol), DMAP (50 mg, 0.393 mmol) and pyridine (1.9 mL, 23.6 mmol) in DCM (30 mL) under an argon atmosphere was stirred at RT for 5 mins. Next, a solution of *O*-benzyl salicyloyl chloride (5.89 mmol, 1.50 equiv. prepared from *O*-benzyl salicylic acid using the general procedure) in DCM (15 mL) was added and the resulting mixture was heated, at reflux, at 50 °C for 16 h. An additional solution of *O*-benzyl salicyloyl chloride (5.89 mmol, 1.50 equiv. prepared from *O*-benzyl salicylic acid using the general procedure) in DCM (15 mL) was then added and the mixture was heated at reflux at 50 °C for a further 16 h to achieve reaction completion. The solvent was then concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. This material was redissolved in ethyl acetate (40 mL) and placed under an argon atmosphere. Palladium on carbon (390 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 1 h. The reaction was then purged with argon, filtered through Celite, washed with methanol and the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (40 mL) and triethylamine (825 μL, 5.89 mmol) added, and stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* as a white solid (520 mg, 54%); $R_f = 0.62$ (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.74 (dd, *J* = 7.7, 1.8 Hz, 1H, Ar-C**H**), 7.44 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H, Ar-C**H**), 7.37 – 7.23 (m, 1H, Ar-C**H**), 7.06 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar-C**H**), 6.46 (brs, 1H, N**H**), 3.60 – 3.36 (m, 2H, C$\mathbf{H_2}$NH), 2.79 – 2.56 (m, 2H, C$\mathbf{H_2}$COO), 1.92 – 1.84 (m, 2H, C$\mathbf{H_2}$), 1.74 – 1.67 (m, 2H, C$\mathbf{H_2}$), 1.64 – 1.52 (m, 4H, 2 × C$\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 172.0 (**C**O), 165.4 (**C**O), 147.2 (Ar-**C**), 131.6 (Ar-**C**H), 130.6 (Ar-**C**H), 129.1 (Ar-**C**), 126.6 (Ar-**C**H), 123.3 (Ar-**C**H), 40.2 (**C**H_2NH), 34.6 (**C**H_2CO), 26.4 (**C**H_2), 25.8 (**C**H_2), 24.7 (**C**H_2), 22.5 (**C**H_2); HRMS (ESI): calcd. For $C_{14}H_{17}NNaO_3$, 270.1101. Found: $[MNa]^+$, 270.1101 (–0.2 ppm error). Spectroscopic data are consistent with those previously reported.[1]

9-Propanoyl-4,5,6,7,8,9-hexahydro-2*H*-1,9-benzoxazacyclododecine-2,10(3*H*)-dione (13)



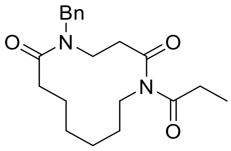
A mixture of lactam **9** (49.4 mg, 0.20 mmol), CuO (1.6 mg, 0.02 mmol) and NMM (0.132 mL, 1.20 mmol) in benzene (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of propionyl chloride **12** (0.60 mmol, 3 equiv.) in benzene (1.0 mL) was added and the resulting mixture was refluxed at 80 °C for 16 h. The mixture was then directly concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate) afforded the *title compound* as a colorless oil (55.5 mg, 92%); R_f = 0.60 (hexane: ethyl acetate = 1:1); δ_H (400 MHz, $CDCl_3$) 7.51 – 7.44 (m, 2H, Ar-C**H**), 7.36 – 7.29 (m, 1H, Ar-C**H**), 7.17 – 7.13 (m, 1H, Ar-C**H**), 4.04 (s, 2H, NC**H**$_2$), 2.65 – 2.39 (m, 2H, C**H**$_2$), 2.20 (q, *J* = 7.2 Hz, 2H, C**H**$_2$), 1.83 (d, *J* = 6.8 Hz, 2H, C**H**$_2$), 1.72 (q, *J* = 6.3 Hz, 2H, C**H**$_2$), 1.56 – 1.39 (m, 4H, 2 × C**H**$_2$), 0.99 (t, *J* = 7.2 Hz, 3H, C**H**$_3$); δ_C (100 MHz, $CDCl_3$) 176.8 (**C**O), 172.3 (**C**O), 169.9 (**C**O), 146.5 (Ar-**C**), 132.2 (Ar-**C**), 131.4 (Ar-**C**H), 128.6 (Ar-**C**H), 126.5 (Ar-**C**H), 123.1 (Ar-**C**H), 44.0 (N**C**H$_2$), 34.1 (**C**H$_2$), 31.4 (**C**H$_2$), 27.4 (**C**H$_2$), 25.6 (**C**H$_2$), 24.0 (**C**H$_2$), 22.9 (**C**H$_2$), 9.6 (**C**H$_3$); HRMS (ESI): calcd. For $C_{17}H_{21}NNaO_4$, 326.1363. Found: $[MNa]^+$, 326.1363 (–0.1 ppm error).

2-Propanoyldecahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazacycloundecine-1,9(2*H*)-dione (14)



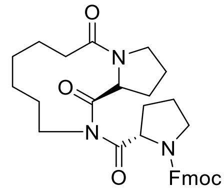
A mixture of lactam **7** (22.4 mg, 0.10 mmol), CuO (0.8 mg, 0.01 mmol) and NMM (0.066 mL, 0.60 mmol) in benzene (0.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of propionyl chloride **12** (0.30 mmol, 3 equiv.) in benzene (0.5 mL) was added and the resulting mixture was refluxed at 80 °C for 16 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 5 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate→ ethyl acetate) afforded the *title compound* as a white solid (23 mg, 72%); R_f = 0.24 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 5.08 (dd, *J* = 8.6, 2.7 Hz, 1H, NC**H**), 4.27 (dt, *J* = 14.8, 6.2 Hz, 1H, NC**H**$_2$), 3.37 (ddd, *J* = 14.8, 7.7, 6.1 Hz, 1H, NC**H**$_2$), 3.74 (ddd, *J* = 12.3, 8.5, 4.1 Hz, 1H, NC**H**$_2$), 3.65 (dt, *J* = 11.7, 7.7 Hz, 1H, NC**H**$_2$), 2.64 – 2.51 (m, 2H, C**H**$_2$), 2.47 – 2.37 (m, 1H, C**H**$_2$), 1.89 (dtt, *J* = 12.6, 7.6, 3.9 Hz, 1H, C**H**$_2$), 2.34 – 2.20 (m, 2H, C**H**$_2$), 2.15 – 1.98 (m, 2H, C**H**$_2$), 1.81 – 1.70 (m, 2H, C**H**$_2$), 1.69 – 1.62 (m, 2H, C**H**$_2$), 1.57 – 1.47 (m, 1H, C**H**$_2$), 1.41 – 1.29 (m, 1H, C**H**$_2$), 1.26 – 1.11 (m, 5H, C**H**$_3$ + C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 179.4 (**C**O), 177.4 (**C**O), 172.6 (**C**O), 63.5 (N**C**H), 47.6 (N**C**H$_2$), 42.2 (**N**CH$_2$), 32.0 (**C**H$_2$), 31.0 (**C**H$_2$), 29.6 (**C**H$_2$), 25.1 (**C**H$_2$), 23.2 (**C**H$_2$), 22.4 (**C**H$_2$), 22.3 (**C**H$_2$), 20.3 (**C**H$_2$), 8.9 (**C**H$_3$); HRMS (ESI): calcd. For $C_{15}H_{24}N_2NaO_3$, 303.1679. Found: $[MNa]^+$, 303.1678 (0.5 ppm error).

1-(1-Oxopropyl)-5-(phenylmethyl)-1,5-diazacyclododecane-2,6-dione (15)



A mixture of lactam **8** (28.8 mg, 0.10 mmol), CuO (0.8 mg, 0.01 mmol) and NMM (0.066 mL, 0.60 mmol) in benzene (0.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of propionyl chloride **12** (0.30 mmol, 3.0 equiv.) in benzene (0.5 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 5 mL) and the combined organic extracts dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 10:1 hexane: ethyl acetate → 1:1 hexane: ethyl acetate) afforded the *title compound* as a colorless oil (32 mg, as 3:1 mixture of rotamers when analyzed by NMR in CDCl$_3$ at RT, 93%); $R_f = 0.62$ (ethyl acetate); To simplify ^{1}H NMR analysis, the product was also analyzed at 120 °C in DMSO which resolved the rotamers; δ_H (400 MHz, DMSO-*d*$_6$, 120 °C) 7.34 (t, *J* = 7.3 Hz, 2H, Ar-C**H**), 7.27 (d, *J* = 6.7 Hz, 1H, Ar-C**H**), 7.22 (d, *J* = 7.6 Hz, 2H, Ar-C**H**), 4.61 (s, 2H, NC**H$_2$**Ph), 3.78 (s, 2H, NC**H$_2$**), 3.00 (s, 2H, NC**H$_2$**), 2.90 (s, 2H, C**H$_2$**), 2.66 (q, *J* = 7.0 Hz, 2H, C**H$_2$**CH$_3$), 2.30 (s, 2H, C**H$_2$**), 1.72 (s, 2H, C**H$_2$**), 1.62 – 1.48 (m, 2H, C**H$_2$**), 1.44 – 1.34 (m, 2H, C**H$_2$**), 1.26 – 1.18 (m, 2H, C**H$_2$**), 1.10 (t, *J* = 7.3 Hz, 3H, C**H$_3$**); Diagnostic ^{1}H NMR resonances recorded in CDCl$_3$ at RT, which confirm the presence of the two rotameric forms can be found at: 7.36 – 7.23 (m, 5H, Ar-C**H**, major rotamer), 7.16 – 7.11 (m, 5H, Ar-C**H**, minor rotamer), 1.21 (t, *J* = 7.2 Hz, 3H, C**H$_3$**, major rotamer), 1.14 (t, *J* = 7.2 Hz, 3H, C**H$_3$**, minor rotamer); δ_C (100 MHz, CDCl$_3$ at RT) data for the major rotamer only: 177.4 (**C**O), 176.7 (**C**O), 175.4 (**C**O), 137.0 (Ar-**C**), 129.0 (Ar-**C**H), 127.7 (Ar-**C**H), 126.5 (Ar-**C**H), 52.0 (N**C**H$_2$Ph), 43.5 (**C**H$_2$), 41.7 (**C**H$_2$), 37.7 (**C**H$_2$), 33.0 (**C**H$_2$), 30.0 (**C**H$_2$), 28.1 (**C**H$_2$), 27.0 (**C**H$_2$), 24.3 (**C**H$_2$), 22.5 (**C**H$_2$), 9.3 (**C**H$_3$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 177.3 (**C**O), 175.1 (**C**O), 174.7 (**C**O), 138.1 (Ar-**C**), 128.7 (Ar-**C**H), 128.5 (Ar-**C**H), 127.5 (Ar-**C**H), 48.9 (N**C**H$_2$Ph), 43.9 (**C**H$_2$), 41.5 (**C**H$_2$), 37.6 (**C**H$_2$), 30.4 (**C**H$_2$), 24.1 (**C**H$_2$), 22.4 (**C**H$_2$), 9.1 (**C**H$_3$); HRMS (ESI): calcd. for $C_{20}H_{29}N_2O_3$, 345.2173. Found: $[MH]^+$, 345.2178 (–1.6 ppm error).

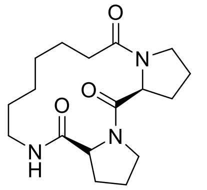
(9*H*-Fluoren-9-yl)methyl 2-(1,9-dioxodecahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazacycloundecine-2(3*H*)-carbonyl)pyrrolidine-1-carboxylate (19)



A mixture of 11 membered lactam **7** (89.7 mg, 0.4 mmol), CuO (3.2 mg, 0.04 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **16** (1.2 mmol, 3.0 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in dry benzene (2.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (129 mg, 60%). R_f = 0.60 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.75 (d, *J* = 7.2 Hz, 2H, Ar-C**H**, major rotamer), 7.64 – 7.59 (m, Ar-C**H**, 2H, major rotamer), 7.55 – 7.52 (m, 2H, Ar-C**H**, minor rotamer), 7.48 – 7.45 (m, 2H, Ar-C**H**, minor rotamer), 7.39 (t, *J* = 7.4 Hz, 2H, Ar-C**H**, major rotamer), 7.30 (tt, *J* = 7.4, 1.1 Hz, 1H, Ar-C**H**, major rotamer), 4.96 (dd, *J* = 8.6, 1.2 Hz, 1H, NC**H**, major rotamer), 4.75 (dd, *J* = 9.1, 2.8 Hz, 1H, NC**H**, minor rotamer), 4.60 (dd, *J* = 8.4, 4.7 Hz, 1H, NC**H**, major rotamer), 4.36 (dd, *J* = 10.4, 7.3 Hz, 2H, C**H**$_2$, major rotamer), 4.24 (t, *J* = 7.2 Hz, 1H, CH$_2$C**H**, major rotamer), 4.14 (ddd, *J* = 14.2, 5.5, 3.6 Hz, 1H, NC**H**$_2$, major rotamer), 3.80 – 3.57 (m, 5H, NC**H**$_2$, both rotamers), 3.27 (ddd, *J* = 14.8, 9.9, 4.9 Hz, 1H, C**H**$_2$, major rotamer), 2.55 (ddd, *J* = 13.7, 9.5, 4.4 Hz, 1H, C**H**$_2$, major rotamer), 2.45 – 1.11 (m, 20H, 8 × C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 179.0 (**C**O), 176.6 (**C**O), 173.3 (**C**O), 154.8 (**C**OO), 2 × 143.8 (Ar-**C**), 2 × 141.3 (Ar-**C**), 2 × 127.8 (Ar-**C**H), 2 × 127.0 (Ar-**C**H), 2 × 125.2 (Ar-**C**H), 2 × 120.0 (Ar-**C**H), 67.7 (O**C**H$_2$), 62.7 (N**C**H), 59.6 (N**C**H), 47.5 (CH$_2$**C**H), 47.2 (**C**H$_2$), 47.1 (**C**H$_2$), 42.3 (**C**H$_2$), 32.3 (**C**H$_2$), 30.7 (**C**H$_2$), 29.8 (**C**H$_2$), 25.4 (**C**H$_2$), 24.6 (**C**H$_2$), 22.9 (**C**H$_2$), 22.4 (**C**H$_2$), 21.7 (**C**H$_2$), 19.2 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 178.9 (**C**O), 175.5 (**C**O), 172.3 (**C**O), 154.2 (**C**OO), 143.9 (Ar-**C**), 143.4 (Ar-**C**), 141.2 (Ar-**C**), 141.2 (Ar-**C**), 125.0 (Ar-**C**H), 120.3 (Ar-**C**H), 68.7 (O**C**H$_2$), 62.6 (N**C**H), 59.5 (N**C**H), 47.5 (CH$_2$**C**H), 47.1 (**C**H$_2$), 46.9 (**C**H$_2$), 32.1 (**C**H$_2$), 31.0 (**C**H$_2$), 30.1 (**C**H$_2$), 24.7 (**C**H$_2$), 23.0 (**C**H$_2$), 22.3 (**C**H$_2$), 21.5 (**C**H$_2$), 19.4

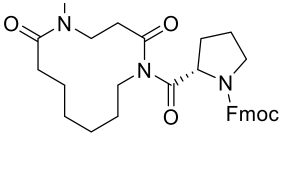
(**C**H$_2$); HRMS (ESI): calcd. for $C_{32}H_{37}N_3NaO_5$, 566.2625. Found: [MNa]$^+$, 566.2636 (–1.8 ppm error).

Dodecahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*][1,4,7]triazacyclotetradecine 5,13,18(6*H*,18a*H*)-trione (20)



The *N*-acylated product **19** (129 mg, 0.33 mmol) was dissolved in DCM (4 mL) and DBU (0.6 mL, 4.0 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:1 ethyl acetate: hexane → ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 3: 1 mixture of rotamers) as a yellow oil (54 mg, 43%); R$_f$ = 0.31 (9:1 ethyl acetate: methanol); $[\alpha]_D^{21}$ = 64.3 (0.7 mg/mL in CHCl$_3$); δ_H (400 MHz, CDCl$_3$) 6.97 (1H, s, N**H**, major rotamer), 4.51 – 4.56 (2H, m, 2 × NC**H**, both rotamers), 4.12 – 4.19 (m, 1H, NHC**H**$_2$, both rotamers), 3.95 – 4.02 (m, 1H, NHC**H**$_2$, both rotamers), 3.63 –3.72 (m, 1H, COC**H**$_2$, both rotamers), 3.48 – 3.55 (m, 2H, NC**H**$_2$, both rotamers), 3.35 – 3.20 (m, 2H, NC**H**$_2$, both rotamers), 3.17 – 3.04 (m, 1H, COC**H**$_2$, both rotamers), 2.36 – 2.46 (m, 2H, C**H**$_2$, both rotamers), 2.17 – 2.31 (m, 4H, C**H**$_2$, both rotamers), 1.85 – 2.14 (m, 12H, C**H**$_2$, both rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 173.3 (**C**O), 171.9 (**C**O), 171.5 (**C**O), 61.3 (N**C**H), 58.1 (N**C**H), 47.5 (**C**H$_2$), 47.3 (**C**H$_2$), 39.9 (**C**H$_2$), 34.6 (**C**H$_2$), 29.7 (**C**H$_2$), 29.3 (**C**H$_2$), 28.6 (**C**H$_2$), 25.8 (**C**H$_2$), 25.4 (**C**H$_2$), 24.2 (**C**H$_2$), 23.8 (**C**H$_2$), 19.0 (**C**H$_2$). Diagnostic ^{13}C NMR resonances for the minor rotamer: 166.5 (**C**O), 164.4 (**C**O), 61.2 (N**C**H), 60.7 (N**C**H), 45.3 (**C**H$_2$), 44.6 (**C**H$_2$), 30.0 (**C**H$_2$), 27.8 (**C**H$_2$), 23.5 (**C**H$_2$), 22.8 (**C**H$_2$), 21.8 (**C**H$_2$), 14.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{17}H_{27}NaN_3O_3$, 344.1943. Found: [MNa]$^+$, 344.1945 (0.4 ppm error).

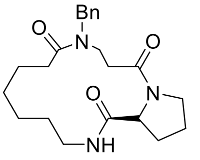
(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazacyclododecane-1-carbonyl)pyrrolidine-1-carboxylate (21)



A mixture of 12 membered lactam **8** (115.4 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.264 mL, 2.4 mmol) in dry benzene (2 mL) under an argon atmosphere was stirred at

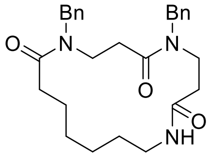
RT for 30 mins. Next, a solution of acid chloride **16** (1.2 mmol, 3.00 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 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. Purification by flash column chromatography (SiO_2, hexane→ 10:1 hexane: ethyl acetate) afforded the *title compound* (as 2:1 mixture rotamers) as a colorless oil (198 mg, 81%). R_f = 0.55 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.78 – 7.44 (m, 7H, Ar-C**H**, both rotamers), 7.42 – 7.10 (m, 14H, Ar-C**H**, both rotamers), 4.86 (d, *J* = 17.2 Hz, 1H, NC**H**, major rotamer), 4.77 (dd, *J* = 8.3, 4.4 Hz, 1H, NC**H**, minor rotamer), 4.74 (ddd, *J* = 16.0, 8.4, 3.7 Hz, 1H, NC**H**, major rotamer), 4.51 – 4.21 (m, 7H, COOC**H**$_2$ + NC**H**$_2$Ph, both rotamers), 4.14 – 4.08 (m, 1H, Fmoc-C**H**, both rotamers), 3.94 – 3.41 (m, 7H, C**H**$_2$, both rotamers), 3.27 – 2.70 (m, 3H, C**H**$_2$, both rotamers), 2.63 – 2.17 (m, 6H, C**H**$_2$, both rotamers), 2.15 – 1.14 (m, 20H, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) for major rotamer only: 177.0 (**C**O), 175.1 (**C**O), 174.8 (**C**O), 155.0 (**C**O), 2 × 144.1 (Ar-**C**), 2 × 141.4 (Ar-**C**), 137.1 (Ar-**C**), 129.0 (Ar-**C**H), 2 × 128.8 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 2 × 127.1 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 2 × 125.2 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.6 (O**C**H$_2$), 60.4 (**C**H), 47.3 (Fmoc-**C**H), 47.1 (**C**H$_2$), 43.8 (**C**H$_2$), 43.4 (**C**H$_2$), 37.2 (**C**H$_2$), 33.0 (**C**H$_2$), 30.5 (**C**H$_2$), 27.6 (**C**H$_2$), 24.6 (**C**H$_2$), 24.5 (**C**H$_2$), 23.1 (**C**H$_2$), 22.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{37}H_{41}N_3NaO_5$, 630.2938. Found: [MNa]$^+$, 630.2922 (2.6 ppm error).

10-Benzyldodecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8]triazacyclopentadecine-1,9,13(2*H*,10*H*)-trione (22)



The *N*-acylated product **21** (161 mg, 0.265 mmol) was dissolved in DCM (3 mL) and DBU (0.390 mL, 2.6 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 10:5:1:1 mixture of rotamers, A:B:C:D) a colorless oil (98 mg, 96%); R_f = 0.25 (9:1 ethyl acetate: methanol); $[\alpha]_D^{21}$ = –3.0 (5.9 mg/mL in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.35 – 7.08 (m, 10H, Ar-C**H**, all rotamers), 7.05 – 7.00 (m, 2H, N**H**, rotamers A and B), 6.62 (t, *J* = 6.3 Hz, 1H, N**H**, rotamer C), 6.33 (t, *J* = 5.2 Hz, 1H, N**H**, rotamer D), 5.05 – 4.47 (m, 4H, NC**H**$_2$Ph, all rotamers), 4.43 (d, *J* = 7.5 Hz, 1H, NC**H**, rotamer A), 4.36 (d, *J* = 3.4 Hz, 1H, NC**H**, rotamer C), 4.34 (d, *J* = 3.5 Hz, 1H, NC**H**, rotamer D), 4.23 – 4.04 (m, 2H, NC**H**$_2$Ph + NC**H**, mix rotamers), 3.62 – 2.85 (m, 8H, COC**H**$_2$+ NC**H**$_2$, mix rotamers), 2.57 – 2.00 (m, 12H, NC**H**$_2$ + C**H**$_2$, mix rotamers), 1.97 – 1.16 (m, 22H, C**H**$_2$, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer A only: 173.5 (**C**O), 170.8 (**C**O), 170.1 (**C**O), 138.7 (Ar-**C**), 2 × 128.7 (Ar-**C**H), 127.1 (Ar-**C**H), 2 × 126.7 (Ar-**C**H), 60.0 (N**C**H), 49.5 (N**C**H$_2$Ph), 47.2 (**C**H$_2$), 43.8 (**C**H$_2$), 37.6 (**C**H$_2$), 33.3 (**C**H$_2$), 29.6 (**C**H$_2$), 27.7 (**C**H$_2$), 26.8 (**C**H$_2$), 26.1 (**C**H$_2$), 24.8 (**C**H$_2$), 23.6 (**C**H$_2$), 22.7 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 174.9 (**C**O), 174.4 (**C**O), 172.5 (**C**O), 171.7 (**C**O), 171.6 (**C**O), 171.3 (**C**O), 171.0 (**C**O), 169.9 (**C**O), 138.0 (Ar-**C**), 137.4 (Ar-**C**), 137.0 (Ar-**C**), 129.0 (Ar-**C**H), 128.9 (Ar-**C**H), 128.6 (Ar-**C**H), 128.1 (Ar-**C**H), 127.6 (Ar-**C**H), 127.5 (Ar-**C**H), 127.4 (Ar-**C**H), 126.3 (Ar-**C**H), 126.2 (Ar-**C**H), 61.1 (N**C**H), 61.0 (N**C**H), 60.5 (N**C**H), 53.1 (N**C**H$_2$Ph), 52.3 (N**C**H$_2$Ph), 49.0 (N**C**H$_2$Ph), 47.6 (**C**H$_2$), 46.9 (**C**H$_2$), 46.9 (**C**H$_2$), 42.9 (**C**H$_2$), 42.6 (**C**H$_2$), 40.1 (**C**H$_2$), 39.3 (**C**H$_2$), 39.0 (**C**H$_2$), 34.5 (**C**H$_2$), 34.3 (**C**H$_2$), 33.3 (**C**H$_2$), 32.6 (**C**H$_2$), 32.1 (**C**H$_2$), 31.9 (**C**H$_2$), 29.3 (**C**H$_2$), 28.9 (**C**H$_2$), 28.7 (**C**H$_2$), 28.4 (**C**H$_2$), 28.2 (**C**H$_2$), 27.3 (**C**H$_2$), 26.3 (**C**H$_2$), 25.7 (**C**H$_2$), 25.5 (**C**H$_2$), 24.7 (**C**H$_2$), 24.5 (**C**H$_2$), 23.2 (**C**H$_2$), 22.8 (**C**H$_2$), 22.8 (**C**H$_2$), 22.7 (**C**H$_2$); HRMS (ESI): calcd. for $C_{22}H_{31}N_3NaO_5$, 408.2258. Found: $[MNa]^+$, 408.2260 (–0.5 ppm error).

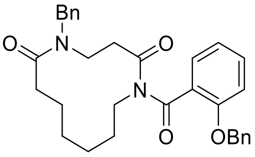
5,9-Dibenzyl-1,5,9-triazacyclohexadecane-2,6,10-trione (24)



A mixture of **8** (115.4 mg, 0.40 mmol), CuO (3.2 mg, 0.04 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **17** (1.2 mmol, 3.00 equiv., prepared using the general procedure) in benzene (2.0 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The reaction mixture was concentrated in vacuo, loaded onto a short silica plug and eluted with 2:1 hexane: ethyl acetate to remove the excess carboxylic acid and NMM. The acylated product was concentrated in *vacuo*, re-dissolved in DCM (4 mL) and DBU (0.6 mL, 4.0 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 ethyl acetate: hexane → ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 4:2:1 mixture of rotamers, A:B:C) as a yellow oil (75 mg, 40%); R_f = 0.42 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.43 – 7.07 (m, 20H, Ar-C**H**, all rotamers), 7.00 – 6.96 (m, 1H, N**H**, rotamer A), 6.85

(t, *J* = 5.7 Hz, 1H, N**H**, rotamer B), 6.16 (t, *J* = 5.3 Hz, 1H, N**H**, rotamer C), 4.67 – 4.50 (m, 5H, NC**H**$_2$Ph, all rotamers), 3.73 – 3.56 (m, 7H, NC**H**$_2$, all rotamers), 3.39 – 3.13 (m, 4H, C**H**$_2$NH, all rotamers), 2.76 – 2.28 (m, 12H, 3 × C**H**$_2$, all rotamers), 1.84 – 1.20 (m, 16H, 6 × C**H**$_2$, all rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.4 (**C**O), 170.9 (**C**O), 170.5 (**C**O), 137.6 (Ar-**C**), 136.4 (Ar-**C**), 2 × 129.2 (Ar-**C**H), 129.0 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 128.2 (Ar-**C**H), 2 ×126.5 (Ar-**C**H), 126.2 (Ar-**C**H), 52.1 (N**C**H$_2$Ph), 49.3 (N**C**H$_2$Ph), 45.9 (**C**H$_2$), 44.9 (**C**H$_2$), 40.3 (**C**H$_2$), 37.4 (**C**H$_2$), 32.8 (**C**H$_2$), 31.1 (**C**H$_2$), 28.4 (**C**H$_2$), 26.5 (**C**H$_2$), 25.6 (**C**H$_2$), 21.6 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 174.1 (**C**O), 173.6 (**C**O), 173.0 (**C**O), 171.9 (**C**O), 171.4 (**C**O), 170.6 (**C**O), 138.2 (Ar-**C**), 138.0 (Ar-**C**), 137.0 (Ar-**C**), 136.0 (Ar-**C**), 128.9 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.9 (Ar-**C**H), 127.6 (Ar-**C**H), 127.5 (Ar-**C**H), 127.5 (Ar-**C**H), 127.5 (Ar-**C**H), 126.3 (Ar-**C**H), 54.1 (N**C**H$_2$Ph), 52.2 (N**C**H$_2$Ph), 49.3 (N**C**H$_2$Ph), 44.7 (N**C**H$_2$Ph), 44.2 (**C**H$_2$), 43.7 (**C**H$_2$), 43.2 (**C**H$_2$), 43.0 (**C**H$_2$), 39.6 (**C**H$_2$), 39.1 (**C**H$_2$), 36.7 (**C**H$_2$), 35.6 (**C**H$_2$), 35.4 (**C**H$_2$), 33.3 (**C**H$_2$), 32.2 (**C**H$_2$), 31.4 (**C**H$_2$), 30.7 (**C**H$_2$), 28.9 (**C**H$_2$), 28.1 (**C**H$_2$), 27.6 (**C**H$_2$), 26.2 (**C**H$_2$), 25.4 (**C**H$_2$), 24.7 (**C**H$_2$), 24.5 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{27}H_{36}NO_3$, 450.2751. Found: $[MH]^+$, 450.2757 (−1.2 ppm error).

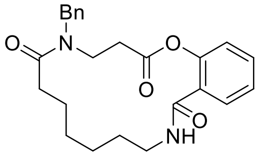
5-Benzyl-1-[2-(benzyloxy) benzoyl]-1,5-diazacyclododecane-2,6-dione (25)



A mixture of lactam **8** (115.4 mg, 0.40 mmol), CuO (6.4 mg, 0.20 mmol) and 4-methylmorpholine (0.260 mL, 2.4 mmol) in benzene (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **18** (1.20 mmol, 3.00 equiv., prepared from 2-benzyloxybenzoic acid using the general procedure) in benzene (2.0 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. Purification by flash column chromatography (SiO_2, hexane → 1:10 hexane: dichloromethane → dichloromethane → 5: 1 dichloromethane: ethyl acetate) afforded the *title compound* (as a 4:3 mixture of rotamers) as a colorless oil (180 mg, 90%). R_f = 0.70 (1: 2 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.59 – 6.93 (m, 14H, Ar-C**H**, both rotamers), 5.10 (s, 2H, OC**H**$_2$Ph, both rotamers), 4.84 (d, *J* = 16.7 Hz, 1H, NC**H**$_2$Ph, major rotamer), 4.63 (s, 1H, NC**H**$_2$Ph, minor rotamer), 4.47 (d, *J* = 16.7 Hz, 1H, NC**H**$_2$Ph, major rotamer), 4.27 (s, 1H, NC**H**$_2$Ph, minor rotamer), 4.12 – 3.99 (m, 1H, C**H**$_2$, major rotamer), 3.94 – 3.62 (m, 2H, C**H**$_2$, both rotamers), 3.30 (s, 1H, C**H**$_2$, major rotamer), 2.96 – 2.64 (m, 1H, C**H**$_2$, both rotamers), 2.59 – 2.05 (m, 2H, C**H$_2$**, both rotamers), 1.93 – 1.32 (m, 8H, 4 × C**H**$_2$, both rotamers), 1.19 – 0.76 (m, 2H, C**H**$_2$, both rotamers);

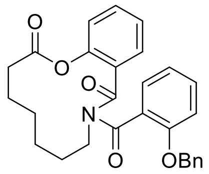
δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.3 (**C**O), 174.4 (**C**O), 171.3 (**C**O), 154.8 (Ar-**C**), 137.3 (Ar-**C**), 136.4 (Ar-**C**), 132.0 (Ar-**C**), 129.4 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 128.8 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 128.3 (Ar-**C**H), 2 × 127.6 (Ar-**C**H), 2 × 127.2 (Ar-**C**H), 126.5 (Ar-**C**H), 121.6 (Ar-**C**H), 112.7 (Ar-**C**H), 70.7 (O**C**H$_2$), 48.0 (N**C**H$_2$Ph), 45.2 (**C**H$_2$), 43.9 (**C**H$_2$), 36.5 (**C**H$_2$), 29.8 (**C**H$_2$), 27.8 (**C**H$_2$), 26.2 (**C**H$_2$), 24.5 (**C**H$_2$), 23.2 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamers: 176.7 (**C**O), 174.0 (**C**O), 172.5 (**C**O), 155.1 (Ar-**C**), 137.9 (Ar-**C**), 136.1 (Ar-**C**), 132.6 (Ar-**C**), 129.4 (Ar-**C**H), 128.8 (Ar-**C**H), 128.7 (Ar-**C**H), 128.4 (Ar-**C**H), 128.2 (Ar-**C**H), 127.6 (Ar-**C**H), 127.4 (Ar-**C**H), 126.4 (Ar-**C**H), 121.5 (Ar-**C**H), 112.8 (Ar-**C**H), 43.5 (N**C**H$_2$Ph), 43.4 (**C**H$_2$), 36.9 (**C**H$_2$), 33.7 (**C**H$_2$), 29.4 (**C**H$_2$), 26.7 (**C**H$_2$), 26.5 (**C**H$_2$), 23.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{31}H_{35}N_2O_4$, 499.2591. Found: [MH]$^+$, 499.2600 (−1.6 ppm error).

5-Benzyl-4,5,8,9,10,11,12,13-octahydro-2*H*-1,5,13-benzoxadiazacyclohexadecine-2,6,14(3*H*,7*H*)-trione (26)



N-acylated product **25** (176 mg, 0.353 mmol) was dissolved in ethyl acetate (3.5 mL) and placed under an argon atmosphere. Palladium on carbon (35.3 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) overnight. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.5 mL) and triethylamine (75 µL, 0.52 mmol) was added, and then stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → 1:2 hexane: ethyl acetate → 10:1 ethyl acetate: menthol) afforded the *title compound* (as a 2:1 mixture of rotamers) as a colorless oil (45.5 mg, 32%); R_f = 0.65 (9:1 ethyl acetate: menthol); δ_H (400 MHz, $CDCl_3$) 8.09 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar-C**H**, major rotamer), 7.51 – 7.41 (m, 2H, Ar-C**H**, both rotamers), 7.37 – 7.23 (m, 9H, Ar-C**H**, both rotamers), 7.09 (ddt, *J* = 15.8, 8.1, 1.4 Hz, 4H, Ar-C**H**, both rotamers), 6.81 (t, *J* = 5.3 Hz, 1H, CON**H**, major rotamer), 4.78 (s, 2H, NC**H$_2$**Ph, major rotamer), 3.77 – 3.69 (m, 1H, NC**H**$_2$, both rotamers), 3.67 – 3.59 (m, 2H, NHC**H**$_2$, both rotamers), 3.51 – 3.37 (m, 3H, OCOC**H**$_2$ + NC**H**$_2$, both rotamers), 3.15 (dd, *J* = 5.9, 4.3 Hz, 2H, NC**H**$_2$, both rotamers), 2.79 – 2.70 (m, 1H, C**H**$_2$, both rotamers), 2.53 – 2.44 (m, 1H, C**H**$_2$, both rotamers), 2.38 – 2.26 (m, 2H, C**H**$_2$, both rotamers), 1.80 (dq, *J* = 17.1, 8.8 Hz, 4H, C**H$_2$**, both rotamers), 1.67 – 1.38 (m, 8H, CH$_2$, both rotamers); Diagnostic ^{1}H NMR resonances for the minor rotamers: 7.63 (dd, *J* = 7.7, 1.7 Hz, 1H, Ar-C**H**, major rotamer), 6.14 (t, *J* = 6.2 Hz, 1H, CON**H**, minor rotamer), 4.64 (s, 2H, NC**H$_2$**Ph, minor rotamer); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 174.6 (**C**O), 171.4 (**C**O), 164.9 (**C**O), 147.8 (Ar-**C**), 137.6 (Ar-**C**), 132.0 (Ar-**C**H), 131.6 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 128.2 (Ar-**C**H), 127.6 (Ar-**C**H), 127.0 (Ar-**C**), 2 × 126.5 (Ar-**C**H), 123.1 (Ar-**C**H), 54.1 (N**C**H$_2$Ph), 43.2 (**C**H$_2$), 40.5 (**C**H$_2$), 33.6 (**C**H$_2$), 32.7 (**C**H$_2$), 29.7 (**C**H$_2$), 29.6 (**C**H$_2$), 26.4 (**C**H$_2$), 23.9 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamers: 173.7 (**C**O), 169.4 (**C**O), 166.3 (**C**O), 147.7 (Ar-**C**), 137.7 (Ar-**C**), 131.7 (Ar-**C**H), 129.1 (Ar-**C**H), 127.7 (Ar-**C**H), 127.0 (Ar-**C**), 126.6 (Ar-**C**H), 123.2 (Ar-**C**H), 49.2 (N**C**H$_2$Ph), 42.9 (**C**H$_2$), 39.6 (**C**H$_2$), 34.8 (**C**H$_2$), 31.5 (**C**H$_2$), 29.5 (**C**H$_2$), 27.3 (**C**H$_2$), 25.2 (**C**H$_2$), 24.5 (**C**H$_2$); HRMS (ESI): calcd. for $C_{24}H_{28}N_2NaO_4$, 431.1941. Found: [MNa]$^+$, 431.1939 (0.6 ppm error).

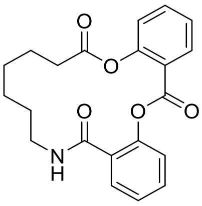
9-[2-(Benzyloxy)benzoyl]-4,5,6,7,8,9,10a,14a-octahydro-2*H*-1,9-benzoxazacyclododecine-2,10(3*H*)-dione (27)



A mixture of lactam **9** (247mg, 1.00 mmol), CuO (8.0 mg, 0.10 mmol) and 4-Methylmorpholine (0.660 mL, 6.0 mmol) in benzene (5.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **18** (3.0 mmol, 3.00 equiv., prepared from 2-benzyloxybenzoic acid using the general procedure) in benzene (5.0 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. Purification by flash column chromatography (SiO$_2$, hexane → 1:10 hexane: dichloromethane → dichloromethane) afforded the title compound as a white solid (315 mg, 69%). R$_f$ = 0.53 (1:1 hexane: ethyl acetate); δ_H (400 MHz, CDCl$_3$) 7.41 (d, *J* = 4.4 Hz, 4H, Ar-C**H**), 7.37 – 7.32 (m, 1H, Ar-C**H**), 7.25 – 7.23 (m, 1H, Ar-C**H**), 7.14 – 7.04 (m, 3H, Ar-C**H**), 6.86 (td, *J* = 7.6, 1.1 Hz, 1H, Ar-C**H**), 6.77 (dd, *J* = 8.6, 1.1Hz, 1H, Ar-C**H**), 6.68 (td, *J* = 7.5, 0.9 Hz, 1H, Ar-C**H**), 6.59 (d, *J* = 8.4 Hz, 1H, Ar-C**H**), 4.97 (s, 2H, OC**H$_2$**), 4.09 (d, *J* = 6.9 Hz, 2H, C**H$_2$**), 2.53 (d, *J* = 6.7 Hz, 2H, C**H$_2$**), 1.91 – 1.42 (m, 8H, 4 × C**H$_2$**); δ_C (100 MHz, CDCl$_3$) 172.6 (**C**O), 172.5 (**C**O), 169.8 (**C**O), 154.7 (Ar-

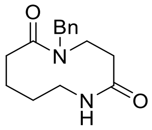
C), 146.5 (Ar-**C**), 136.1 (Ar-**C**), 132.2 (Ar-**C**H), 131.3 (Ar-**C**H), 130.7 (Ar-**C**), 130.1 (Ar-**C**), 129.8 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 128.3 (Ar-**C**H), 2 × 127.4 (Ar-**C**H), 126.8 (Ar-**C**H), 125.6 (Ar-**C**H), 122.3 (Ar-**C**H), 121.0 (Ar-**C**H), 111.7 (Ar-**C**H), 70.4 (O**C**H$_2$), 45.2 (**C**H$_2$), 33.9 (**C**H$_2$), 27.7 (**C**H$_2$), 25.4 (**C**H$_2$), 23.9 (**C**H$_2$), 23.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{28}H_{28}NO_5$, 458.1962. Found: $[MH]^+$, 458.1963 (–0.1ppm error).

8,9,10,11,12,13-Hexahydro-4a*H*,6*H*-dibenzo[*b*,*f*][1,5,9]dioxazacyclohexadecine-6,14,20(7*H*,20a*H*)-trione (28)



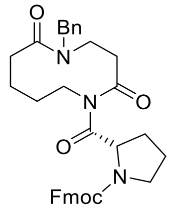
9-[2-(Benzyloxy)benzoyl]-4,5,6,7,8,9,10a,14a-octahydro-2H-1,9-benzoxaza- cyclododecine-2,10(3H)-dione **27** (315 mg, 0.689 mmol) was dissolved in ethyl acetate (7.0 mL) and placed under an argon atmosphere. Palladium on carbon (70 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 18 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (7.0 mL) and triethylamine (147 µL, 1.05 mmol) was added, and then stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate) afforded the *title compound* as a yellow oil (91 mg, 35%); R_f = 0.67 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.36 (dd, *J* = 7.9, 1.7 Hz, 1H, Ar-C**H**), 7.65 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1H, Ar-C**H**), 7.59 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar-C**H**), 7.49 (ddd, *J* = 8.1, 7.5, 1.7 Hz, 1H, Ar-C**H**), 7.39 (ddd, *J* = 7.9, 7.5, 1.2 Hz, 1H, Ar-C**H**), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-C**H**), 7.20 (dd, *J* = 8.1, 1.1 Hz, 1H, Ar-C**H**), 7.15 (dd, *J* = 8.1, 1.1 Hz, 1H, Ar-C**H**), 5.98 (s, 1H, N**H**), 3.56 – 3.32 (m, 2H, C**H**$_2$), 2.75 – 2.51 (m, 2H, C**H**$_2$), 1.87 – 1.79 (m, 2H, C**H**$_2$), 1.66 – 1.59 (m, 2H, C**H**$_2$), 1.52 (qd, *J* = 6.5, 2.7 Hz, 2H, C**H**$_2$), 1.44 (qd, *J* = 6.5, 2.5 Hz, 2H, C**H**$_2$); δ_C (100 MHz, $CDCl_3$) 172.3 (**C**O), 166.6 (**C**O), 162.3 (**C**O), 152.1 (Ar-**C**), 148.0 (Ar-**C**), 134.9 (Ar-**C**H), 133.0 (Ar-**C**H), 131.8 (Ar-**C**H), 130.8 (Ar-**C**), 128.5 (Ar-**C**H), 126.5 (Ar-**C**H), 126.3 (Ar-**C**H), 124.8 (Ar-**C**H), 123.1 (Ar-**C**H), 121.6 (Ar-**C**), 38.5 (**C**H$_2$), 32.8 (**C**H$_2$), 28.4 (**C**H$_2$), 27.2 (**C**H$_2$), 24.3 (**C**H$_2$), 23.6 (**C**H$_2$); HRMS (ESI): calcd. for $C_{21}H_{22}NO_5$, 368.1492. Found: $[MH]^+$, 368.1492 (0.2 ppm error).

5-Benzyl-1,5-diazecane-2,6-dione (29)



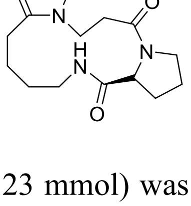
A mixture of δ-valerolactam (495.6 mg, 5.0 mmol), DMAP (61 mg, 0.5 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (35 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **17** (7.5 mmol, 1.50 equiv., freshly prepared from 3-[benzyl({[(9H-fluoren-9-yl)methoxy]carbonyl})amino]propanoic acid using the general procedure) in DCM (18 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over MgSO4 and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (50 mL) and DBU (7.6 mL, 50 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 10:1 mixture of rotamers) as a white solid (730 mg, 56%); R$_f$ = 0.26 (9:1 ethyl acetate: methanol); δ$_H$ (400 MHz, CDCl$_3$) 7.35 – 7.17 (m, 5H, Ar-C**H**, both rotamers), 5.95 (d, *J* = 10.3 Hz, 1H, N**H**, minor rotamer), 5.32 (d, *J* = 9.1 Hz, 1H, N**H**, major rotamer), 4.89 (d, *J* = 14.5 Hz, 1H, NC**H**$_2$Ph, both rotamers), 4.41 (d, *J* = 14.5 Hz, 1H, NC**H**$_2$Ph, both rotamers), 3.97 – 3.82 (m, 2H, C**H$_2$**, both rotamers), 3.35 – 3.27 (m, 1H, C**H$_2$**, both rotamers), 2.93 – 2.82 (m, 1H, C**H$_2$**, both rotamers), 2.74 – 2.61 (m, 1H, C**H$_2$,** both rotamers), 2.27 – 2.10 (m, 3H, C**H$_2$** + C**H**$_2$, both rotamers), 1.79 – 1.43 (m, 4H, C**H$_2$**, both rotamers); δ$_C$ (100 MHz, CDCl$_3$) data for the major rotamer only: 174.1 (**C**O), 171.1 (**C**O), 138.2 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 2 × 128.3 (Ar-**C**H), 128.0 (Ar-**C**H), 49.6 (N**C**H$_2$Ph), 45.5 (**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$_2$); ^{13}C NMR resonances for the minor rotamer: 176.4 (**C**O), 171.4 (**C**O), 136.7 (Ar-**C**), 129.0 (Ar-**C**H), 127.8 (Ar-**C**H), 126.8 (Ar-**C**H), 60.5 (N**C**H$_2$Ph), 54.4 (**C**H$_2$), 42.6 (**C**H$_2$), 40.2 (**C**H$_2$), 35.2 (**C**H$_2$), 27.4 (**C**H$_2$), 25.1 (**C**H$_2$), 21.2 (**C**H$_2$), 14.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{15}H_{20}N_2NaO_2$, 283.1417. Found: [MNa]$^+$, 283.1416 (0.3 ppm error). Spectroscopic data are consistent with those previously reported.[2]

(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazecane-1-carbonyl)pyrrolidine-1-carboxylate (30)



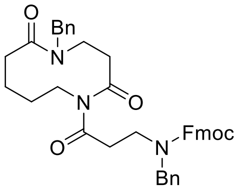
A mixture of 5-benzyl-1,5-diazecane-2,6-dione **29** (103.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (3.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **16** (1.2 mmol, 1.50 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 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*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → 1:3 hexane: ethyl acetate) afforded the *title compound* as a pale yellow oil (150 mg, 65%). R_f = 0.20 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.77 – 7.11 (m, 13H, Ar-C**H**), 4.79 (dd, *J* = 8.7, 3.6 Hz, 1H, NC**H**), 4.43 – 4.21 (m, 4H, NC**H₂**Ph + COOC**H₂**), 4.00 – 3.86 (m, 1H, Fmoc-C**H**), 3.82 – 3.48 (m, 4H, C**H₂**), 3.34 – 3.02 (m, 4H, C**H₂**), 2.46 – 2.14 (m, 4H, C**H₂**), 1.86 – 1.54 (m, 6H, C**H₂**); δ_C (100 MHz, $CDCl_3$) 173.4 (**C**O), 173.4 (**C**O), 171.3 (**C**O), 155.0 (**C**OO), 144.0 (Ar-**C**), 143.8 (Ar-**C**), 141.4 (Ar-**C**), 141.4 (Ar-**C**), 137.3 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 128.4 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 2 × 127.5 (Ar-**C**H), 2 × 125.3 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.8 (O**C**H₂), 60.0 (O**C**H), 47.2 (N**C**H₂Ph), 47.1 (Fmoc-**C**H), 47.0 (**C**H₂), 45.2 (**C**H₂), 43.4 (**C**H₂), 38.6 (**C**H₂), 30.0 (**C**H₂), 29.2 (**C**H₂), 24.8 (**C**H₂), 24.3 (**C**H₂), 24.3 (**C**H₂); HRMS (ESI): calcd. for $C_{35}H_{37}N_3NaO_5$, 602.2625. Found: $[MNa]^+$, 602.2634 (–1.4 ppm error).

8-Benzyldecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8]triazacyclotridecine-1,7,11(2*H*,8*H*)-trione (31)



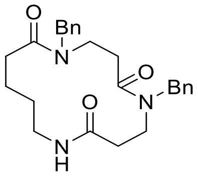
The *N*-acylated product **30** (133 mg, 0.23 mmol) was then re-dissolved in DCM (4 mL) and DBU (0.6 mL, 4 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 5:4 hexane: ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 2:1 mixture of rotamers) a colorless oil (83 mg, 98%); R_f = 0.21 (9:1 ethyl acetate: methanol); $[\alpha]_D^{21}$ = –1.8 (5.3 mg/mL in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.39 – 7.16 (m, 9H, Ar-C**H**, both rotamers), 7.07 (t, *J* = 4.5 Hz, 1H, N**H**, major rotamer), 4.77 (d, *J* =17.1 Hz, 1H, NC**H**, major rotamer), 4.68 (d, *J* = 6.9 Hz, 1H, NC**H**, minor rotamer), 4.59 – 4.49 (m, 2H, NC**H₂**Ph, both rotamers), 3.97 – 3.20 (m, 6H, C**H₂**, both rotamers), 3.12 – 2.23 (m, 10H, C**H₂**, both rotamers), 2.21 – 1.50 (m, 15H, C**H₂**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer: 176.3 (**C**O), 171.4 (**C**O), 170.1 (**C**O), 136.4 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 128.3 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 61.4 (NC**H**), 49.9 (N**C**H₂Ph), 48.0 (**C**H₂), 47.5 (NH₂), 39.1(**C**H₂), 33.5(**C**H₂), 32.0 (**C**H₂), 29.0 (**C**H₂), 25.3 (**C**H₂), 25.0 (**C**H₂), 22.3 (**C**H₂); ^{13}C NMR resonances for the minor rotamer: 172.7 (**C**O), 171.8 (**C**O), 169.8 (**C**O), 137.7 (Ar-**C**), 128.9 (Ar-**C**H), 127.9 (Ar-**C**H), 127.6 (Ar-**C**H), 59.6 (N**C**H₂Ph), 47.9 (N**C**H₂Ph), 40.7 (**C**H₂), 33.5 (**C**H₂), 33.0 (**C**H₂), 29.1 (**C**H₂), 26.8 (**C**H₂), 26.3 (**C**H₂), 23.8 (**C**H₂); HRMS (ESI): calcd. for $C_{20}H_{27}N_3NaO_3$, 380.1945. Found: $[MNa]^+$, 380.1942 (0.6 ppm error).

(9*H*-Fluoren-9-yl)methyl benzyl[3-(5-benzyl-2,6-dioxo-1,5-diazecan-1-yl)-3-oxopropyl]carbamate (32)



A mixture of 5-benzyl-1,5-diazecane-2,6-dione **29** (103.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (3.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **17** (1.2 mmol, 3.00 equiv., freshly prepared using the general procedure) in benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 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*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate) afforded the *title compound* (exist as a 2:1 mixture of rotamers in $CDCl_3$) as a yellow oil (144 mg, 56%). R_f = 0.70 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.82 – 6.79 (m, 25H, Ar-C**H**, both rotamers), 4.73 (d, *J* = 4.7 Hz, 1H, NC**H₂**Ph, major rotamer), 4.55 (d, *J* = 6.0 Hz, 1H, NC**H₂**Ph, major rotamer), 4.53 – 4.41 (m, 2H, NC**H₂**Ph, both rotamers), 4.39 (s, 1H, OC**H₂**, both rotamers), 4.28 – 4.17 (m, 1H, OC**H₂**, both rotamers), 3.78 (s, 1H, OCH₂C**H**), 3.60 – 3.21 (m, 6H, 3 × C**H₂**, both rotamers), 3.14 – 3.08 (m, 1H, C**H**$_2$, both rotamers), 2.80 (t, *J* = 6.8 Hz, 1H, C**H**$_2$, both rotamers), 2.40 – 1.83 (m, 2H, C**H**$_2$, both rotamers), 1.92 – 1.45 (m, 6H, 2 × 3**H**$_2$, both rotamers); δ$_C$ (100 MHz, CDCl$_3$) for major rotamer only: 174.1 (**C**O), 172.8 (**C**O), 171.3 (**C**O), 156.1 (**C**OO), 144.0 (Ar-**C**), 143.9 (Ar-**C**), 141.5 (Ar-**C**), 137.6 (Ar-**C**), 137.3 (Ar-**C**), 2 × 128.9 (Ar-**C**H), 2 × 128.8 (Ar-**C**H), 2 × 128.1 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.7 (Ar-**C**), 2 × 127.5 (Ar-**C**H), 127.3 (Ar-**C**H), 2 × 127.2 (Ar-**C**H), 2 × 124.9 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.4 (O**C**H$_2$), 51.8 (N**C**H$_2$Ph), 47.6 (Fmoc-Ar-**C**H), 47.4 (N**C**H$_2$Ph), 44.1 (**C**H$_2$), 43.5 (**C**H$_2$), 42.8 (**C**H$_2$), 38.9 (**C**H$_2$), 35.6 (**C**H$_2$), 35.4 (**C**H$_2$), 29.4 (**C**H$_2$), 24.3 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamers: 141.6 (Ar-**C**), 60.7 (O**C**H$_2$), 47.6 (Fmoc-Ar-**C**H), 35.7 (**C**H$_2$), 29.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{40}H_{41}N_3NaO_5$, 666.2938. Found: [MNa]$^+$, 666.2943 (–0.6 ppm error)

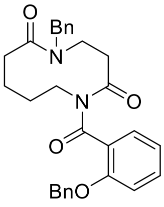
5,9-Dibenzyl-1,5,9-triazacyclotetradecane-2,6,10-trione (33)



The *N*-acylated product **2-25** (134 mg, 0.208 mmol) was then re-dissolved in DCM (4 mL) and DBU (0.60 mL, 4.00 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 10:5:1 mixture of rotamers, A:B:C) a colorless oil (74 mg, 85%); R$_f$ = 0.72 (ethyl acetate); δ$_H$ (400 MHz, CDCl$_3$) 7.38 – 6.97 (m, 22H, Ar-C**H**, all rotamers), 6.94 (t, *J* = 5.4 Hz, 1H, N**H**, rotamer B), 6.84 (t, *J* = 5.9 Hz, 1H, N**H**, rotamer A), 6.61 (t, *J* = 5.3 Hz, 1H, N**H**, rotamer C), 4.71 (s, 2H, NC**H**$_2$Ph, rotamer A), 4.62 (s, 2H, NC**H**$_2$Ph, rotamer C), 4.60 (s, 2H, NC**H**$_2$Ph, rotamer C), 4.56 (s, 2H, NC**H**$_2$Ph, rotamer A), 4.54 (s, 2H, NC**H**$_2$Ph, rotamer B), 4.30 (s, 2H, NC**H**$_2$Ph, rotamer B), 3.75 – 3.50 (m, 8H, C**H**$_2$, all rotamers), 3.38 – 3.26 (m, 4H, C**H**$_2$, all rotamers), 2.68 – 2.37 (m, 12H, C**H**$_2$, all rotamers), 1.82 – 1.52 (m, 9H, C**H**$_2$, all rotamers); δ$_C$ (100 MHz, CDCl$_3$) data for the major rotamer only: 174.1 (**C**O), 173.0 (**C**O), 171.3 (**C**O), 137.1 (Ar-**C**), 137.0 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 128.8 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 2 × 126.2 (Ar-**C**H), 126.1 (Ar-**C**H), 53.6 (N**C**H$_2$Ph), 53.4 (N**C**H$_2$Ph), 44.6 (**C**H$_2$), 44.0 (**C**H$_2$), 38.6 (**C**H$_2$), 35.6 (**C**H$_2$), 33.5 (**C**H$_2$), 31.8 (**C**H$_2$), 29.0 (**C**H$_2$), 22.8 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 174.3 (**C**O), 173.5 (**C**O), 173.4 (**C**O), 171.0 (**C**O), 170.7 (**C**O), 170.2 (**C**O), 137.7 (Ar-**C**), 137.6 (Ar-**C**), 137.6 (Ar-**C**), 135.8 (Ar-**C**), 129.2 (Ar-**C**H), 128.7 (Ar-**C**H), 128.7 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-

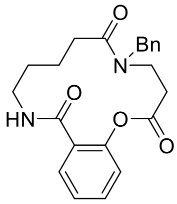
CH), 127.6 (Ar-**C**H), 127.6 (Ar-**C**H), 127.4 (Ar-**C**H), 126.5 (Ar-**C**H), 126.1 (Ar-**C**H), 51.3 (N**C**H$_2$Ph), 50.8 (N**C**H$_2$Ph), 48.9 (N**C**H$_2$Ph), 48.7 (N**C**H$_2$Ph), 44.5 (N**C**H$_2$), 43.9 (N**C**H$_2$), 43.1 (N**C**H$_2$), 42.2 (N**C**H$_2$), 39.6 (NH**C**H$_2$), 38.4 (NH**C**H$_2$), 35.2 (CO**C**H$_2$), 35.1 (CO**C**H$_2$), 33.2 (CO**C**H$_2$), 33.0 (CO**C**H$_2$), 32.6 (**C**H$_2$), 32.3 (**C**H$_2$), 28.1 (**C**H$_2$), 27.8 (**C**H$_2$), 24.0 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{25}H_{31}N_3NaO_3$, 444.2258. Found: $[MNa]^+$, 444.2261 (–0.7 ppm error).

Benzyl-1-[2-(benzyloxy)benzoyl]-1,5-diazecane-2,6-dione (34)



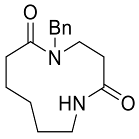
A mixture of 5-benzyl-1,5-diazecane-2,6-dione **29** (103.7 mg, 0.40 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (3.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **18** (1.20 mmol, 1.50 equiv., freshly prepared from 2-benzyloxybenzoic acid using the general procedure) in benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 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*. Purification by flash column chromatography (SiO_2, 3:2 hexane:ethyl acetate) afforded the *title compound* as a yellow oil (173 mg, 92%). $R_f = 0.72$ (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.46 – 7.40 (m, 1H, Ar-C**H**), 7.38 – 7.25 (m, 9H, Ar-C**H**), 7.21 – 7.17 (m, 2H, Ar-C**H**), 7.07 – 7.00 (m, 2H, Ar-C**H**), 5.10 (s, 2H, OC**H$_2$**Ph), 4.12 – 1.39 (m, 14H, 6 × C**H$_2$** + NC**H$_2$**Ph); δ_C (100 MHz, $CDCl_3$) 173.3 (**C**O), 173.3 (**C**O), 171.3 (**C**O), 155.2 (Ar-**C**), 137.3 (Ar-**C**), 135.9 (Ar-**C**), 132.5(Ar-**C**H), 2 × 128.8 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 128.5 (Ar-**C**H), 2 × 128.3 (Ar-**C**H), 2 × 127.5 (Ar-**C**H), 126.5 (Ar-**C**), 121.6 (Ar-**C**H), 113.1 (Ar-**C**H), 70.9 (O**C**H$_2$), 47.8 (N**C**H$_2$Ph), 46.8 (**C**H$_2$), 43.0 (**C**H$_2$), 38.9 (**C**H$_2$), 29.1 (**C**H$_2$), 24.7 (**C**H$_2$), 23.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{29}H_{30}N_2NaO_4$, 493.2098. Found: $[MNa]^+$, 493.2099 (–0.1 ppm error).

5-Benzyl-4,5,8,9,10,11-hexahydro-2*H*-1,5,11-benzoxadiazacyclotetradecine-2,6,12(3*H*,7*H*)-trione (35)



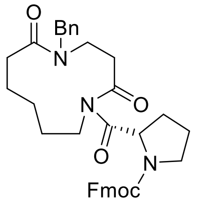
The *N*-acylated product **34** (121 mg, 0.257 mmol) was dissolved in ethyl acetate (2.5 mL) and placed under an argon atmosphere. Palladium on carbon (25 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (2.5 mL) and triethylamine (54 µL, 0.385 mmol) added, and stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, 1:3 hexane: ethyl acetate → ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (93 mg, 95%); R_f = 0.52 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.97 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar-C**H**, major rotamer), 7.52 (dd, *J* = 7.6, 1.7 Hz, 1H, Ar-C**H**, minor rotamer), 7.46 (td, *J* = 7.8, 1.8 Hz, 1H, Ar-C**H**, major rotamer), 7.41 (td, *J* = 7.8, 1.7 Hz, 1H, Ar-C**H**, minor rotamer), 7.36 – 7.21 (m, 6H, Ar-C**H**, both rotamers), 7.11 – 7.03 (m, 3H, Ar-**H**, both rotamers), 6.55 (t, *J* = 6.1 Hz, 1H, N**H**, major rotamer), 6.35 (t, *J* = 6.1 Hz, 1H, N**H**, minor rotamer), 4.60 (s, 2H, N**H$_2$**Ph, both rotamers), 3.74 (t, *J* = 7.0 Hz, 2H, C**H$_2$**, minor rotamer), 3.60 (dd, *J* = 6.4, 4.2 Hz, 2H, C**H$_2$**, major rotamer), 3.57 – 3.45 (m, 2H, C**H$_2$**, both rotamers), 3.04 (t, *J* = 5.3 Hz, 2H, C**H$_2$**, major rotamer), 2.69 (t, *J* = 7.0 Hz, 2H, C**H$_2$**, minor rotamer), 2.61 – 2.52 (m, 2H, C**H$_2$**, minor rotamer), 2.46 – 2.32 (m, 2H, C**H$_2$**, major rotamer), 1.85 – 1.55 (m, 5H, 2 × C**H$_2$**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.7 (**C**O), 171.4 (**C**O), 165.3 (**C**O), 147.4 (Ar-**C**), 137.3 (Ar-**C**), 131.9 (Ar-**C**H), 131.3 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 127.9 (Ar-**C**), 2 × 126.7 (Ar-**C**H), 126.4 (Ar-**C**H), 126.4 (Ar-**C**H), 123.1 (Ar-**C**H), 54.4 (N**C**H$_2$Ph), 43.1 (**C**H$_2$), 38.7 (**C**H$_2$), 33.7 (**C**H$_2$), 33.5 (**C**H$_2$), 28.3 (**C**H$_2$), 23.4 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 173.7 (**C**O), 169.4 (**C**O), 166.8 (**C**O), 147.3 (Ar-**C**), 137.2 (Ar-**C**), 130.0 (Ar-**C**), 128.8 (Ar-**C**H), 128.5 (Ar-**C**H), 128.0 (Ar-**C**H), 127.6 (Ar-**C**H), 122.8 (Ar-**C**H), 47.9 (N**C**H$_2$Ph), 42.7 (**C**H$_2$), 37.6 (**C**H$_2$), 34.4 (**C**H$_2$), 33.6 (**C**H$_2$), 29.0 (**C**H$_2$), 22.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{22}H_{24}N_2NaO_4$, 403.1628. Found: [MNa]$^+$, 403.1634 (–1.5 ppm error).

5-Benzyl-1,5-diazacycloundecane-2,6-dione (36)



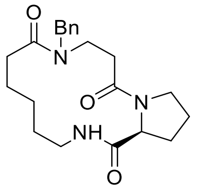
A mixture of ε-caprolactam (565.8 mg, 5.0 mmol), DMAP (61mg, 0.5 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (35 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **17** (7.5 mmol, 1.50 equiv, freshly prepared from 3-[benzyl({[(9H-fluoren-9-yl)methoxy]carbonyl})amino]propanoic acid using the general procedure) in DCM (18 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (50 mL) and DBU (7.6 mL, 50 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a pale yellow solid (1.22 g, 89%). R_f = 0.37 (9:1 ethyl acetate: methanol); δ_H (400 MHz, $CDCl_3$) 7.37 – 7.24 (m, 5H, Ar-C**H**, both rotamers), 5.92 (t, N**H**, *J* = 6.1 Hz, 1H, both rotamers), 5.03 – 4.75 (m, 1H, NC$\mathbf{H_2}$Ph, both rotamers), 4.48 – 4.30 (m, 1H, NC$\mathbf{H_2}$Ph, both rotamers), 4.05 – 3.17 (m, 8H, NC$\mathbf{H_2}$ + C$\mathbf{H}_2$, both rotamers), 2.74 – 2.34 (m, 6H, C$\mathbf{H_2}$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 173.5 (**C**O), 171.5 (**C**O), 138.4 (Ar-**C**), 2 × 129.0 (Ar-**C**H), 2 × 128.3 (Ar-**C**H), 127.9 (Ar-**C**H), 49.0 (N**C**H_2Ph), 45.1 (**C**H_2), 41.7 (**C**H_2), 37.0 (**C**H_2), 28.5 (**C**H_2), 25.3 (**C**H_2), 24.4 (**C**H_2), 22.8 (**C**H_2); Diagnostic ^{13}C NMR resonances for the minor rotamer: 175.4 (**C**O), 171.1 (**C**O), 137.0 (Ar-**C**), 127.7 (Ar-**C**H), 126.6 (Ar-**C**H), 54.0 (N**C**H_2Ph), 42.9 (**C**H_2), 37.5 (**C**H_2), 34.7 (**C**H_2), 33.8 (**C**H_2), 26.0 (**C**H_2), 23.5 (**C**H_2), 22.4 (**C**H_2); HRMS (ESI): calcd. for $C_{16}H_{22}N_2NaO_2$, 297.1573. Found: $[MNa]^+$, 297.1575 (–0.6 ppm error). Spectroscopic data are consistent with those previously reported.[2]

(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazacycloundecane-1 carbonyl)pyrrolidine-1-carboxylate (37)



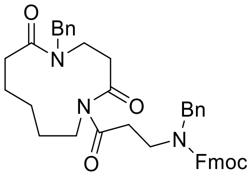
A mixture of 11-membered ring lactam **36** (109.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.264 mL, 2.4 mmol) in dry benzene (2 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **16** (1.2 mmol, 3.0 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 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. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate→ 2:3 hexane: ethyl acetate) afforded the *title compound* (as a 5:2 mixture of rotamers,) as a colorless oil (194 mg, 82%). R_f = 0.55 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.79 – 7.45 (m, 7H, Ar-C**H**, both rotamers), 7.43 – 7.09 (m, 14H, Ar-C**H**, both rotamers), 4.74 (ddd, *J* = 16.0, 8.4, 3.7 Hz, 1H, NC**H**, major rotamer), 4.67 (dd, *J* = 10.9, 6.4 Hz, 1H, NC**H**, minor rotamer), 4.48 – 4.22 (m, OC**H$_2$** + NC**H$_2$**Ph, 7H, both rotamers), 4.11 (t, *J* = 6.1 Hz, 1H, Fmoc-C**H**, minor rotamer), 4.01 – 3.88 (m, 1H, Fmoc-C**H**, major rotamer), 3.84 – 3.01 (m, 9H, C**H$_2$**, both rotamers), 2.83 – 2.08 (m, 7H, C**H$_2$**, both rotamers), 2.06 – 1.19 (m, 15H, C**H$_2$**, both rotamers); δ_C (100 MHz, $CDCl_3$) for major rotamers only: 178.8 (**C**O), 176.2 (**C**O), 173.6 (**C**O), 155.0 (**C**OO), 144.1 (Ar-**C**), 143.9 (Ar-**C**), 2 × 141.4 (Ar-**C**), 137.3 (Ar-**C**), 2 × 129.1 (Ar-CH), 2 × 128.7 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 127.5 (Ar-CH), 2 × 127.1 (Ar-**C**H), 2 × 126.7 (Ar-**C**H), 125.3 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.7 (COO**C**H$_2$), 60.3 (CO**C**H), 47.3 (N**C**H$_2$Ph), 47.3 (Fmoc-**C**H), 47.1 (**C**H$_2$), 45.1 (**C**H$_2$), 44.0 (**C**H$_2$), 43.2 (**C**H$_2$), 32.0 (**C**H$_2$), 30.8 (**C**H$_2$), 29.6 (**C**H$_2$), 27.7 (**C**H$_2$), 24.3 (**C**H$_2$), 23.6(**C**H$_2$); HRMS (ESI): calcd. for $C_{36}H_{39}N_3NaO_5$, 616.2782. Found: $[MNa]^+$, 616.3785 (–0.5 ppm error).

9-Benzyldodecahydropyrrolo[2,1-*c*][1,4,8]triazacyclotetradecine-1,8,12(9*H*)-trione (38)



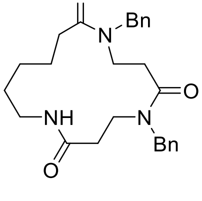
The *N*-acylated product **37** (155 mg, 0.261 mmol) was re-dissolved in DCM (3 mL) and DBU (0.390 mL, 2.6 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 20:1 mixture of rotamers) a colorless oil (87 mg, 90%); R_f = 0.18 (9:1 ethyl acetate: methanol); $[\alpha]_D^{21}$ = –1.9 (0.8 mg/mL in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.36 – 7.27 (m, 3H, Ar-C**H**, both rotamers), 7.20 – 7.16 (m, 2H, Ar-C**H**, both rotamers), 4.83 (d, *J* = 16.8 Hz, 1H, NC**H**$_2$Ph, major rotamer), 4.63 (d, *J* = 16.9 Hz, 1H, NC**H**$_2$Ph, major rotamer), 4.79 – 4.67 (m, 2H, NC**H$_2$**Ph, minor rotamer), 4.57 (d, *J* = 1.9 Hz, 1H, NC**H**, minor rotamer), 4.51 (dd, *J* = 8.5, 2.1 Hz, 1H, NC**H**, major rotamer), 4.43 (ddd, *J* = 13.2, 9.8, 3.2 Hz, 1H, NC**H$_2$**, major rotamer), 4.34 – 4.30 (m, 1H, NC**H**$_2$, minor rotamer), 3.75 (ddd, *J* = 9.7, 8.0, 2.5 Hz, 1H, NC**H**$_2$, major rotamer), 3.40 (qd, *J* = 9.8, 5.8 Hz, 2H, NC**H$_2$**, major rotamer), 3.33 – 3.18 (m, 1H, NHC**H**$_2$, major rotamer), 3.00 (ddd, *J* = 13.6, 6.2, 4.5 Hz, 1H, NHC**H**$_2$, major rotamer), 2.89 (ddd, *J* = 14.8, 6.2, 3.5 Hz, 1H, C**H**$_2$, major rotamer), 2.55 (ddd, *J* = 14.8, 11.5, 3.0 Hz, 1H, C**H$_2$**, major rotamer), 2.41 (ddd, *J* = 14.5, 9.7, 4.5 Hz, 1H, C**H**$_2$, major rotamer), 2.28 (ddt, *J* = 11.4, 8.7, 3.0 Hz, 1H, C**H$_2$**, major rotamer), 2.14 (ddd, *J* = 15.2, 5.7, 3.2 Hz, 1H, C**H**$_2$, major rotamer), 2.08 – 1.73 (m, 4H, C**H$_2$**, both rotamers), 1.69 – 1.58 (m, 1H, C**H**$_2$, major rotamer), 1.43 (dddd, *J* = 16.0, 8.4, 5.5, 2.8 Hz, 1H, C**H**$_2$, major rotamer), 1.38 – 1.14 (m, 3H, C**H$_2$**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.0 (**C**O), 171.4 (**C**O), 171.1 (**C**O), 136.9 (Ar-**C**), 2 × 129.0 (Ar-**C**H), 127.7 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 61.0 (N**C**H), 52.5 (N**C**H$_2$Ph), 47.4 (**C**H$_2$), 42.6 (**C**H$_2$), 36.8 (**C**H$_2$), 33.8 (**C**H$_2$), 32.4 (**C**H$_2$), 28.4 (**C**H$_2$), 26.9 (**C**H$_2$), 24.8 (**C**H$_2$), 23.4 (**C**H$_2$), 21.8 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 173.8 (**C**O), 171.7 (**C**O), 171.5 (**C**O), 137.7 (Ar-**C**), 128.8 (Ar-**C**H), 127.4 (Ar-**C**H), 126.6 (Ar-**C**H), 61.2 (N**C**H), 53.2 (N**C**H$_2$Ph), 46.8 (**C**H$_2$), 42.0 (**C**H$_2$), 38.1 (**C**H$_2$), 34.8 (**C**H$_2$), 31.8 (**C**H$_2$), 29.7 (**C**H$_2$), 26.4 (**C**H$_2$), 25.1 (**C**H$_2$), 24.3 (**C**H$_2$), 22.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{21}H_{29}N_3NaO_3$, 394.2101. Found: $[MNa]^+$, 394.2101 (0.0 ppm error).

(9*H*-Fluoren-9-yl)methyl benzyl[3-(5-benzyl-2,6-dioxo-1,5-diazacycloundecan-1-yl)-3-oxopropyl]carbamate (39)



A mixture of 5-benzyl-1,5-diazacycloundecane-2,6-dione **36** (109.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (3.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **17** (1.2 mmol, 3.00 equiv., freshly prepared using the general procedure) in benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 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. Purification by flash column chromatography (SiO_2, 2:1 hexane: ethyl acetate→1:1 hexane: ethyl acetate) afforded the title compound as a colorless oil (138 mg, 53%). $R_f = 0.65$ (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.79 – 6.94 (m, 18H, Ar-C**H**), 4.91 – 4.15 (m, 7H, $OCH_2C\mathbf{H}$ + $O\mathbf{CH_2}$ + 2 × $N\mathbf{CH_2}Ph$), 3.94 – 3.02 (m, 6H, 3 × $C\mathbf{H_2}$), 2.89 – 2.08 (m, 4H, 2 × $C\mathbf{H_2}$), 1.95 – 1.16 (m, 8H, 4 × $C\mathbf{H_2}$); δ_C (100 MHz, $CDCl_3$) 175.0 (**C**O), 174.5 (**C**O), 172.8 (**C**O), 156.1 (**C**OO), 144.0 (Ar-**C**), 143.9 (Ar-**C**), 141.5 (Ar-**C**), 141.4 (Ar-**C**), 137.5 (Ar-**C**), 137.5 (Ar-**C**), 129.0 (Ar-**C**H), 128.8 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 128.2 (Ar-**C**H), 2 × 127.8 (Ar-**C**H), 2 × 127.4 (Ar-**C**H), 127.2 (Ar-**C**H), 127.1 (Ar-**C**H), 2 × 126.7 (Ar-**C**H), 2 × 124.9 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.4 ($O\mathbf{C}H_2$), 51.7 ($N\mathbf{C}H_2Ph$), 47.7 ($N\mathbf{C}H_2Ph$), 47.3 (Fmoc-Ar-**C**H), 44.1 ($\mathbf{C}H_2$), 44.0 ($\mathbf{C}H_2$), 43.1 ($\mathbf{C}H_2$), 37.6 ($\mathbf{C}H_2$), 35.7 ($\mathbf{C}H_2$), 31.9 ($\mathbf{C}H_2$), 26.7 ($\mathbf{C}H_2$), 25.3 ($\mathbf{C}H_2$), 22.9 ($\mathbf{C}H_2$); HRMS (ESI): calcd. for $C_{41}H_{43}N_3NaO_5$, 680.3095. Found: $[MNa]^+$, 680.3110 (–2.2 ppm error).

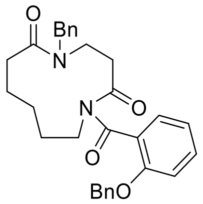
5,9-Dibenzyl-1,5,9-triazacyclopentadecane-2,6,10-trione (40)



The *N*-acylated product **39** (71.6 mg, 0.11 mmol) was dissolved in DCM (4 mL) and DBU (0.6 mL, 4 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → 10:1

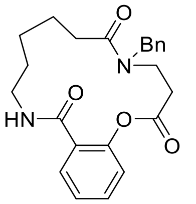
ethyl acetate: methanol) afforded the *title compound* as (as a 2:1 mixture of rotamers) a colorless oil (38 mg, 79%); R_f = 0.32 (9:1 ethyl acetate: methanol); δ_H (400 MHz, CDCl$_3$) 7.40 – 7.04 (m, 15H, Ar-C**H**, both rotamers), 6.72 (t, *J* = 5.9 Hz, 1H, N**H**, major rotamer), 6.49 (t, *J* = 5.8 Hz, 1H, N**H**, minor rotamer), 4.85 (s, 2H, NC$\mathbf{H_2}$Ph, major rotamer), 4.75 (s, 2H, NC$\mathbf{H_2}$Ph, minor rotamer), 4.59 (s, 2H, NC$\mathbf{H_2}$Ph, major rotamer), 4.57 (s, 2H, NC$\mathbf{H_2}$Ph, minor rotamer), 3.80 – 3.23 (m, 10H, NHC$\mathbf{H_2}$ + 2 × NC$\mathbf{H_2}$, both rotamers), 2.88 – 2.37 (m, 10H, 3 × C$\mathbf{H_2}$, both rotamers), 1.82 – 1.29 (m, 11H, 3 × C$\mathbf{H_2}$, both rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 174.5 (**CO**), 173.7 (**CO**), 170.8 (**CO**), 137.6 (Ar-**C**), 136.4 (Ar-**C**), 2 × 129.1 (Ar-**C**H), 2 × 129.0 (Ar-**C**H), 128.2 (Ar-**C**H), 126.7 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 2 × 126.2 (Ar-**C**H), 54.6 (N**C**H$_2$Ph), 51.4 (N**C**H$_2$Ph), 44.4 (**C**H$_2$), 42.0 (**C**H$_2$), 39.0 (**C**H$_2$), 35.2 (**C**H$_2$), 32.5 (**C**H$_2$), 31.5 (**C**H$_2$), 28.5 (**C**H$_2$), 25.6 (**C**H$_2$), 25.0 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamer: 174.5 (**CO**), 171.7 (**CO**), 170.6 (**CO**), 138.0 (Ar-**C**), 137.2 (Ar-**C**), 129.0 (Ar-**C**H), 128.7 (Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 53.7 (N**C**H$_2$Ph), 49.4 (N**C**H$_2$Ph), 44.7 (**C**H$_2$), 44.2 (**C**H$_2$), 37.6 (**C**H$_2$), 36.9(**C**H$_2$), 32.3 (**C**H$_2$), 31.9 (**C**H$_2$), 26.8 (**C**H$_2$), 24.1 (**C**H$_2$), 23.3 (**C**H$_2$); HRMS (ESI): calcd. for $C_{26}H_{33}N_3NaO_3$, 458.2414. Found: [MNa]$^+$, 458.2416 (–0.3 ppm error).

5-Benzyl-1-[2-(benzyloxy)benzoyl]-1,5-diazacycloundecane-2,6-dione (41)



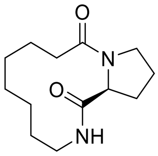
A mixture of 11-membered ring lactam **36** (109.7 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.264 mL, 2.4 mmol) in dry benzene (2 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **18** (1.2 mmol, 3.0 equiv., freshly prepared from 2-benzyloxybenzoic acid using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 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. Purification by flash column chromatography (SiO$_2$, 2:1 hexane: ethyl acetate→ 3:2 hexane: ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (180 mg, 93%). R_f = 0.65 (ethyl acetate); δ_H (400 MHz, CDCl$_3$) 7.51 – 7.27 (m, 9H, Ar-C**H**, both rotamers), 7.25 – 7.18 (m, 2H, Ar-C**H**, both rotamers), 7.11 – 6.90 (m, 3H, Ar-C**H**, both rotamers), 5.09 (s, 2H, OC$\mathbf{H_2}$Ph, both rotamers), 4.82 (d, *J* = 16.6 Hz, 1H, NC$\mathbf{H_2}$Ph, major rotamer), 4.38 (d, *J* = 16.6 Hz, 1H, NC**H**$_2$Ph, major rotamer), 4.17 – 3.55 (m, 4H, C**H$_2$**, both rotamers), 3.34 – 2.54 (m, 2H, C**H$_2$**, both rotamers), 2.40 – 1.11 (m, 9H, C**H$_2$**, both rotamers); δ_C (100 MHz, CDCl$_3$) for major rotamer: 174.8 (**C**O), 173.1 (**C**O), 172.5 (**C**O), 154.8 (Ar-**C**), 137.6 (Ar-**C**), 136.0 (Ar-**C**), 132.4 (Ar-**C**H), 2 × 128.7 (Ar-**C**H), 2 × 128.6 (Ar-**C**H), 2 × 128.2 (Ar-**C**H), 2 ×127.2 (Ar-**C**H), 126.6 (Ar-**C**), 121.5 (Ar-**C**H), 112.8 (Ar-**C**H), 70.6 (O**C**H$_2$), 47.7 (N**C**H$_2$Ph), 46.4 (N**C**H$_2$), 44.3 (N**C**H$_2$), 37.1 (CO**C**H$_2$), 32.2 (CO**C**H$_2$), 29.1 (**C**H$_2$), 25.3 (**C**H$_2$), 23.8 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 178.2 (N**C**O), 174.4 (N**C**O), 170.3 (N**C**O), 154.8 (Ar-**C**OBn), 137.3 (Ar-**C**), 136.2 (Ar-**C**), 132.2 (Ar-**C**H), 129.6(Ar-**C**H), 129.2 (Ar-**C**H), 128.9 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 127.6 (Ar-**C**H), 127.3 (Ar-**C**H), 127.2 (Ar-**C**H), 126.3 (Ar-**C)**, 112.9 (Ar-**C**H), 70.7 (O**C**H$_2$Ph), 44.7 (N**C**H$_2$Ph), 36.5 (**C**H$_2$), 26.4 (**C**H$_2$), 22.8 (**C**H$_2$), 22.4 (**C**H$_2$); HRMS (ESI): calcd. for $C_{30}H_{32}N_2NaO_4$, 507.2254. Found: [MNa]$^+$, 507.2261 (–1.3 ppm error).

5-Benzyl-4,5,7,8,9,10,11,12-octahydro-1,5,12-benzoxadiazacyclopentadecine-2,6,13(3*H*)-trione (42)



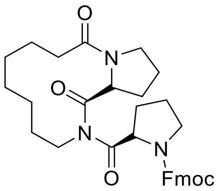
This *N*-acylated product **41** (175 mg, 0.362 mmol) was re-dissolved in ethyl acetate (4.0 mL) and placed under an argon atmosphere. Palladium on carbon (36 mg, Pd 10% on carbon) was then added and the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 16 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (4.0 mL) and triethylamine (76 µL, 0.543 mmol) added, and stirred at RT for 4 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO$_2$, 1:3 hexane: ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a colorless oil (82 mg, 57%); R$_f$ = 0.45 (ethyl acetate); δ_H (400 MHz, CDCl$_3$) 7.86 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar-C**H**, major rotamer), 7.44 (td, *J* = 7.8, 1.7 Hz, 1H, Ar-C**H**, major rotamer), 7.53 (dd, *J* = 7.6, 1.8 Hz, 1H, Ar-C**H**, minor rotamer), 7.34 – 7.22 (m, 5H, Ar-C**H**, both rotamers), 7.14 – 7.09 (m, 2H, Ar-C**H**, both rotamers), 6.97 (dd, *J* = 8.1, 1.0 Hz, 1H, Ar-C**H**, major rotamer), 6.49 (t, *J* = 6.0 Hz, 1H, N**H**, major rotamer), 6.24 (t, *J* = 6.1 Hz, 1H, N**H**, minor rotamer), 4.72 (s, 2H, NC**H$_2$**Ph, major rotamer), 4.61 (s, 2H, NC**H$_2$**Ph, minor rotamer), 3.74 (t, *J* = 6.8 Hz, 2H, C**H$_2$**, minor rotamer), 3.61 – 3.55 (m, 3H, C**H₂**, major rotamer), 3.44 (q, *J* = 6.0 Hz, 2H, C**H₂**, major rotamer), 3.14 – 3.05 (m, 2H, C**H₂**, major rotamer), 2.79 (t, *J* = 6.8 Hz, 2H, C**H₂**, minor rotamer), 2.51 (t, *J* = 7.4 Hz, 2H, C**H₂**, minor rotamer), 2.47 – 2.42 (m, 2H, C**H₂**, major rotamer), 1.80 – 1.71 (m, 2H, C**H₂**, both rotamers), 1.59 (dt, *J* = 11.6, 6.4 Hz, 2H, C**H₂**, both rotamers), 1.46 – 1.35 (m, 2H, C**H₂**, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 174.5 (**C**O), 171.9 (**C**O), 165.5 (**C**O), 147.6 (Ar-**C**), 137.3 (Ar-**C**), 131.8 (Ar-**C**H), 130.7 (Ar-**C**H), 128.9 (Ar-**C**), 2 × 128.9 (Ar-**C**H), 127.6 (Ar-**C**H), 126.6 (Ar-**C**H), 2 × 126.6 (Ar-**C**H), 122.9 (Ar-**C**H), 54.0 (N**C**H₂Ph), 42.6 (**C**H₂), 39.5 (**C**H₂), 33.1 (**C**H₂), 33.1 (**C**H₂), 29.2 (**C**H₂), 25.4 (**C**H₂), 25.1 (**C**H₂); Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.9 (**C**O), 169.9 (**C**O), 166.4 (**C**O), 147.9 (Ar-**C**), 137.4 (Ar-**C**), 131.4 (Ar-**C**H), 129.6 (Ar-**C**H), 128.8 (Ar-**C**H), 128.2 (Ar-**C**H), 127.5 (Ar-**C**H), 126.3 (Ar-**C**H), 123.1(Ar-**C**H), 48.7 (N**C**H₂Ph), 42.1 (**C**H₂), 37.9 (**C**H₂), 34.8 (**C**H₂), 33.6 (**C**H₂), 28.2 (**C**H₂), 25.8 (**C**H₂), 24.5 (**C**H₂); HRMS (ESI): calcd. for $C_{23}H_{26}N_2NaO_4$, 417.1785. Found: $[MNa]^+$, 417.1784 (0.1 ppm error).

Dodecahydropyrrolo[1,2-*a*][1,4]diazacyclododecine-1,10-dione (43)



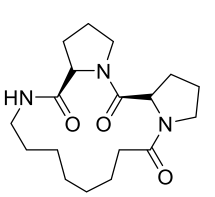
A mixture of azocan-2-one (706 mg, 5 mmol), DMAP (61 mg, 0.5 mmol) and pyridine (2.42 mL, 30 mmol) in DCM (35 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **16** (7.5 mmol, 1.50 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in DCM (18 mL) was added and the resulting mixture was refluxed at 50 °C for 16 h. The mixture was then diluted with DCM (100 mL) and washed with 10% aq. HCl (100 mL). The aqueous layer was then extracted with DCM (3 × 100 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (50 mL) and DBU (7.6 mL, 50 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate → ethyl acetate → 10:1 ethyl acetate: methanol) afforded the *title compound* (as a 3:2 mixture of rotamers) as a white solid (940 mg, 79%); $R_f = 0.25$ (9:1 ethyl acetate: methanol); $[\alpha]_D^{21}$ = 2.4 (2.9 mg/mL in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.51 (d, *J* = 9.1 Hz, 1H, N**H**, minor rotamer), 5.85 (d, *J* = 9.6 Hz, 1H, N**H**, major rotamer), 4.81 (dd, *J* = 8.0, 1.5 Hz, 1H, NC**H**, minor rotamer), 4.37 (dd, *J* = 8.7, 2.8 Hz, 1H, NC**H**, major rotamer), 3.88 – 3.50 (m, 4H, C**H₂**, both rotamers), 3.45 (dd, *J* = 9.7, 9.1 Hz, 1H, C**H**₂, both rotamers), 3.02 (dd, *J* = 14.0, 5.4 Hz, 1H, C**H**₂, both rotamers), 2.84 – 2.65 (m, 1H, C**H**$_2$, both rotamers), 2.51 – 2.44 (m, 1H, C**H**$_2$, both rotamers), 2.43 – 2.33 (m, 2H, C**H$_2$**, both rotamers), 2.32 – 2.06 (m, 6H, C**H$_2$**, both rotamers), 1.84 – 1.02 (m, 24H, C**H$_2$**, both rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer: 173.8 (**C**O), 171.8 (**C**O), 62.0 (N**C**H), 47.0 (**C**H$_2$), 39.9 (**C**H$_2$), 31.8 **C**H$_2$), 31.2 (**C**H$_2$), 27.9 (**C**H$_2$), 24.6 (**C**H$_2$), 24.6 (**C**H$_2$), 24.5 (**C**H$_2$), 24.4 (**C**H$_2$), 22.9 (**C**H$_2$); ^{13}C data for the minor rotamer: 174.7 (**C**O), 171.1 (**C**O), 58.5 (N**C**H), 47.3 (**C**H$_2$), 39.1 (**C**H$_2$), 35.0 (**C**H$_2$), 27.5 (**C**H$_2$), 26.9 (**C**H$_2$), 25.2 (**C**H$_2$), 25.1 (**C**H$_2$), 25.0 (**C**H$_2$), 23.8 (**C**H$_2$), 23.2 (**C**H$_2$); HRMS (ESI): calcd. for $C_{13}H_{22}N_2NaO_2$, 261.1573. Found: [MNa]$^+$, 261.1570 (1.3 ppm error).

(9*H*-Fluoren-9-yl)methyl 2-(1,10-dioxododecahydropyrrolo[1,2*a*][1,4] diazacyclododecine-2(1*H*)-carbonyl)pyrrolidine-1-carboxylate (44)



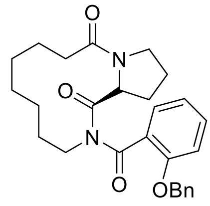
A mixture of 12 membered lactam **43** (95.3 mg, 0.4 mmol), CuO (3.2 mg, 0.04 mmol) and NMM (0.260 mL, 2.4 mmol) in benzene (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **18** (1.2 mmol, 3.0 equiv., freshly prepared from Fmoc-Pro-OH using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts dried over MgSO$_4$ and concentrated in vacuo. Purification by flash column chromatography (SiO$_2$, 1:1 hexane: ethyl acetate→ ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* (as a 5:1 mixture of rotamers) as a colorless oil (90 mg, 40%). R$_f$ = 0.55 (9:1 ethyl acetate: methanol); δ_H (400 MHz, CDCl$_3$); 7.75 (t, *J* = 7.1 Hz, 3H, Ar-C**H**, both rotamers), 7.65 – 7.55 (m, 3H, Ar-C**H**, both rotamers), 7.43 – 7.34 (m, 3H, Ar-C**H**, both rotamers), 7.33 – 7.26 (m, 3H, Ar-C**H**, both rotamers), 5.54 (d, *J* = 8.8 Hz, 1H, NC**H**, minor rotamer), 5.40 (dd, *J* = 8.8, 1.7 Hz, 1H, NC**H**, major rotamer), 4.77 (dd, *J*= 8.6, 4.0 Hz, 1H, NC**H**, major rotamer), 4.58 (dd, *J* = 10.8, 7.1 Hz, 1H, NC**H**, minor rotamer), 4.49 – 4.30 (m, 3H, OC**H$_2$**, both rotamers), 4.25 (t, *J* = 7.2 Hz, 1H, OCH$_2$C**H**, major rotamer), 3.84 – 3.58 (m, 5H, NC**H$_2$**, both rotamers), 3.29 (ddd, *J* = 14.8, 6.5, 2.8 Hz, 1H, NC**H**$_2$, major rotamer), 2.46 (dt, *J* = 14.5, 7.4 Hz, 1H, NC**H**$_2$, major rotamer), 2.39 – 2.26 (m, 2H, COC**H$_2$**, both rotamers), 2.15 – 1.08 (m, 25H, 9 × C**H$_2$**, both rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 177.6 (**C**O), 176.1 (**C**O), 172.7 (**C**O), 154.8 (**C**OO), 2 × 144.1 (Ar-**C**), 2 × 141.4 (Ar-**C**), 2 × 127.8 (Ar-**C**H), 2 × 127.1 (Ar-**C**H), 2 × 125.3 (Ar-**C**H), 2 × 120.1 (Ar-**C**H), 67.7 (O**C**H$_2$), 62.8 (N**C**H), 59.9 (N**C**H), 47.3 (OCH$_2$**C**H), 47.0 (**C**H$_2$), 47.0 (**C**H$_2$), 44.3 (**C**H$_2$), 32.6 (**C**H$_2$), 31.6 (**C**H$_2$), 30.0 (**C**H$_2$), 27.3 (**C**H$_2$), 26.3 (**C**H$_2$), 25.7 (**C**H$_2$), 25.2 (**C**H$_2$), 24.4 (**C**H$_2$), 23.9 (**C**H$_2$), 21.9 (**C**H$_2$); ^{13}C NMR resonances for the minor rotamers: 177.0 (**C**O), 175.2 (**C**O), 172.2 (**C**O), 154.3 (**C**OO), 144.0 (Ar-**C**), 143.5 (Ar-**C**), 141.3 (Ar-**C**), 141.2 (Ar-**C**), 127.9 (Ar-**C**H), 127.8 (Ar-**C**H), 127.1 (Ar-**C**H), 127.0 (Ar-**C**H), 120.2 (Ar-**C**H), 68.2 (O**C**H$_2$), 47.7 (OCH$_2$**C**H), 47.2 (**C**H$_2$), 46.9 (**C**H$_2$), 44.1 (**C**H$_2$), 31.4 (**C**H$_2$), 31.2 (**C**H$_2$), 29.8 (**C**H$_2$), 27.0 (**C**H$_2$), 25.8 (**C**H$_2$), 25.0 (**C**H$_2$), 23.2 (**C**H$_2$), 22.9 (**C**H$_2$); HRMS (ESI): calcd. for $C_{33}H_{39}N_3NaO_5$, 580.2782. Found: [MNa]$^+$, 580.2790 (–1.4 ppm error).

Tetradecahydro-1*H*-dipyrrolo[1,2-*a*:1',2'-*d*][1,4,7]triazacyclopentadecine-5,14,19(19a*H*)-trione (45)



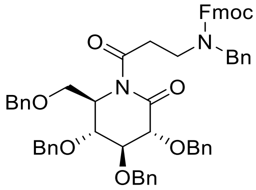
The *N*-acylated product **44** (85 mg, 0.15 mmol) was then re-dissolved in DCM (4 mL) and DBU (0.6 mL, 4 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO$_2$, ethyl acetate → 9:1 ethyl acetate: methanol) afforded the *title compound* as (as a 10:1:1:1 mixture of rotamers, A:B:C:D) a colorless oil (39 mg, 72%); R$_f$ = 0.18 (9:1 ethyl acetate: methanol); $[\alpha]_D^{21}$ = –13.2 (5.4 mg/mL in CHCl$_3$); δ_H (400 MHz, CDCl$_3$) 8.57 (d, *J* = 4.2 Hz, 1H, N**H**, rotamer A), 7.45 (d, *J* = 7.3 Hz, 1H, N**H**, rotamer B), 6.15 (t, *J* = 5.7 Hz, 1H, N**H**, rotamer C), 4.80 (dd, *J* = 8.4, 2.9 Hz, 1H, NC**H**, rotamer B), 4.71 (dd, *J* = 8.0, 2.0 Hz, 1H, NC**H**, rotamer C), 4.58 – 4.49 (m, 1H, NC**H**, rotamer D), 4.50 – 4.41 (m, 1H, NC**H**, rotamer B), 4.36 (td, *J* = 8.6, 1.6 Hz, 1H, NC**H**, rotamer C), 4.24 (d, *J* = 7.8 Hz, 1H, NC**H**, rotamer A), 4.11 (t, *J* = 7.7 Hz, 1H, NC**H**, rotamer A), 3.77 – 3.20 (m, 8H, NC**H$_2$**+ NHC**H$_2$**, all rotamers), 2.92 – 2.47 (m, 3H, COC**H$_2$**, all rotamers), 2.44 – 0.76 (m, 36H, 7 × C**H$_2$**, all rotamers); δ_C (100 MHz, CDCl$_3$) data for the major rotamer only: 173.2 (**C**O), 171.2 (**C**O), 171.0 (**C**O), 61.9 (N**C**H), 59.3 (N**C**H), 47.7 (**C**H$_2$), 47.0 (**C**H$_2$), 38.9 (**C**H$_2$), 34.7 (**C**H$_2$), 32.3 (**C**H$_2$), 28.8 (**C**H$_2$), 28.3 (**C**H$_2$), 28.2 (**C**H$_2$), 26.3 (**C**H$_2$), 25.7 (**C**H$_2$), 24.2 (**C**H$_2$), 22.5 (**C**H$_2$), 22.0 (**C**H$_2$); HRMS (ESI): calcd. for $C_{18}H_{29}N_3NaO_3$, 358.2101. Found: [MNa]$^+$, 358.2104 (–0.7 ppm error).

2-[2-(Benzyloxy)benzoyl]dodecahydropyrrolo[1,2-*a*][1,4]diazacyclododecine-1,10-dione (46)



A mixture of 12-membered lactam **43** (95.3 mg, 0.4 mmol), CuO (6.4 mg, 0.08 mmol) and NMM (0.264 mL, 2.4 mmol) in dry benzene (2 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **18** (1.2 mmol, 3.0 equiv., freshly prepared from 2-benzyloxybenzoic acid using the general procedure) in dry benzene (2 mL) was added and the resulting mixture was refluxed at 80 °C for 18 h. The mixture was then diluted with DCM (30 mL) and washed with 10% aq. HCl (30 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. Purification by flash column chromatography (SiO_2, 1:1 hexane: ethyl acetate→ ethyl acetate) afforded the *title compound* (as a 10:1 mixture of rotamers) as a pale-yellow oil (130 mg, 73%). $R_f = 0.40$ (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.95 (dd, *J* = 7.7, 1.8 Hz, 1H, Ar-C**H**, minor rotamer), 7.44 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H, Ar-C**H**, major rotamer), 7.38 – 7.27 (m, 6H, Ar-C**H**, both rotamers), 7.08 – 7.01 (m, 2H, Ar-C**H**, both rotamers), 5.10 – 4.95 (m, 2H, OC**H**$_2$Ph, both rotamers), 4.40 (ddd, *J* = 14.2, 10.9, 3.0 Hz, 1H, NC**H**, major rotamer), 3.96 (ddd, *J* = 13.4, 7.6, 2.7 Hz, 1H, NC**H**, minor rotamer), 3.65 (dt, *J* = 11.8, 5.7 Hz, 2H, C**H**$_2$, both rotamers), 3.53 – 3.42 (m, 1H, C**H**$_2$, both rotamers), 3.25 (dt, *J* = 14.4, 4.0 Hz, 1H, C**H**$_2$, both rotamers), 2.41 (dt, *J* = 13.9, 7.2 Hz, 1H, C**H**$_2$, both rotamers), 2.09 – 1.91 (m, 2H, C**H**$_2$, both rotamers), 1.71 – 1.50 (m, 6H, C**H**$_2$, both rotamers), 1.43 – 1.08 (m, 8H, C**H**$_2$, both rotamers); δ_C (100 MHz, $CDCl_3$) data for the major rotamer only: 175.9 (**C**O), 172.9 (**C**O), 172.6 (**C**O), 154.4 (Ar-**C**), 135.7 (Ar-**C**), 132.3 (Ar-**C**H), 128.7 (Ar-**C**H), 128.7 (Ar-**C**H), 2 × 128.5 (Ar-**C**H), 2 × 127.7 (Ar-**C**H), 125.8 (Ar-**C**), 121.4 (Ar-**C**H), 112.2 (Ar-**C**H), 70.6 (O**C**H$_2$Ph), 61.9 (N**C**H), 46.8 (**C**H$_2$), 46.5 (**C**H$_2$), 32.3 (**C**H$_2$), 30.7 (**C**H$_2$), 26.9 (**C**H$_2$), 26.7 (**C**H$_2$), 26.2 (**C**H$_2$), 24.9 (**C**H$_2$), 23.2 (**C**H$_2$), 22.1 (**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 177.0 (**C**O), 171.2 (**C**O), 154.8 (Ar-**C**), 135.9 (Ar-**C**), 132.5 (Ar-**C**H), 128.1 (Ar-**C**H), 127.4 (Ar-**C**), 127.2 (Ar-**C**H), 121.8 (Ar-**C**H), 112.4 (Ar-**C**H), 70.8 (O**C**H$_2$Ph), 60.4 (N**C**H), 58.0 (**C**H$_2$), 44.8 (**C**H$_2$), 34.7 (**C**H$_2$), 27.4 (**C**H$_2$), 25.9 (**C**H$_2$), 25.1 (**C**H$_2$), 23.6 (**C**H$_2$), 22.8 (**C**H$_2$), 21.1 (**C**H$_2$); HRMS (ESI): calcd. for $C_{27}H_{32}N_2NaO_4$, 471.2254. Found: [MNa]$^+$, 471.2249 (1.1 ppm error).

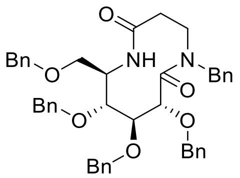
(9*H*-Fluoren-9-yl)methyl 3,4,5-tris(benzyloxy)-2-[(benzyloxy)methyl]-6-oxopiperidine-1-carboxylate (49)



A mixture of lactam **48**[3] (107.5 mg, 0.2 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride (1.0 mmol, 3.0 equiv., freshly prepared from acid using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The mixture was then diluted with DCM (10 mL) and washed with 10% aq. HCl (10 mL). The aqueous layer was then extracted with DCM (3 × 10 mL) and the combined organic extracts 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 5:4 rotamers) as a colorless oil (132 mg, 72%). R_f = 0.60 (1:1 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.77 – 7.71 (m, 2H, Fmoc-C**H**, both rotamers), 7.63 (d, *J* = 7.1 Hz, 1H, Fmoc-C**H**, both rotamers), 7.49 – 7.19 (m, 36H, Ar-C**H**, both rotamers), 7.12 (d, *J* = 6.4 Hz, 1H, Fmoc-C**H**, both rotamers), 5.04 – 4.93 (m, 2H, OC**H**₂Ph, both rotamers), 4.75 (dd, *J* = 13.7, 10.1 Hz, 1H, CONC**H**, major rotamer), 4.65 (t, *J* = 10.3 Hz, 1H, COOCH₂C**H**, major rotamer), 4.60 – 4.36 (m, 11H, 3 × OC**H**₂Ph + NC**H**₂Ph + OC**H**₂CH, both rotamers), 4.24 (dt, *J* = 12.9, 6.6 Hz, 1H, OC**H**, both rotamers), 4.01 (dd, *J* = 4.0, 2.2 Hz, 1H, OC**H**, major rotamer), 3.88 (dd, *J* = 8.9, 4.3 Hz, 1H, OC**H**, major rotamer), 3.78 (dd, *J* = 10.5, 8.8 Hz, 1H, OC**H**, minor rotamer), 3.67 – 3.56 (m, 2H, BnOC**H**₂, both rotamers), 3.47 (td, *J* = 9.8, 5.3 Hz, 2H, NC**H**₂, both rotamers), 3.40 – 3.09 (m, 2H, COC**H**₂, both rotamers); δ_C (101 MHz, $CDCl_3$) for major rotamer only: 173.6 (N**C**O), 172.1 (N**C**O), 156.2 (O**C**O), 144.1 (Ar-**C**), 141.4 (Ar-**C**), 138.0 (Ar-**C**), 137.8 (Ar-**C**), 137.7 (Ar-**C**), 137.5 (Ar-**C**), 128.8 (Ar-**C**H), 128.6 (Ar-**C**H), 128.5 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.4 (Ar-**C**H), 127.3 (Ar-**C**H), 127.2 (Ar-**C**H), 125.1 (Ar-**C**H), 120.0 (Ar-**C**H), 81.7 (O**C**H), 79.8 (O**C**H), 76.5 (O**C**H), 74.4 (O**C**H₂), 73.6 (O**C**H₂), 73.3 (O**C**H₂), 71.7 (O**C**H₂), 69.3 (O**C**H₂), 67.6 (O**C**H₂), 55.5 (N**C**H₂), 50.6 (N**C**H), 47.4 (Ar-C**C**H), 43.2 (N**C**H₂), 37.7 (CO**C**H₂); Diagnostic ^{13}C NMR resonances for the minor rotamer: 173.5 (N**C**O), 172.1 (N**C**O), 156.6 (O**C**O), 144.2 (Ar-**C**), 141.4 (Ar-**C**), 137.8 (Ar-**C**), 137.8 (Ar-**C**), 137.7 (Ar-**C**), 137.4 (Ar-**C**), 128.7 (Ar-**C**H), 128.6 (Ar-**C**H), 128.0 (Ar-**C**H), 127.7 (Ar-**C**H), 127.5 (Ar-**C**H), 127.2 (Ar-**C**H), 125.1 (Ar-**C**H), 120.1 (Ar-**C**H), 81.5 (O**C**H), 79.6 (O**C**H), 74.5

(O**C**H$_2$), 73.8 (O**C**H$_2$), 73.4 (O**C**H$_2$), 71.9 (O**C**H$_2$), 69.6 (O**C**H$_2$), 67.6 (O**C**H$_2$), 55.7 (N**C**H$_2$), 50.8 (N**C**H$_2$), 47.5 (Ar-C**C**H), 42.2 (N**C**H$_2$), 38.2(CO**C**H$_2$); HRMS (ESI): calcd. for $C_{59}H_{56}N_2NaO_8$, 943.3929. Found: $[MNa]^+$, 943.3966 (–4.0 ppm error).

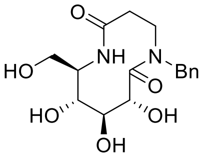
5-Benzyl-7,8,9-tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione (50)



The *N*-acylated product (120 mg, 0.13 mmol) was then re-dissolved in DCM (1.3 mL) and DBU (0.194 mL, 1.3 mmol) was added, followed by stirring at RT overnight, before the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 10:1 hexane: ethyl acetate →1:2 hexane: ethyl acetate) afforded the *title compound* as (as a 10:3:2 mixture of rotamers A:B:C) a colorless oil (61 mg, 67%); R_f = 0.24 (1:1 hexane: ethyl acetate); $[\alpha]_D^{21}$ = –7.4 (10.9 mg/mL in $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3408, 3062, 3030, 2924, 2864, 1660, 1453, 1098, 736, 698; δ_H (400 MHz, $CDCl_3$) 7.56 – 7.06 (m, 57H, Ar-C**H**, all rotamers), 6.90 (dd, *J* = 7.2, 2.3 Hz, 2H, Ar-C**H**, all rotamers), 5.93 (d, *J* = 10.3 Hz, 1H, CON**H**, rotamer A), 5.56 (d, *J* = 10.3 Hz, 1H, CON**H**, rotamer C), 5.43 (d, *J* = 10.2 Hz, 1H, CON**H**, rotamer B), 5.22 – 3.68 (m, 36H, 5 × OC**H**$_2$ + NC**H**$_2$+ 3 × OC**H** + NHC**H**, all rotamers), 3.63 – 3.23 (m, 3H, NC**H**$_2$, all rotamers), 2.84 – 2.71 (m, 2H, C**H**$_2$, rotamer A), 2.50 – 2.41 (m, 2H, C**H**$_2$, rotamer B), 2.34 – 2.25 (m, 2H, C**H**$_2$, rotamer C); δ_C (101 MHz, $CDCl_3$) data for the major rotamer only: 172.0 (NH**C**O), 169.6 (N**C**O), 138.9 (Ar-**C**), 138.2 (Ar-**C**), 138.2 (Ar-**C**), 137.8 (Ar-**C**), 136.1 (Ar-**C**), 128.9 (Ar-**C**H), 128.8 (Ar-**C**H), 128.6 (Ar-**C**H), 128.5 (Ar-**C**H), 128.5 (Ar-**C**H), 128.4 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 127.9 (Ar-**C**H), 126.9 (Ar-**C**H), 78.8 (O**C**H), 78.5 (O**C**H), 74.2 (O**C**H$_2$), 74.0 (O**C**H$_2$), 73.2 (O**C**H$_2$), 72.7 (O**C**H), 72.2 (O**C**H$_2$), 69.2 (O**C**H$_2$), 53.1 (NH**C**H), 51.2 (N**C**H$_2$Ph), 41.1 (N**C**H$_2$), 34.9 (CO**C**H$_2$); Diagnostic ^{13}C NMR resonances for the minor rotamer: 171.8 (NH**C**O), 171.7 (NH**C**O), 171.5 (N**C**O), 166.2 (N**C**O), 151.9 (Ar-**C**), 138.5 (Ar-**C**), 138.2 (Ar-**C**), 138.1 (Ar-**C**), 138.1 (Ar-**C**), 138.0 (Ar-**C**), 138.0 (Ar-**C**), 137.4 (Ar-**C**), 137.4 (Ar-**C**), 135.9 (Ar-**C**), 129.4 (Ar-**C**H), 129.2 (Ar-**C**H), 129.0 (Ar-**C**H), 128.7 (Ar-**C**H), 128.7 (Ar-**C**H), 128.4 (Ar-**C**H), 128.3 (Ar-**C**H), 128.2 (Ar-**C**H), 128.2 (Ar-**C**H), 128.2 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.5 (Ar-**C**H), 127.5 (Ar-**C**H), 127.5 (Ar-**C**H), 105.9 (O**C**H), 90.6 (O**C**H), 81.9 (O**C**H), 81.5 (O**C**H), 76.2 (O**C**H), 75.8 (O**C**H), 75.8 (O**C**H), 74.9 (O**C**H$_2$), 74.2 (O**C**H), 73.9 (O**C**H$_2$), 73.6 (O**C**H$_2$), 73.1 (O**C**H$_2$), 71.6 (O**C**H$_2$), 70.1 (O**C**H$_2$), 68.2 (O**C**H$_2$), 67.3 (O**C**H$_2$), 53.3 (NH**C**H), 52.6 (NH**C**H), 50.8

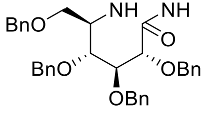
(N**C**H$_2$Ph), 50.4 (N**C**H$_2$Ph), 49.9 (N**C**H$_2$Ph), 47.3 (N**C**H$_2$), 44.9 (N**C**H$_2$), 44.1 (N**C**H$_2$), 37.9 (CO**C**H$_2$), 37.7 (CO**C**H$_2$), 36.0 (CO**C**H$_2$), 29.8 (CO**C**H$_2$); HRMS (ESI): calcd. for $C_{44}H_{46}N_2NaO_6$, 721.3248. Found: $[MNa]^+$, 721.3268 (–2.7 ppm error).

5-Benzyl-7,8,9-trihydroxy-10-(hydroxymethyl)-1,5-diazecane-2,6-dione (51)



5-Benzyl-7,8,9-tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione **50** (122 mg, 0.175 mmol) was dissolved in methanol (3 mL) and ethanol (1 mL), then palladium hydroxide on carbon (20 mg, 20% w/w) was added, together with 1 drop 1 M aqueous HCl solution. The mixture was stirred for 48 hours under a positive pressure of hydrogen (via balloon). The mixture was then filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 ethyl acetate: methanol → 3:1 ethyl acetate: methanol) afforded the *title compound* as a pale yellow oil (37 mg, 62%); R_f = 0.26 (3:1 ethyl acetate: methanol); $[\alpha]_D^{21} = -11.5$ (2.2 mg/mL in methanol); $[\alpha]_D^{21} = -14.0$ (2.7 mg/mL in methanol); ν_{max}/cm^{-1} (thin film) 3307, 1634, 1496, 1453, 1364, 1076, 1049, 735, 698; δ_H (400 MHz, methanol-*d$_4$*) 7.37 – 7.10 (m, 5H, Ar-C**H**), 5.38 (d, *J* = 15.1 Hz, 1H, CON**H**), 4.82 – 4.92 (m, 1H, COC**H**OH), 4.17 (s, 1H, C**H**OH), 3.96 (s, 1H, C**H**OH), 3.86 – 3.67 (m, 4H, C**H$_2$**OH + NC**H$_2$**Ph), 3.54 (dd, *J* = 8.8, 3.5 Hz, 1H, NHC**H**), 3.47 – 3.24 (m, 2H, NC**H$_2$**), 2.51 (td, *J* = 12.4, 2.9 Hz, 1H, COC**H$_2$**), 2.21 (dd, *J* = 12.5, 4.2 Hz, 1H, COC**H$_2$**); δ_c (101 MHz, methanol-*d$_4$*) 176.2 (NH**C**O), 174.3 (**N**CO), 138.2 (Ar-**C**), 129.7 (Ar-CH) × 2, 128.8 (Ar-**C**H) × 2, 128.6 (Ar-**C**H), 81.0 (CO**C**HOH), 75.2 (**C**HOH), 65.0 (**C**HOH), 63.2 (**C**H$_2$OH), 52.8 (NH**C**H), 49.8 (N**C**H$_2$Ph), 45.6 (N**C**H$_2$), 37.4 (CO**C**H$_2$); HRMS (ESI): calcd. for $C_{16}H_{22}N_2NaO_6$, 361.1370. Found: $[MNa]^+$, 361.1372 (–0.5 ppm error).

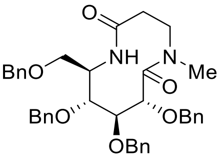
7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione (56)



A mixture of lactam **48**[3] (107.5 mg, 0.2 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **52** (0.6 mmol, 3.0 equiv., freshly prepared from

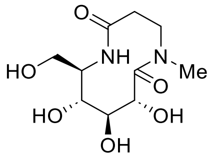
Fmoc-β-alanine using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane: ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues (28% starting lactam left), and concentrated *in vacuo*. The crude material (128 mg) was then re-dissolved in DCM (2 mL) and DBU (300 mL, 2.0 mmol) was added, followed by stirring at RT for 30 min, before 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 colorless oil (36 mg, 30%); R$_f$ = 0.21 (1:1 hexane: ethyl acetate); $[\alpha]_D^{21}$ = 6.4 (9.6 mg/mL in CHCl$_3$); δ_H (400 MHz, CDCl$_3$-*d*) 7.31 – 7.08 (m, 20H, Ar-C**H**), 6.78 (dd, *J* = 10.2, 2.8 Hz, 1H, N**H**), 5.85 (d, *J* = 10.4 Hz, 1H, N**H**), 4.82 (t, *J* = 10.7 Hz, 2H, OC**H$_2$**CH), 4.60 – 4.50 (m, 3H, OC**H$_2$** + OC**H**), 4.46 – 4.33 (m, 4H, OC**H$_2$**), 4.26 – 4.04 (m, 1H, OC**H**), 3.92 – 3.82 (m, 3H,OC**H$_2$** + OC**H**), 3.61 (dd, *J* = 8.8, 6.3 Hz, 1H, NHC**H**), 3.31 (dd, *J* = 9.2, 2.8 Hz, 1H, COC**H$_2$**), 3.15 – 3.02 (m, 1H, COC**H$_2$**), 2.68 (ddd, *J* = 14.2, 8.1, 3.4 Hz, 1H, NHC**H$_2$**), 2.39 (dt, *J* = 14.3, 8.6 Hz, 1H, NHC**H$_2$**); δ_C (101 MHz, CDCl$_3$-*d*) 173.6 (NH**C**O), 169.5 (NH**C**O), 138.6 (Ar-**C**), 138.4 (Ar-**C**), 138.2 (Ar-**C**), 137.3 (Ar-**C**), 128.5 (Ar-**C**H), 128.3 (Ar-**C**H), 128.3 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 127.6 (Ar-**C**H), 85.1 (O**C**H), 83.6 (O**C**H), 76.1 (O**C**H), 75.6 (O**C**H$_2$), 75.3 (O**C**H$_2$), 73.4 (O**C**H$_2$), 73.3 (O**C**H$_2$), 69.5 (O**C**H$_2$CH), 53.0 (NH**C**H), 36.9 (CO**C**H$_2$), 34.0 (NH**C**H$_2$); HRMS (ESI): calcd. for $C_{37}H_{40}N_2NaO_6$, 631.2779. Found: $[MNa]^+$, 631.2786 (–1.2 ppm error).

(7*R*,8*S*,9*R*,10*R*)-7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione (57)



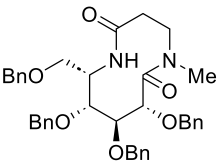
A mixture of lactam **48**[3] (107.5 mg, 0.2 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **53** (0.6 mmol, 3.0 equiv., freshly prepared from Fmoc-*N*-methyl-β-alanine using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane:ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. The crude material (166 mg) was then re-dissolved in DCM (2 mL) and DBU (300 mL, 2.0 mmol) was added, followed by stirring at RT for 30 min, before the solvent was removed in vacuo. Purification by flash column chromatography (SiO_2, 2:1 dichloromethane: ethyl acetate) afforded the title compound (mixture of 4 rotamers, ≈10:1:1:1) as a colorless oil (66 mg, 53%); $[\alpha]_D^{21}$ = 2.2 (30.8 mg/mL in $CHCl_3$); δ_H (400 MHz, $CDCl_3$-*d*) 7.51 – 7.18 (m, 30 H, Ar-C**H**, all rotamers), 6.29 (d, *J* = 10.1 Hz, 1H, N**H**, minor rotamer), 5.89 (d, *J* = 10.0 Hz, 1H, N**H**, major rotamer), 5.64 (d, *J* = 10.2 Hz, 1H, N**H**, minor rotamer), 5.28 (d, *J* = 10.4 Hz, 1H, N**H**, minor rotamer), 5.02 – 4.83 (m, 3H, 3 × OC**H**, all rotamers), 4.72 – 4.32 (m, 10H, 5 × OC**H₂**, all rotamers) 4.26 – 4.11 (m, 2H, C**H₂**, all rotamers), 3.83 – 3.35 (m, 3H, C**H** + C**H₂**, all rotamers), 3.00 (s, 3H, NC**H₃**, minor rotamer), 2.90 (s, 3H, NC**H₃**, minor rotamer), 2.84 (s, 3H, NC**H₃**, minor rotamer), 2.59 (s, 3H, NC**H₃**, major rotamer); δ_C (101 MHz, $CDCl_3$-*d*) data for the major rotamer only: 171.7 (NH**C**O), 169.4 (NH**C**O), 138.9 (Ar-**C**), 138.4 (Ar-**C**), 138.2 (Ar-**C**), 138.0 (Ar-**C**), 128.5 (Ar-**C**H), 128.5 (Ar-**C**H), 128.4 (Ar-**C**H), 128.4 (Ar-**C**H), 128.2 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.7 (Ar-**C**H), 127.7 (Ar-**C**H), 78.4 (O**C**H), 78.2 (O**C**H), 74.1 (O**C**H_2), 74.1 (O**C**H_2), 73.2 (O**C**H_2), 72.4 (O**C**H), 72.0 (O**C**H_2), 69.1 (O**C**H_2CH), 53.0 (NH**C**H), 43.7 (CO**C**H_2), 35.7 (N**C**H_3), 34.9 (NH**C**H_2); HRMS (ESI): calcd. for $C_{38}H_{42}N_2NaO_6$, 645.2935. Found: $[MNa]^+$, 645.2939 (–0.7 ppm error).

(7*R*,8*S*,9*R*,10*R*)-7,8,9-trihydroxy-10-(hydroxymethyl)-5-methyl-1,5-diazecane-2,6-dione (58)



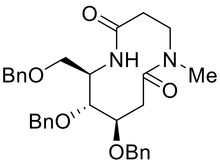
7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione **57** (66 mg, 0.106 mmol) was dissolved in methanol (1 mL) and ethanol (0.3 mL), then palladium hydroxide on carbon (10 mg, 20% w/w) was added, together with 1 drop 1 M aqueous HCl solution. The mixture was stirred for 48 hours under a positive pressure of hydrogen (via balloon). The mixture was then filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, 3:1 ethyl acetate: methanol) afforded the *title compound* as a pale-yellow oil (20 mg, 72%); R_f = 0.26 (3:1 ethyl acetate: methanol); δ_H (400 MHz, methanol-*d₄*) 4.64 – 3.98 (m, 4H, 4 × C**H**), 3.96 – 3.58 (m, 2H, C**H₂**OH), 3.29 – 3.22 (m, 2H, C**H₂**), 3.07 – 2.86 (m, 2H, C**H₂**), 2.72 (s, 3H, NC**H₃**); δ_C (101 MHz, methanol-*d₄*) 174.8 (**C**O), 171.5 (**C**O), 73.3 (**C**HOH), 72.8 (**C**HOH), 68.6 (**C**HOH), 63.4 (**C**H_2OH), 54.5 (**C**HNH), 45.9 (N**C**H_3), 34.3 (**C**H_2), 31.5 (**C**H_2); HRMS (ESI): calcd. for $C_{10}H_{19}N_2O_6$, 263.1238. Found: $[MH]^+$, 263.1232 (2.2 ppm error).

(7*R*,8*S*,9*R*,10*S*)-7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione (59)



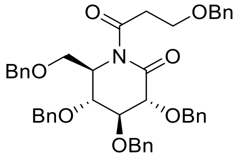
A mixture of lactam **54**[4] (87 mg, 0.16 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (2.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **53** (0.6 mmol, freshly prepared from Fmoc-*N*-methyl-β-alanine using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 2:1 hexane: ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues, and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (2 mL) and DBU (275 µL, 2.0 mmol) was added, followed by stirring at RT for 30 min, before the solvent was removed in vacuo. Purification by flash column chromatography (SiO_2, 1:2 hexane: ethyl acetate) afforded the title compound as a colorless oil (41 mg, 41%); $[\alpha]_D^{21}$ = 2.8 (30.8 mg/mL in $CHCl_3$); δ_H (400 MHz, $CDCl_3$-*d*) 7.41 – 7.18 (m, 20H, Ar-C**H**), 5.80 (d, J = 9.5 Hz, 1H, N**H**), 4.90 (d, J = 11.6 Hz, 1H, OC**H**), 4.83 (d, J = 11.9 Hz, 1H, OC**H**), 4.71 (d, J = 10.6 Hz, 1H, OC**H**), 4.64 (ddd, J = 19.0, 10.5, 3.7 Hz, 3H, OC**H**$_2$ + OC**H**$_2$), 4.50 (d, J = 11.7 Hz, 1H, OC**H**$_2$), 4.41 (dd, J = 8.6, 4.0 Hz, 1H, OC**H**$_2$), 4.37 (d, J = 11.7 Hz, 1H, OC**H**$_2$), 4.05 (dd, J = 11.3, 9.6 Hz, 2H, OC**H**$_2$), 3.69 (d, J = 4.0 Hz, 1H, OC**H**$_2$), 3.44 – 3.25 (m, 3H, OC**H**$_2$ + C**H**$_2$), 2.94 – 2.83 (m, 1H, NHC**H**), 2.77 (s, 3H, NC**H**$_3$), 2.20 – 2.10 (m, 2H, C**H**$_2$); δ_C (101 MHz, $CDCl_3$-*d*) 170.7 (NH**C**O), 170.4 (NH**C**O), 138.3 (2 × Ar-**C**), 138.2 (Ar-**C**), 137.6 (Ar-**C**), 129.2 (2 × Ar-**C**H), 128.5 (2 × Ar-**C**H), 128.4 (4 × Ar-**C**H), 128.4 (3 × Ar-**C**H), 128.3 (2 × Ar-**C**H), 128.0 (2 × Ar-**C**H), 127.9 (Ar-**C**H), 127.8 (2 × Ar-**C**H), 127.7 (Ar-**C**H), 127.6 (Ar-**C**H), 78.0 (O**C**H), 75.9 (O**C**H), 75.3 (O**C**H), 75.0 (O**C**H$_2$), 73.1 (O**C**H$_2$), 72.6 (O**C**H$_2$), 71.9 (O**C**H$_2$), 69.2 (O**C**H$_2$), 46.9 (**C**H$_2$), 46.9 (NH**C**H), 36.9 (**C**H$_2$), 34.0 (N**C**H$_3$); HRMS (ESI): calcd. For $C_{38}H_{42}N_2NaO_6$, 645.2935. Found: $[MNa]^+$, 645.2942 (–1.0 ppm error).

(8*S*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione (60)



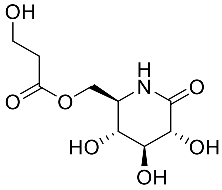
A mixture of sugar lactam **55**[5] (84 mg, 0.19 mmol), DMAP (2.4 mg, 0.02 mmol) and pyridine (0.097 mL, 1.2 mmol) in dry DCM (1.0 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of acid chloride **53** (0.6 mmol, freshly prepared from Fmoc-*N*-methyl-β-alanine using the general procedure) in dry DCM (1.0 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The solvent was concentrated *in vacuo*, loaded onto a short silica plug and eluted with 1:1 hexane: ethyl acetate, to remove the majority of excess carboxylic acid and pyridine residues and concentrated *in vacuo*. The crude material was then re-dissolved in DCM (2 mL) and DBU (275 μL, 2.0 mmol) was added, followed by stirring at RT for 30 min, before the solvent was removed in vacuo. Purification by flash column chromatography (SiO_2, 9:1 ethyl acetate: methanol) afforded *the title compound* (exist as a 3:1 mixture of rotamers in $CDCl_3$ at 50 °C) as a colorless oil (35 mg, 36%); $[\alpha]_D^{21}$ = 24.5 (1.8 mg/mL in $CHCl_3$); δ_H (400 MHz, $CDCl_3$-*d* at 50 °C) 7.37 – 7.14 (m, 15H, Ar-C**H**, both rotamers), 6.13 – 5.87 (m, 1H, N**H**, both rotamers), 5.05 – 4.26 (m, 6H, OC$\mathbf{H_2}$ + 2 × OC**H**, both rotamers), 4.16 – 3.33 (m, 6H, 2 × OC$\mathbf{H_2}$ + C**H**$_2$, both rotamers), 2.96 (s, 3H, NC$\mathbf{H_3}$, major rotamer), 2.81 (s, 3H, NC$\mathbf{H_3}$, minor rotamer), 2.56 – 1.47 (m, 5H, NHC**H** + 2 × C$\mathbf{H_2}$, both rotamers); δ_C (101 MHz, $CDCl_3$-*d* at 50 °C) for major rotamer only: 172.1 (**C**O, brs), 170.5 (**C**O, brs), 138.9 (Ar-**C**), 138.8 (Ar-**C**), 138.0 (Ar-**C**), 128.5 – 127.4 (multiple peaks, Ar-**C**H), 79.1 (O**C**H), 76.3 (O**C**H), 75.3 (O**C**H$_2$, brs), 73.5 (O**C**H$_2$, brs), 73.0 (O**C**H$_2$, brs), 69.8 (O**C**H$_2$), 48.2 (NH**C**H), 36.9 (**C**H$_2$, brs), 34.0 (N**C**H$_3$, brs), 30.6 (**C**H$_2$), 29.9 (**C**H$_2$); Diagnostic 13C NMR resonances for the minor rotamer:172.5 (**C**O), 169.6 (**C**O), 138.2 (Ar-**C**), 23.3 (**C**H$_2$); HRMS (ESI): calcd. For $C_{31}H_{36}N_2NaO_5$, 539.2516. Found: $[MNa]^+$, 539.2519 (–0.4 ppm error).

3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]-1-[3(benzyloxy) propanoyl] piperidin-2-one (62)



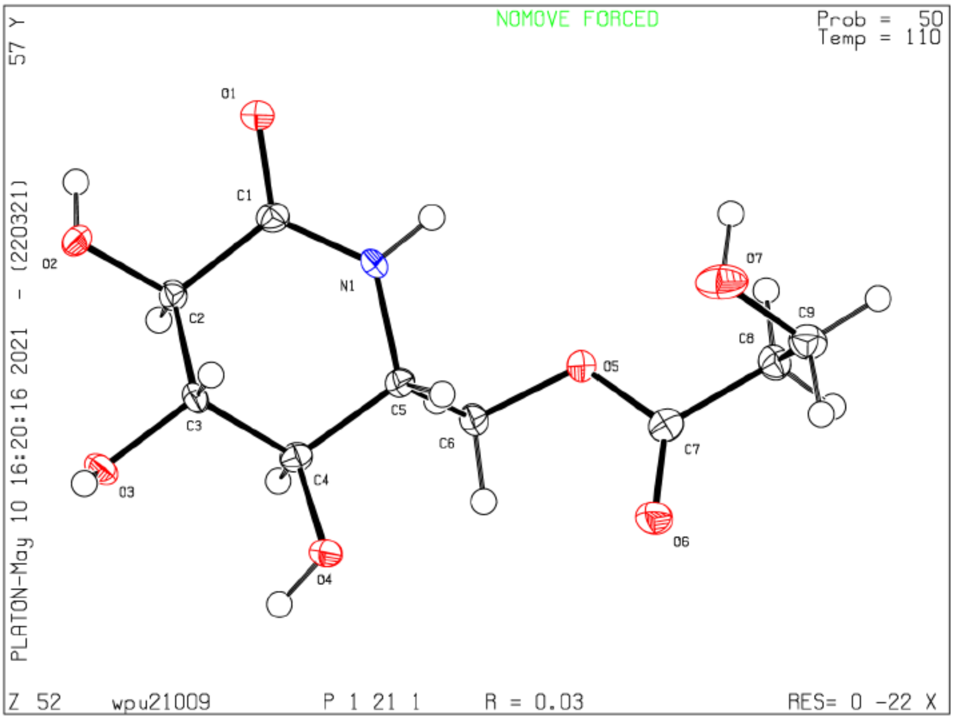
A mixture of lactam **48**[3] (161.3 mg, 0.3 mmol), DMAP (3.7 mg, 0.03 mmol) and pyridine (0.146 mL, 1.8 mmol) in dry DCM (1.5 mL) under an argon atmosphere was stirred at RT for 30 mins. Next, a solution of propanoic acid chloride **61** (0.9 mmol, 3.00 eq. prepared using the general procedure) in dry DCM (1.5 mL) was added and the resulting mixture was refluxed at 50 °C for 18 h. The solvent was concentrated *in vacuo*, and purification by flash column chromatography (SiO_2, 3:1 hexane: ethyl acetate→ ethyl acetate) afforded the title compound **62** as a colorless oil (135 mg, 50%). 27% yield of the stating lactam **48** was also recovered. R_f = 0.70 (1:2 hexane: ethyl acetate); δ_H (400 MHz, $CDCl_3$-*d*) 7.41 – 7.18 (m, 25H, Ar-C**H**), 4.97 (d, *J* = 11.3 Hz, 2H, OC**H**$_2$), 4.72 (d, *J* = 11.4 Hz, 1H, OC**H**$_2$), 4.61 (d, *J* = 11.4 Hz, 1H, OC**H**$_2$), 4.54 (s, 5H, OC**H**$_2$), 4.39 (d, *J* = 1.9 Hz, 2H, OC**H**$_2$), 4.35 (d, *J* = 8.5 Hz, 1H, OC**H**$_2$), 4.00 (dd, *J* = 4.1, 2.0 Hz, 1H, OC**H**), 3.88 – 3.74 (m, 3H, 2 × OC**H** + NC**H**), 3.60 (dd, *J* = 9.6, 6.5 Hz, 1H, OC**H**$_2$CH), 3.46 (dd, *J* = 9.6, 3.9 Hz, 1H, OC**H**$_2$CH), 3.29 (td, *J* = 6.2, 3.7 Hz, 2H, COC**H**$_2$); δ_C (101 MHz, $CDCl_3$-*d*) 173.6 (N**C**O), 172.2 (N**C**O), 138.4 (Ar-**C**), 138.0 (Ar-**C**), 137.7 (Ar-**C**), 137.6 (Ar-**C**), 137.5 (Ar-**C**), 128.6 (Ar-**C**H), 128.5 (Ar-**C**H), 128.5 (Ar-**C**H), 128.3 (Ar-**C**H), 128.1 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 128.0 (Ar-**C**H), 127.9 (Ar-**C**H), 127.8 (Ar-**C**H), 127.8 (Ar-**C**H), 127.7 (Ar-**C**H), 81.8 (O**C**H), 79.8 (O**C**H), 76.5 (O**C**H), 74.4 (O**C**H$_2$), 73.7 (O**C**H$_2$), 73.4 (O**C**H$_2$), 73.2 (O**C**H$_2$), 71.7 (O**C**H$_2$), 69.5 (O**C**H$_2$), 65.7 (O**C**H$_2$), 55.6 (N**C**H), 39.7 (CO**C**H$_2$).

3,4,5-Trihydroxy-6-(hydroxymethyl)-1-(3-hydroxypropanoyl)piperidin-2-one (65)



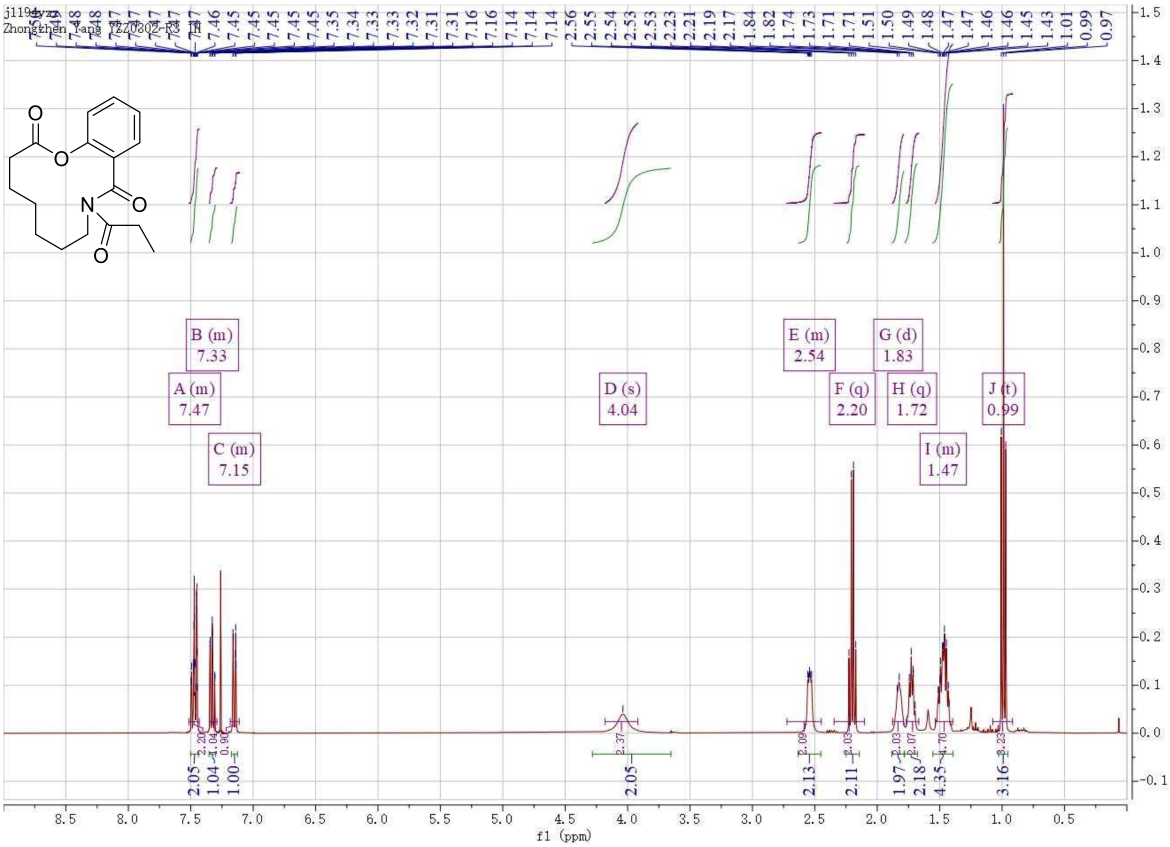
Imide **62** was dissolved in MeOH (5.0 mL)/EtOH (1.5 mL) and placed under an argon atmosphere. Palladium hydroxide on coal (30 mg, 20% w/w) was added, together with a few aqueous HCl solution (1M). Then the reaction vessel was backfilled with hydrogen (via balloon) several times, then stirred at RT under a slight positive pressure of hydrogen (balloon) for 48 h. The reaction was then purged with argon, filtered through Celite, washed with methanol where the solvent was removed *in vacuo*. The crude material was then re-dissolved in chloroform (3.0 mL, not dissolved well) and triethylamine (60 µL, 0.3 mmol) added, and stirred at RT for 16 h, then reduced *in vacuo*. Purification by flash column chromatography (SiO_2, ethyl acetate → 3:1 ethyl acetate: methanol) afforded the title compound as a colorless oil (53 mg, 71%); R_f= 0.20 (3:1 ethyl acetate: methanol); δ_H (400 MHz, methanol-*d*$_4$) 4.39 (dd, *J* = 11.6, 2.6 Hz, 1H, HOC**H**), 4.21 (dd, *J* = 11.6, 5.2 Hz, 1H, HOC**H**), 3.91 – 3.86 (m, 1H, HOC**H**), 3.83 (t, *J* = 6.0 Hz, 2H, HOC**H$_2$**), 3.67 – 3.59 (m, 2H, OC**H$_2$**), 3.47 – 3.42 (m, 1H, NHC**H**), 2.61 – 2.56 (m, 2H, COC**H$_2$**); δ_C (101 MHz, methanol-*d*$_4$) 174.0 (NH**C**O), 173.5 (**C**OO), 75.3 (HO**C**H), 72.5 (HO**C**H), 69.7 (HO**C**H), 64.7 (HO**C**H$_2$), 58.6 (O**C**H$_2$), 56.5 (NH**C**H), 38.3 (CO**C**H$_2$); HRMS (ESI): calcd. for $C_9H_{14}NO_7$, 248.0776. Found: $[MH]^+$, 248.0762 (5.4 ppm error). X-ray crystallographic data for this compound can be accessed via www.ccdc.cam.ac.uk/data_request/cif (CCDC 2303504).

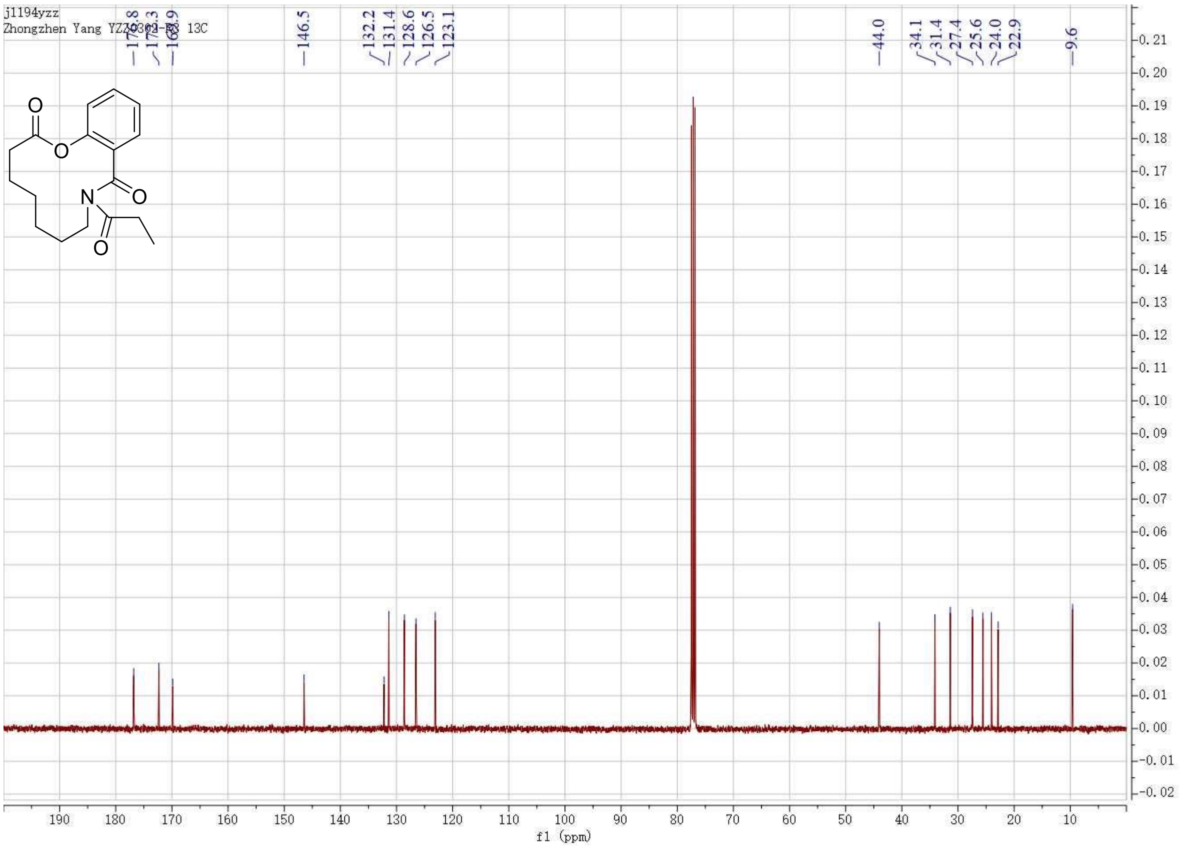
Datablock wpu21009 - ellipsoid plot



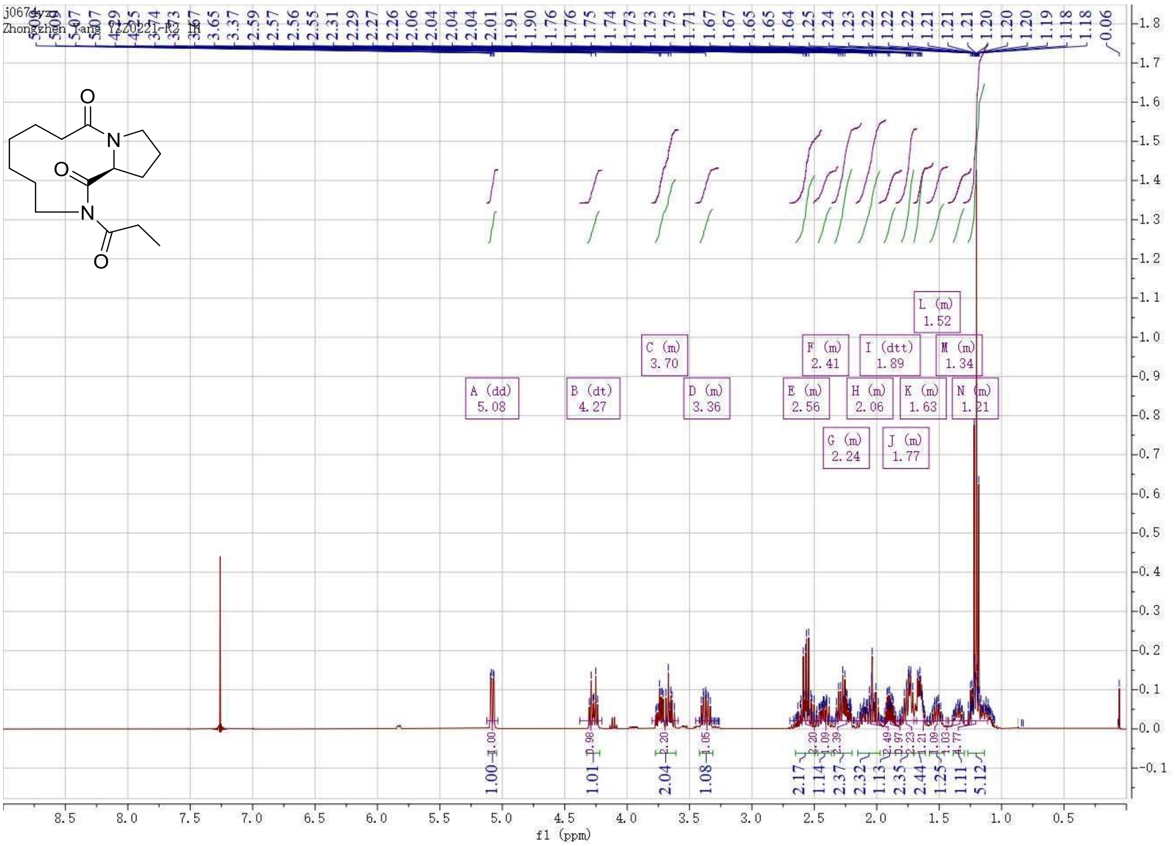
4) ^{1}H and ^{13}C NMR spectra

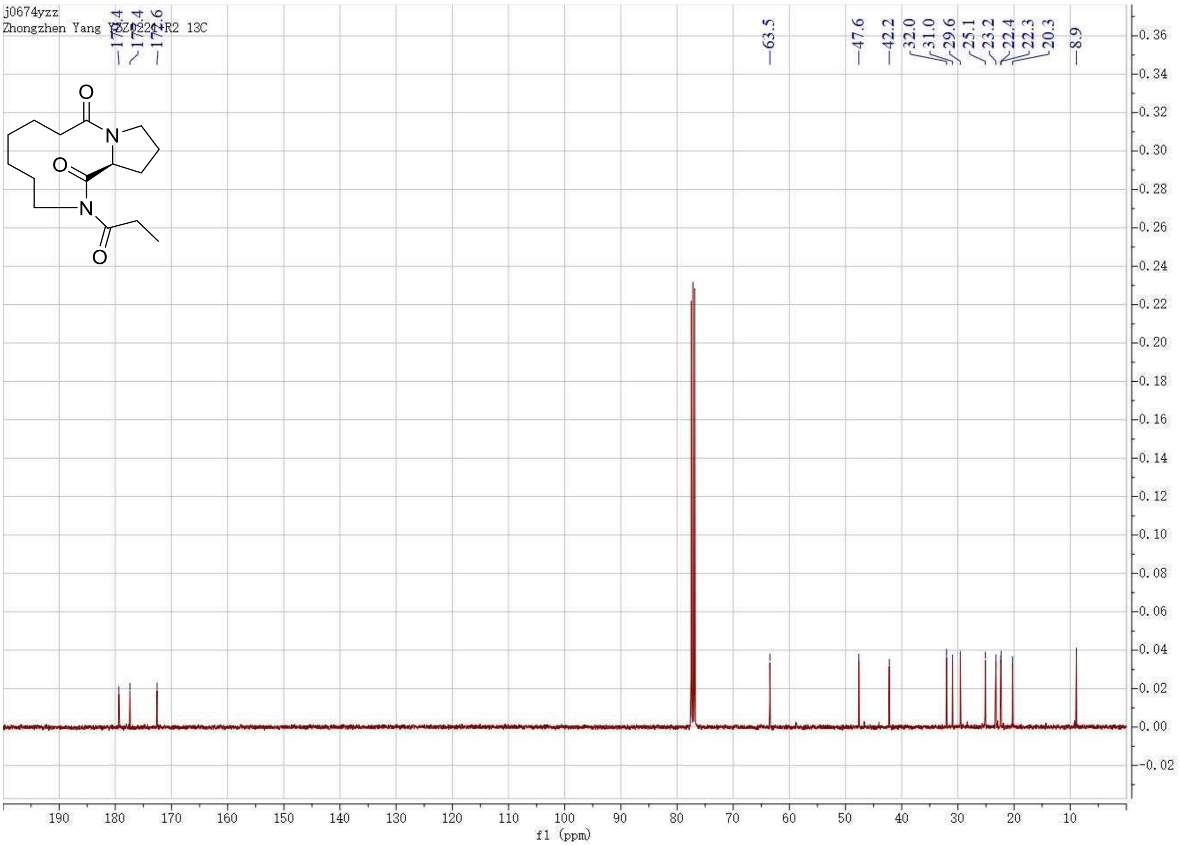
9-Propanoyl-4,5,6,7,8,9-hexahydro-2*H*-1,9-benzoxazacyclododecine-2,10(3*H*)-dione (13)



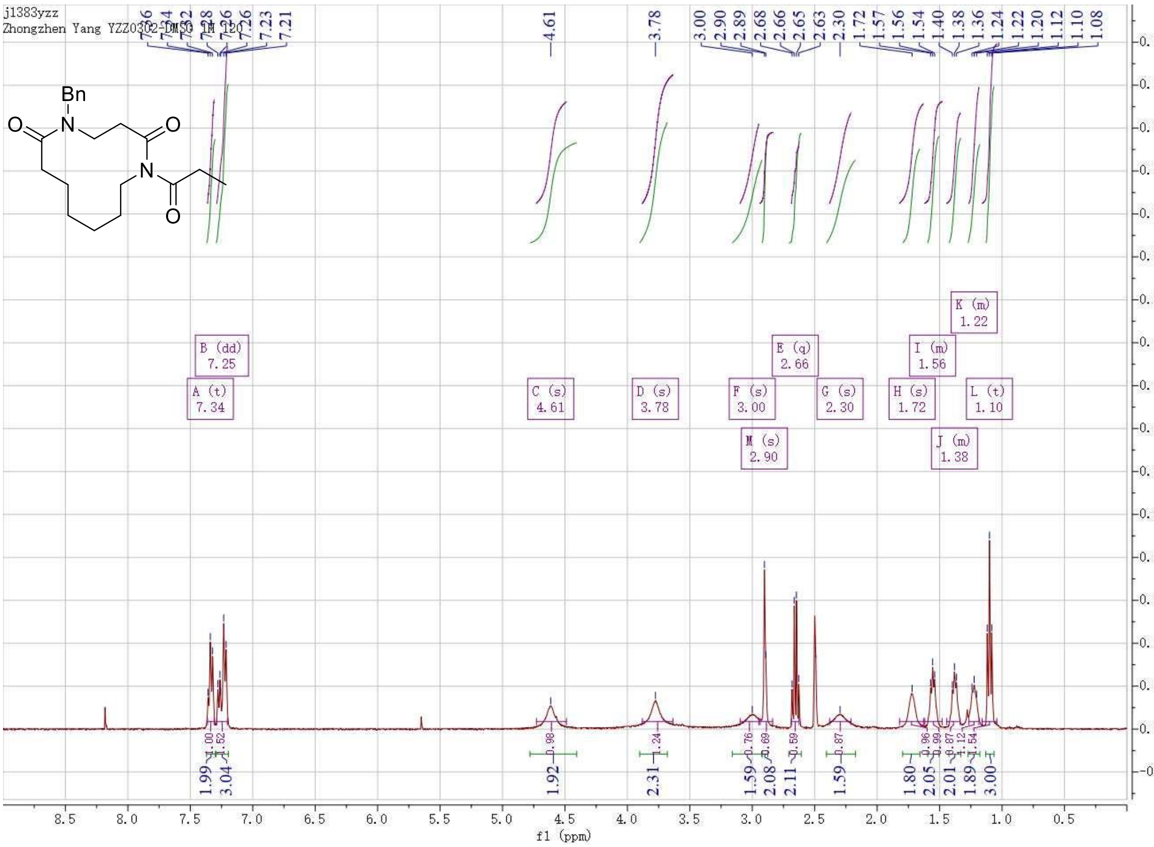


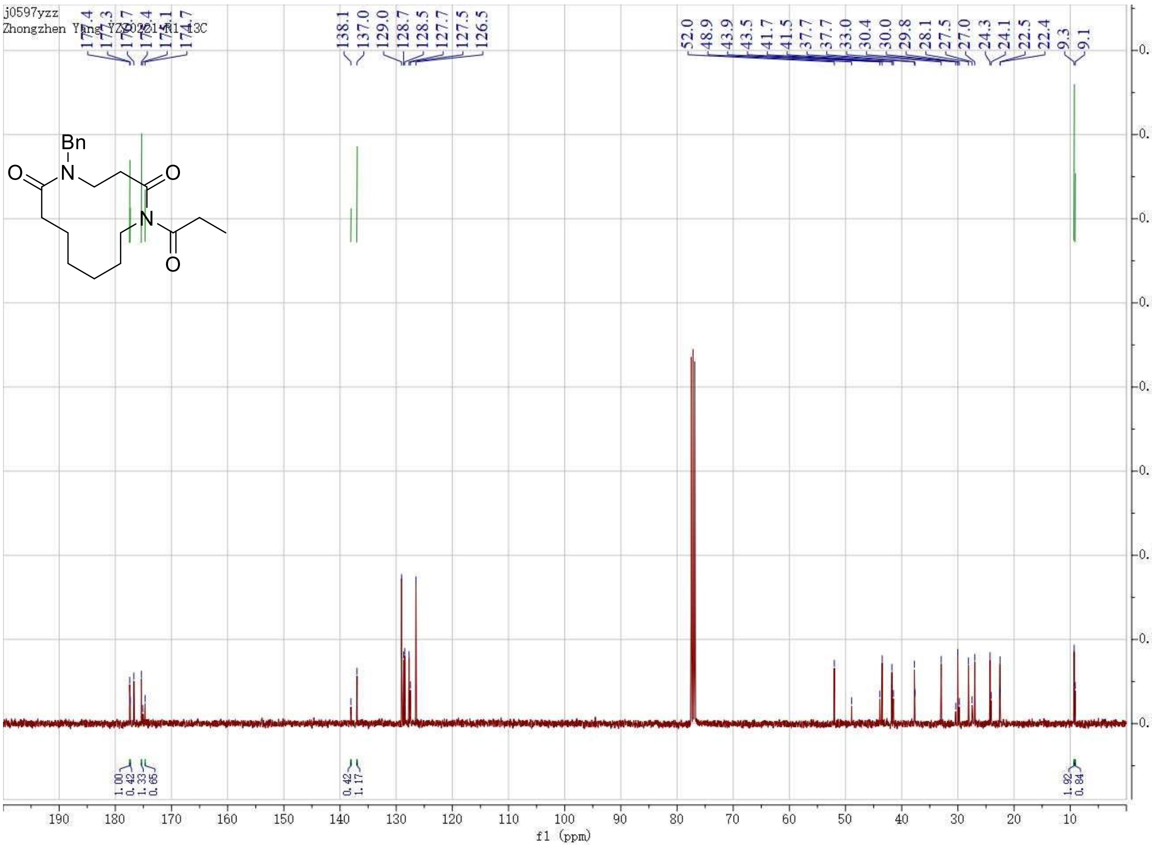
2-Propanoyldecahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazacycloundecine-1,9(2*H*)-dione (14)



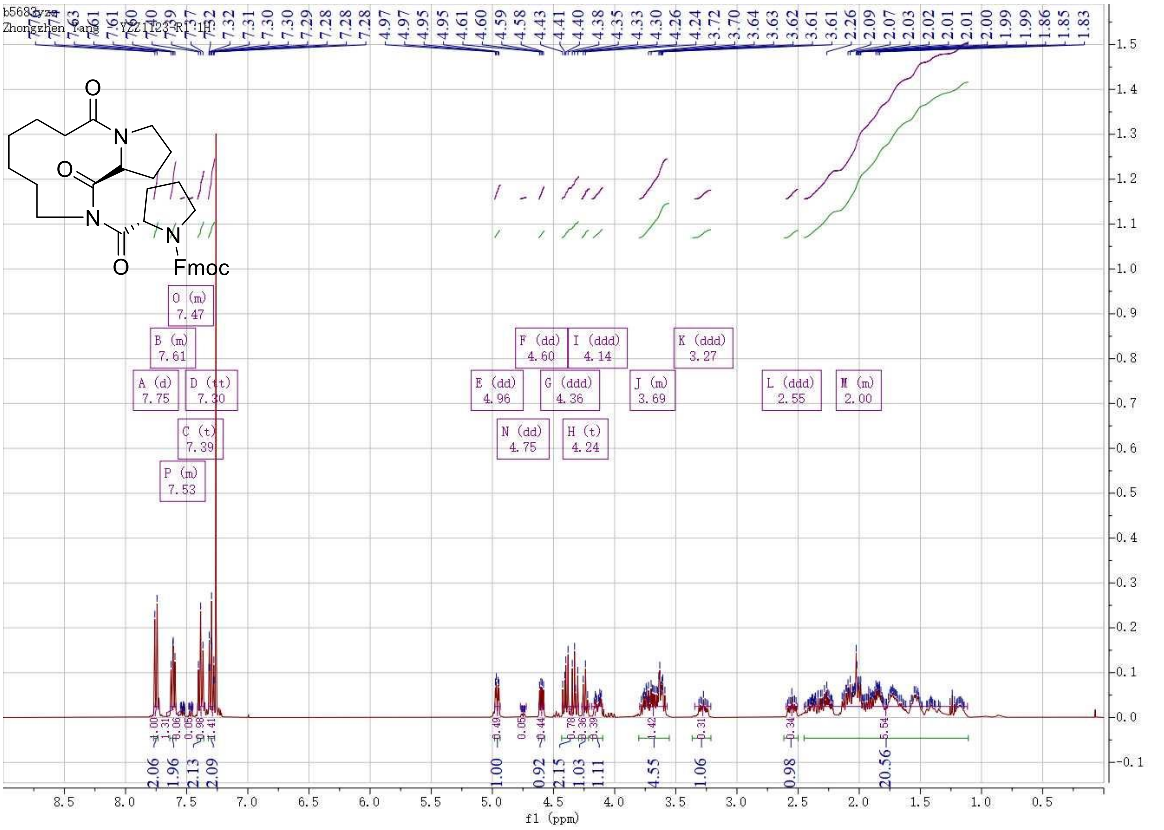


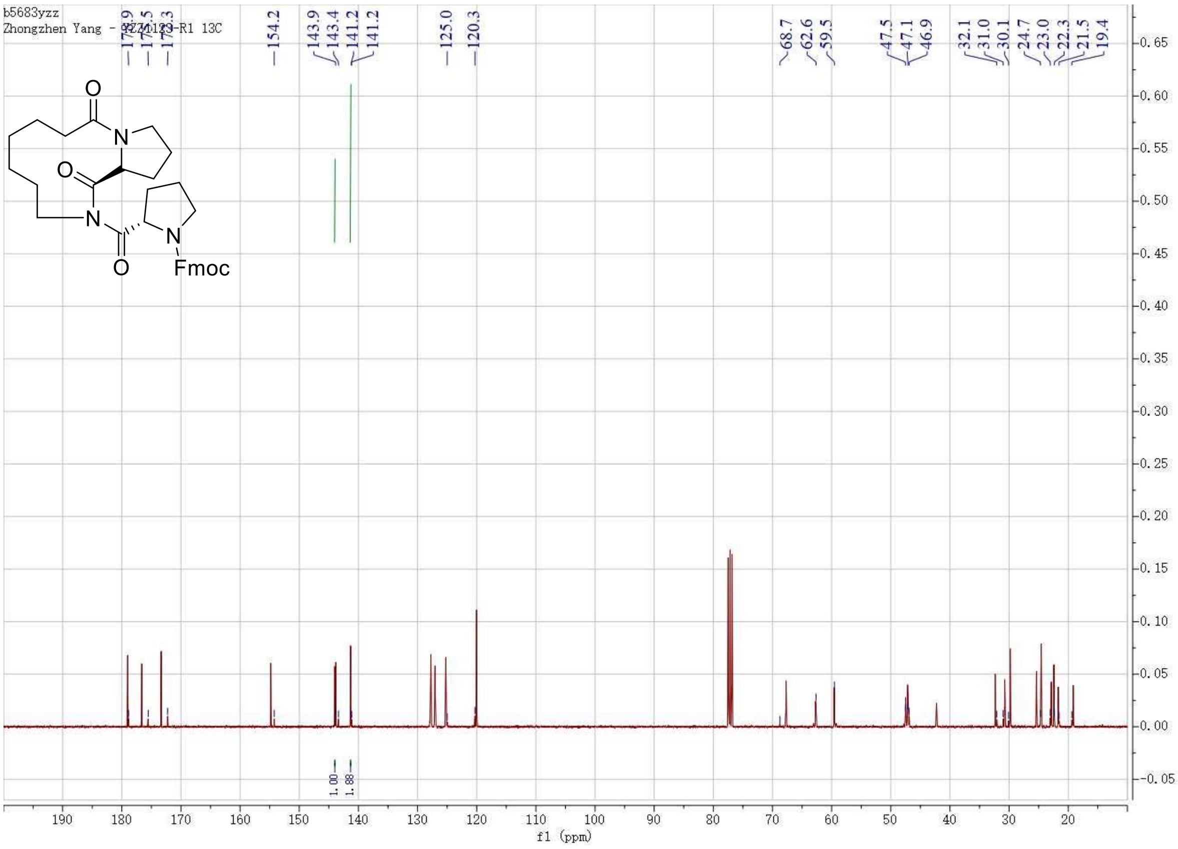
1-(1-Oxopropyl)-5-(phenylmethyl)-1,5-diazacyclododecane-2,6-dione (15) (^{1}H NMR in DMSO-d_6 at 120 °C; 13C NMR in CDCl3 at RT and shows a 3:1 mixture of rotamers).



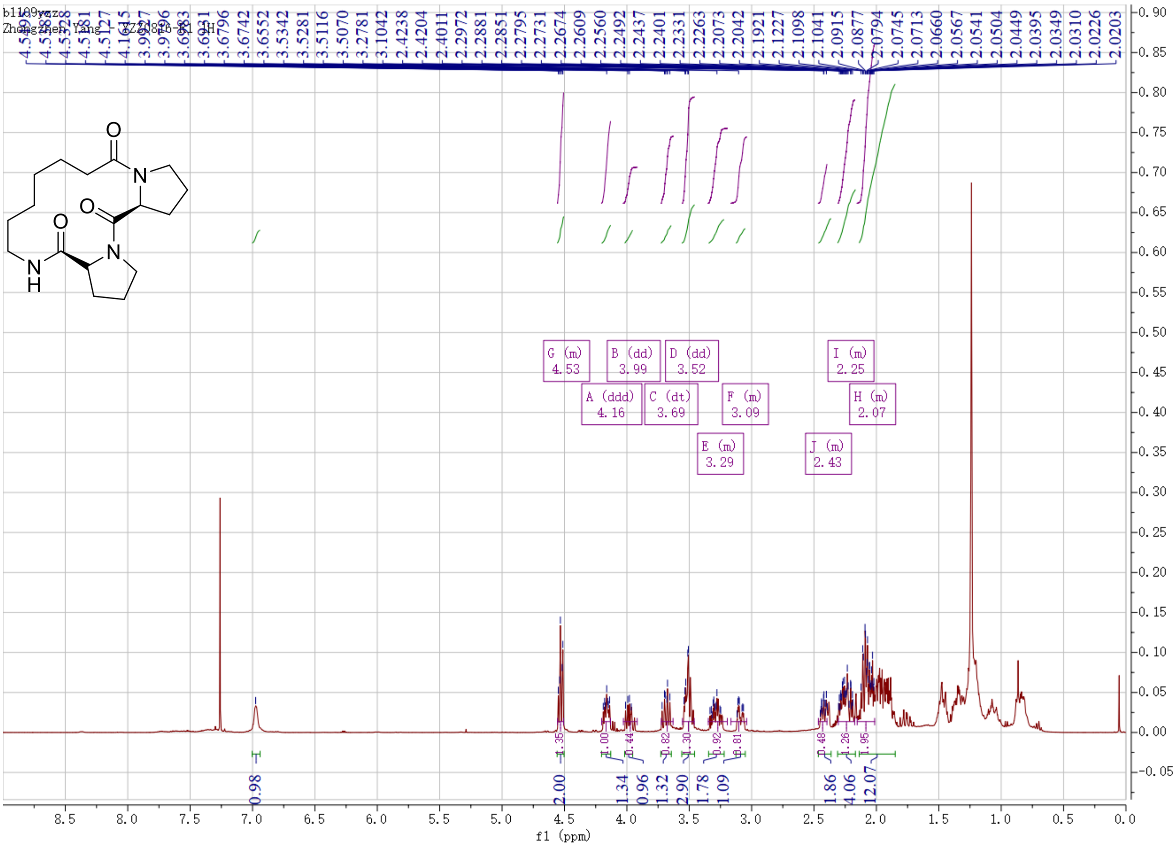


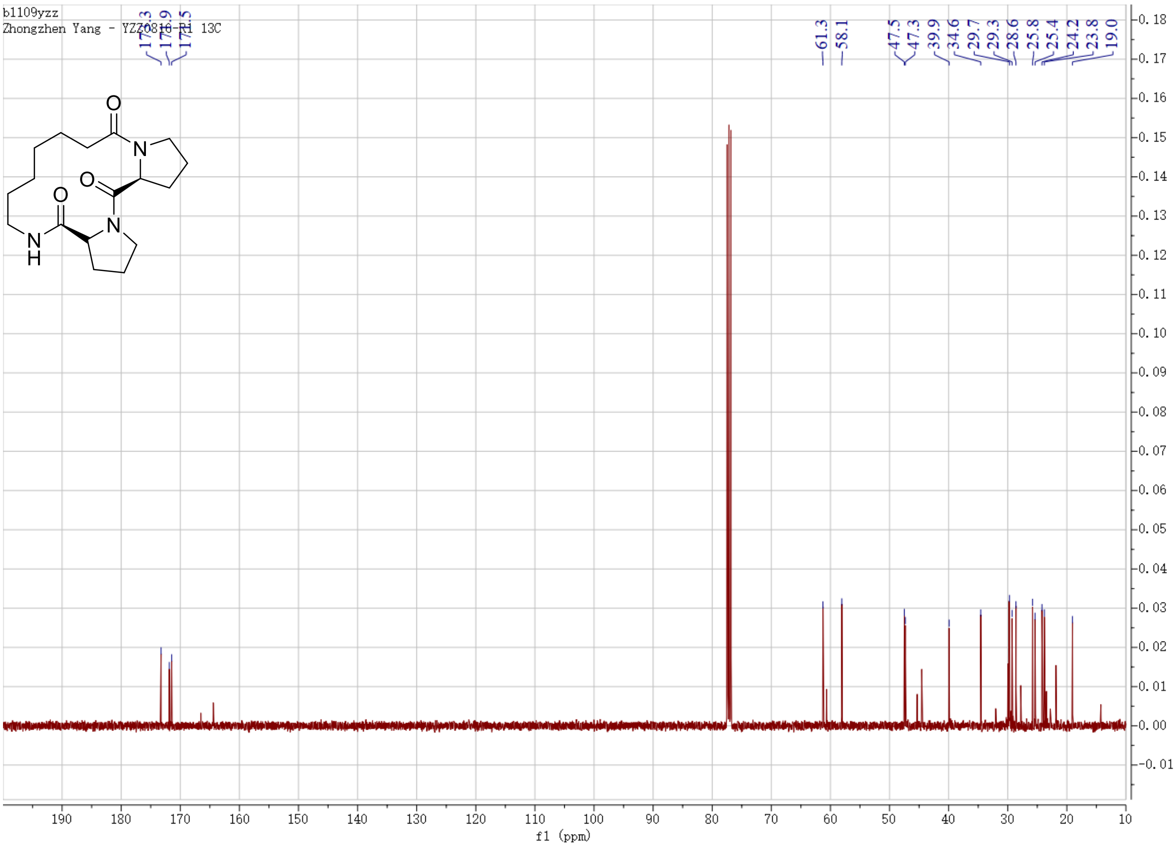
(9*H*-Fluoren-9-yl)methyl 2-(1,9-dioxodecahydro-1*H*-pyrrolo[1,2-*a*][1,4]diazacycloundecine-2(3*H*)-carbonyl)pyrrolidine-1-carboxylate (19) (as a 10:1 mixture of rotamers)



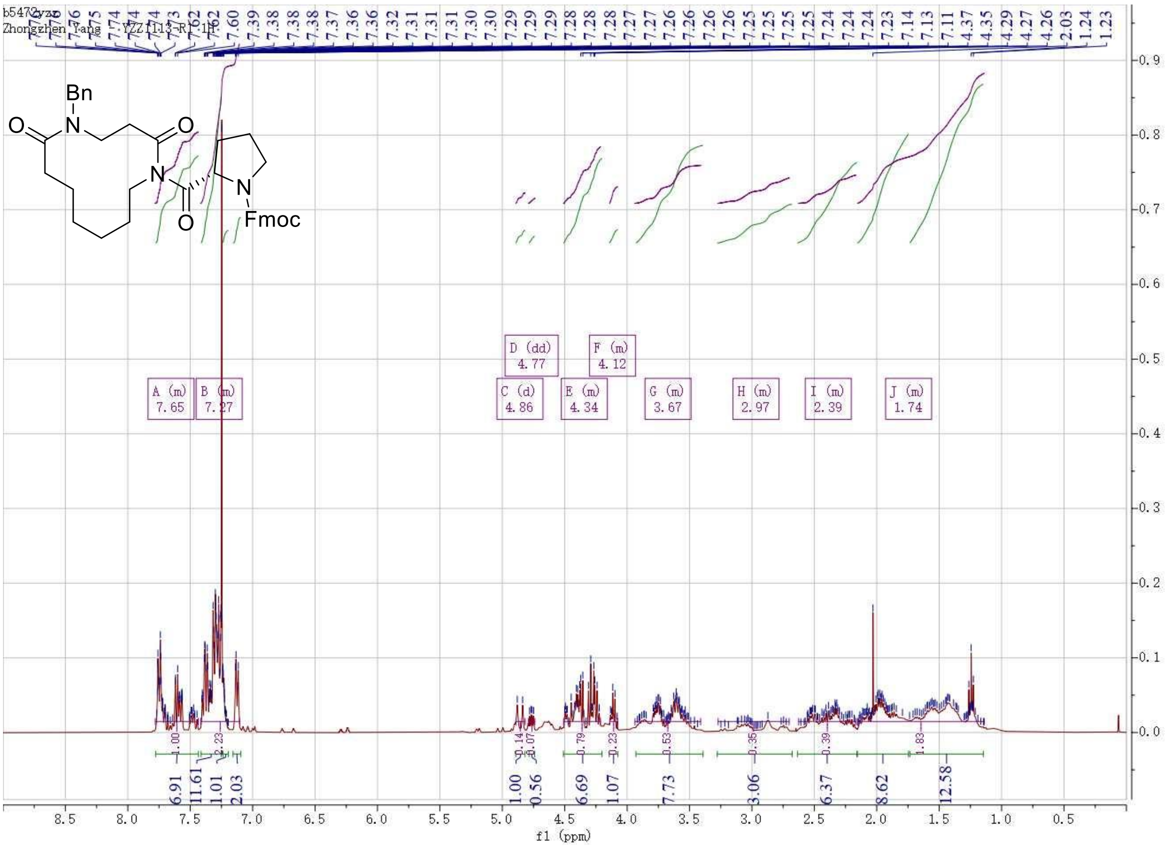


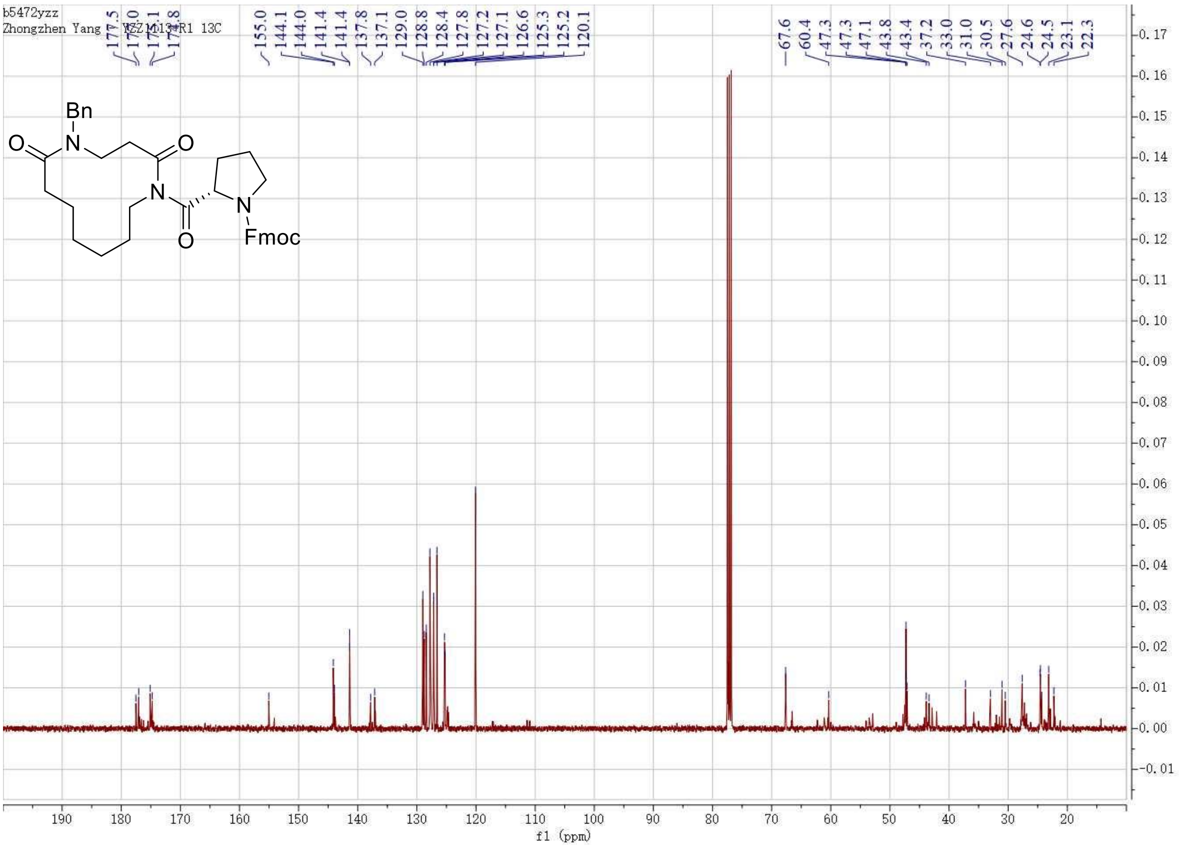
Dodecahydro-1*H*,5*H*-dipyrrolo[1,2-*a*:1',2'-*d*][1,4,7]triazacyclotetradecine 5,13,18(6*H*,18a*H*)-trione (20) (as a 3: 1 mixture of rotamers)



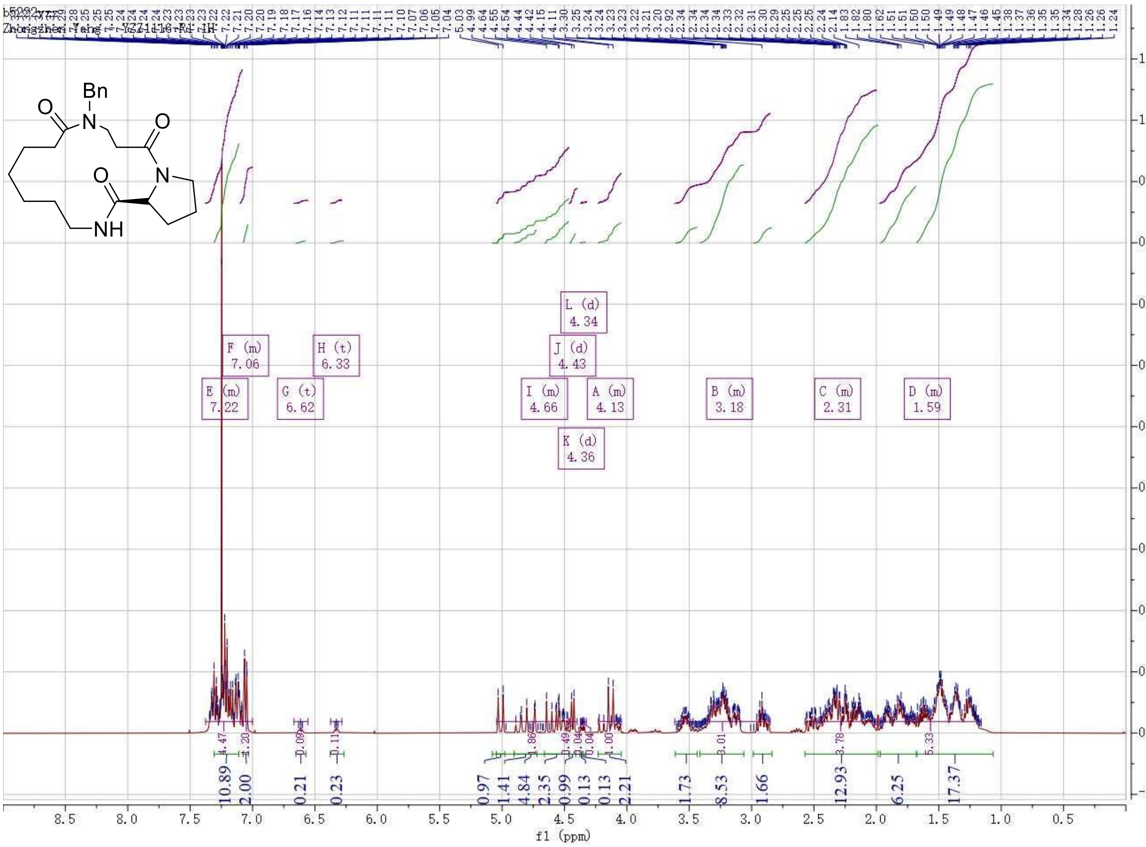


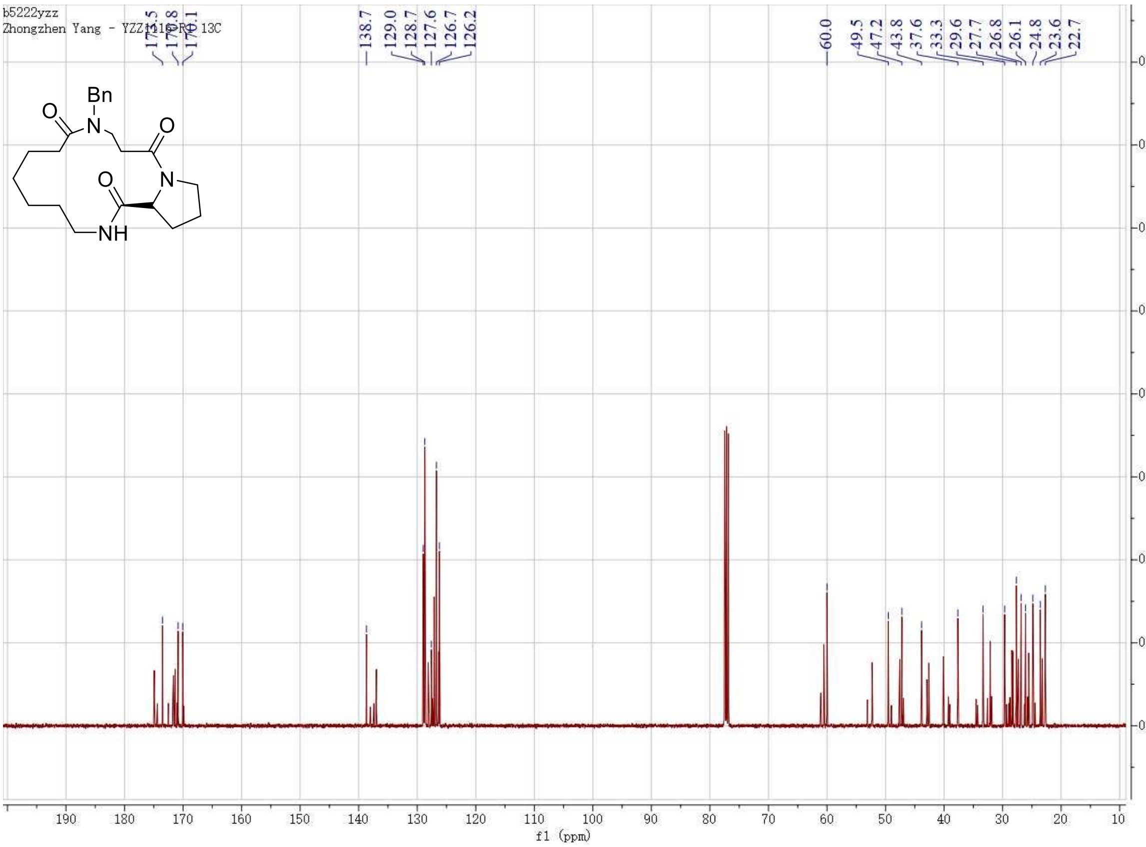
(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazacyclododecane-1-carbonyl)pyrrolidine-1-carboxylate (21) (as 2:1 mixture rotamers)



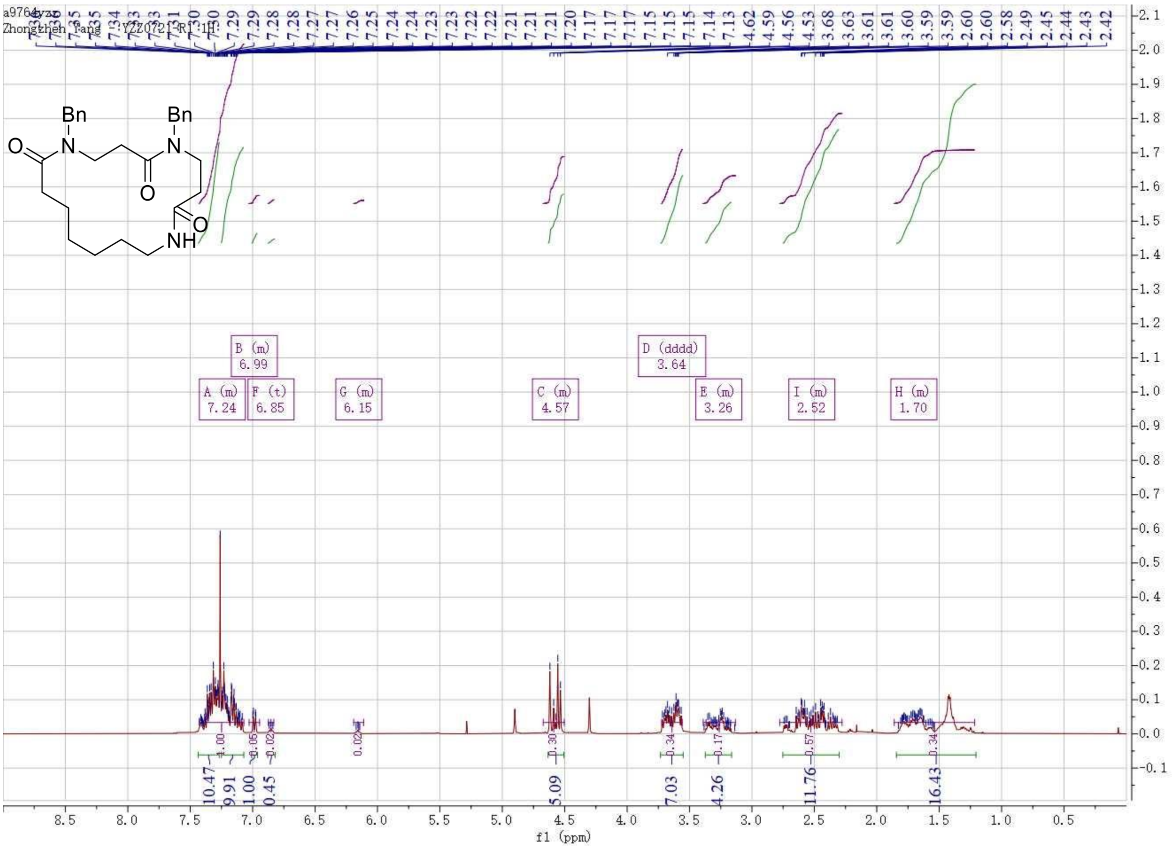


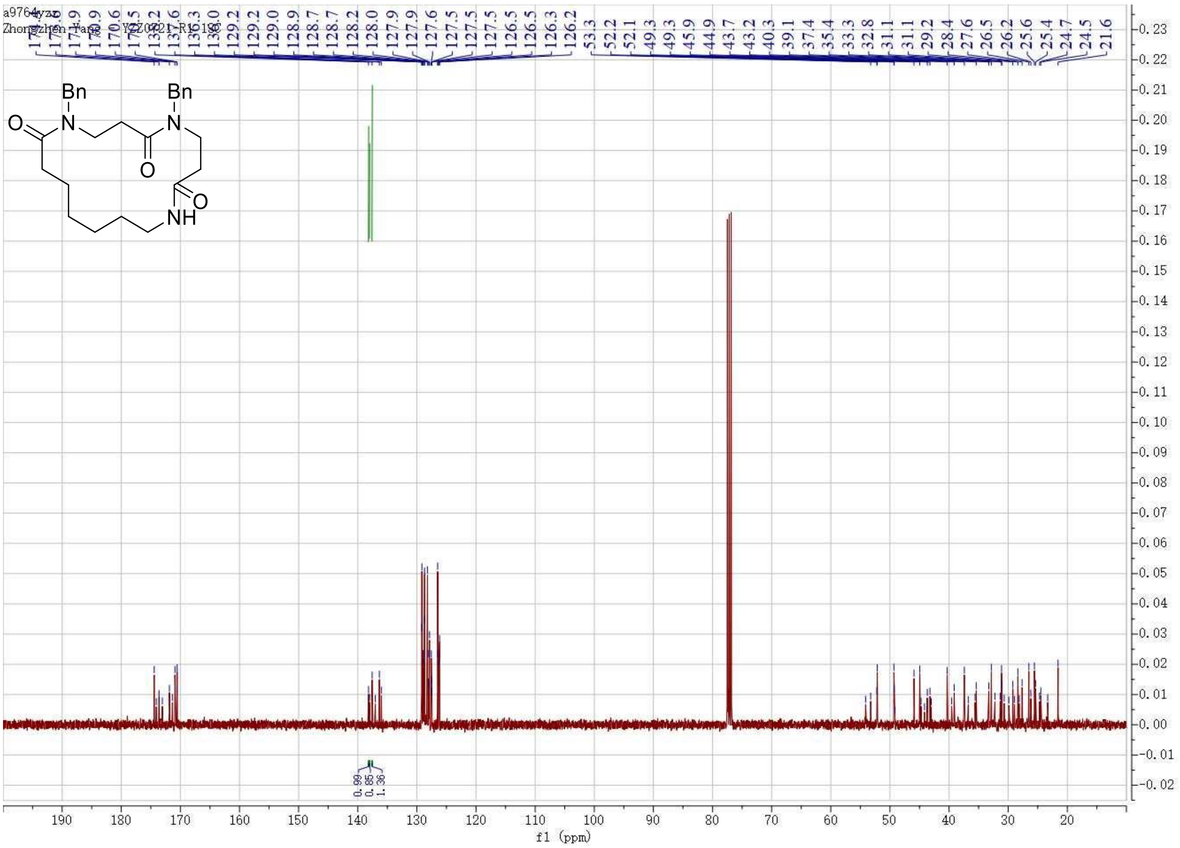
10-Benzyldodecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8]triazacyclopentadecine-1,9,13(2*H*,10*H*)-trione (22) (as a 10:5:1:1 mixture of rotamers)



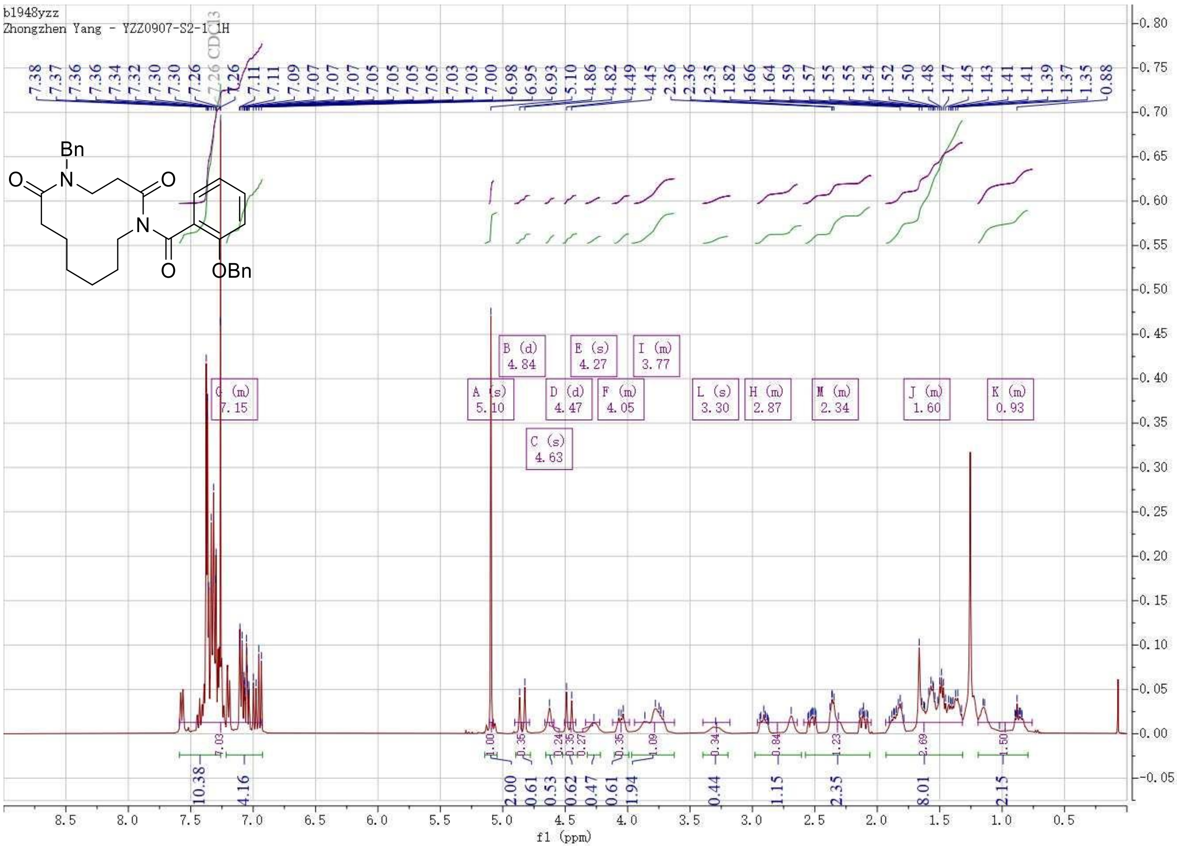


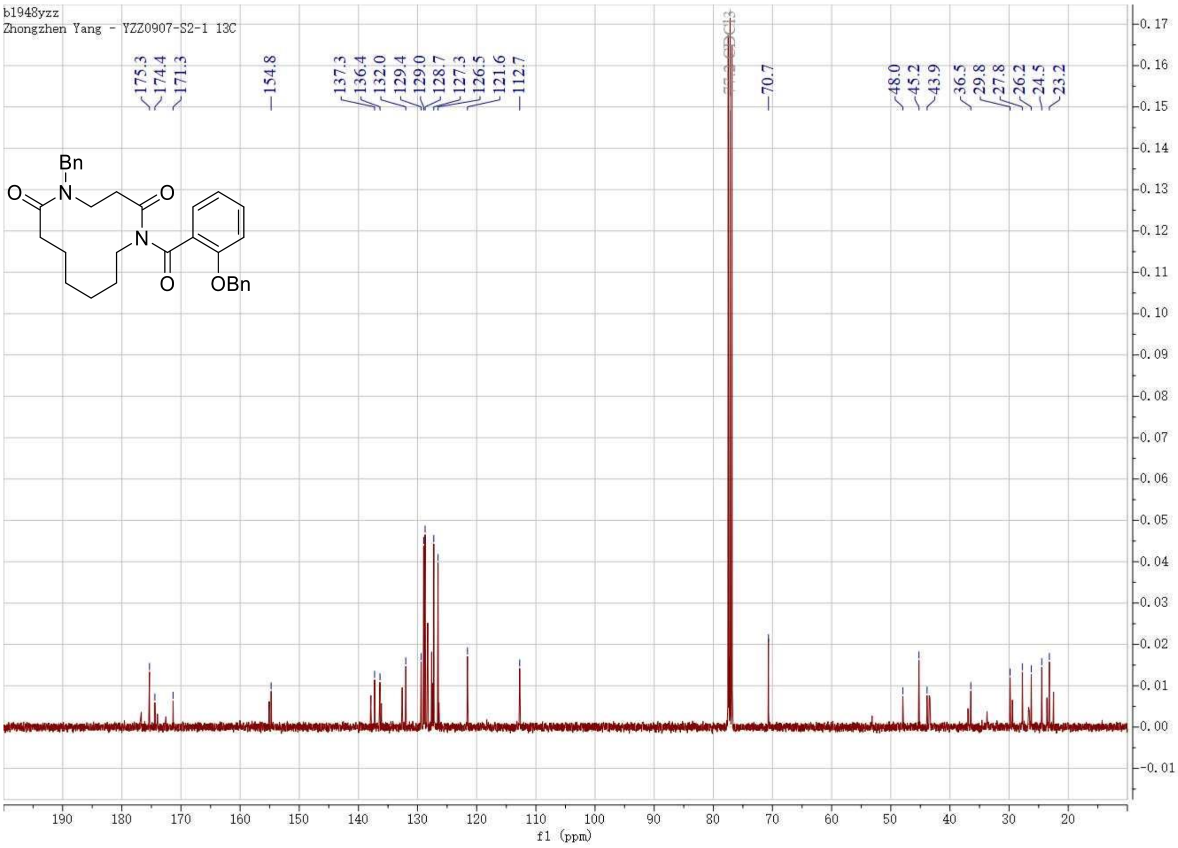
5,9-Dibenzyl-1,5,9-triazacyclohexadecane-2,6,10-trione (24) (as a 4:2:1 mixture of rotamers)



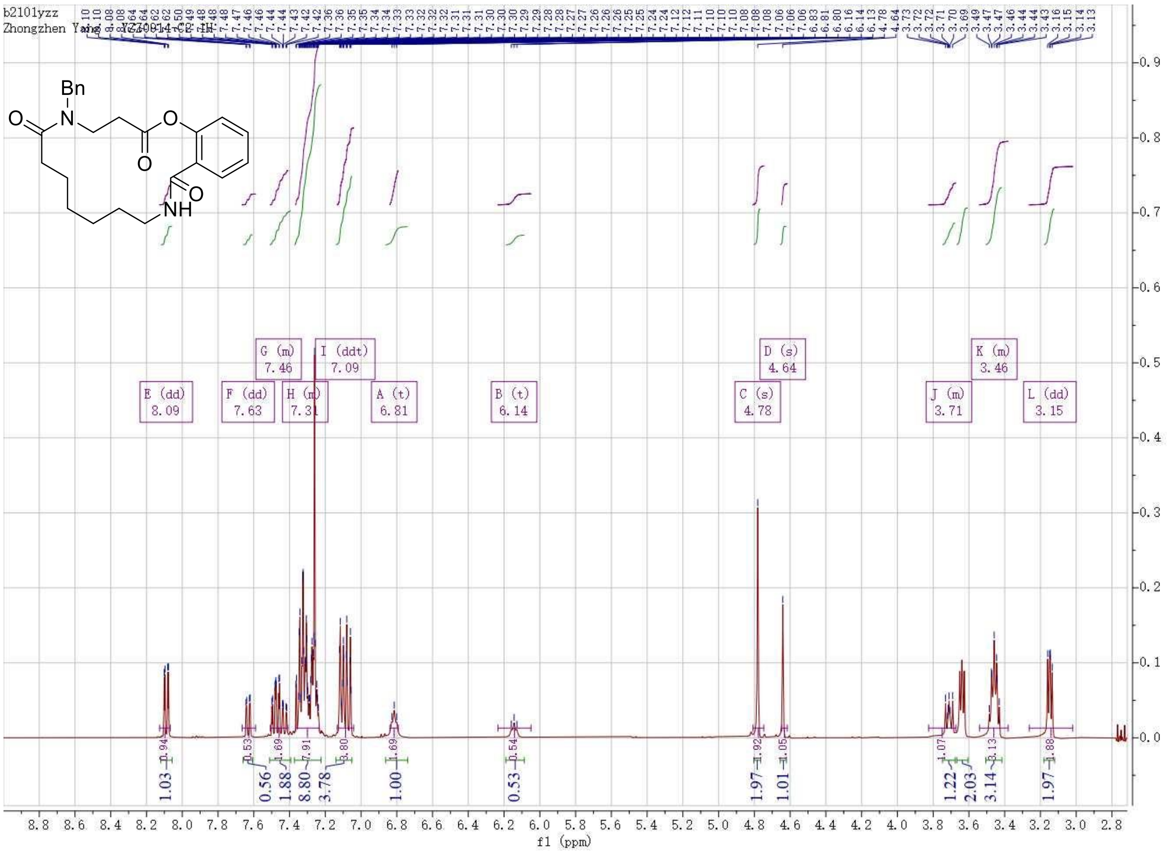


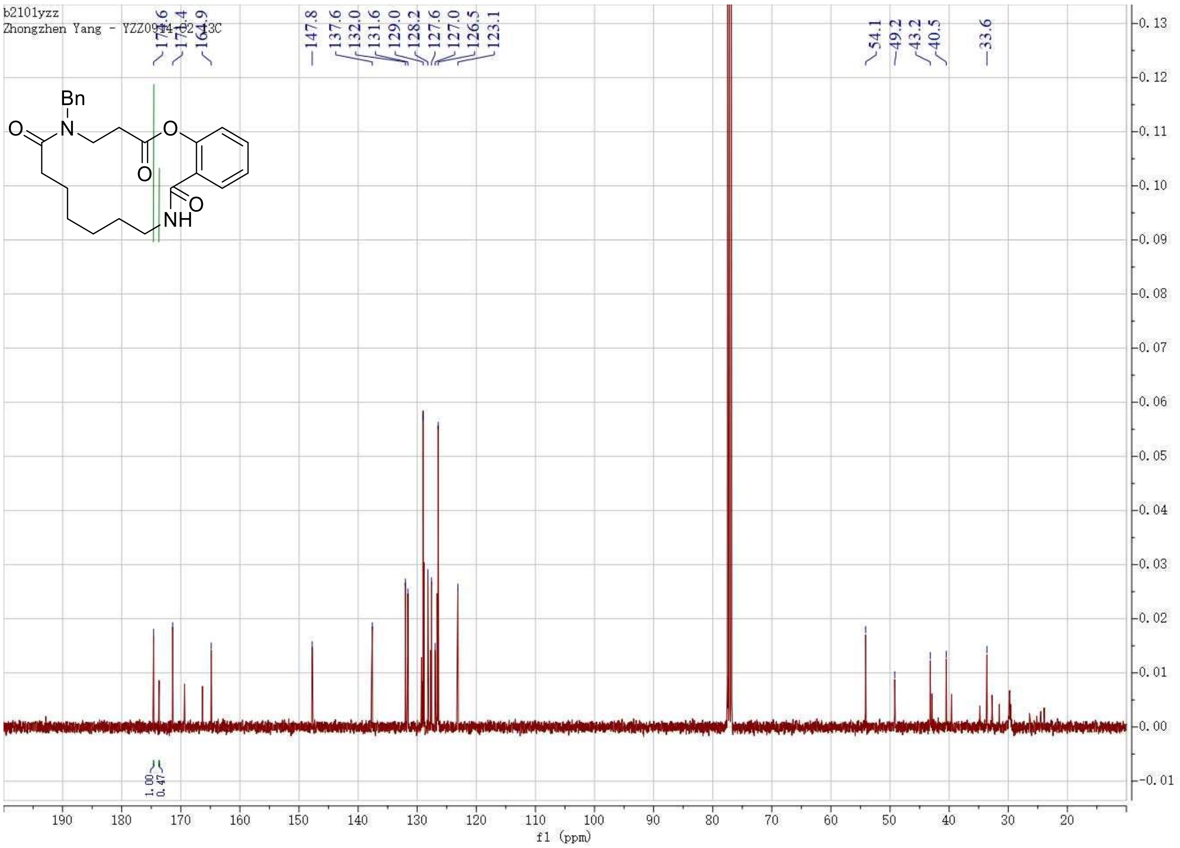
5-Benzyl-1-[2-(benzyloxy) benzoyl]-1,5-diazacyclododecane-2,6-dione (25) (as a 4:3 mixture of rotamers)



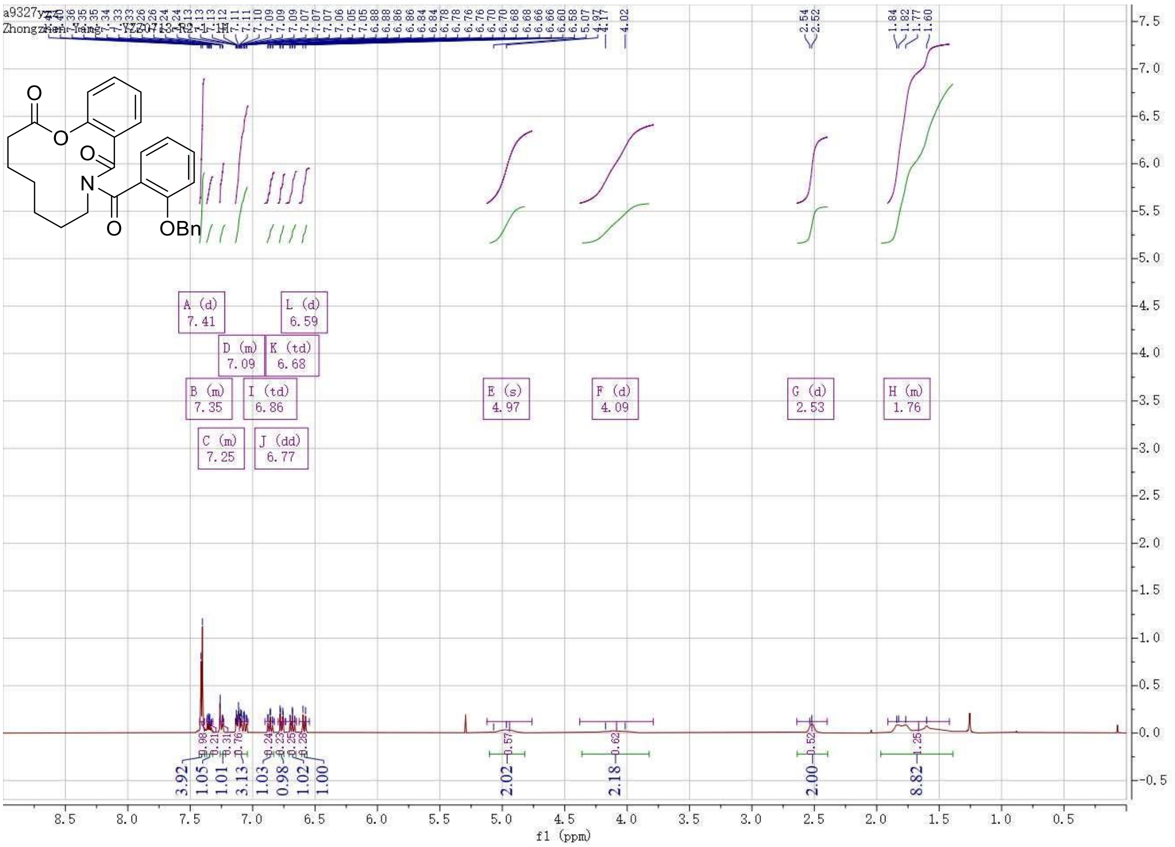


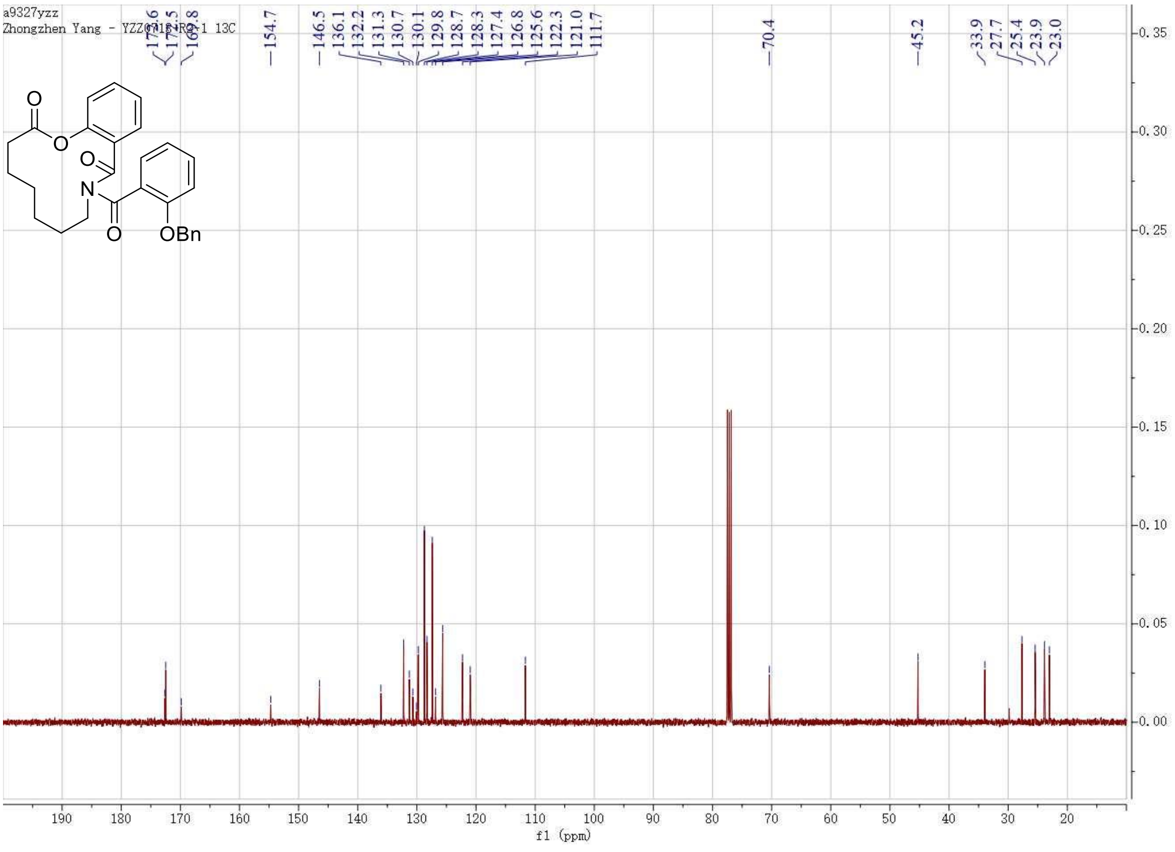
5-Benzyl-4,5,8,9,10,11,12,13-octahydro-2*H*-1,5,13-benzoxadiazacyclohexadecine-2,6,14(3*H*,7*H*)-trione (26)



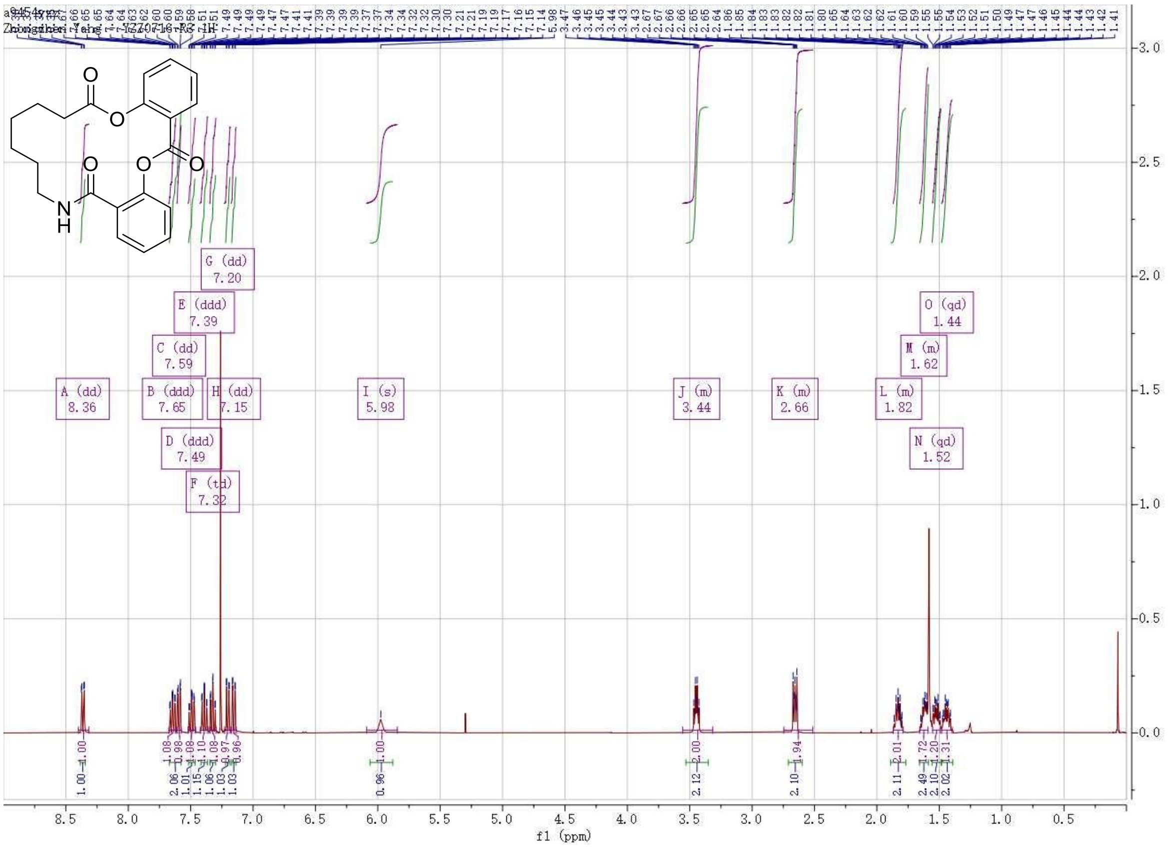


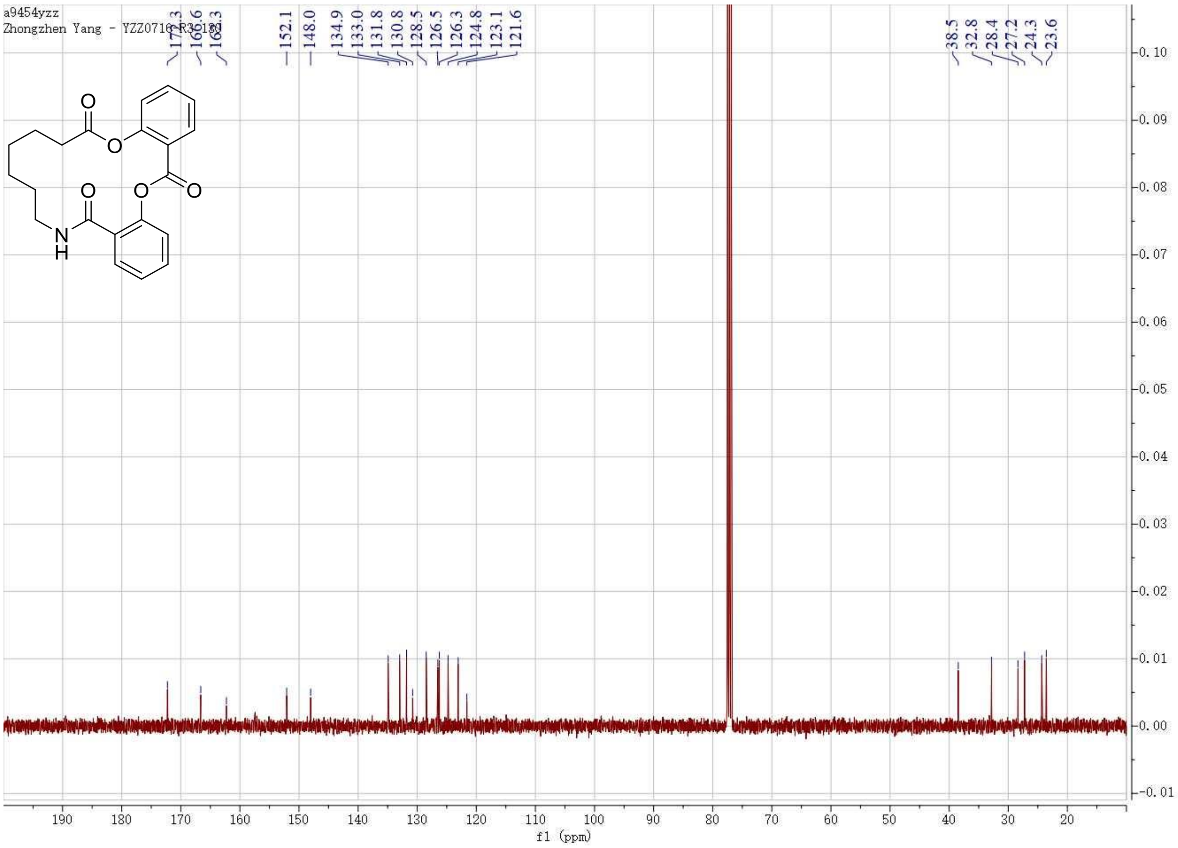
9-[2-(Benzyloxy)benzoyl]-4,5,6,7,8,9,10a,14a-octahydro-2*H*-1,9-benzoxaza-cyclododecine-2,10(3*H*)-dione (27)



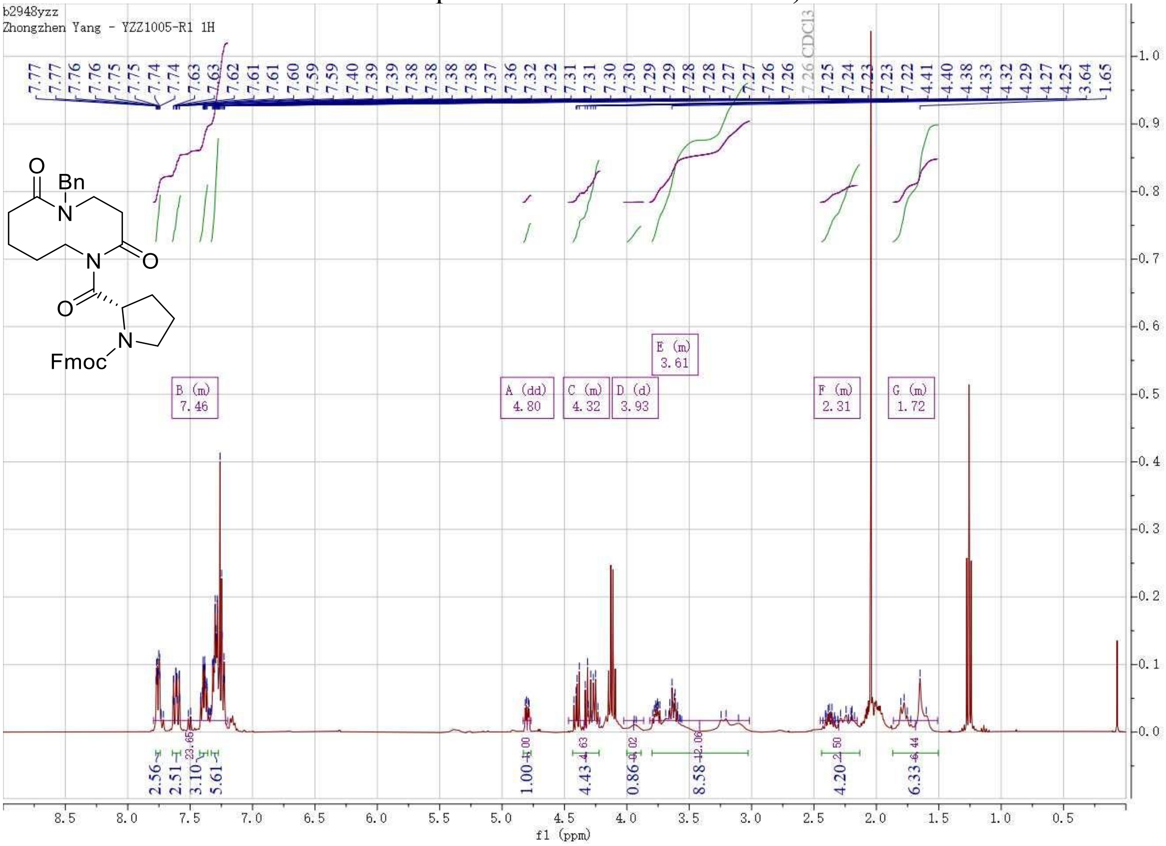


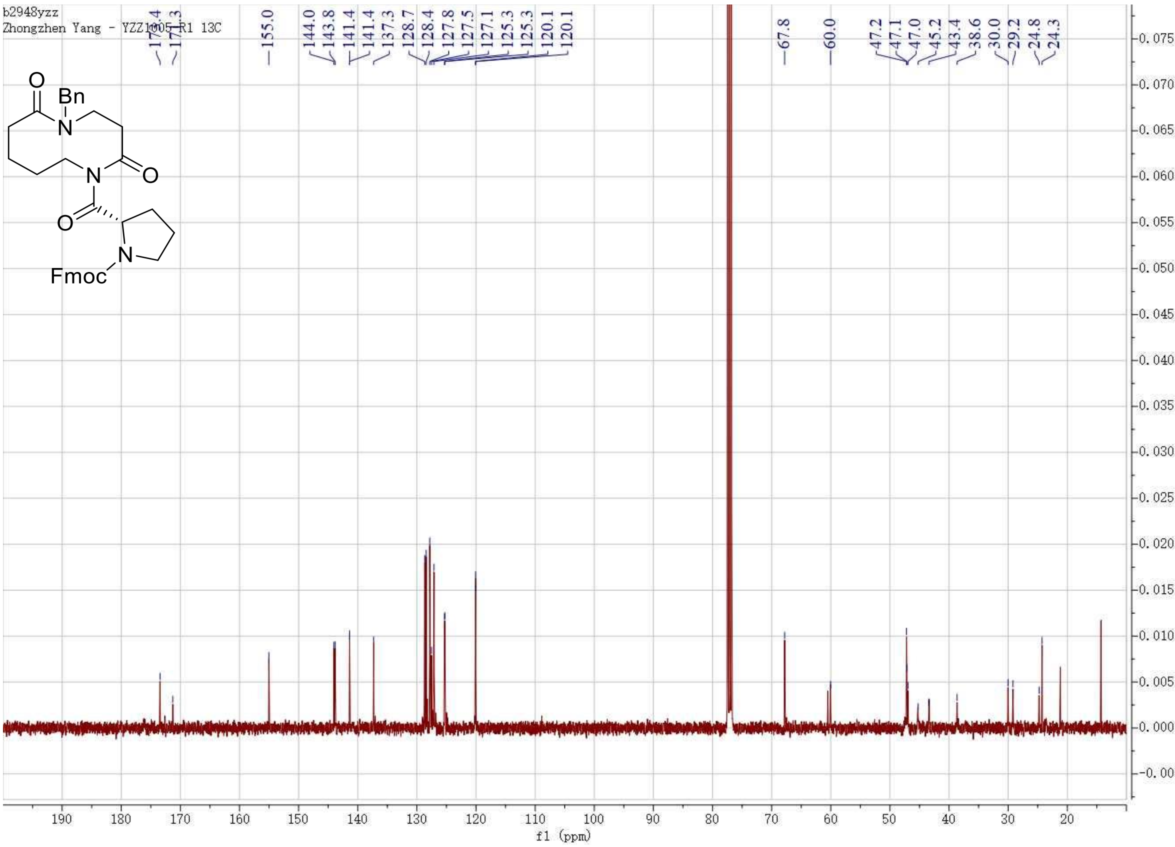
8,9,10,11,12,13-Hexahydro-4a*H*,6*H*-dibenzo[*b*,*f*][1,5,9]dioxazacyclohexadecine-6,14,20(7*H*,20a*H*)-trione (28)



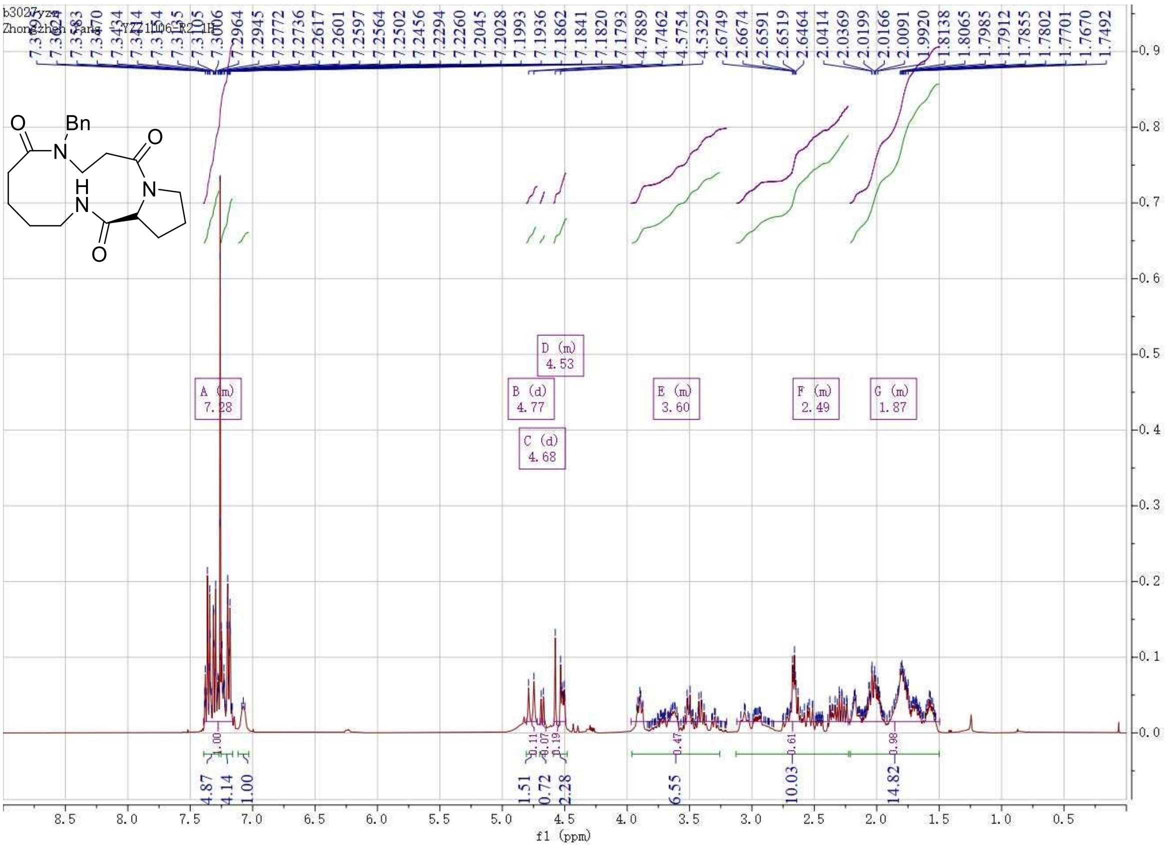


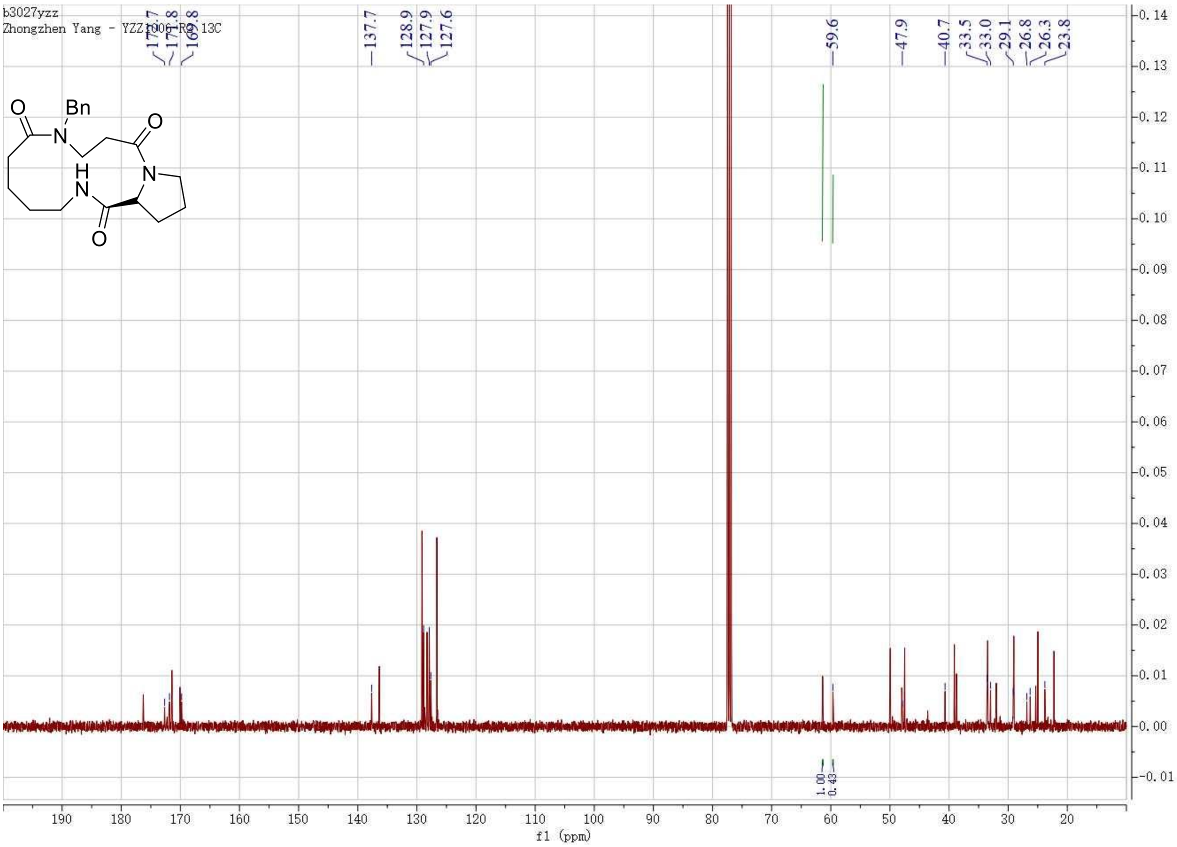
(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazecane-1-carbonyl)pyrrolidine-1-carboxylate (30) (some EtOAc is clearly evident in the NMR spectra of this material, but it was used in this form in its subsequent transformation into **31**)



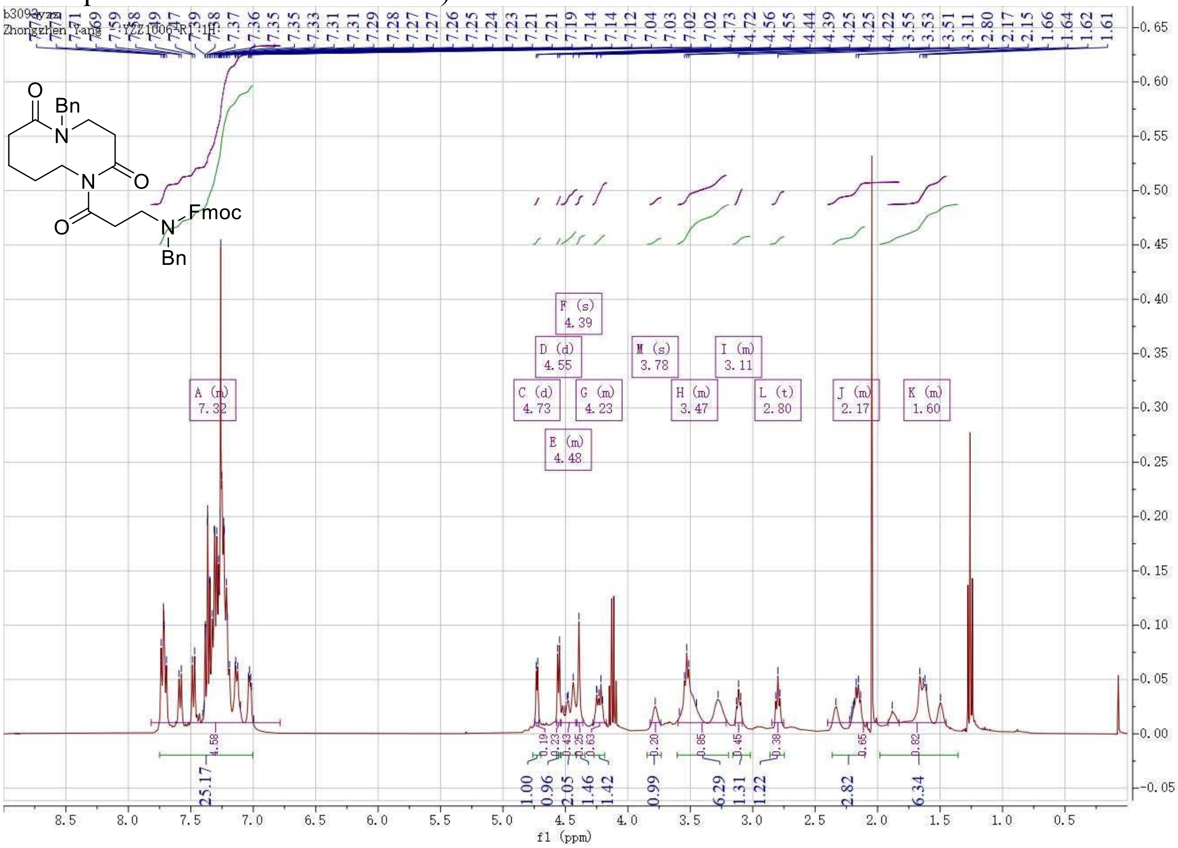


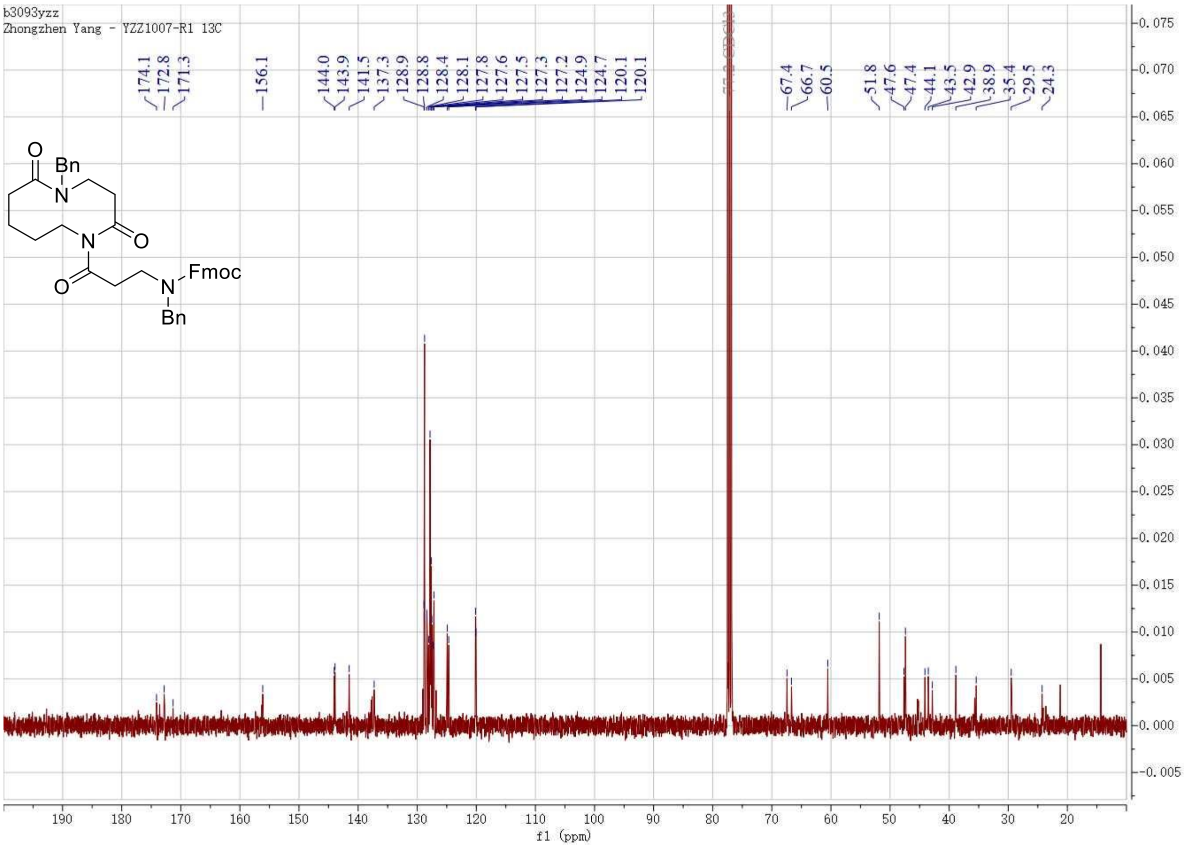
8-Benzyldecahydro-1*H*-pyrrolo[2,1-*c*][1,4,8]triazacyclotridecine-1,7,11(2*H*,8*H*)-trione (31) (as a 2:1 mixture of rotamers)



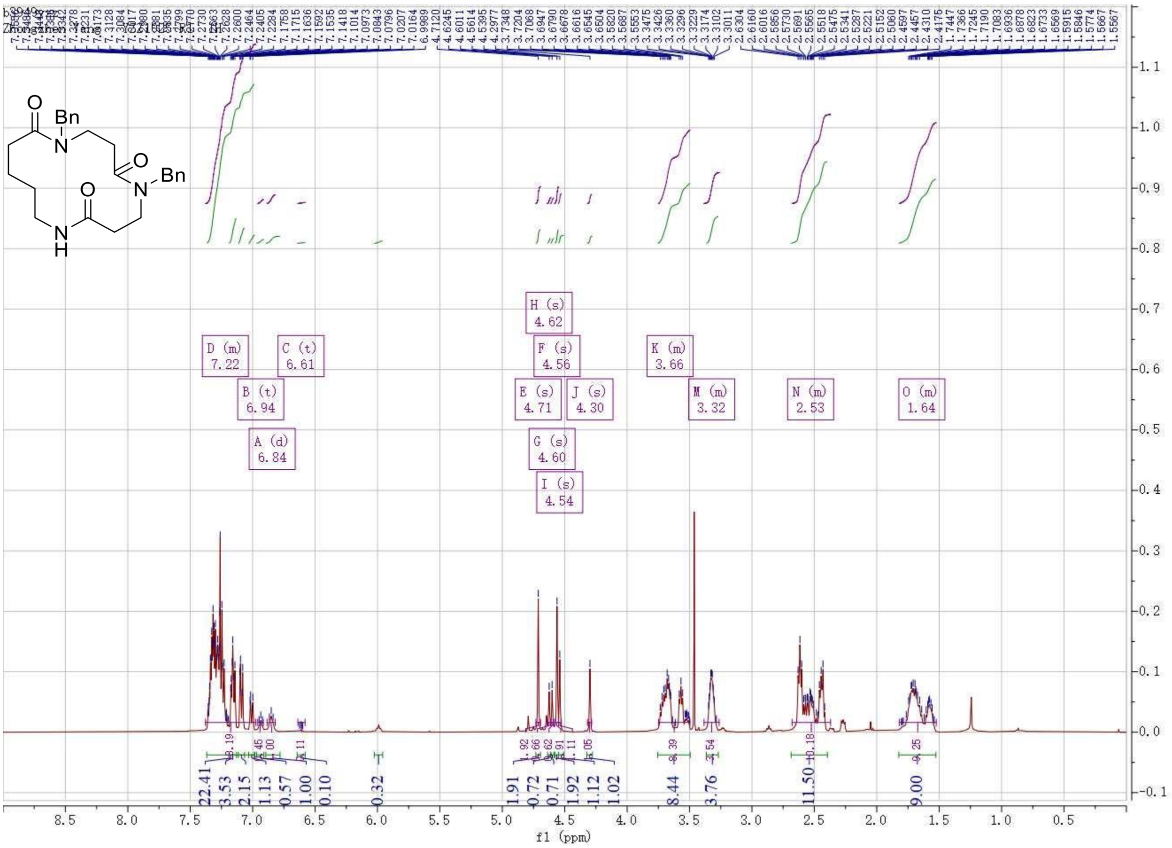


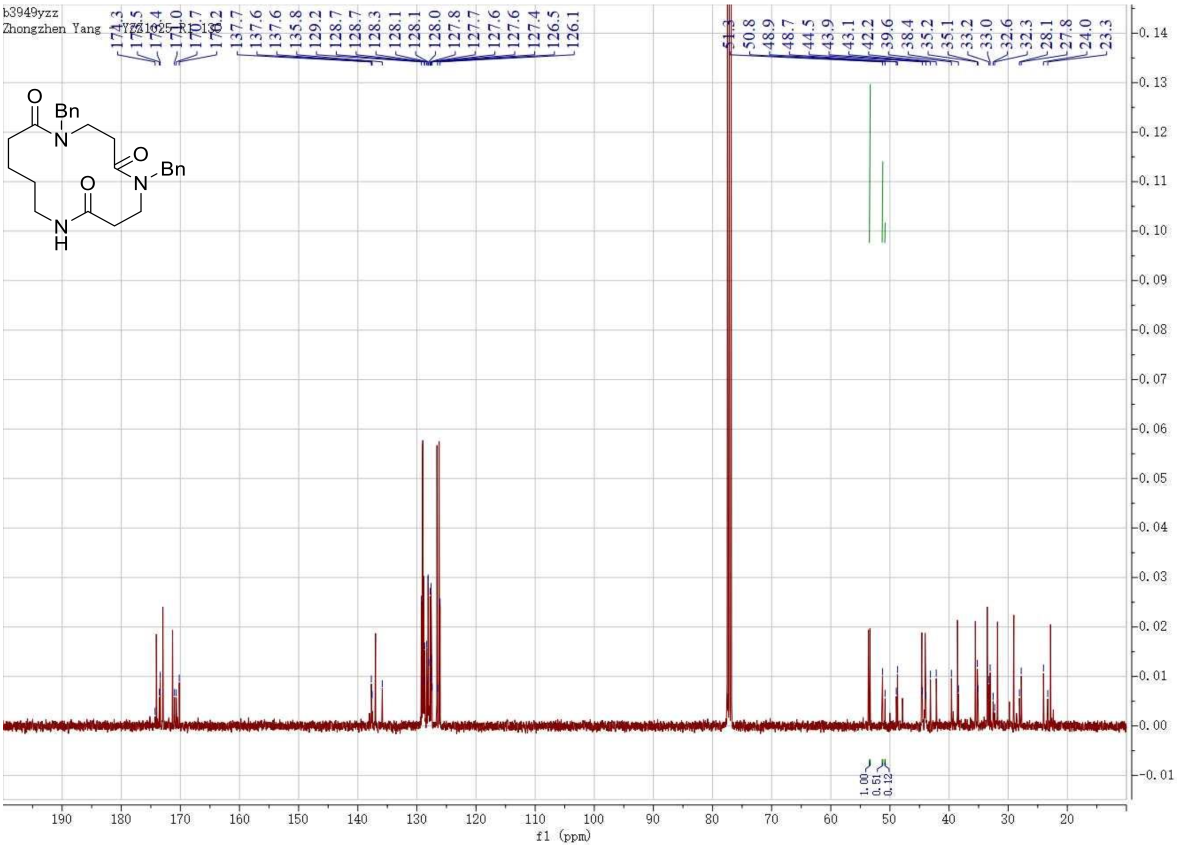
(9*H*-Fluoren-9-yl)methyl benzyl[3-(5-benzyl-2,6-dioxo-1,5-diazecan-1-yl)-3-oxopropyl]carbamate (32) (exist as a 2:1 mixture of rotamers in $CDCl_3$. Some EtOAc is clearly evident in the NMR spectra of this material, but it was used in this form in its subsequent transformation into **33**)



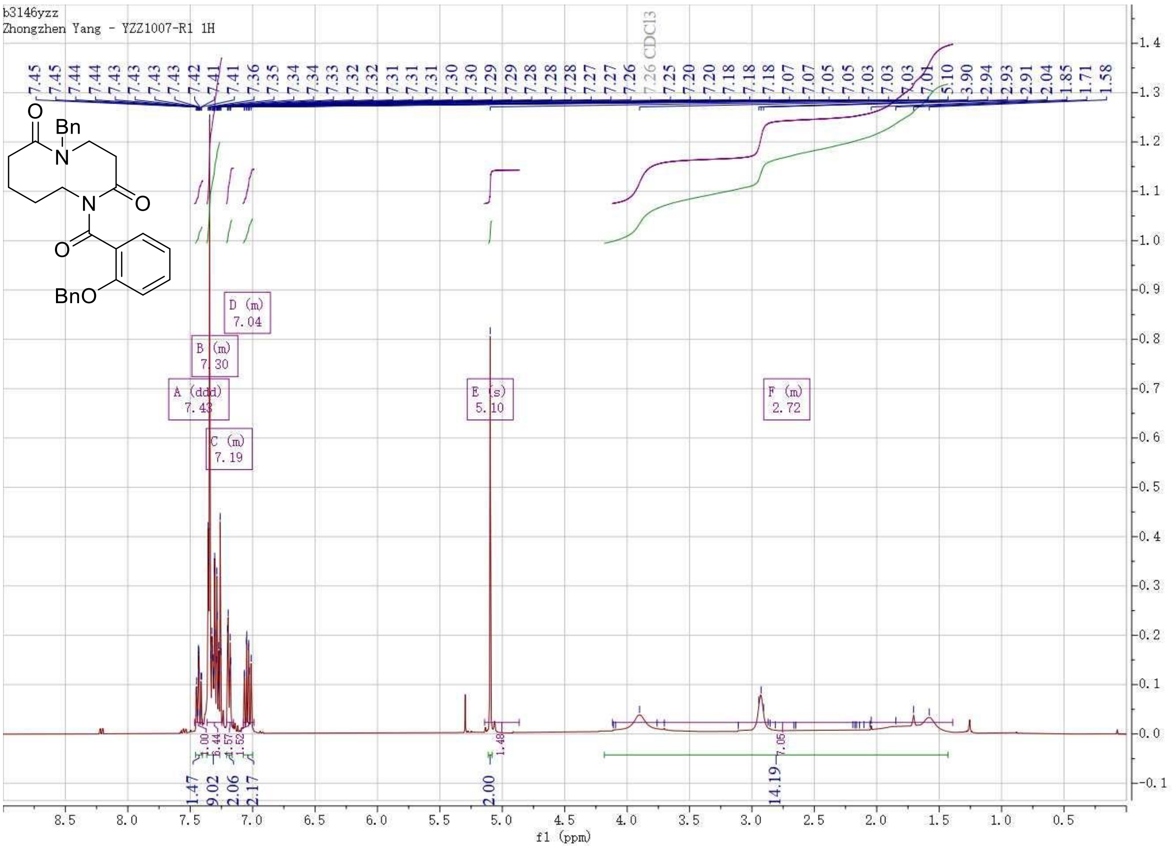


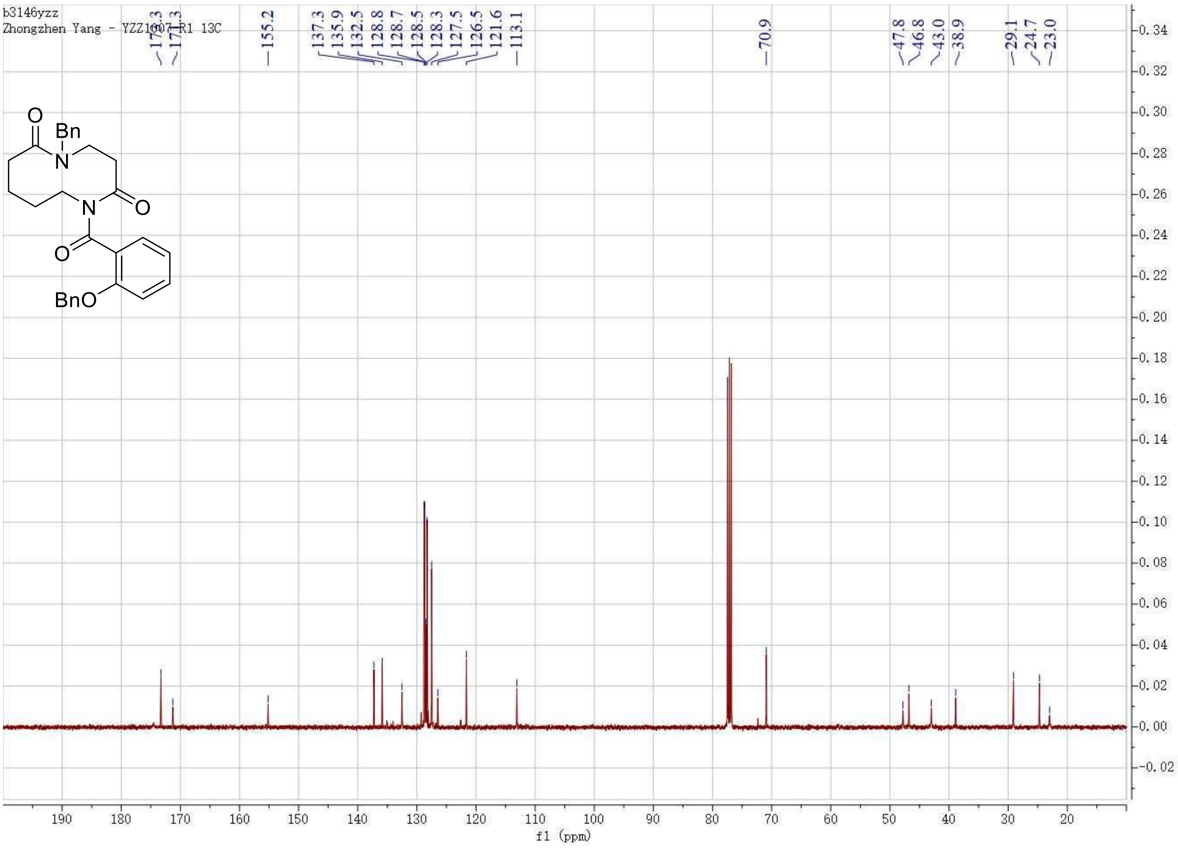
5,9-Dibenzyl-1,5,9-triazacyclotetradecane-2,6,10-trione (33) (as a 10:5:1 mixture of rotamers).



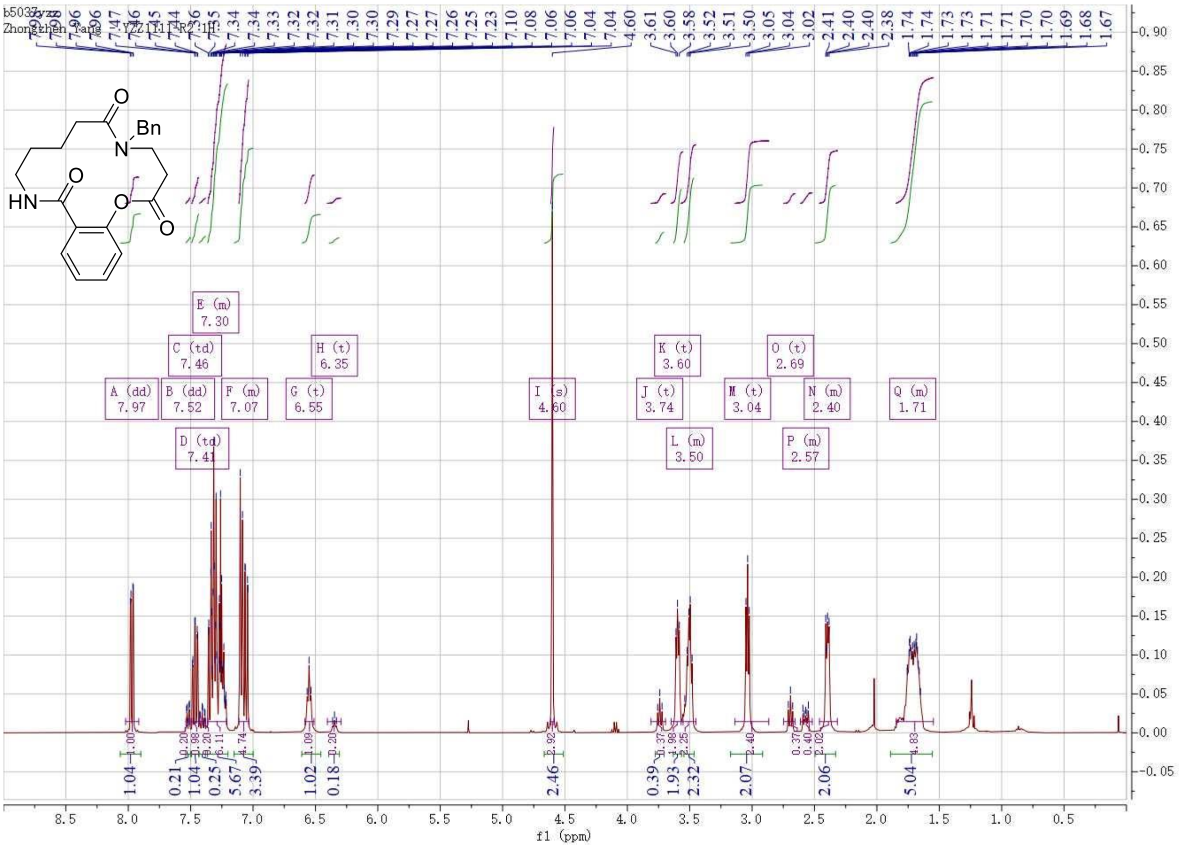


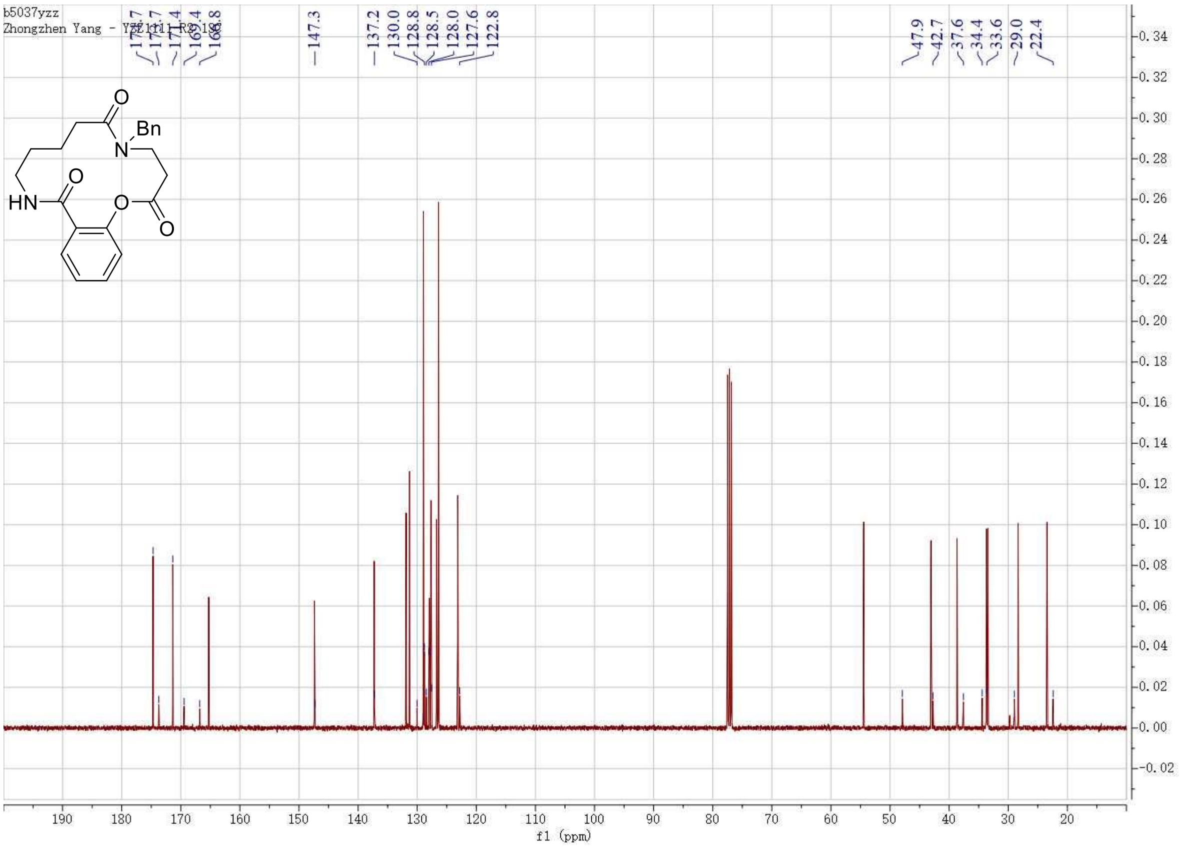
Benzyl-1-[2-(benzyloxy)benzoyl]-1,5-diazecane-2,6-dione (34) – the ^{1}H NMR resonances are very broad in the ^{1}H NMR spectrum due to rotameric broadening.



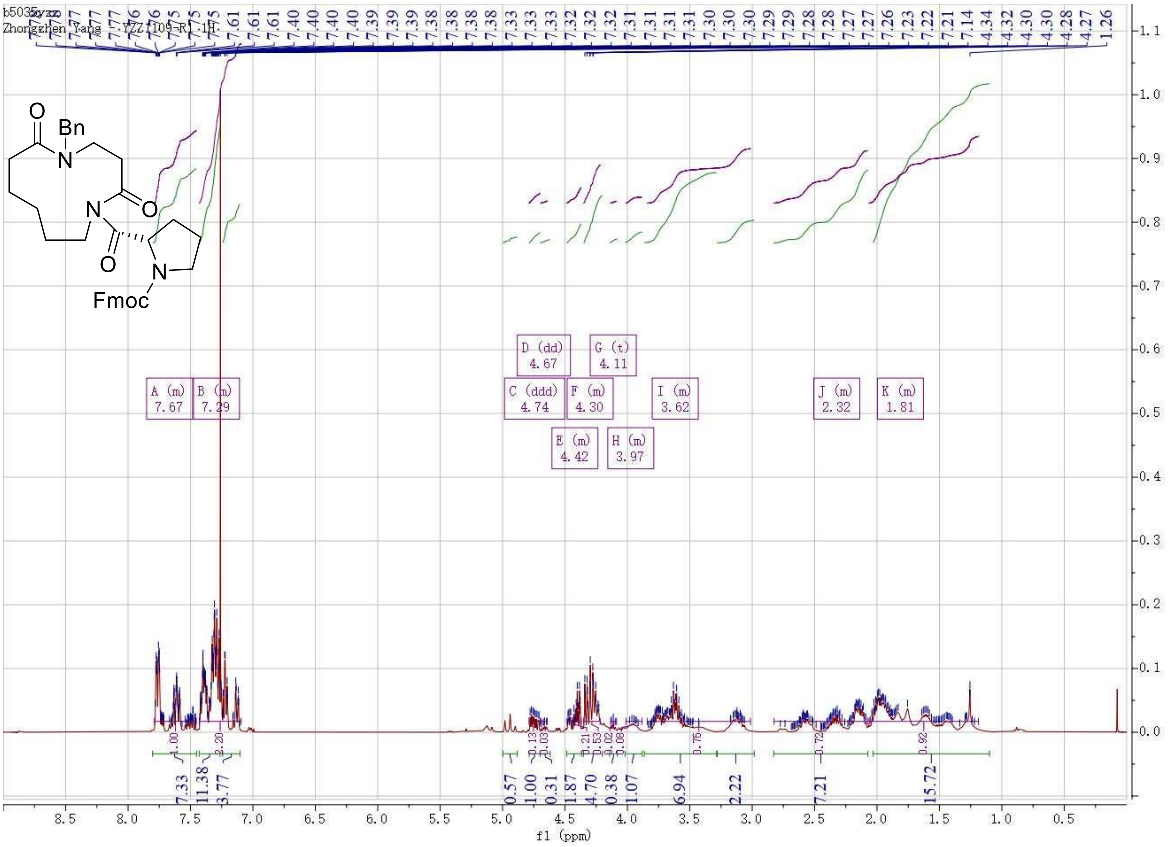


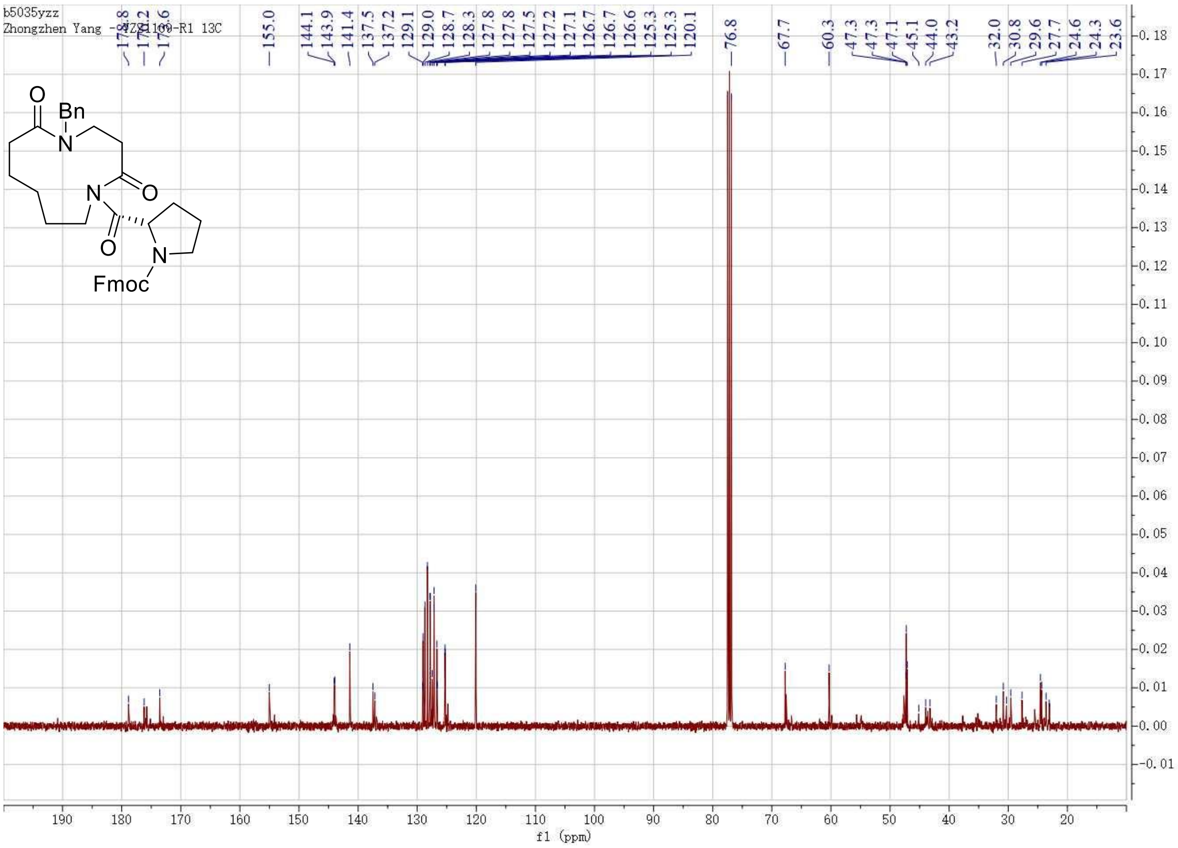
5-Benzyl-4,5,8,9,10,11-hexahydro-2*H*-1,5,11-benzoxadiazacyclotetradecine-2,6,12(3*H*,7*H*)-trione (35) (as a 10:1 mixture of rotamers)





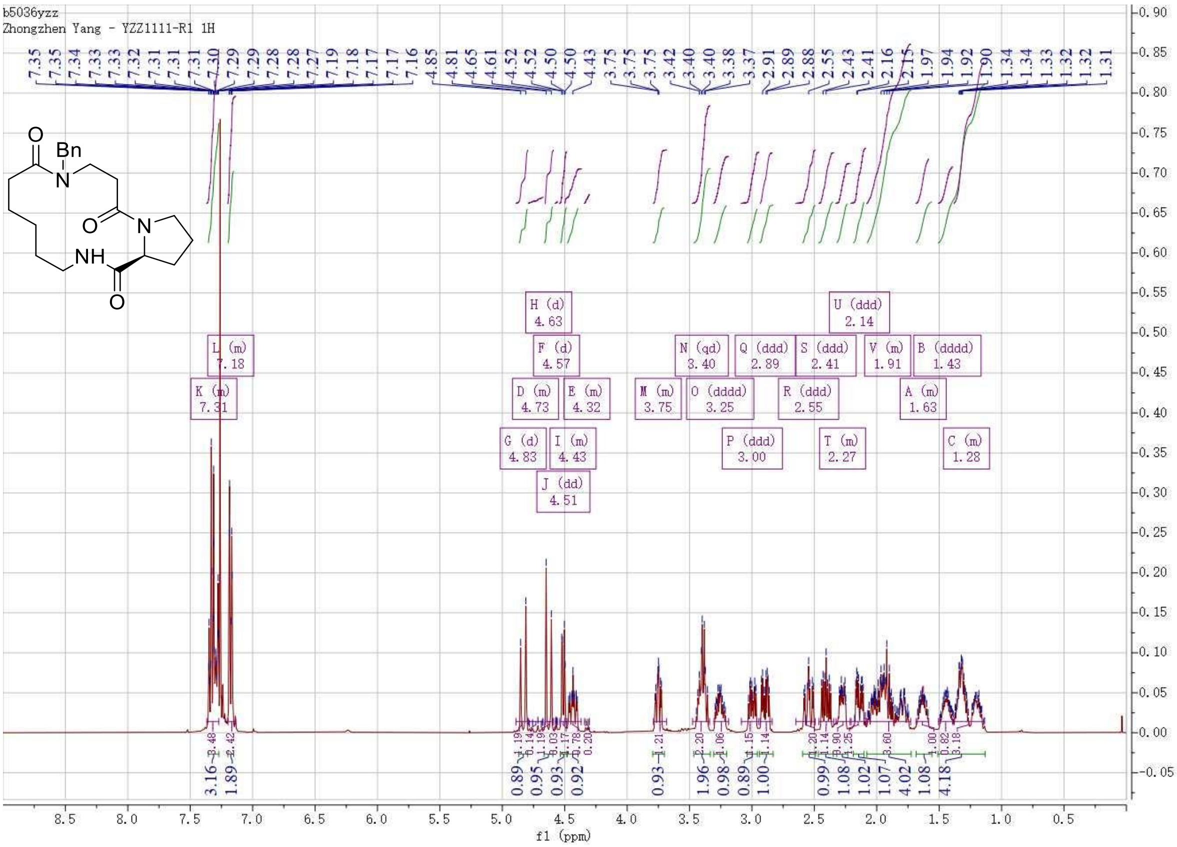
(9*H*-Fluoren-9-yl)methyl 2-(5-benzyl-2,6-dioxo-1,5-diazacycloundecane-1 carbonyl)pyrrolidine-1-carboxylate (37) (as a 5:2 mixture of rotamers)

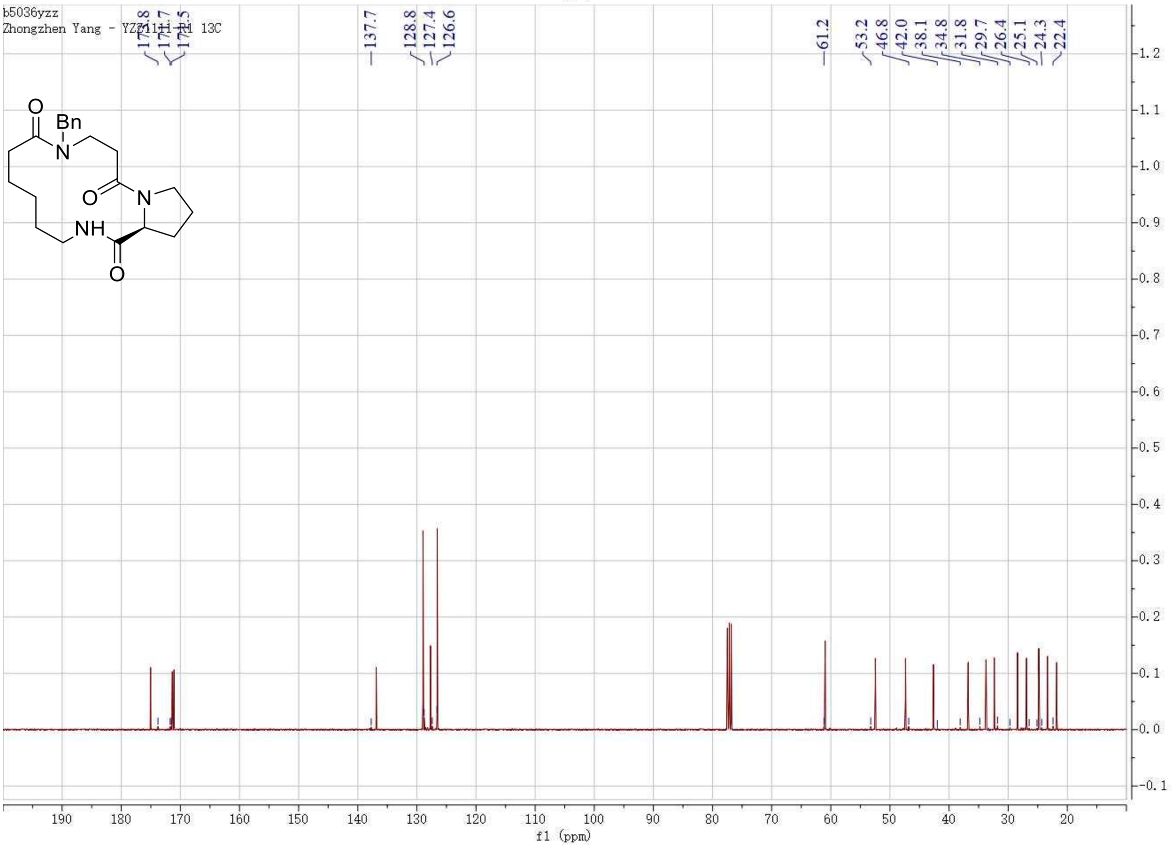




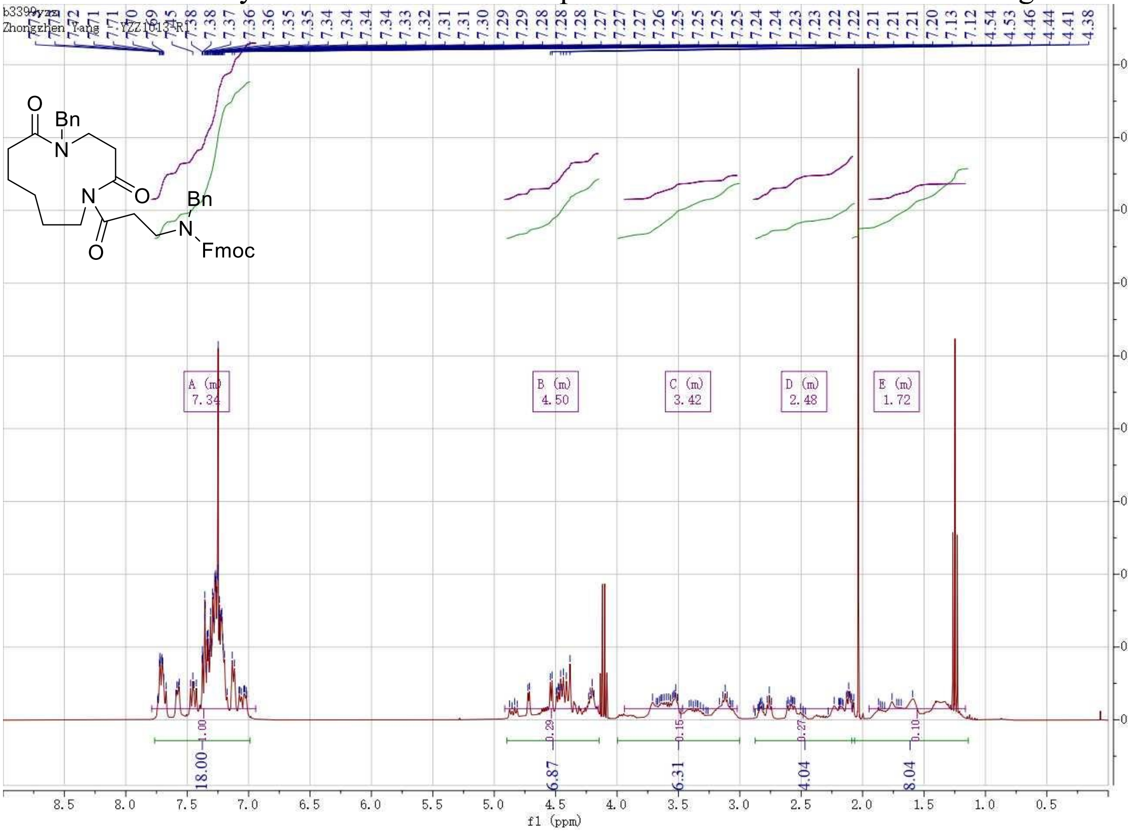
9-Benzyldodecahydropyrrolo[2,1-*c*][1,4,8]triazacyclotetradecine-1,8,12(9*H*)-trione (38)

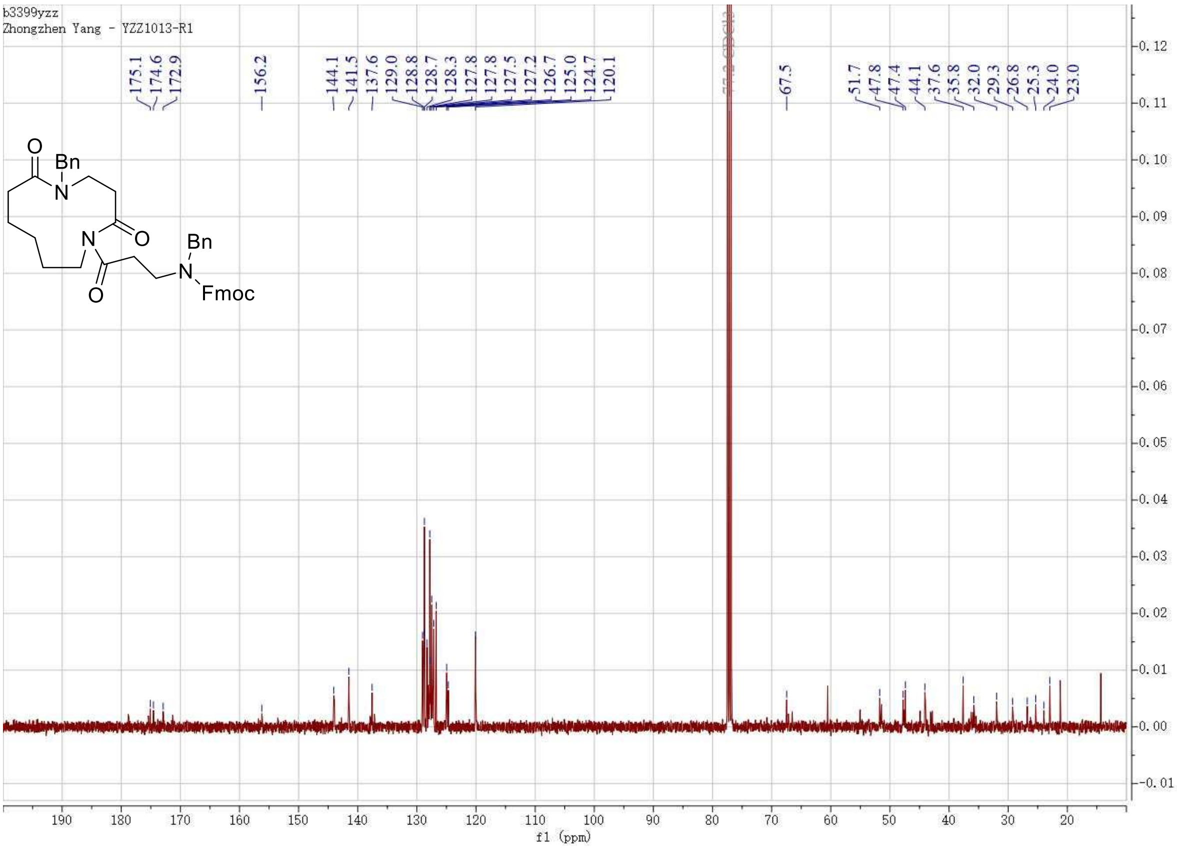
(as a 20:1 mixture of rotamers)



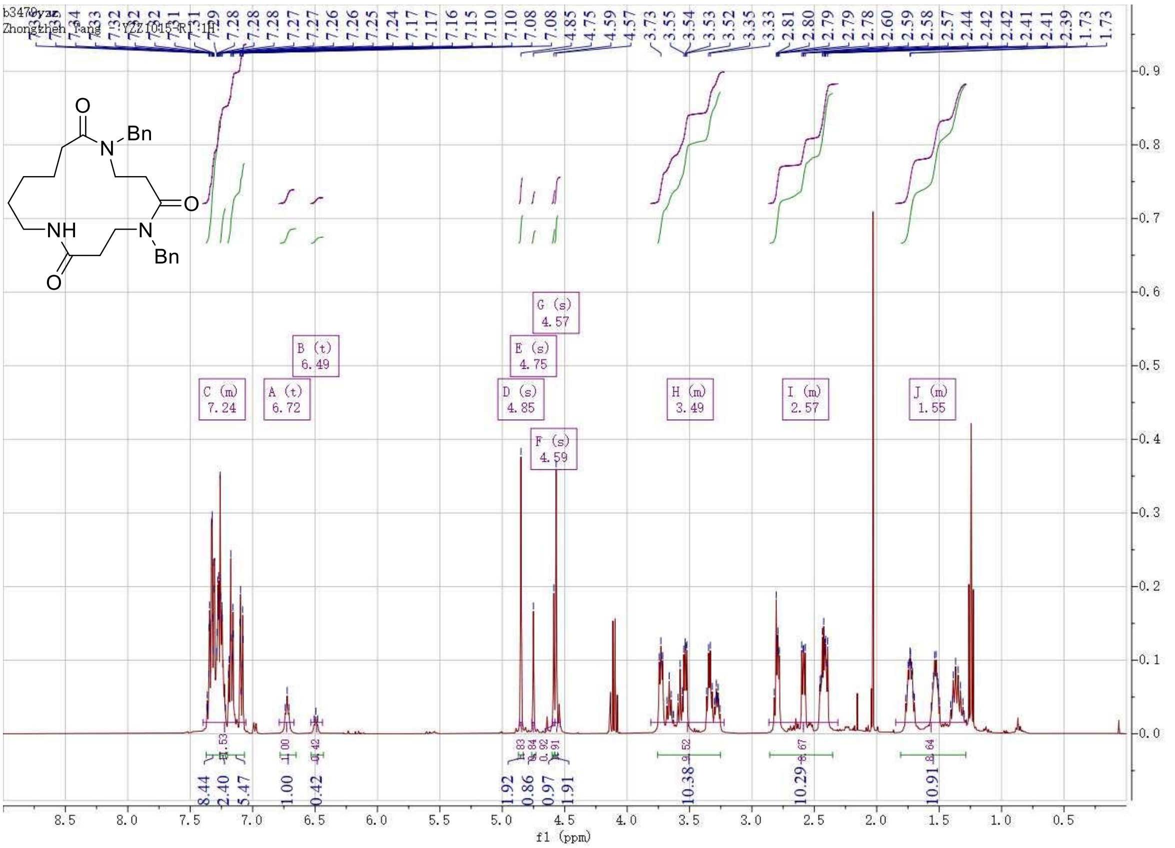


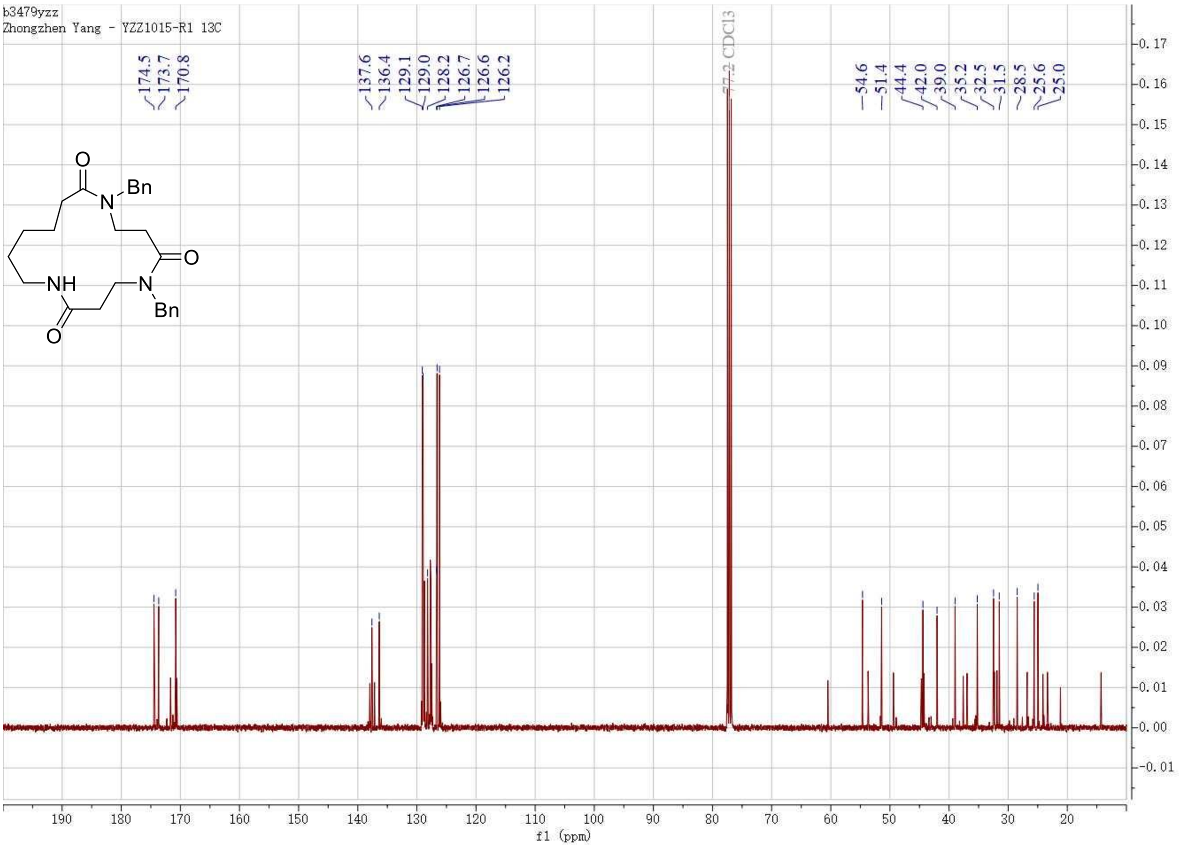
(9*H*-Fluoren-9-yl)methyl benzyl[3-(5-benzyl-2,6-dioxo-1,5-diazacycloundecan-1-yl)-3-oxopropyl]carbamate (39). Some EtOAc is clearly evident in the NMR spectra of this material, but it was used in this form in its subsequent transformation into **40**). The ^{1}H NMR resonances are very broad in the ^{1}H NMR spectrum due to rotameric broadening.



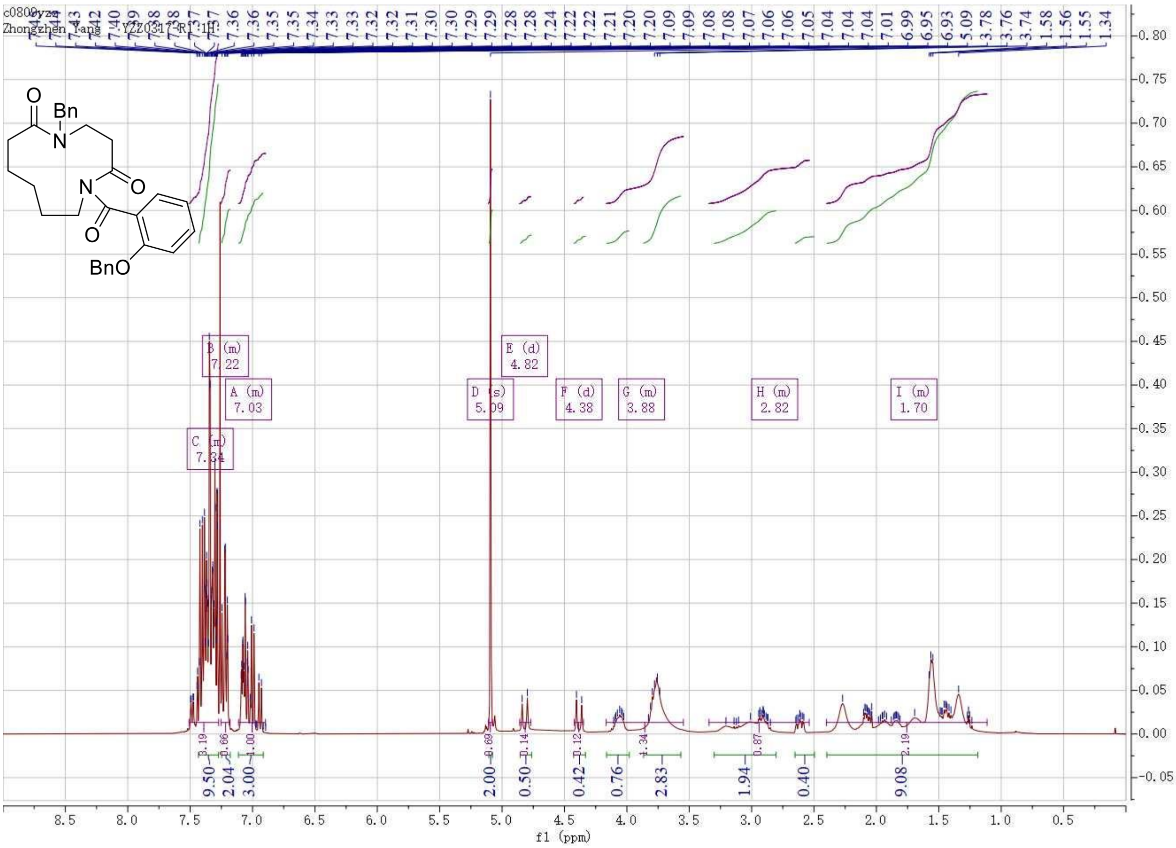


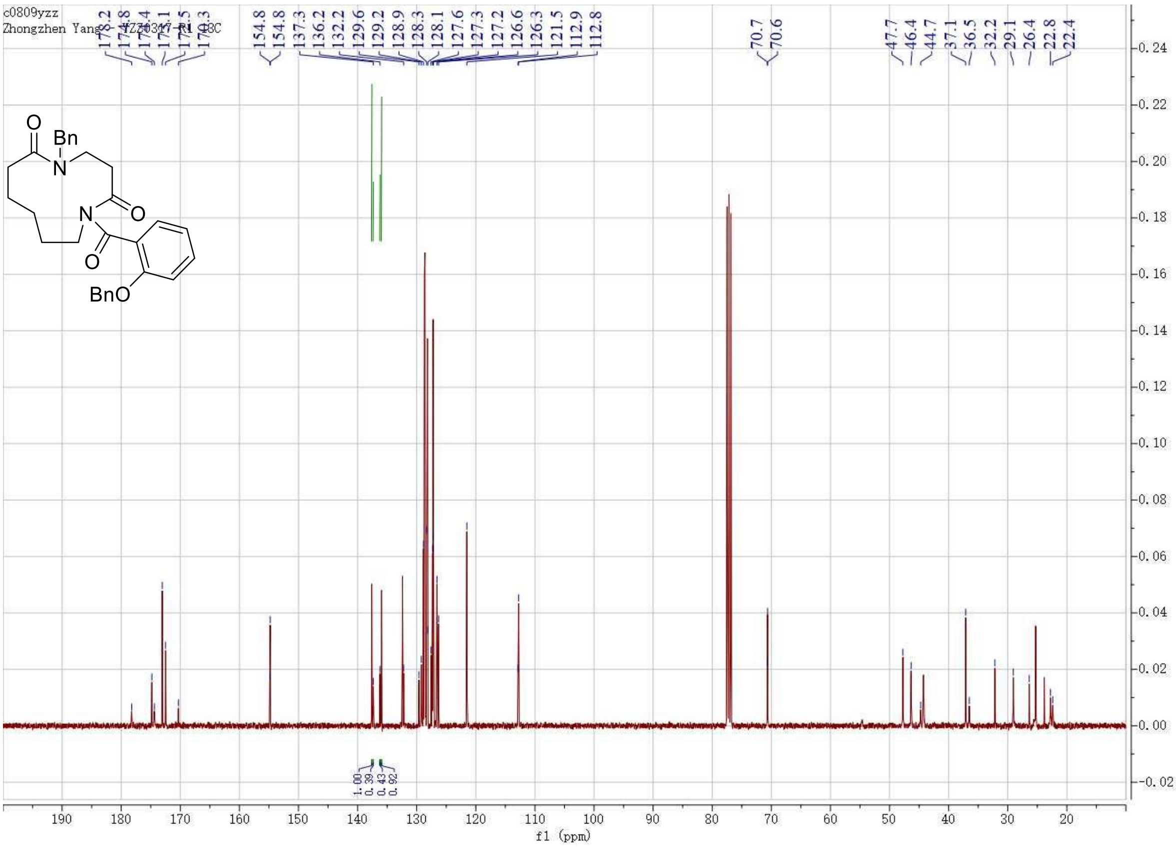
5,9-Dibenzyl-1,5,9-triazacyclopentadecane-2,6,10-trione (40) (as a 2:1 mixture of rotamers)



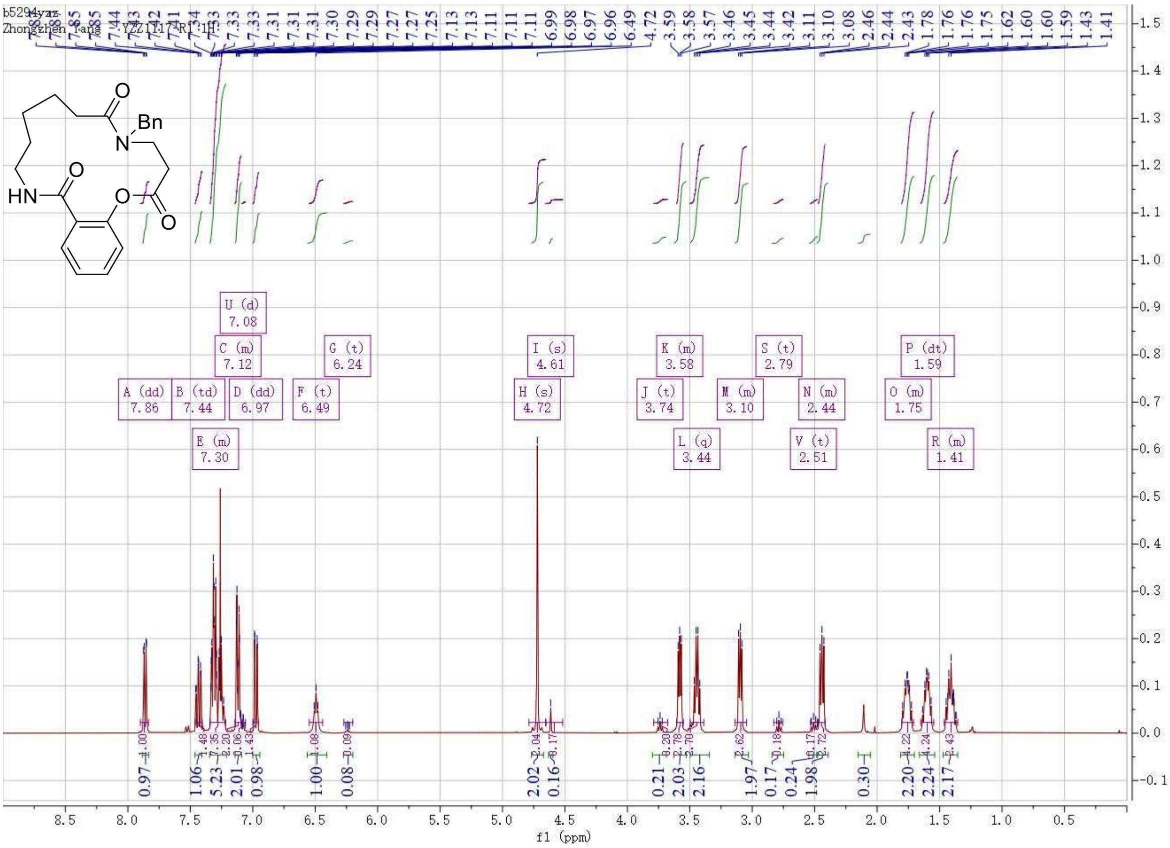


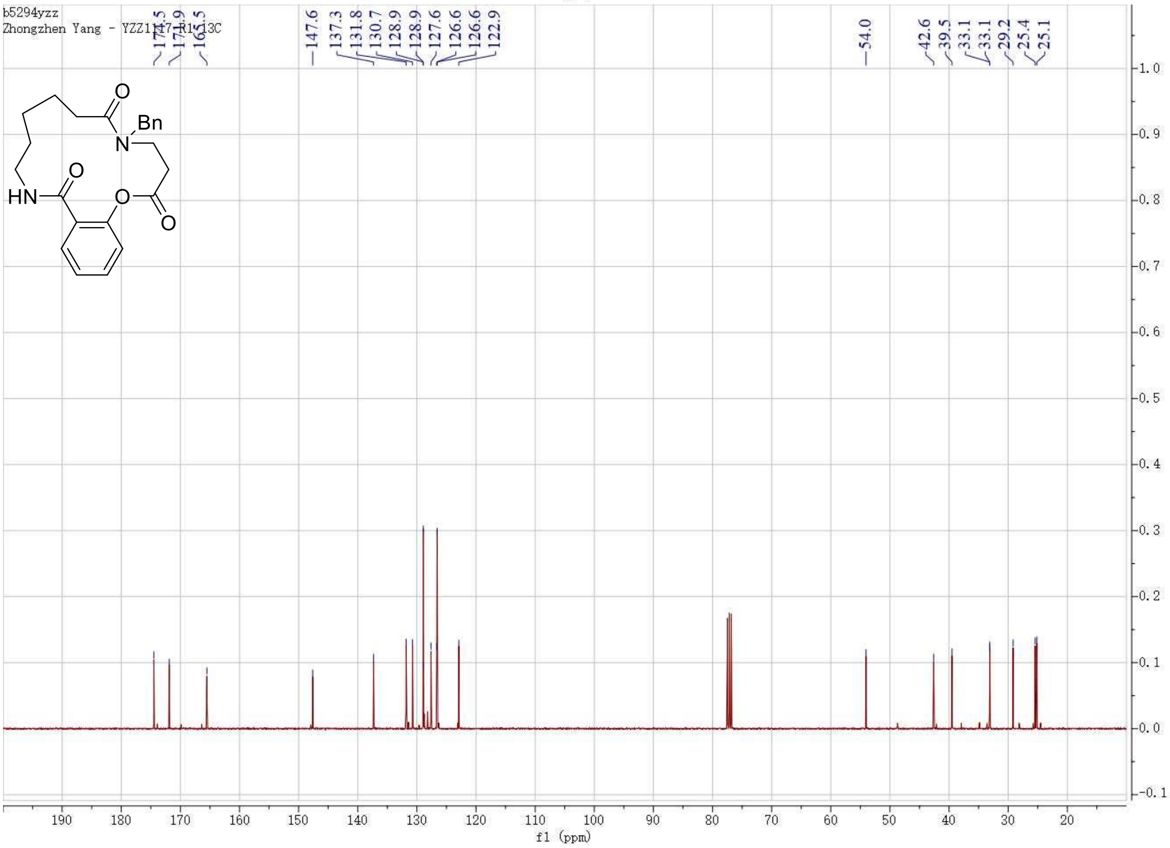
5-Benzyl-1-[2-(benzyloxy)benzoyl]-1,5-diazacycloundecane-2,6-dione (41) (as a 10:1 mixture of rotamers)



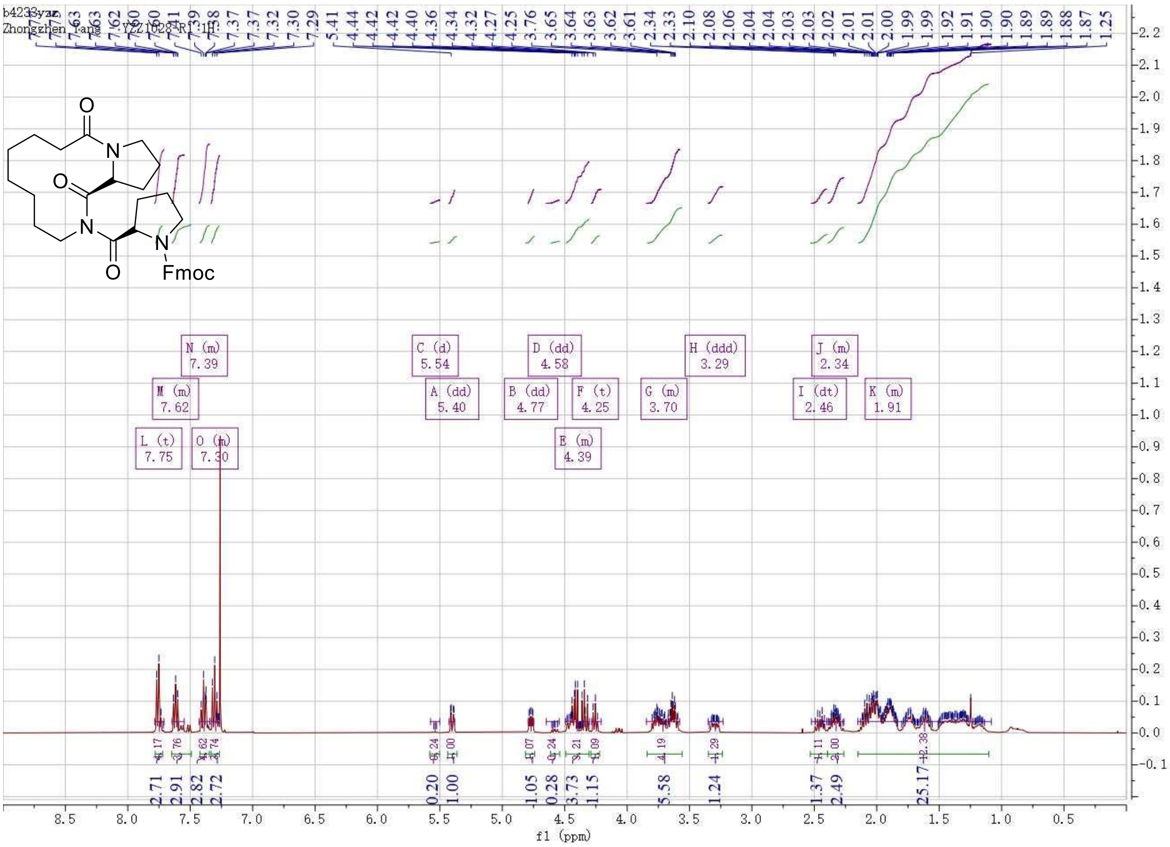


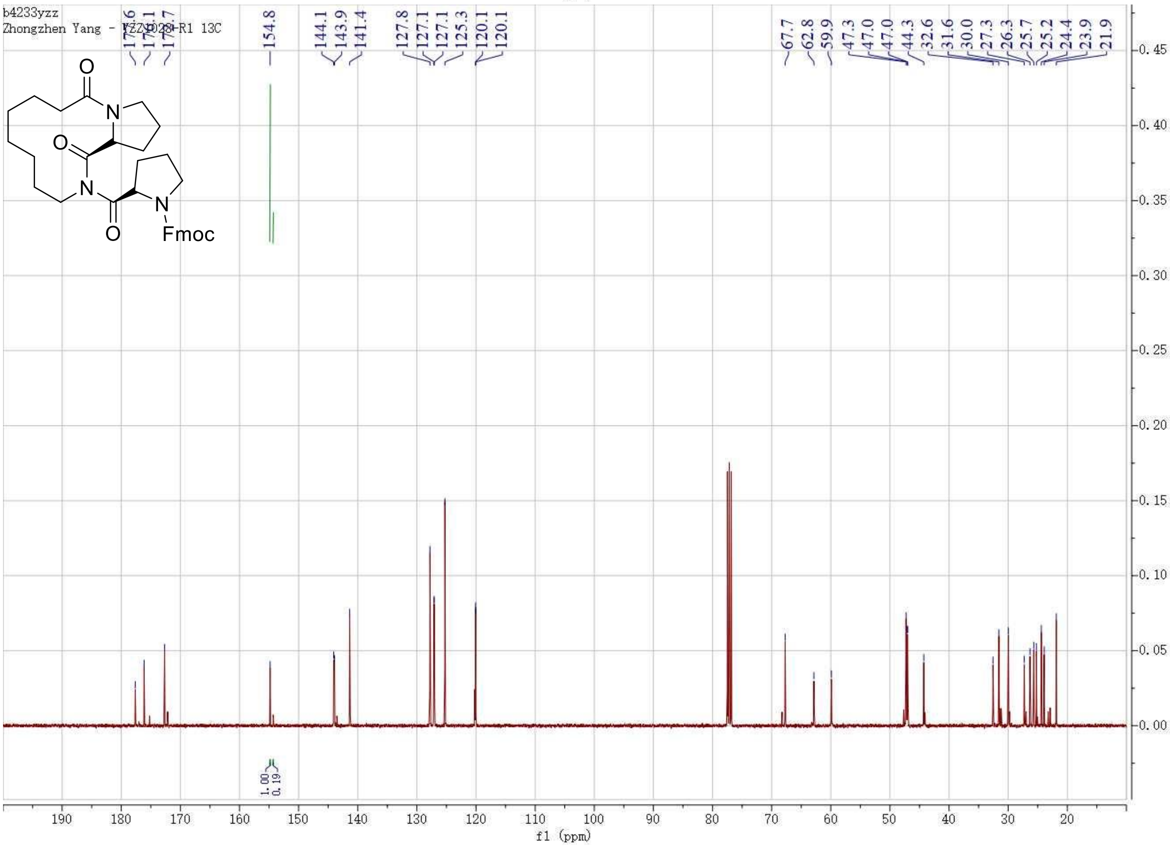
5-Benzyl-4,5,7,8,9,10,11,12-octahydro-1,5,12-benzoxadiazacyclopentadecine-2,6,13(3*H*)-trione (42) (as a 10:1 mixture of rotamers)



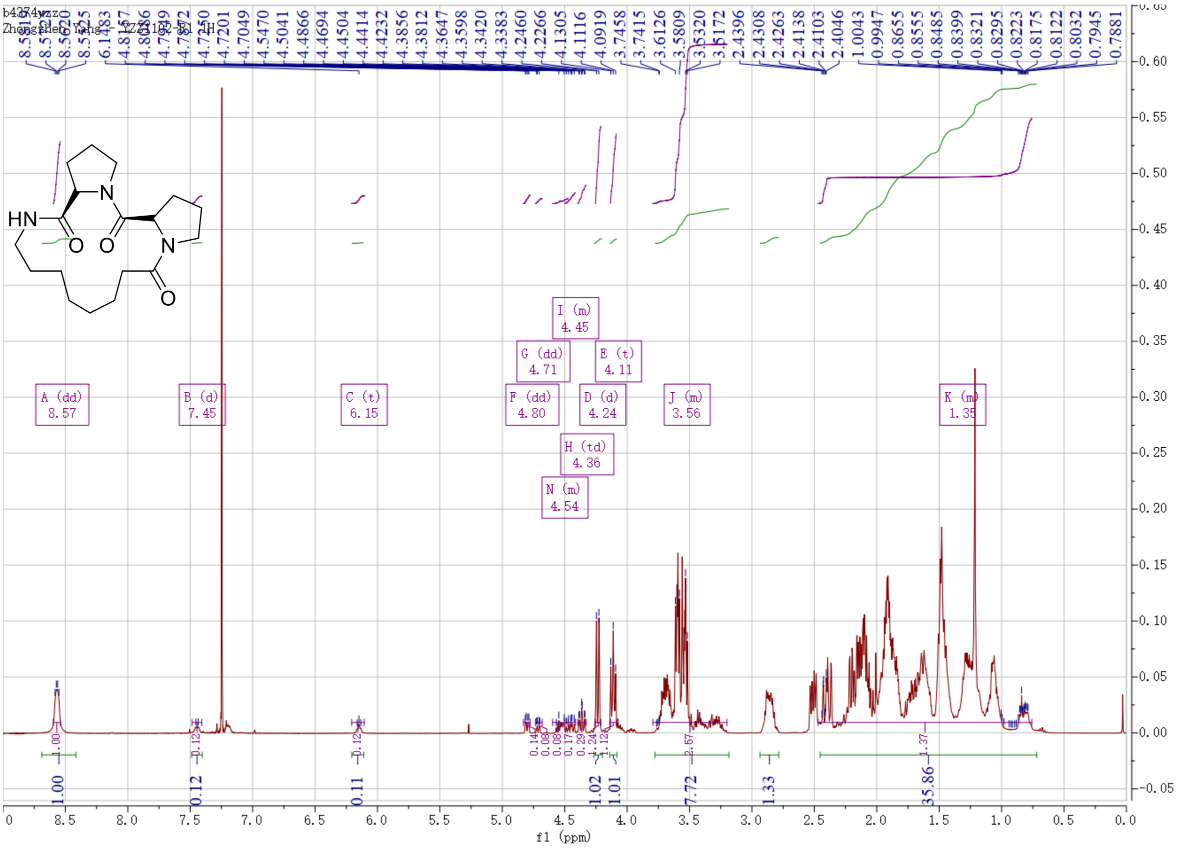


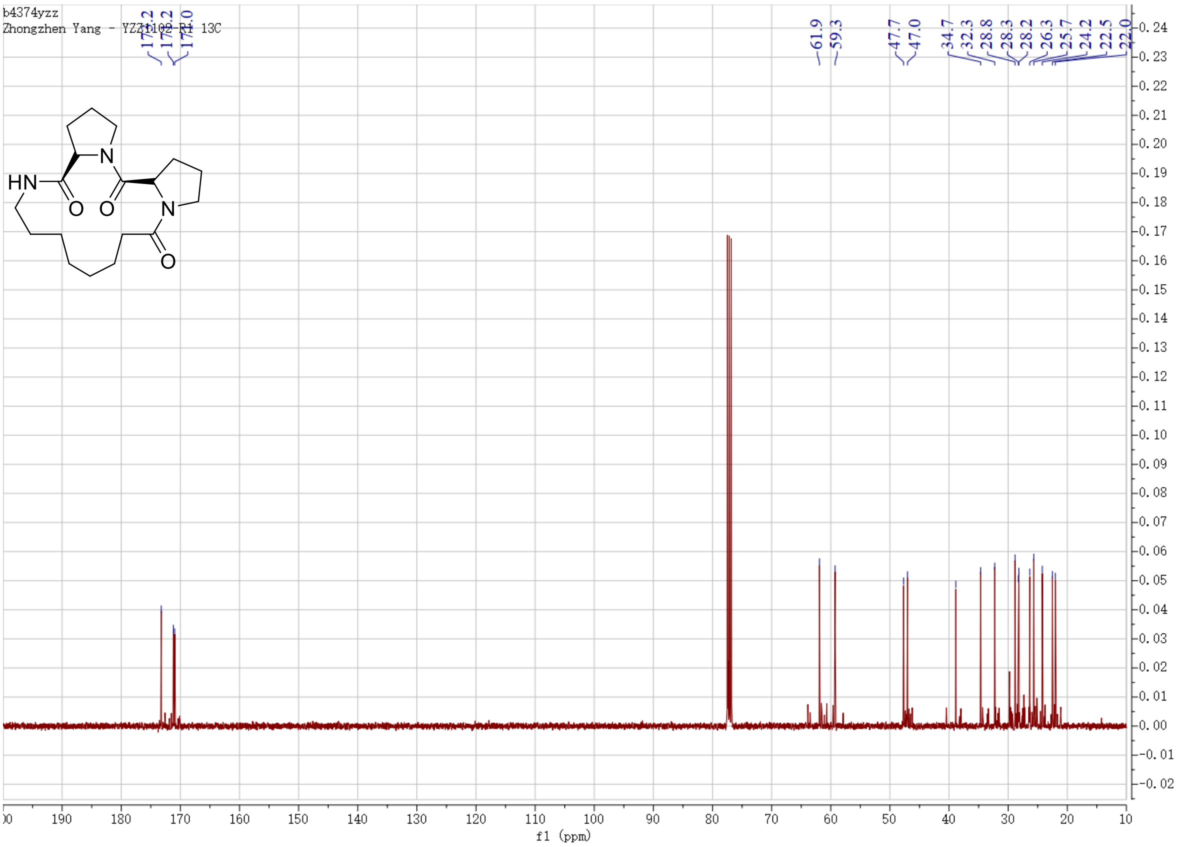
(9*H*-Fluoren-9-yl)methyl 2-(1,10-dioxododecahydropyrrolo[1,2*a*][1,4] diazacyclododecine-2(1*H*)-carbonyl)pyrrolidine-1-carboxylate (44) (as a 5:1 mixture of rotamers)



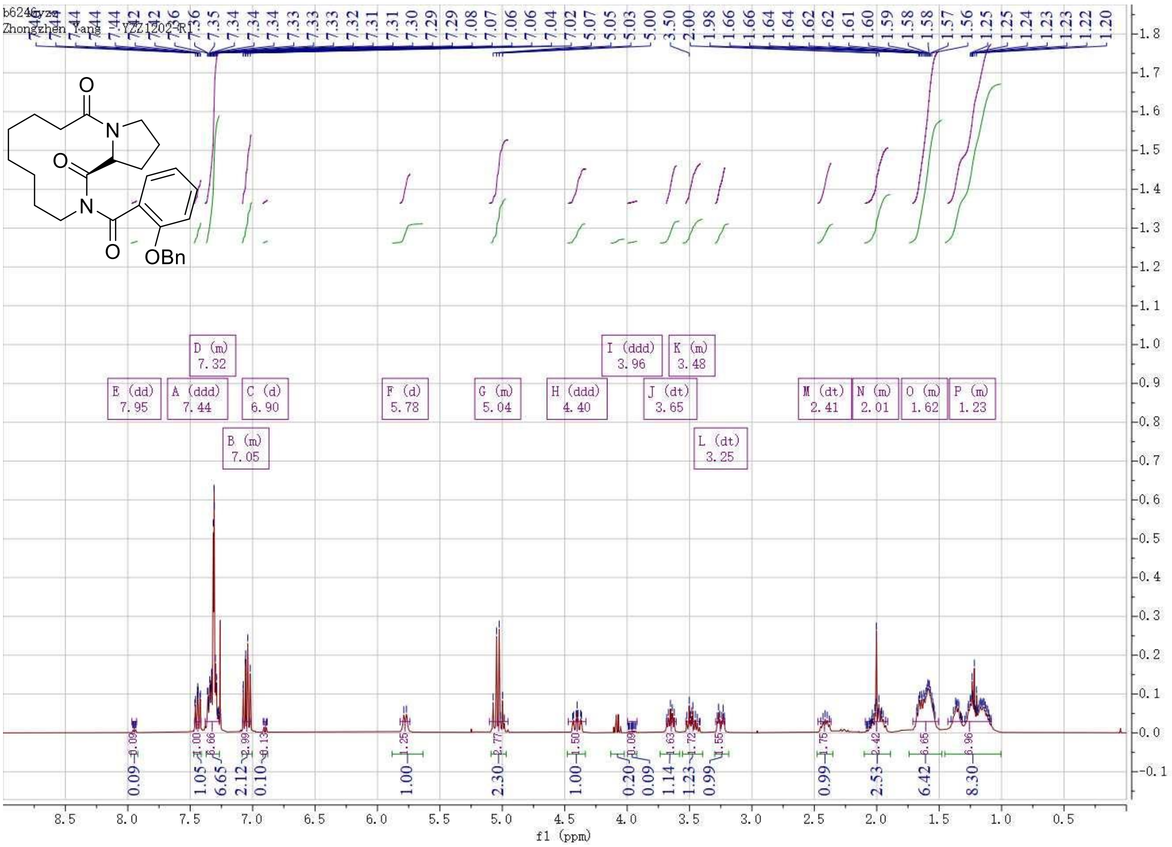


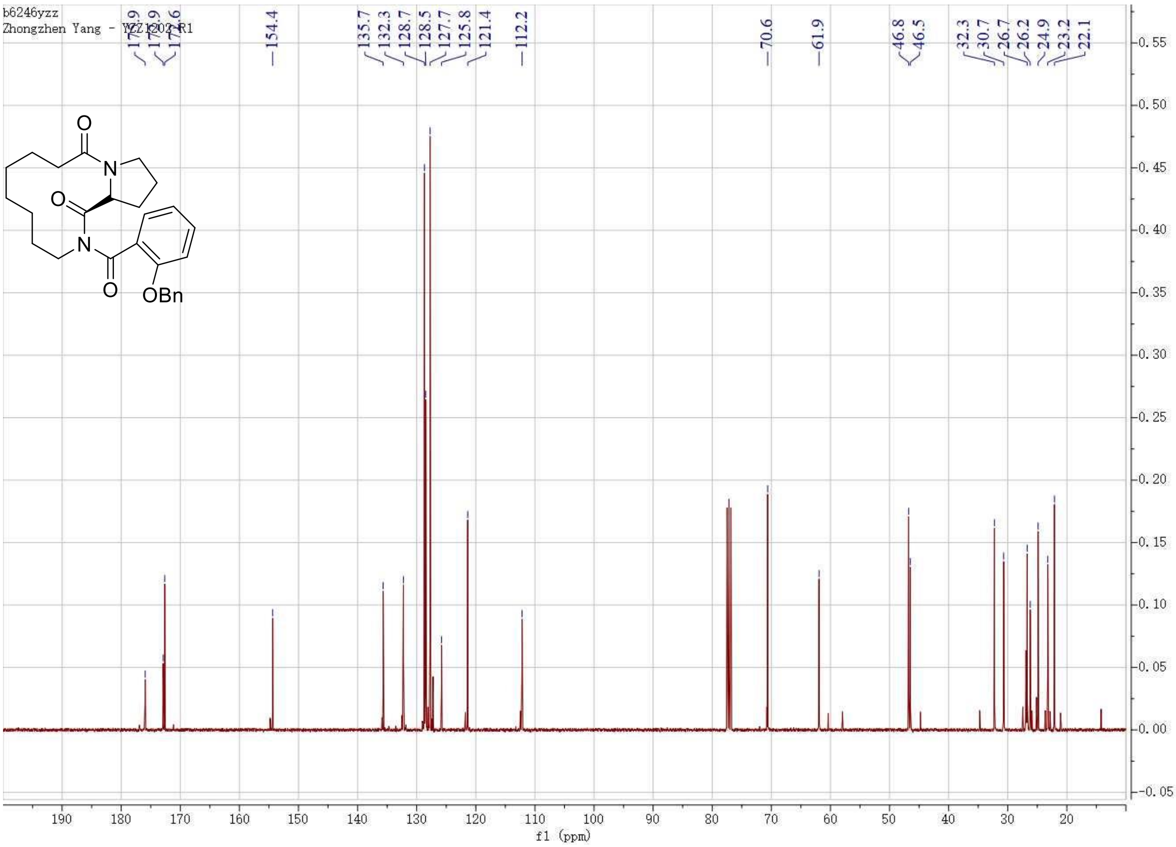
Tetradecahydro-1*H*-dipyrrolo[1,2-*a*:1',2'-*d*][1,4,7]triazacyclopentadecine-5,14,19(19a*H*)-trione (45) (as a 10:1:1:1 mixture of rotamers)



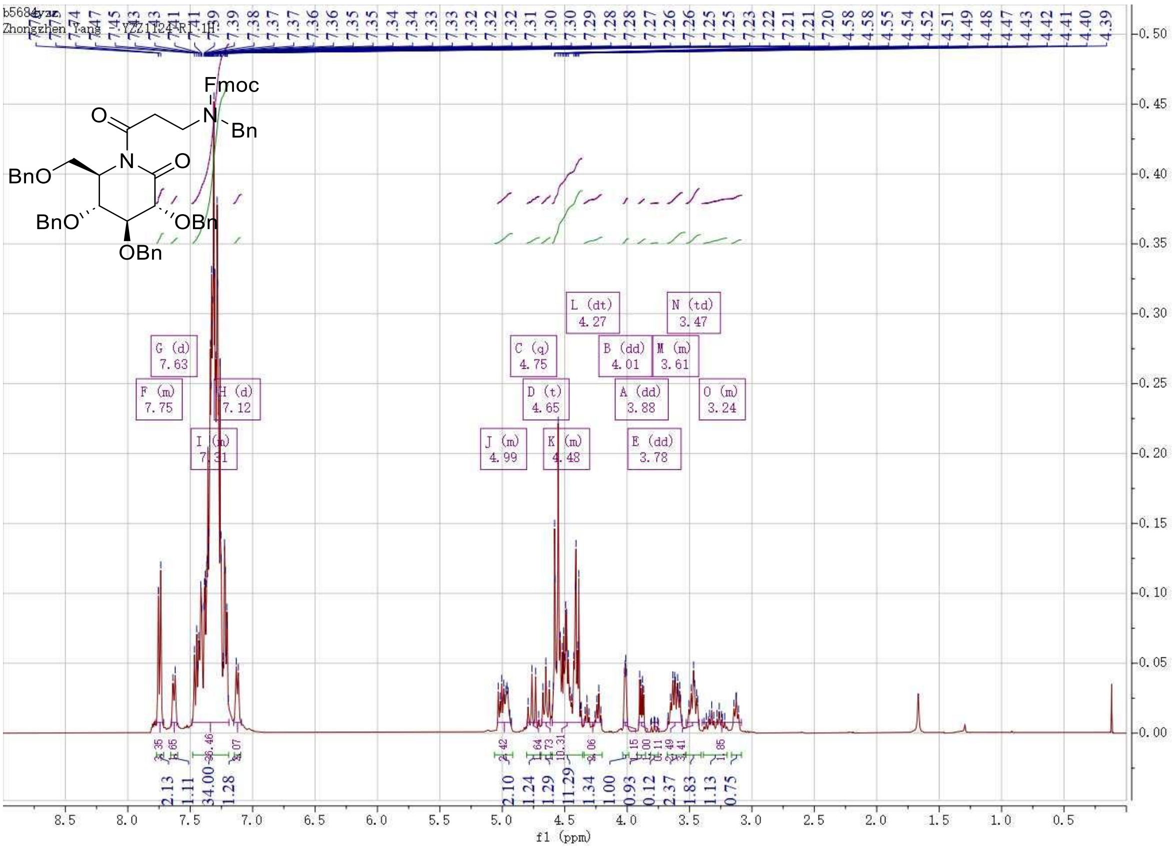


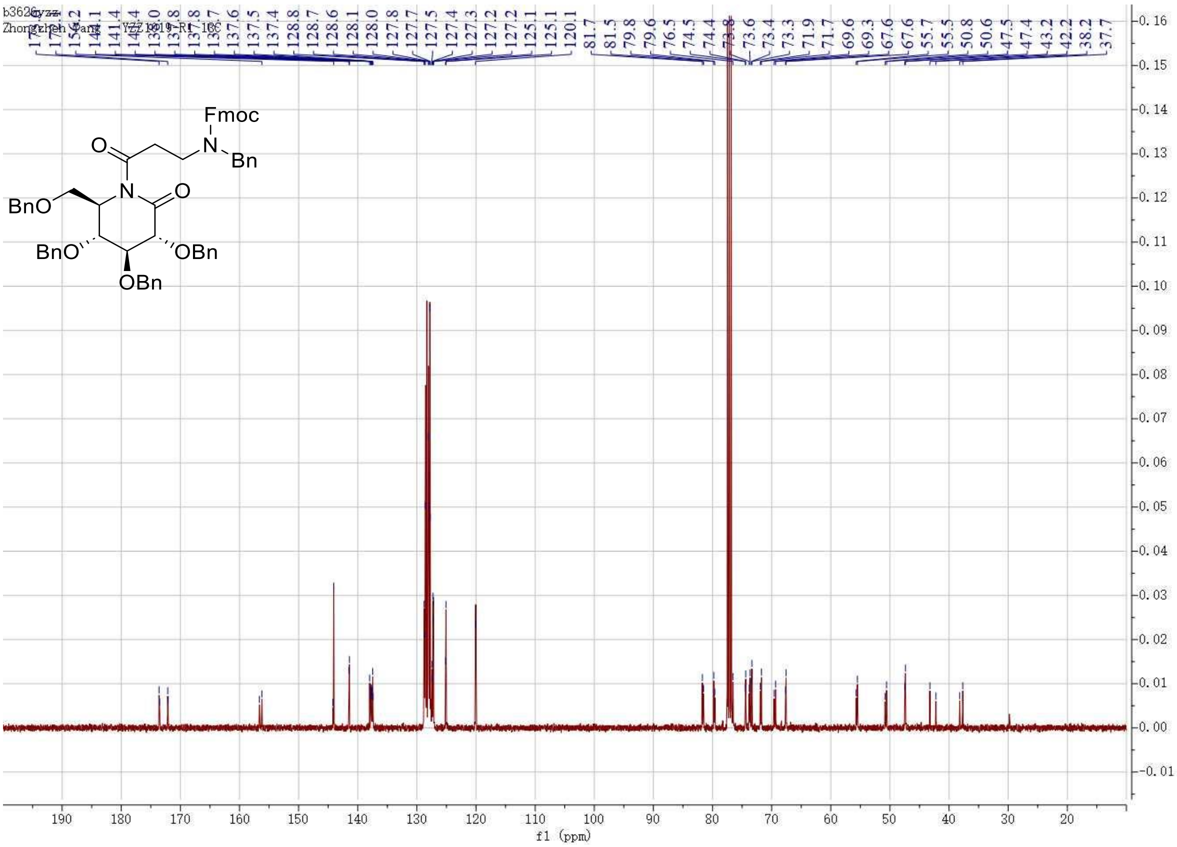
2-[2-(Benzyloxy)benzoyl]dodecahydropyrrolo[1,2-*a*][1,4]diazacyclododecine-1,10-dione (46) (as a 10:1 mixture of rotamers)



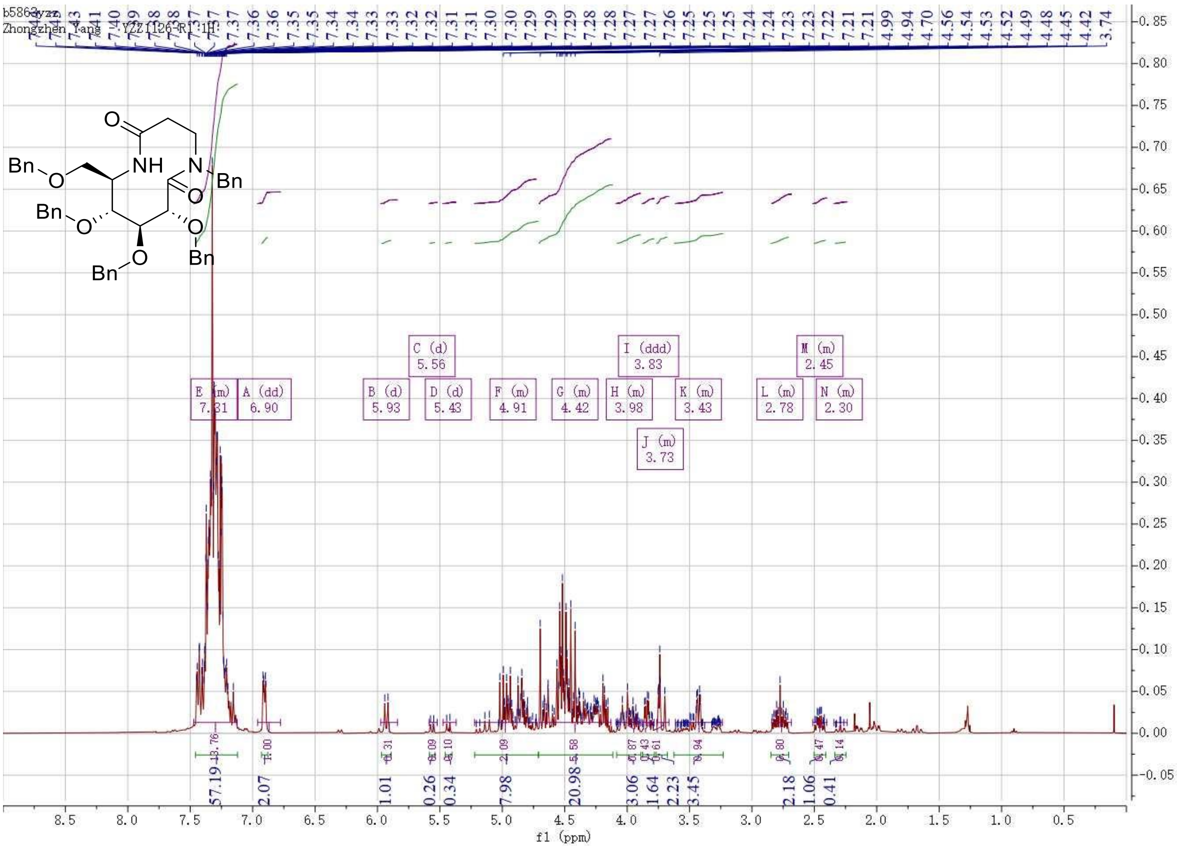


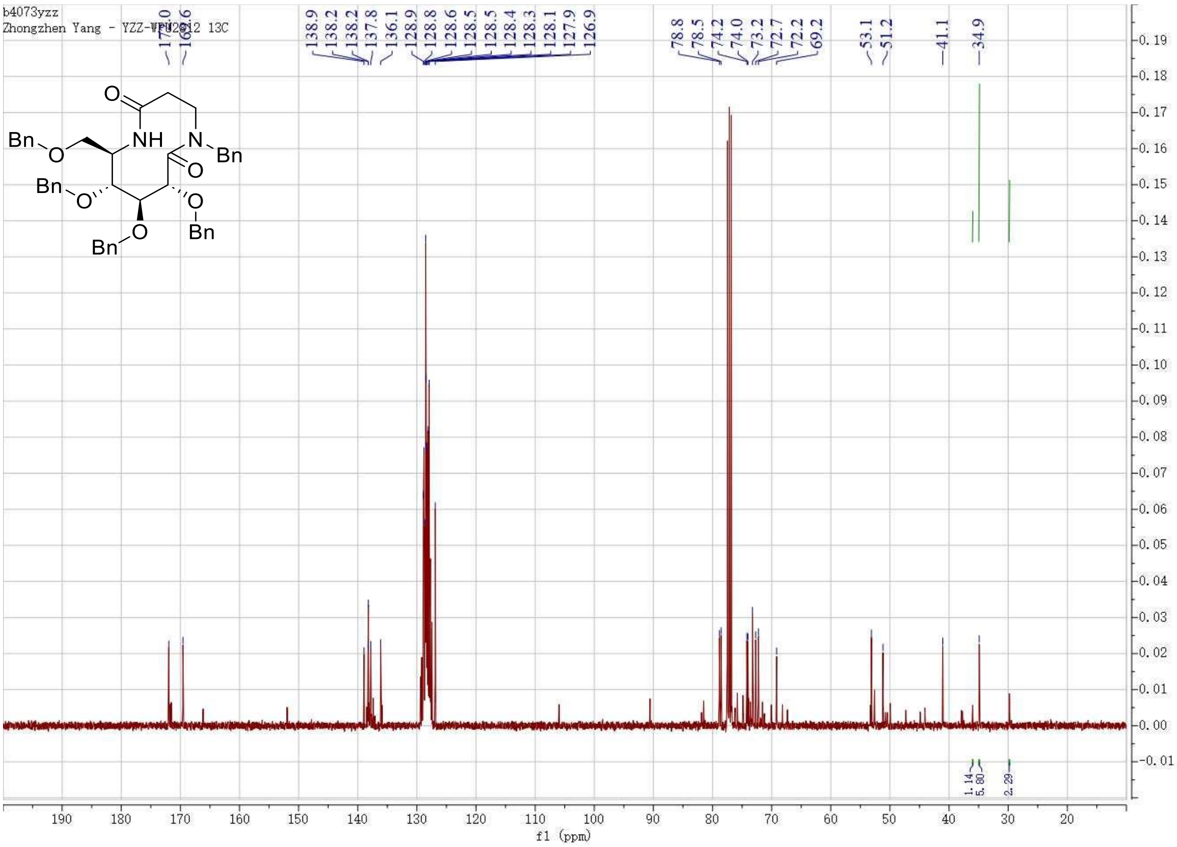
9*H*-Fluoren-9-yl)methyl 3,4,5-tris(benzyloxy)-2-[(benzyloxy)methyl]-6-oxopiperidine-1-carboxylate (49) (as a 5:4 mixture of rotamers)



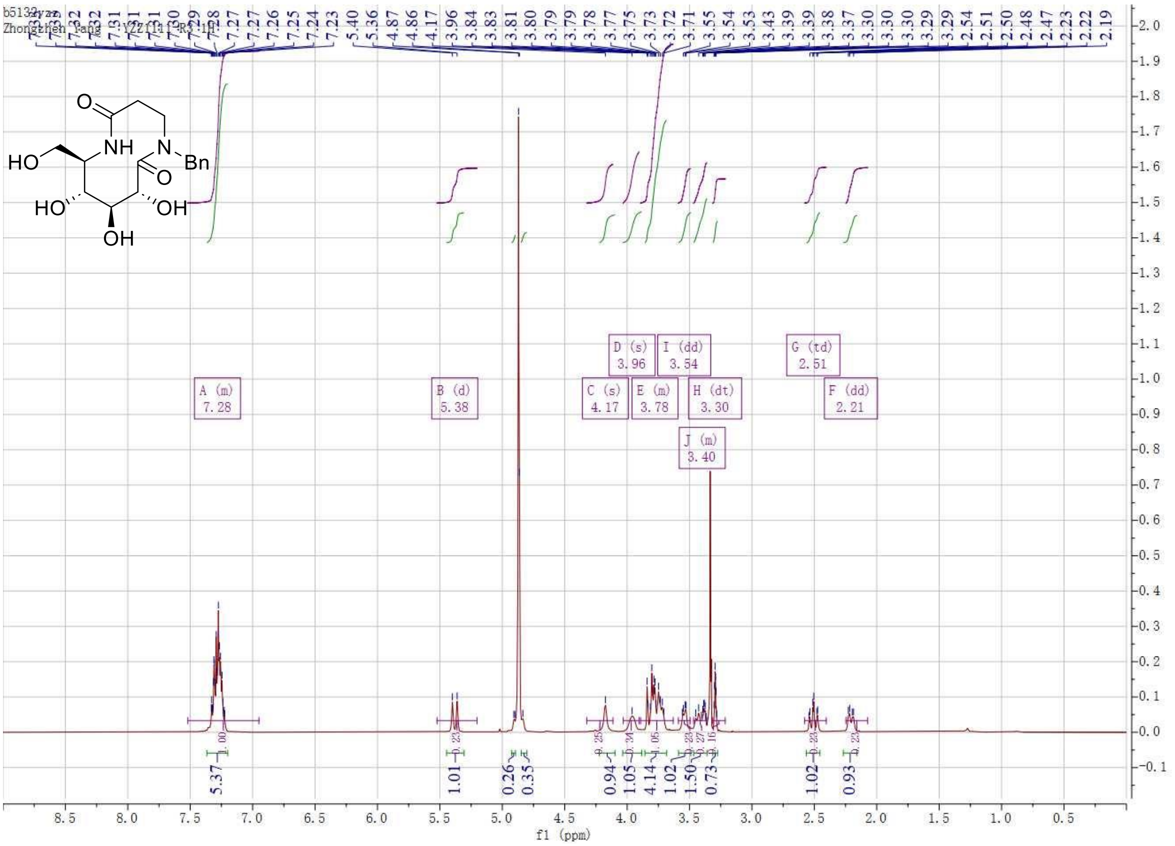


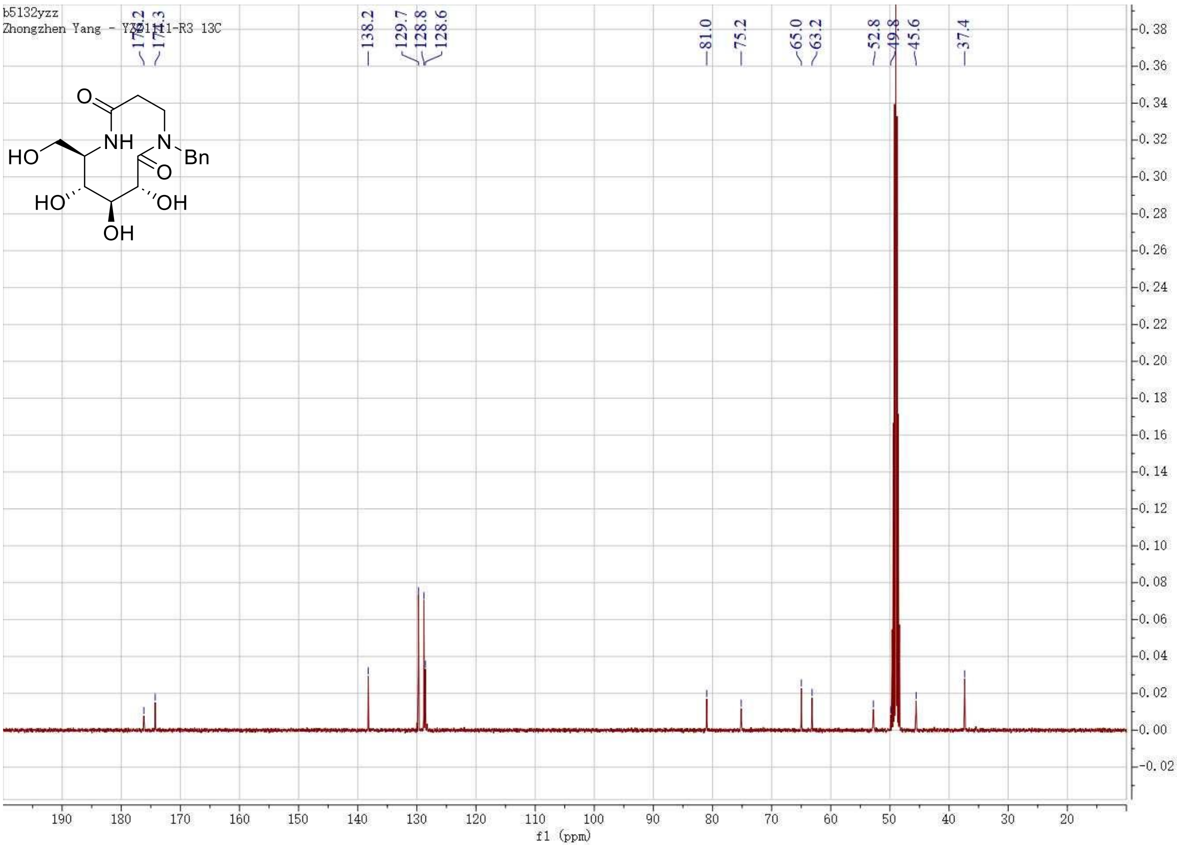
5-Benzyl-7,8,9-tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione (50) (as a 10:3:2 mixture of rotamers A:B:C)



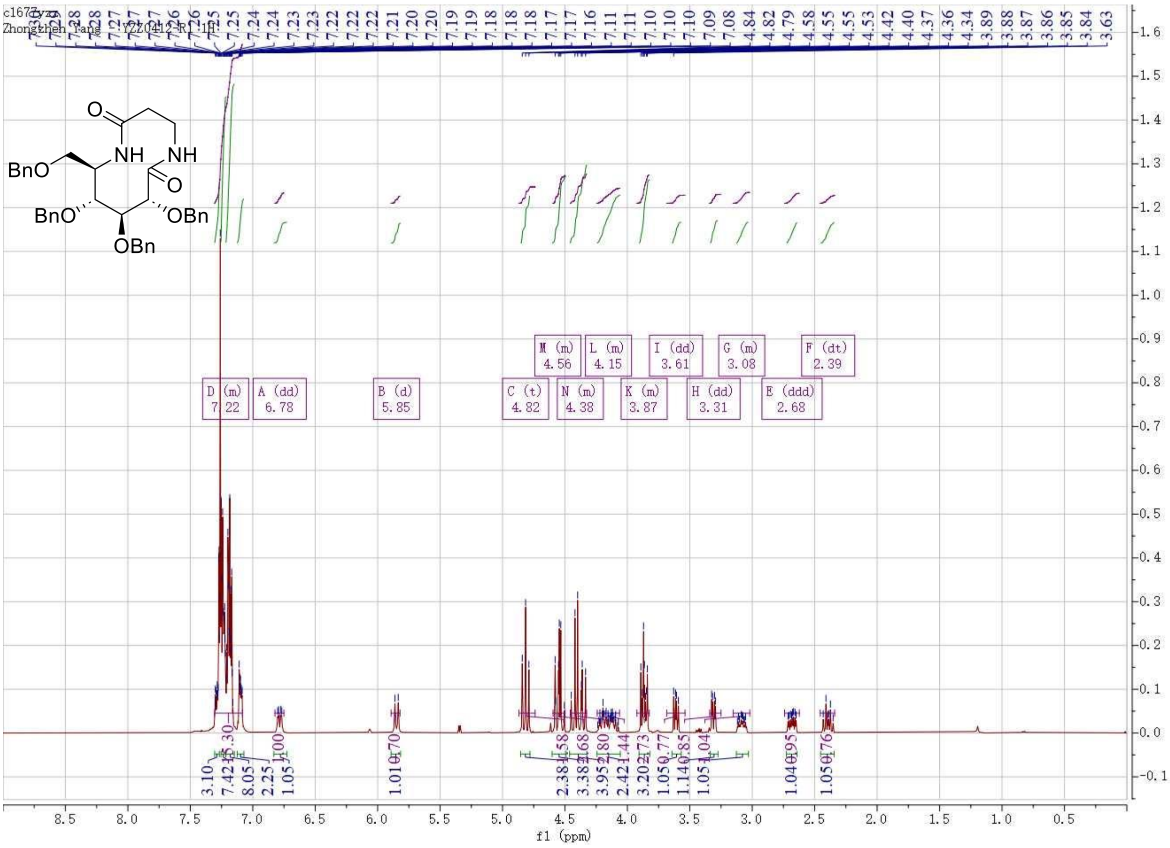


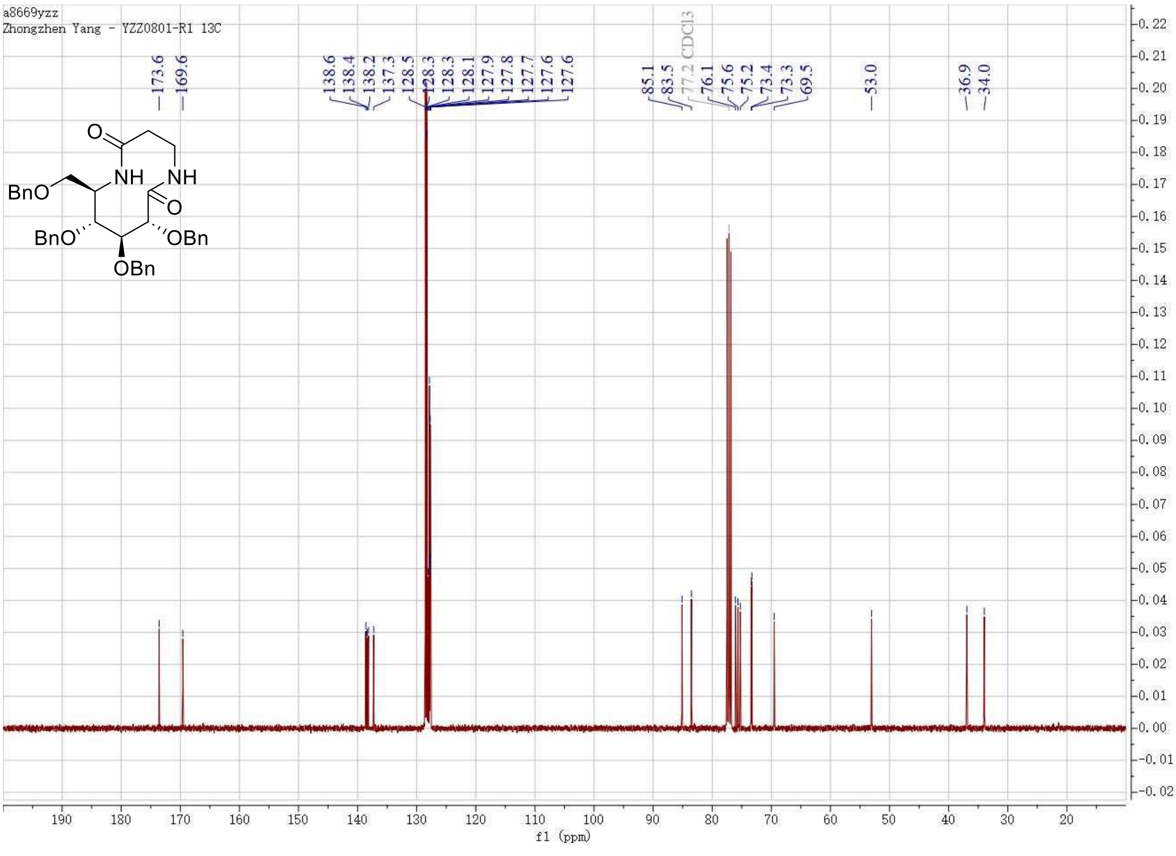
5-Benzyl-7,8,9-trihydroxy-10-(hydroxymethyl)-1,5-diazecane-2,6-dione (51)





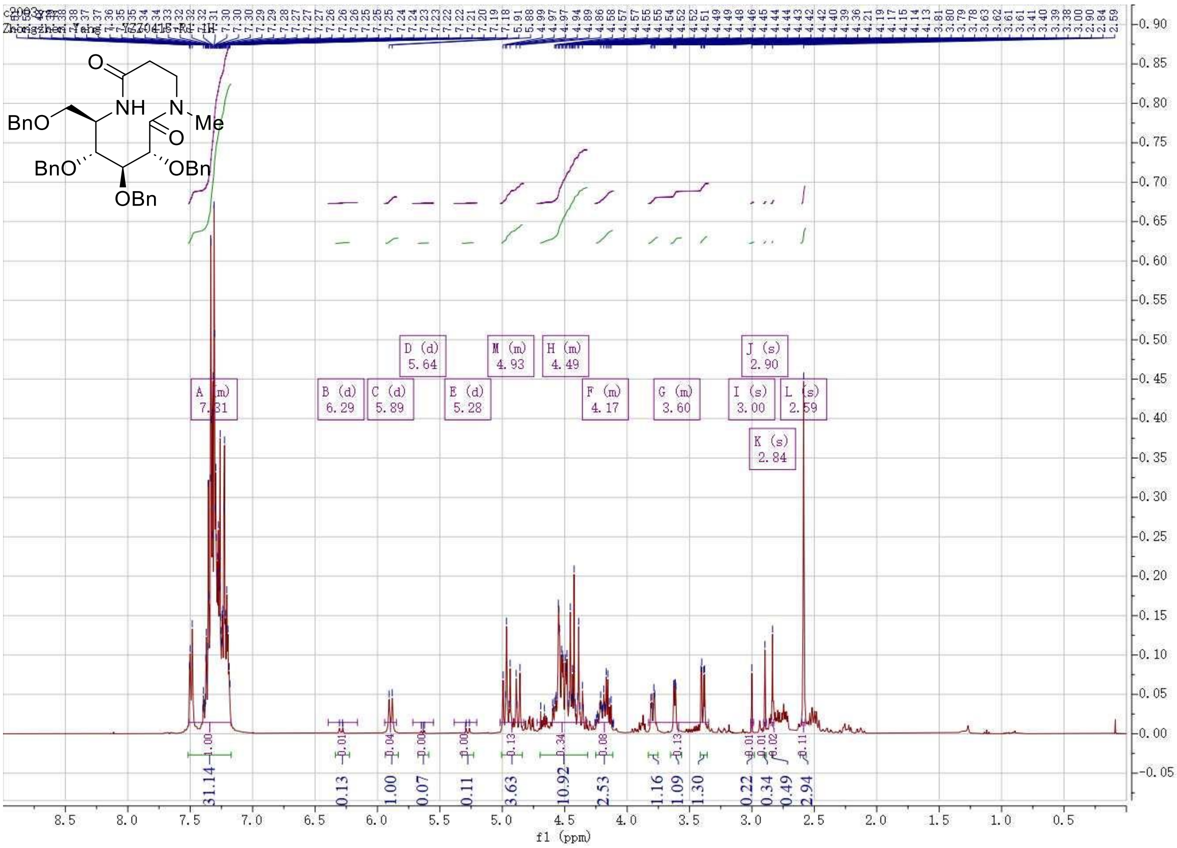
7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-1,5-diazecane-2,6-dione (56)

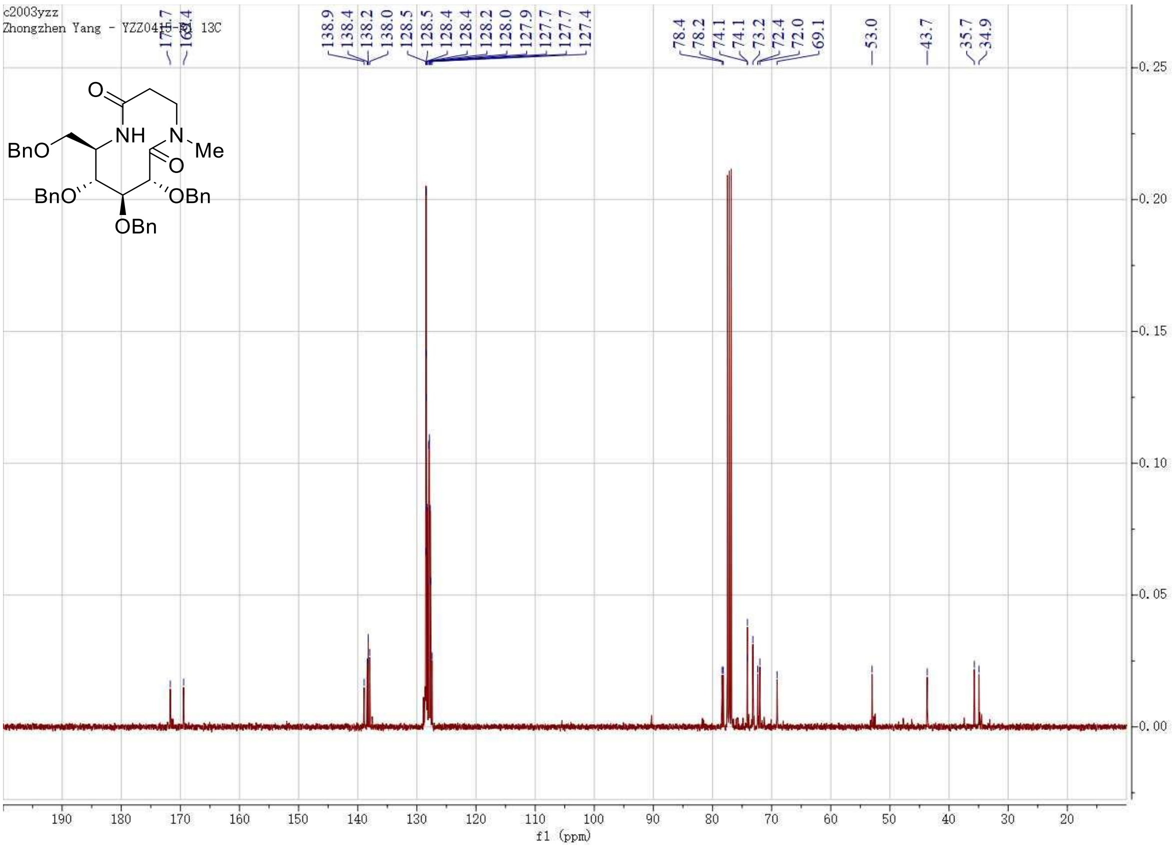




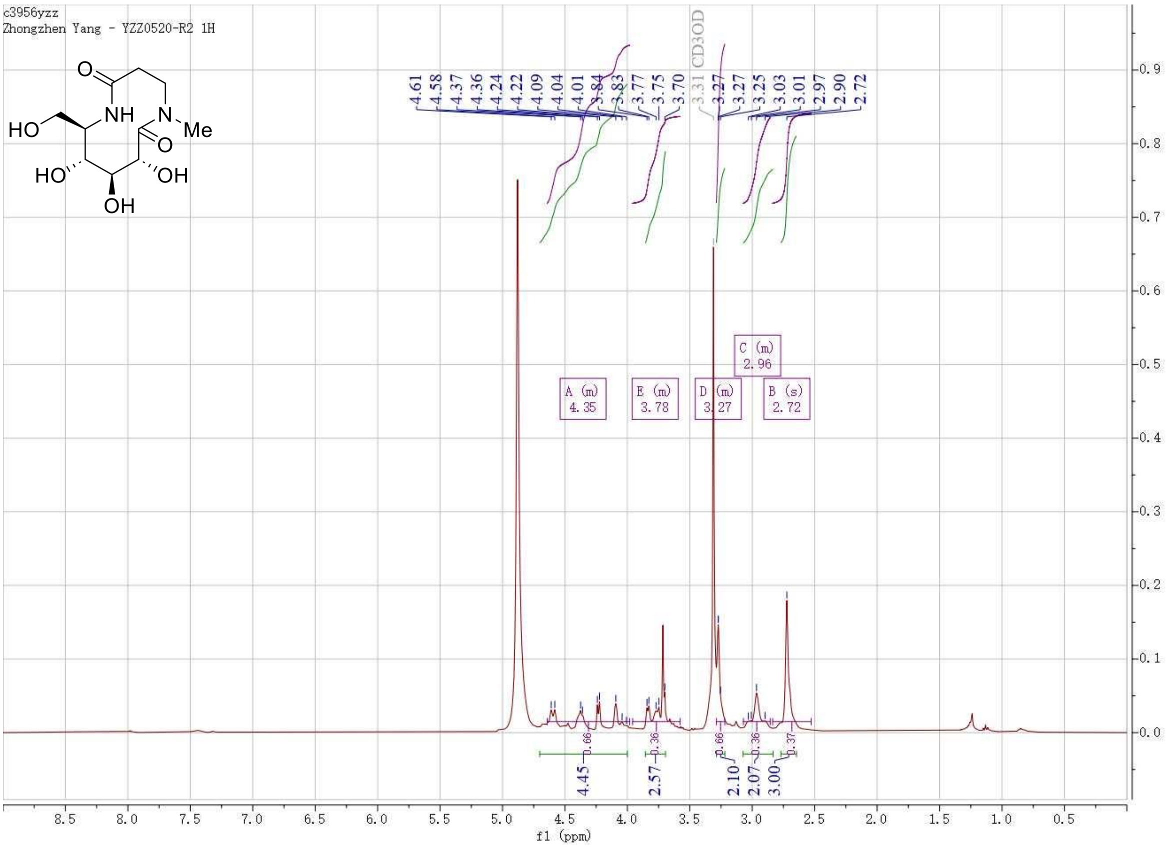
7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione (57)

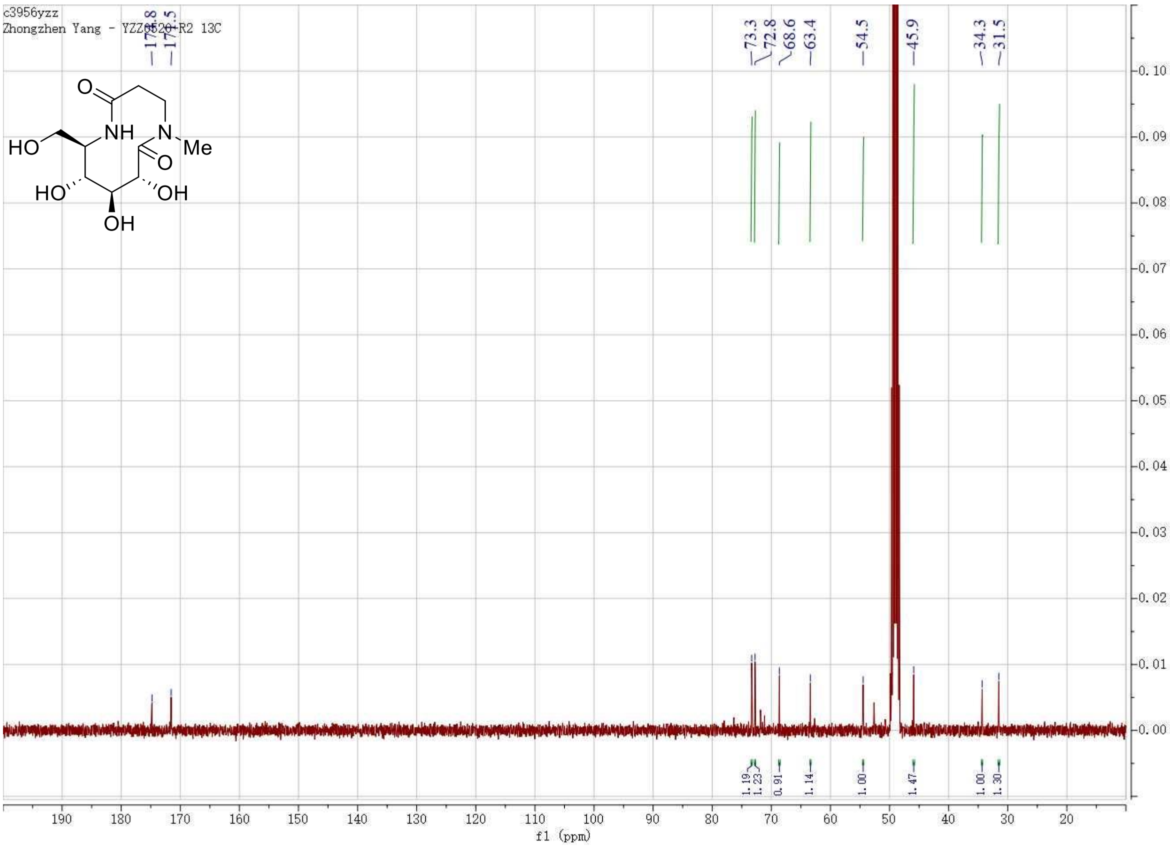
(mixture of 4 rotamers, ≈10:1:1:1)



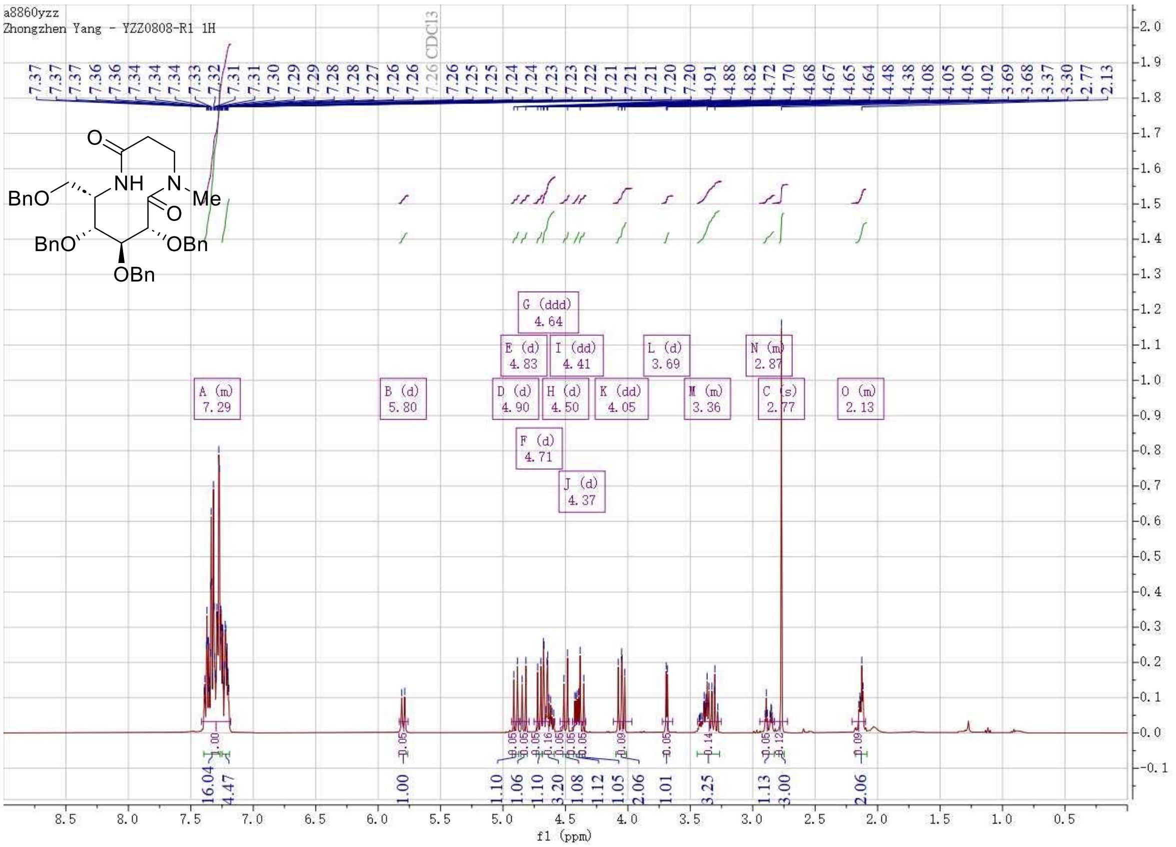


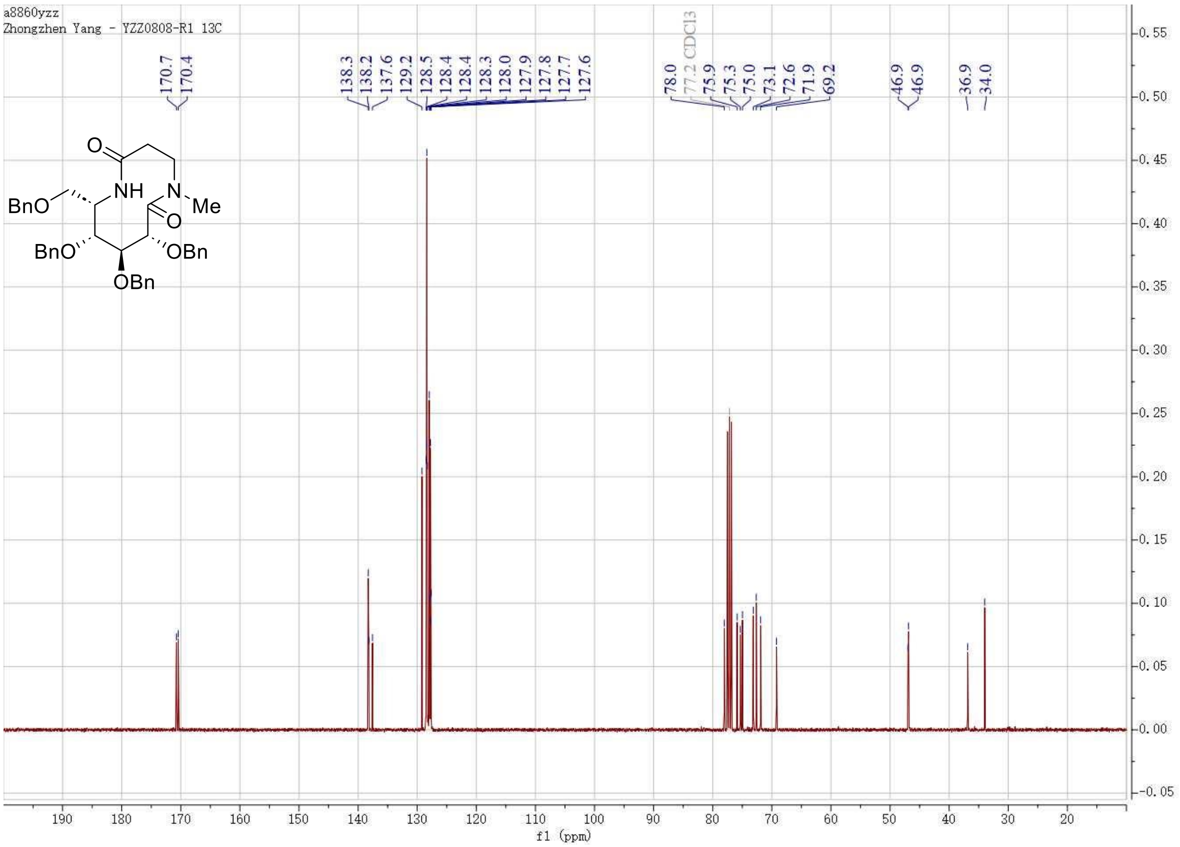
(7*R*,8*S*,9*R*,10*R*)-7,8,9-trihydroxy-10-(hydroxymethyl)-5-methyl-1,5-diazecane-2,6-dione (58)



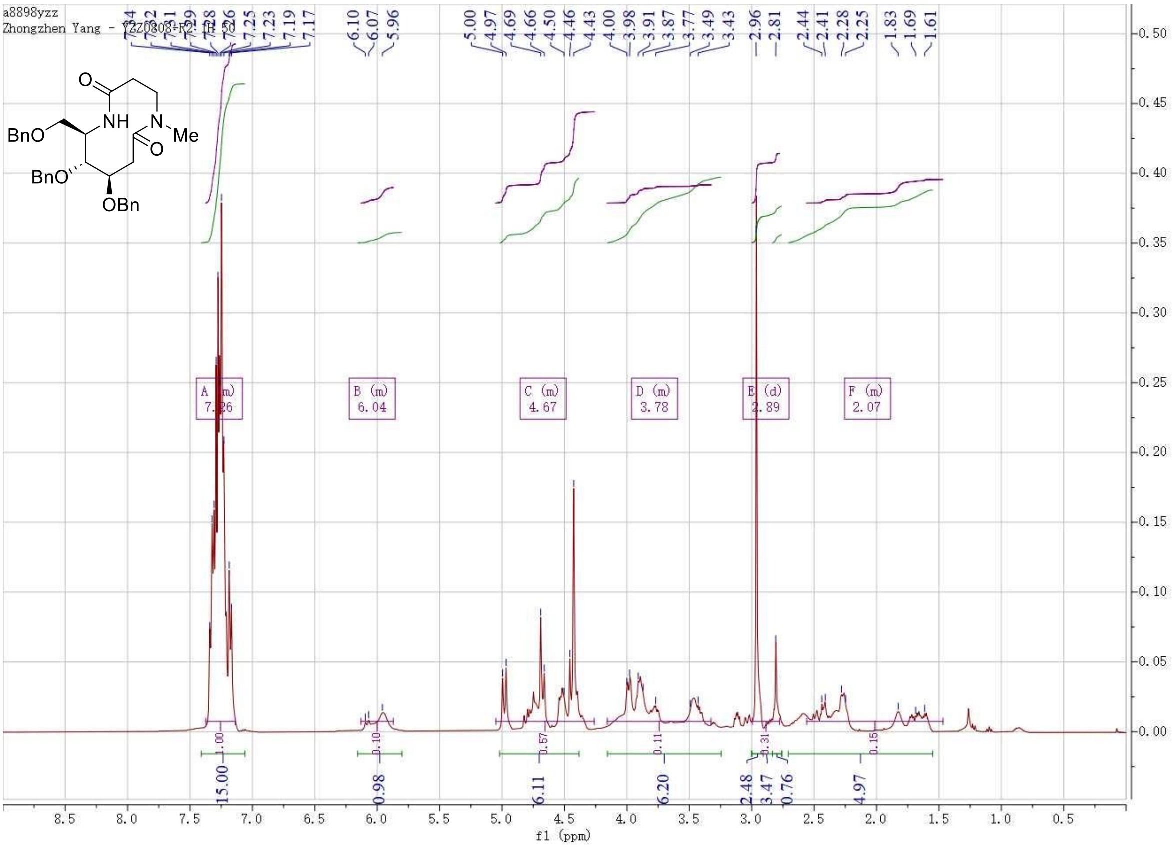


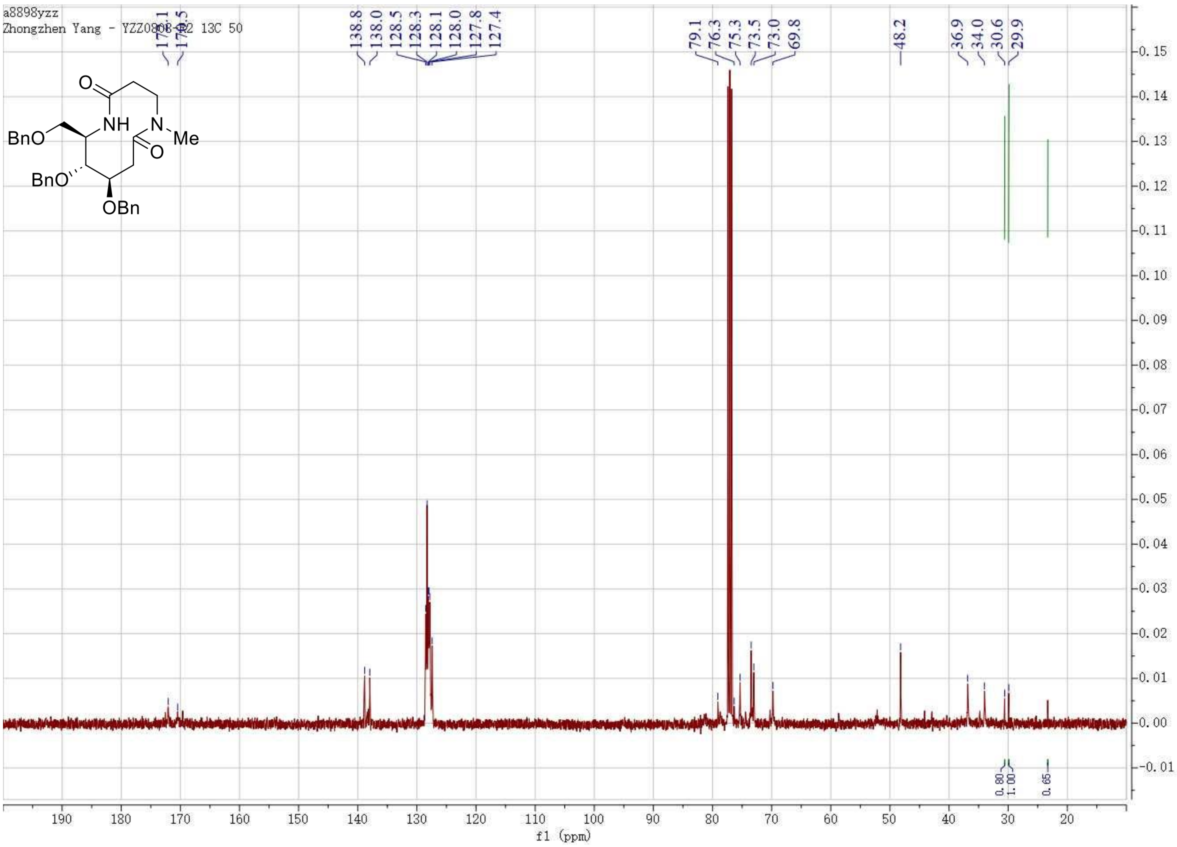
(7*R*,8*S*,9*R*,10*S*)-7,8,9-Tris(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione (59)



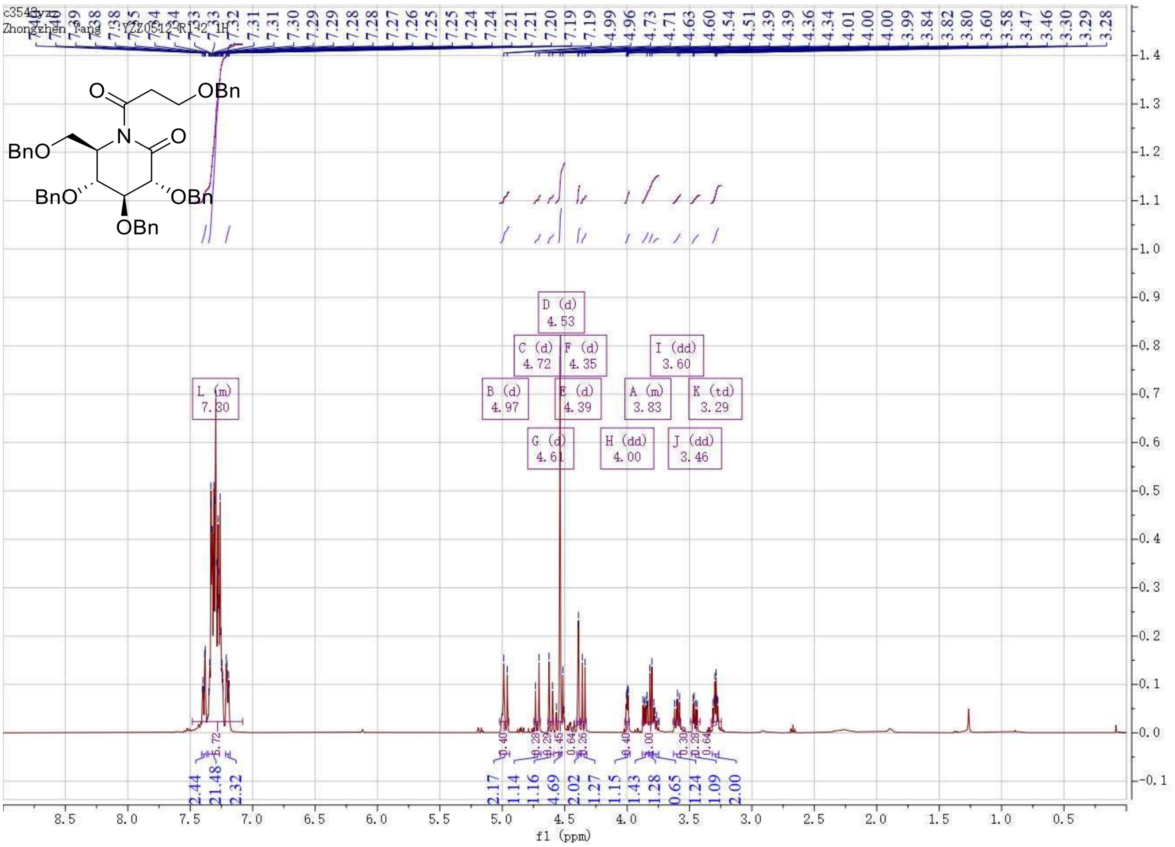


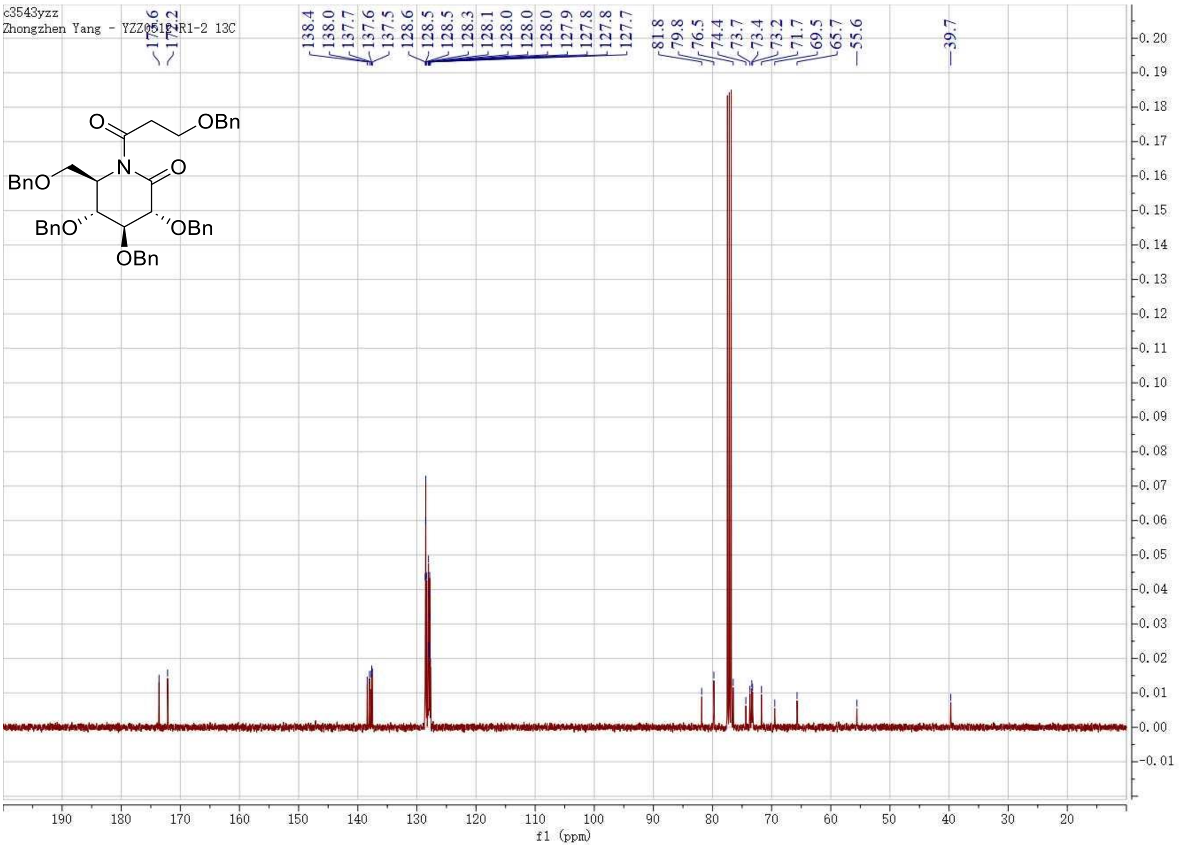
(8*S*,9*R*,10*R*)-8,9-Bis(benzyloxy)-10-[(benzyloxy)methyl]-5-methyl-1,5-diazecane-2,6-dione (60) (exist as a 3:1 mixture of rotamers in $CDCl_3$ at 50 °C; both NMR spectra are severely affected by rotameric broadening).



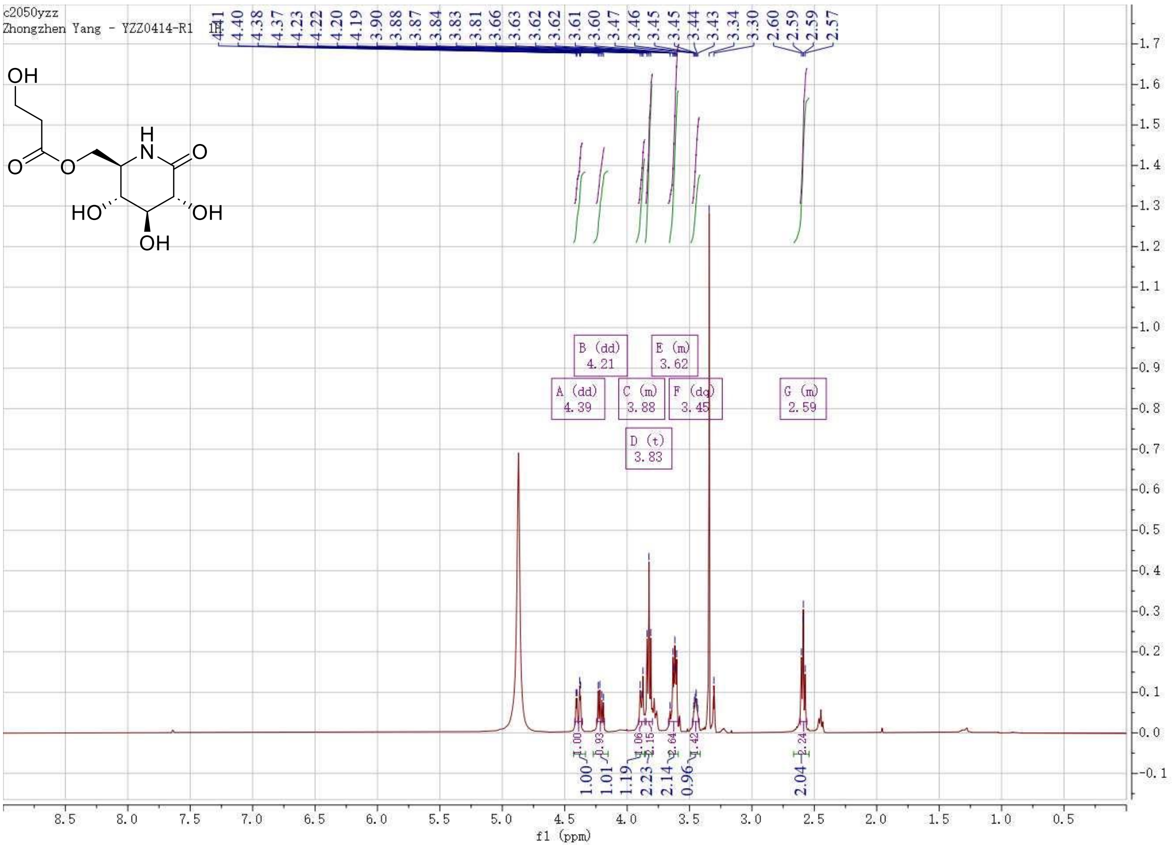


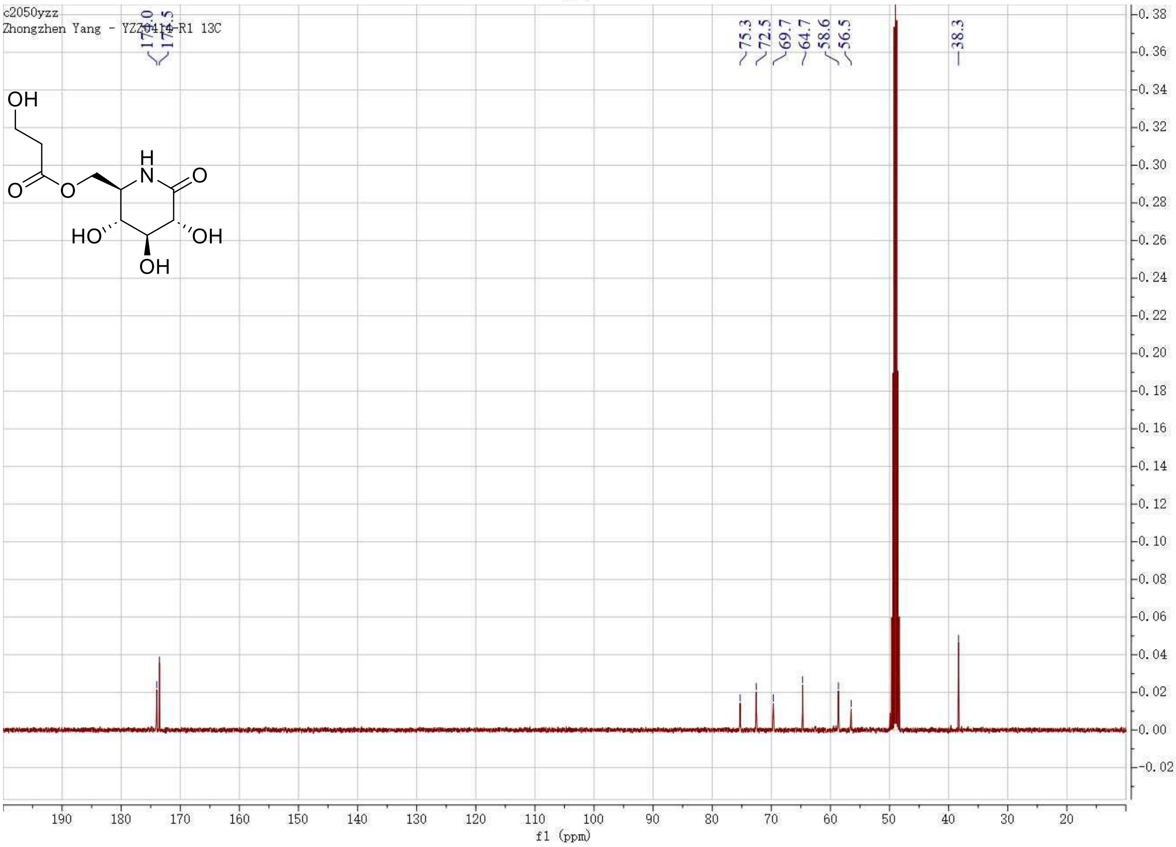
3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]-1-[3(benzyloxy) propanoyl] piperidin-2-one (62)





3,4,5-Trihydroxy-6-(hydroxymethyl)-1-(3-hydroxypropanoyl)piperidin-2-one (65)





5) Bioassay Information

E. coli MIC Assay Protocol

Stock solution preparation:

20 μL stock solutions of each macrocycle were prepared in 50% (v/v) DMSO/ sterile H_2O at 5 μM, 10 μM, 50 μM, 100 μM, 200 μM, 300 μM, 400 μM, 500 μM and 1 mM. Stocks were stored at –20 °C.

***E. coli* K12 BW25113 pre-culture set up:**

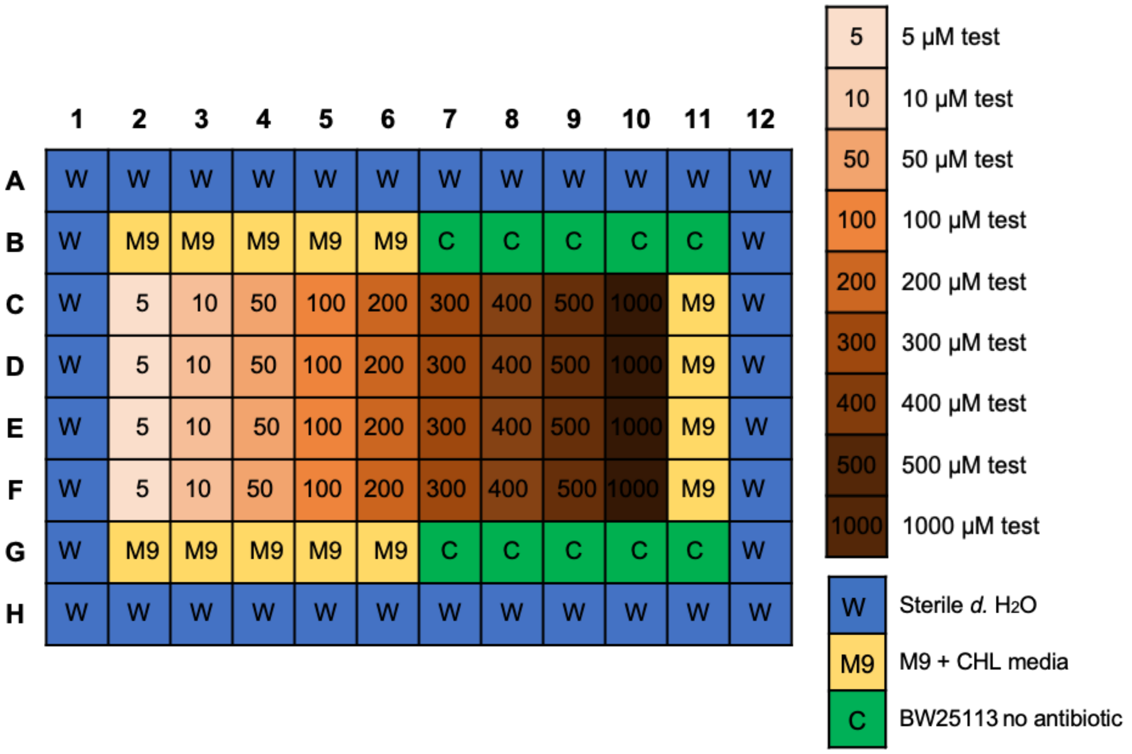
A single colony of freshly streaked BW25113 cells were inoculated into 5 mL of supplemented M9 minimal media at pH 7.2. The pre-culture was incubated at 37 °C at 180 rpm agitation, overnight.

***E. coli* BW25113 culture set up:**

25 mL of supplemented M9 minimal media (pH 7.2) was inoculated to an OD_{600nm} of 0.025 with pre-culture.

Plate design:

Plate details: Thermo Scientific Nunc 2.0 96-Well Plate. Flat bottomed, CAT. # 267427, LOT 175233.



	1	2	3	4	5	6	7	8	9	10	11	12
A	W	W	W	W	W	W	W	W	W	W	W	W
B	W	M9	M9	M9	M9	M9	C	C	C	C	C	W
C	W	5	10	50	100	200	300	400	500	1000	M9	W
D	W	5	10	50	100	200	300	400	500	1000	M9	W
E	W	5	10	50	100	200	300	400	500	1000	M9	W
F	W	5	10	50	100	200	300	400	500	1000	M9	W
G	W	M9	M9	M9	M9	M9	C	C	C	C	C	W
H	W	W	W	W	W	W	W	W	W	W	W	W

5	5 μM test
10	10 μM test
50	50 μM test
100	100 μM test
200	200 μM test
300	300 μM test
400	400 μM test
500	500 μM test
1000	1000 μM test
W	Sterile *d.* H_2O
M9	M9 + CHL media
C	BW25113 no antibiotic

Figure S1: Plate design. Each sample ran in quadruplicate against control wells.

Table S5: Well coding description

Code	**Contents**
5-1000	2 μL of respective medium-ring or macrocycle stock, 198 μL BW25113 culture*
M9	4 μL chlorofenacol*, 196 μL M9 supplemented media
C	200 μL BW25113 culture*
W	200 μL sterile H_2O

*: Inoculated to OD_{600nm} of 0.025

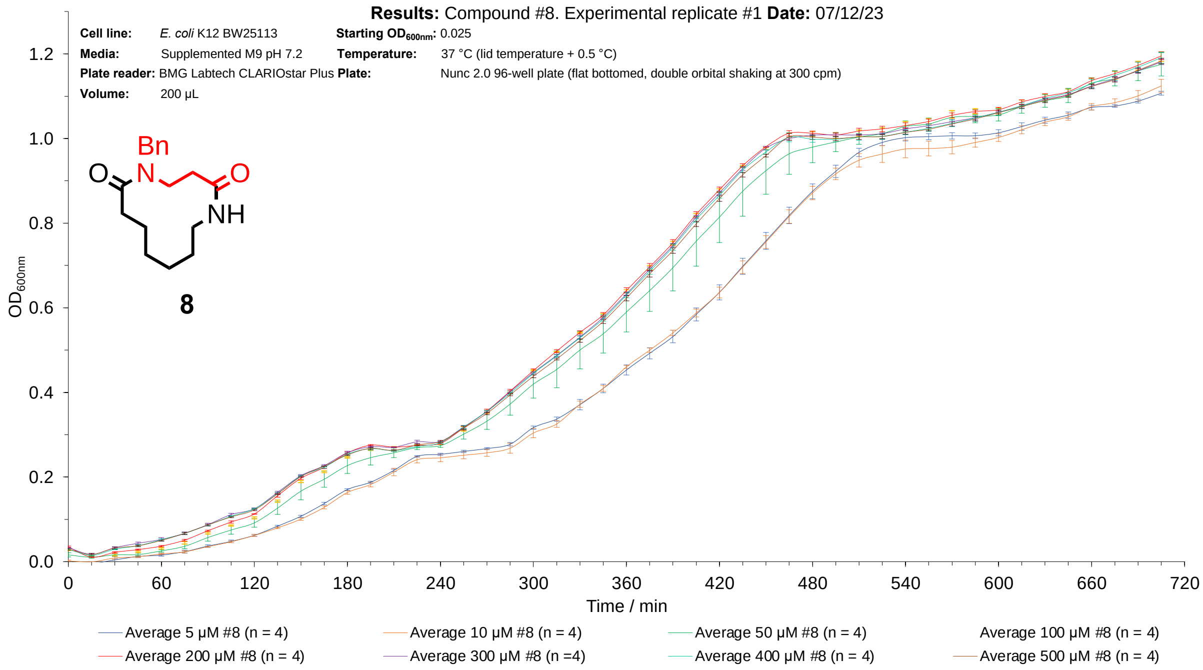
*: Normal chlorofenacol working concentration for selection = 35 μg/mL

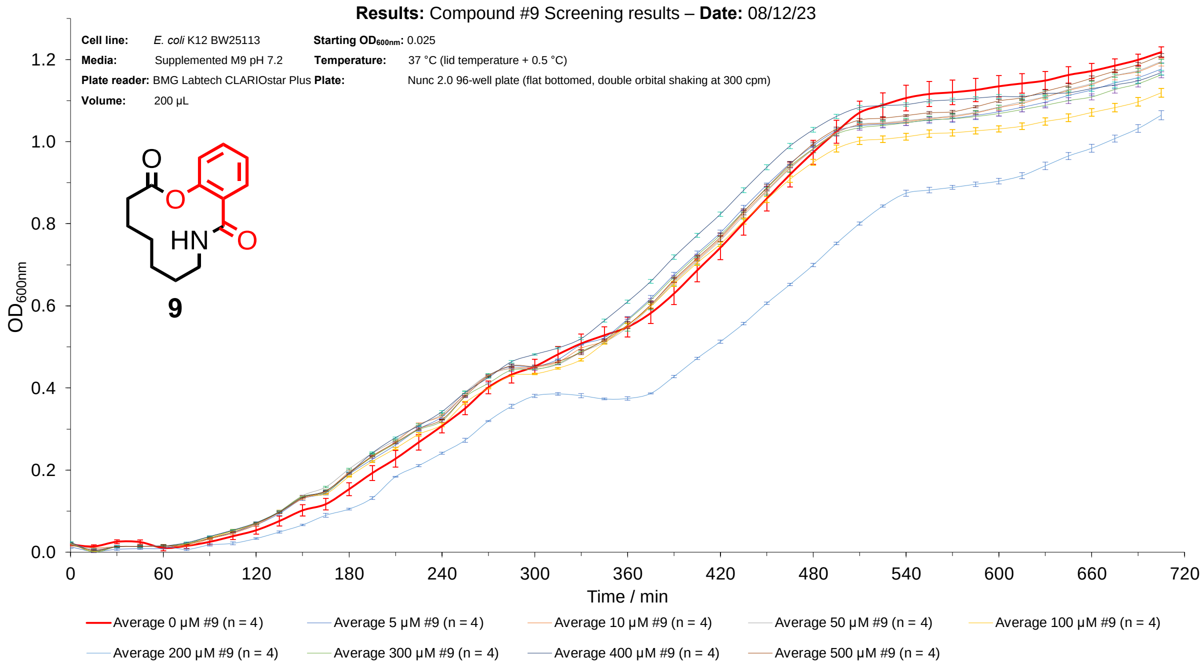
Plate reader assay:

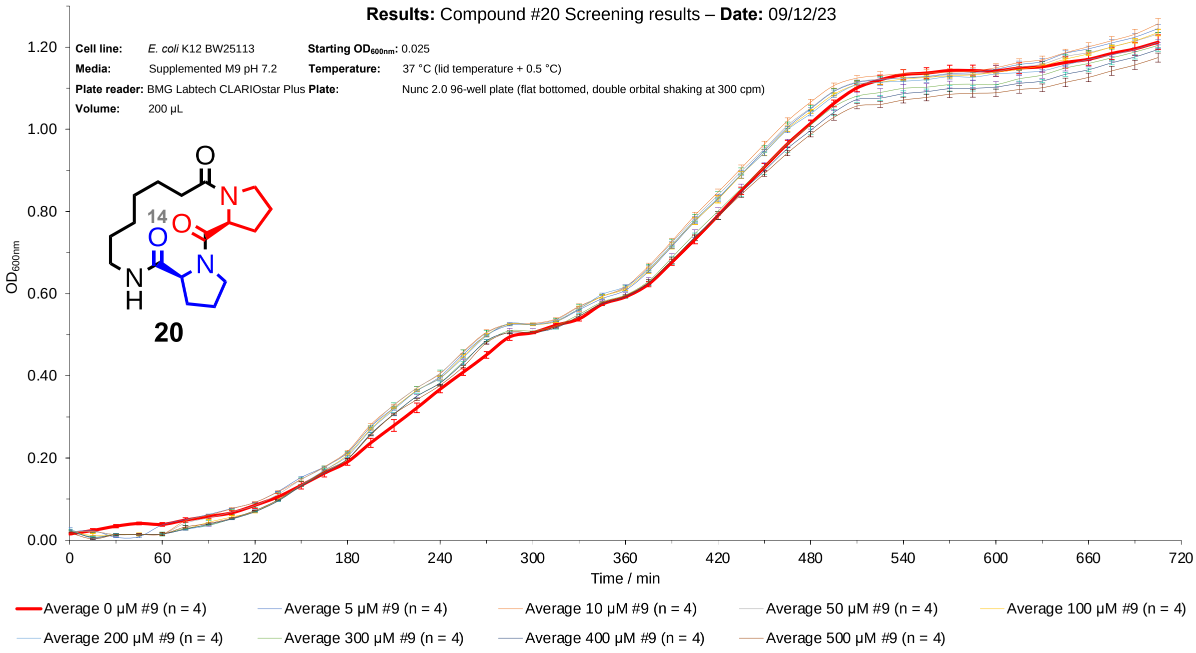
Incubator in plate reader pre-heated to 37 °C before insertion of 96-well plate. OD_{600nm} measurements taken every 15 mins for 12 h, at 37 °C. Measurements taken in a spiral pattern with 300 cpm double orbital plate shaking.

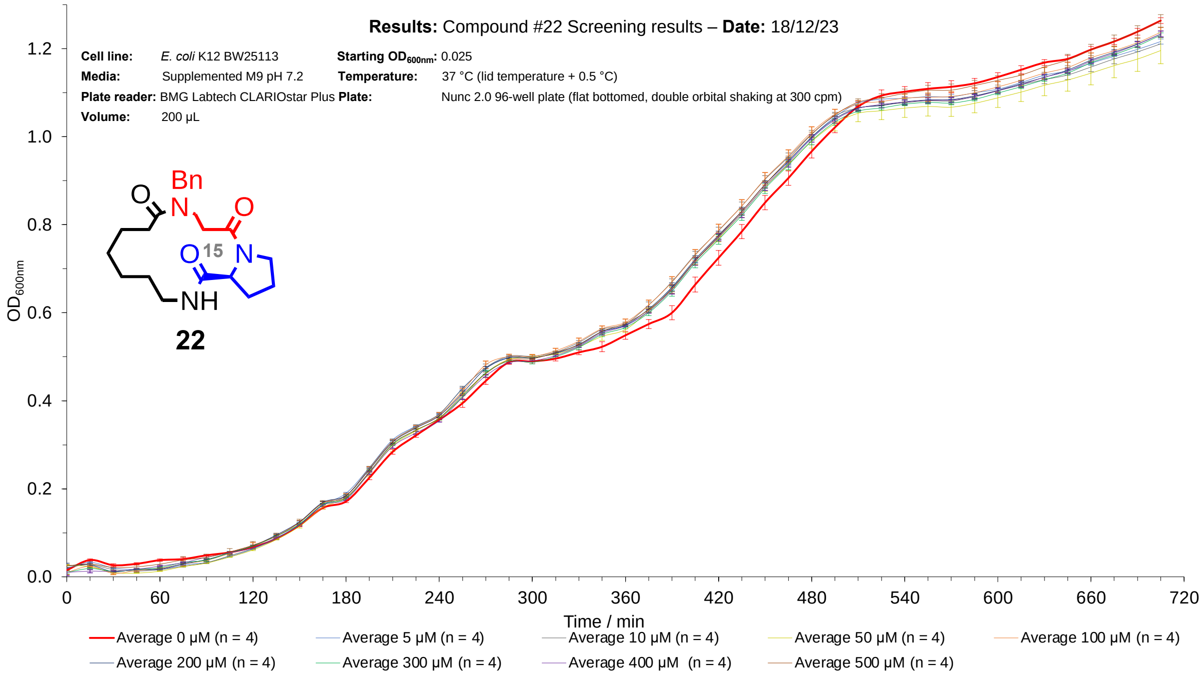
***E. coli* MIC Assay Results**

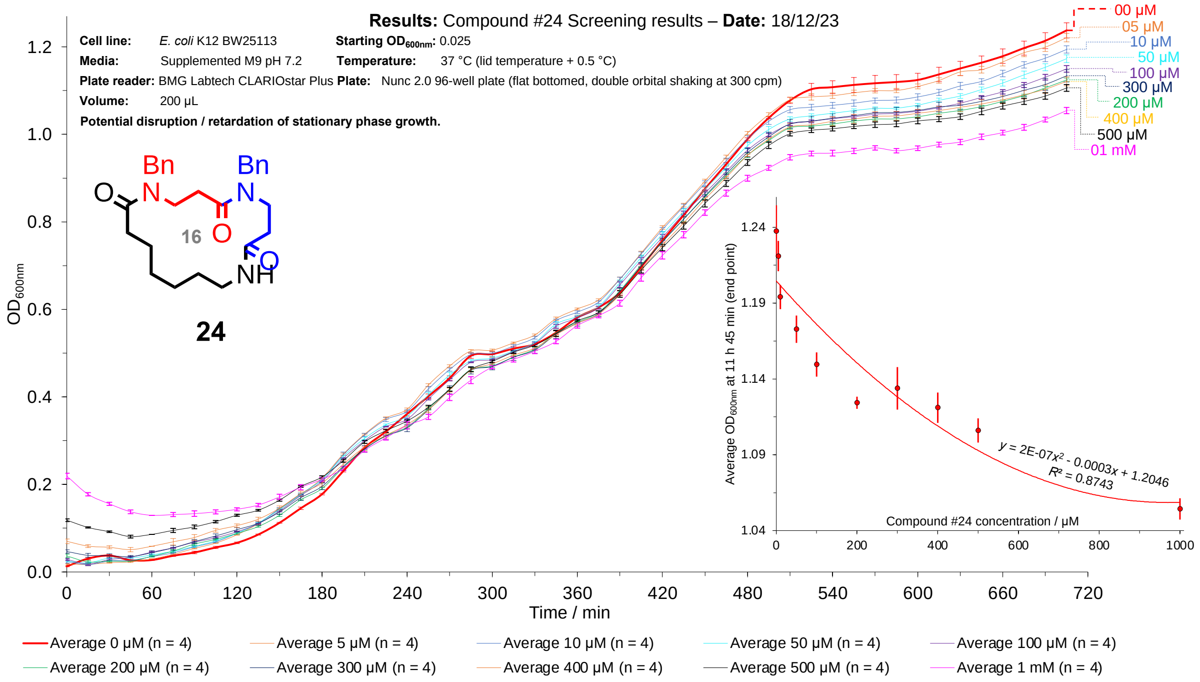
***E. coli* MIC Curves**

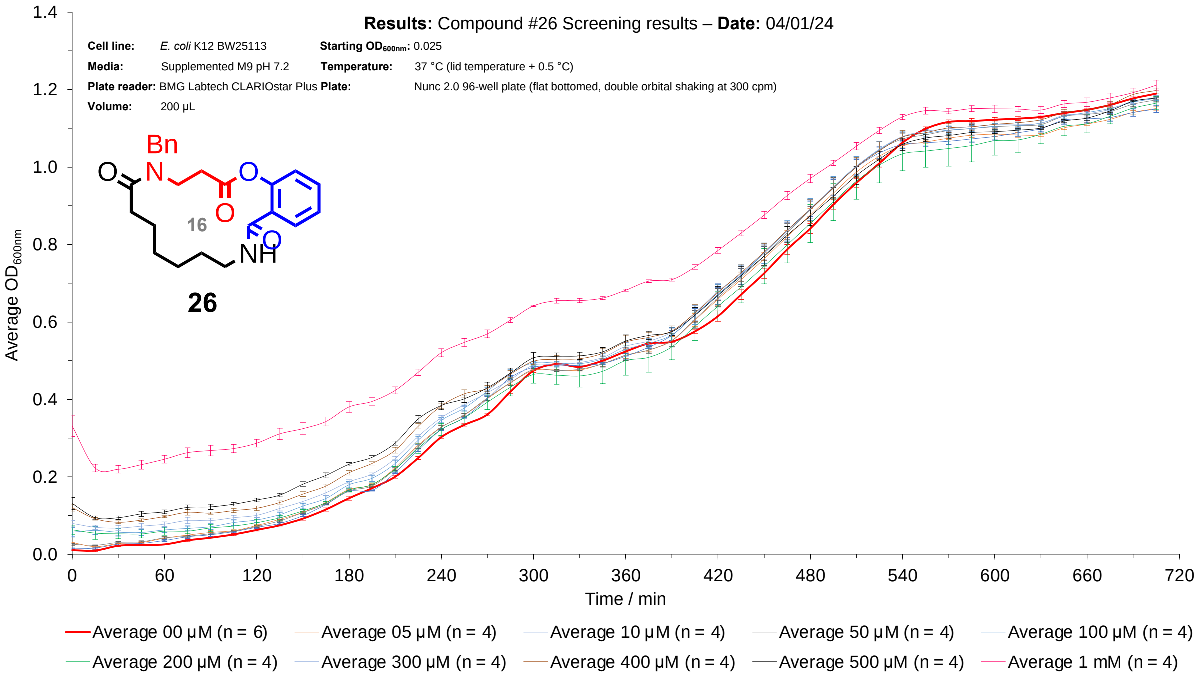


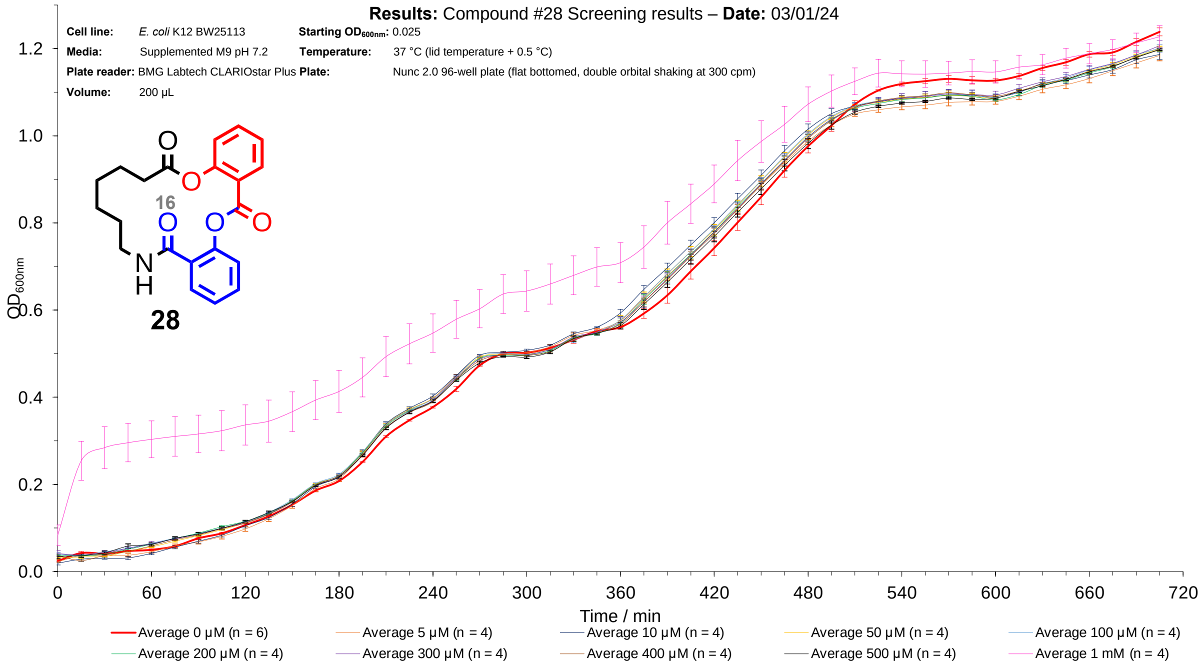


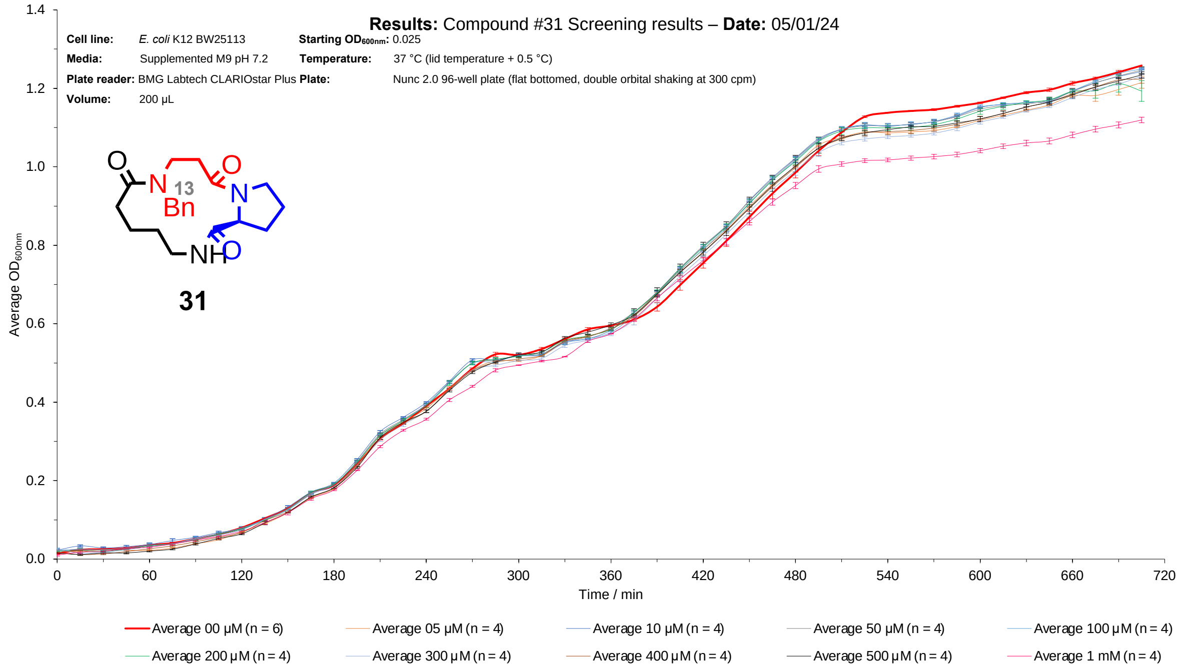

Results: Compound #20 Screening results – **Date:** 09/12/23
Cell line: E. coli K12 BW25113
Starting OD$_{600nm}$: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL
OD$_{600nm}$
1.20
1.00
0.80
0.60
0.40
0.20
0.00
0
60
120
180
240
300
360
420
480
540
600
660
720
Time / min
O
N
14
O
O
N
N
H
20
Average 0 µM #9 (n = 4)
Average 5 µM #9 (n = 4)
Average 10 µM #9 (n = 4)
Average 50 µM #9 (n = 4)
Average 100 µM #9 (n = 4)
Average 200 µM #9 (n = 4)
Average 300 µM #9 (n = 4)
Average 400 µM #9 (n = 4)
Average 500 µM #9 (n = 4)

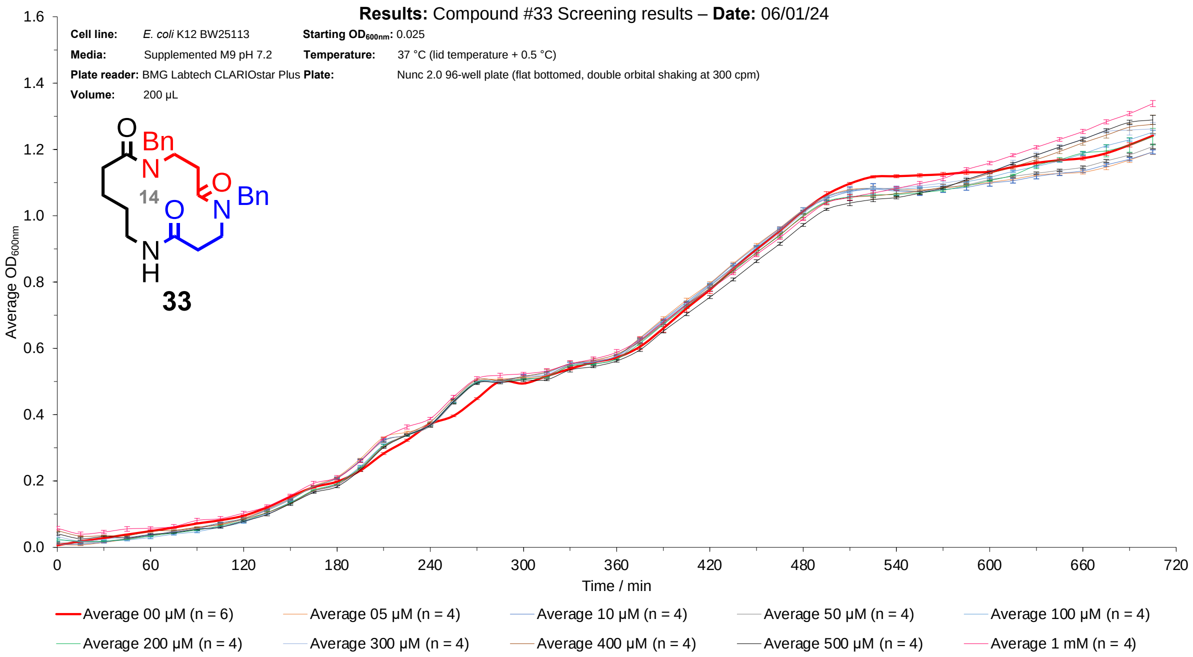

Results: Compound #22 Screening results – **Date:** 18/12/23
Cell line: E. coli K12 BW25113
Starting OD$_{600nm}$: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL
OD$_{600nm}$
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
240
300
360
420
480
540
600
660
720
Time / min
Bn
O
N
O
O
15
N
NH
22
Average 0 µM (n = 4)
Average 5 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)

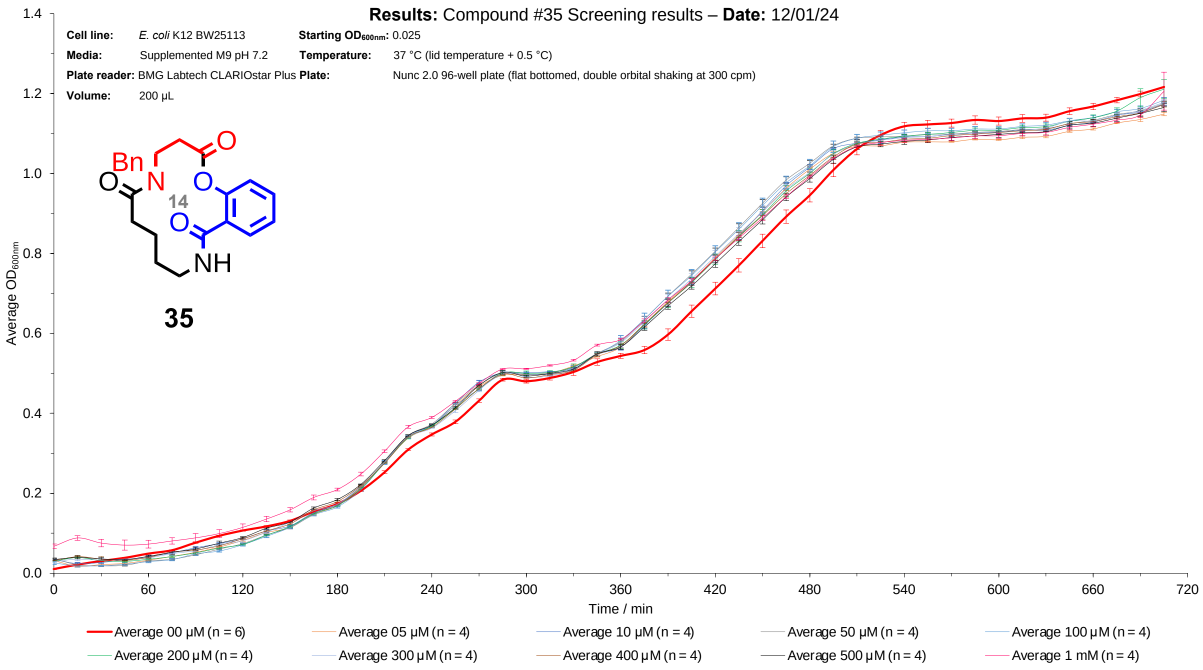

Results: Compound #24 Screening results – Date: 18/12/23
Cell line: E. coli K12 BW25113
Starting OD600nm: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL
Potential disruption / retardation of stationary phase growth.
Bn
Bn
O
N
N
O
16
O
NH
24
OD600nm
0.0
0.2
0.4
0.6
0.8
1.0
1.2
0
60
120
180
240
300
360
420
480
540
600
660
720
Time / min
00 µM
05 µM
10 µM
50 µM
100 µM
300 µM
200 µM
400 µM
500 µM
01 mM
Average OD600nm at 11 h 45 min (end point)
1.04
1.09
1.14
1.19
1.24
0
200
400
600
800
1000
Compound #24 concentration / µM
y = 2E-07x² - 0.0003x + 1.2046
R² = 0.8743
Average 0 µM (n = 4)
Average 5 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)
Average 1 mM (n = 4)

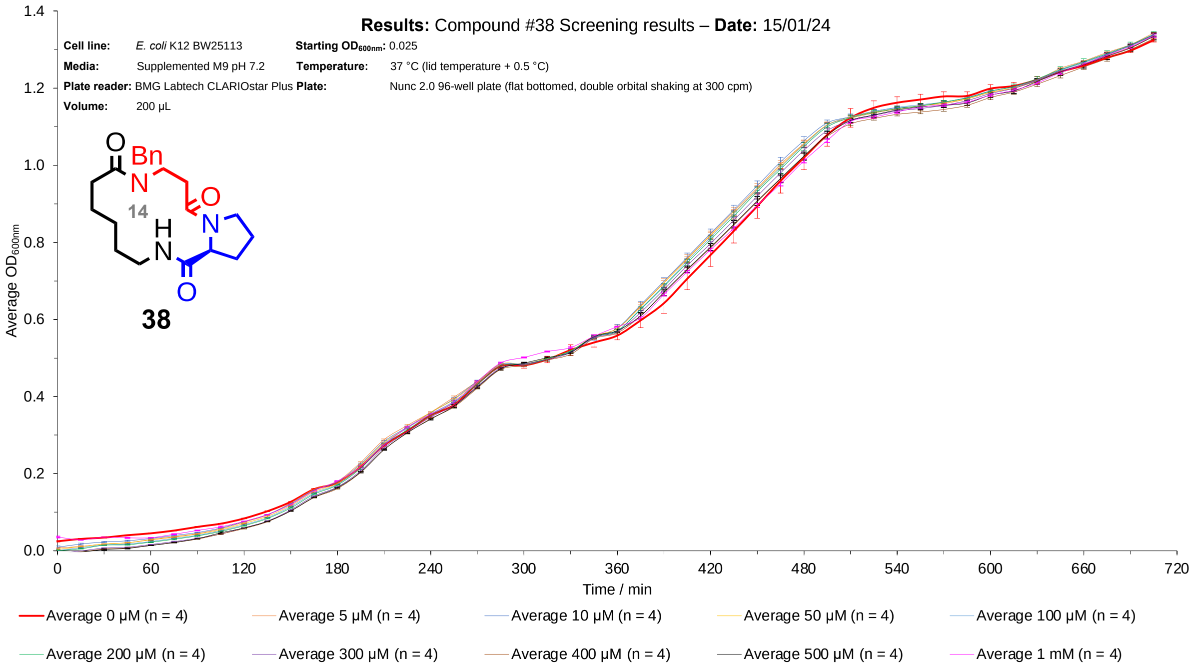

Results: Compound #26 Screening results – Date: 04/01/24
Cell line: E. coli K12 BW25113
Starting OD600nm: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL
Bn
O
N
O
16
O
O
NH
26
Average OD600nm
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0
60
120
180
240
300
360
420
480
540
600
660
720
Time / min
Average 00 µM (n = 6)
Average 05 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)
Average 1 mM (n = 4)


Results: Compound #28 Screening results – Date: 03/01/24
Cell line: E. coli K12 BW25113
Media: Supplemented M9 pH 7.2
Plate reader: BMG Labtech CLARIOstar Plus
Volume: 200 µL
Starting OD600nm: 0.025
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
O
O
16
O
O
O
N
H
28
OD600nm
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
240
300
360
420
480
540
600
660
720
Time / min
Average 0 µM (n = 6)
Average 5 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)
Average 1 mM (n = 4)


Results: Compound #31 Screening results – Date: 05/01/24
Cell line: E. coli K12 BW25113
Media: Supplemented M9 pH 7.2
Plate reader: BMG Labtech CLARIOstar Plus
Volume: 200 µL
Starting OD600nm: 0.025
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
O
N
13
Bn
O
N
NH
O
31
Average OD600nm
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
240
300
360
420
480
540
600
660
720
Time / min
Average 00 µM (n = 6)
Average 05 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)
Average 1 mM (n = 4)

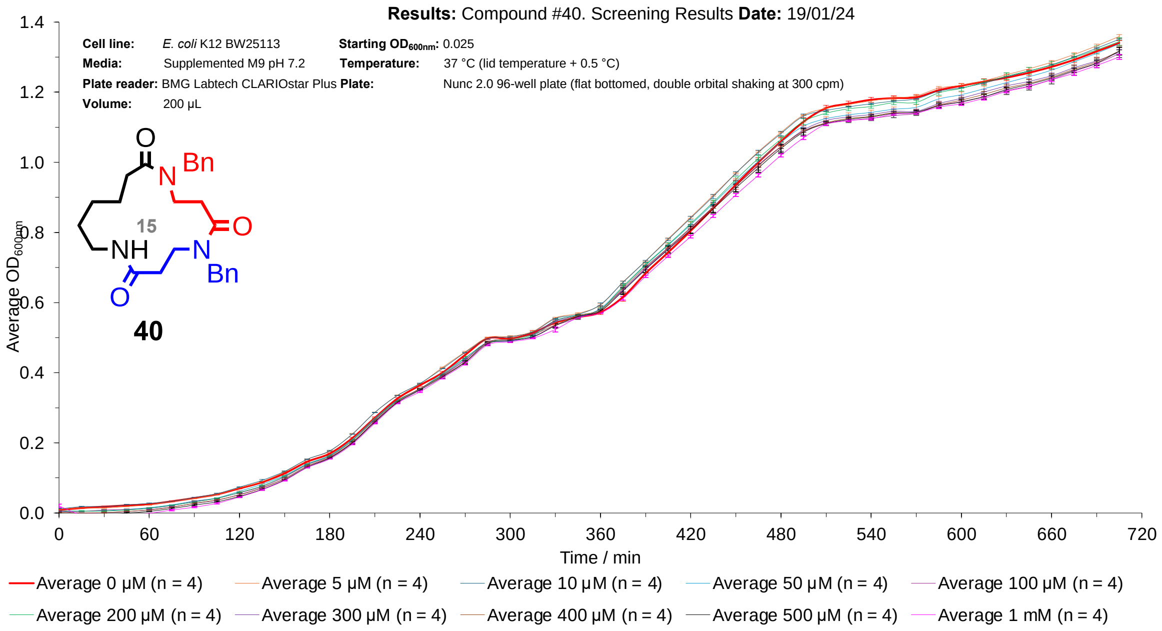

Results: Compound #33 Screening results – Date: 06/01/24
Cell line: E. coli K12 BW25113
Starting OD600nm: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL
O
Bn
N
O
N
Bn
14
O
N
H
33
Average OD600nm
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
240
300
360
420
480
540
600
660
720
Time / min
Average 00 µM (n = 6)
Average 05 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)
Average 1 mM (n = 4)


Results: Compound #35 Screening results – Date: 12/01/24
Cell line: E. coli K12 BW25113
Starting OD600nm: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL
Bn
O
O
N
O
14
O
NH
35
Average OD600nm
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
240
300
360
420
480
540
600
660
720
Time / min
Average 00 µM (n = 6)
Average 05 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)
Average 1 mM (n = 4)



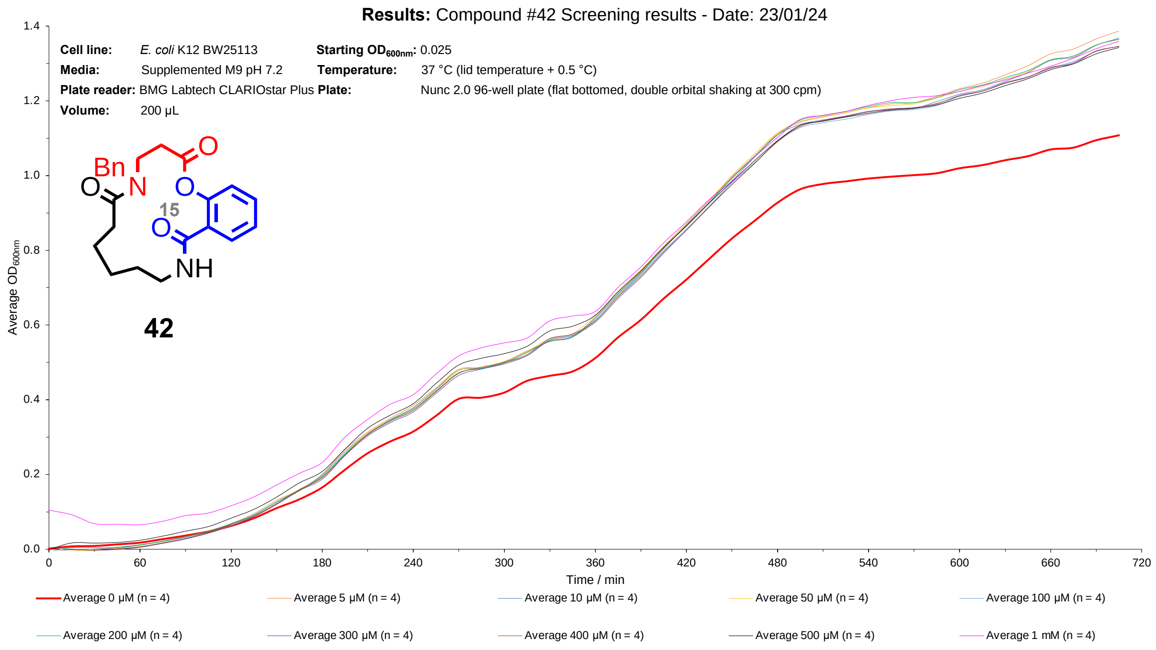
Results: Compound #38 Screening results – **Date:** 15/01/24

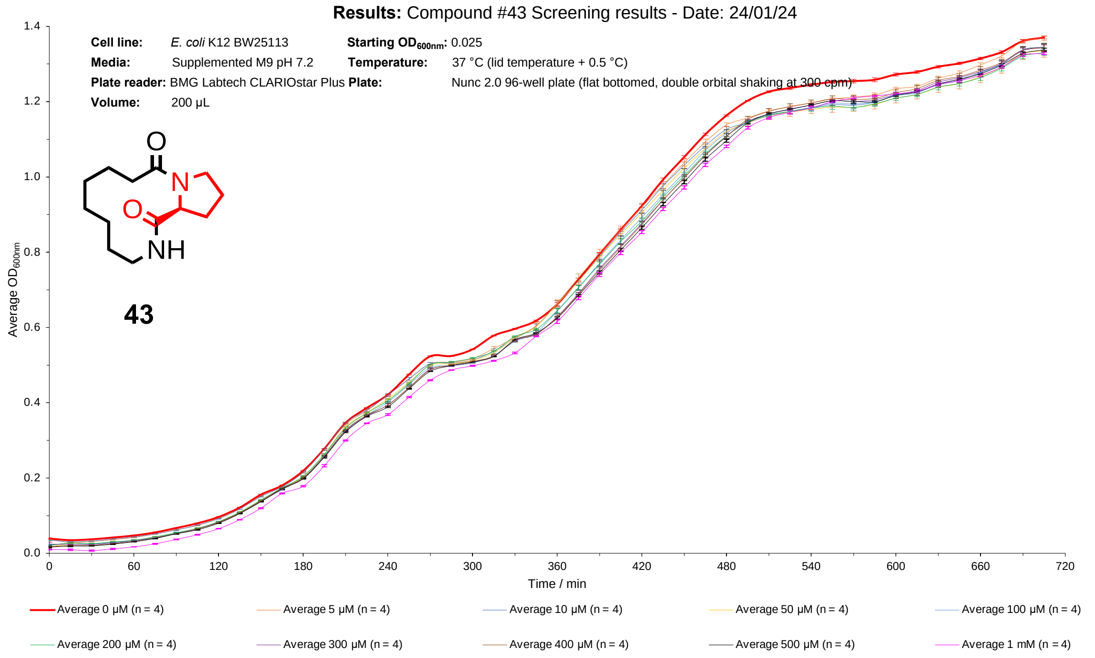
Cell line: *E. coli* K12 BW25113
Starting OD$_{600nm}$: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL

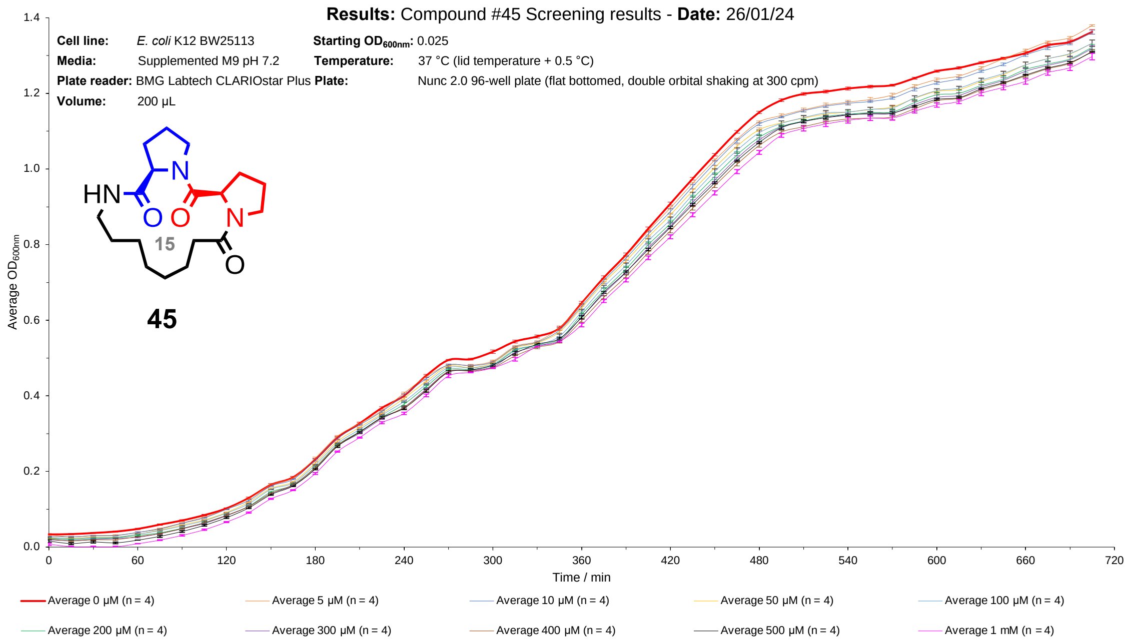


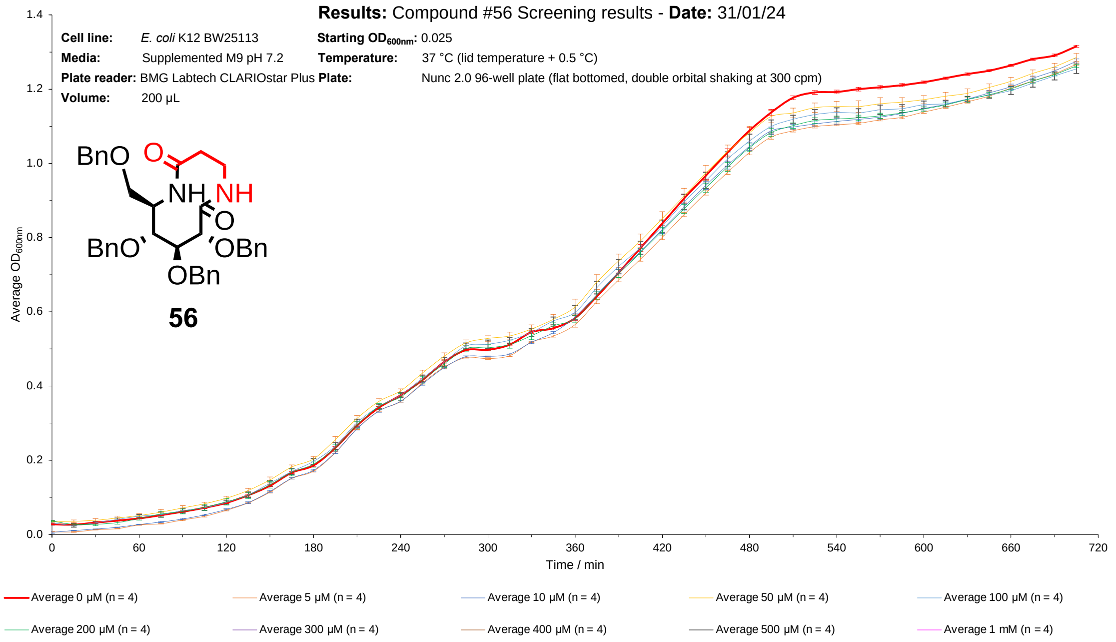
Results: Compound #40. Screening Results **Date:** 19/01/24

Cell line: *E. coli* K12 BW25113
Starting OD$_{600nm}$: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL

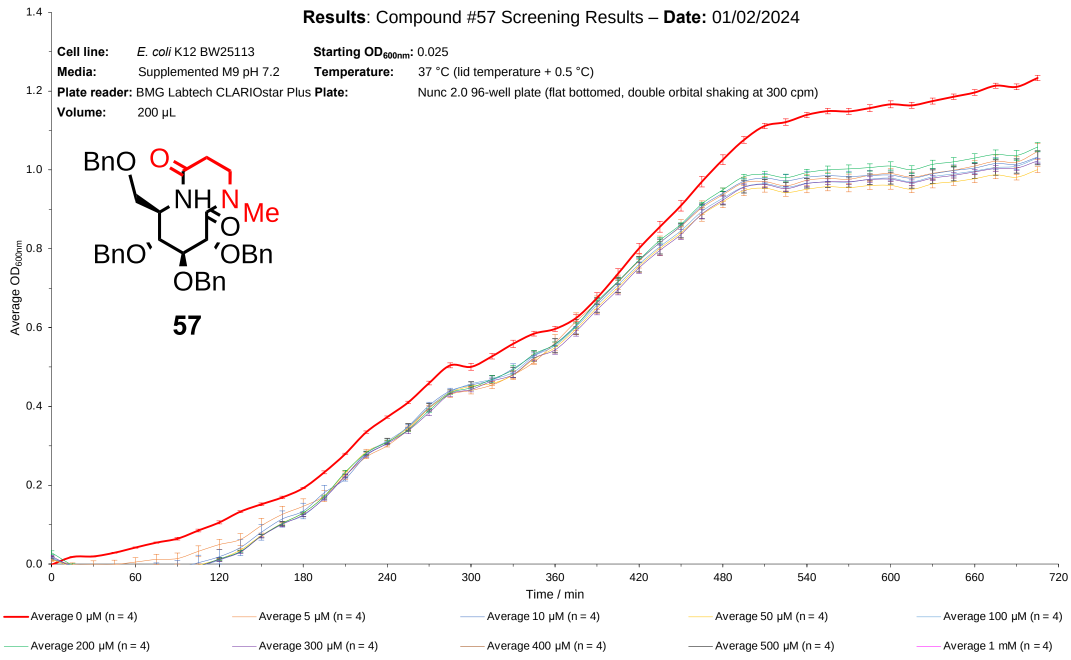

Results: Compound #42 Screening results - Date: 23/01/24
Cell line: E. coli K12 BW25113
Starting OD600nm: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL
Bn
N
O
O
O
15
O
NH
42
Average OD600nm
Time / min
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0
60
120
180
240
300
360
420
480
540
600
660
720
Average 0 µM (n = 4)
Average 5 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)
Average 1 mM (n = 4)


Results: Compound #43 Screening results - Date: 24/01/24
Cell line: E. coli K12 BW25113
Starting OD600nm: 0.025
Media: Supplemented M9 pH 7.2
Temperature: 37 °C (lid temperature + 0.5 °C)
Plate reader: BMG Labtech CLARIOstar Plus
Plate: Nunc 2.0 96-well plate (flat bottomed, double orbital shaking at 300 cpm)
Volume: 200 µL
O
N
O
NH
43
Average OD600nm
Time / min
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
0
60
120
180
240
300
360
420
480
540
600
660
720
Average 0 µM (n = 4)
Average 5 µM (n = 4)
Average 10 µM (n = 4)
Average 50 µM (n = 4)
Average 100 µM (n = 4)
Average 200 µM (n = 4)
Average 300 µM (n = 4)
Average 400 µM (n = 4)
Average 500 µM (n = 4)
Average 1 mM (n = 4)





Compound **56** was insoluble in the assay conditions at concentrations >200 µM.



Compound **57** was insoluble in assay conditions at concentrations >300 µM.

6) References

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