Stereoselective Synthesis of Fissoldhimine Alkaloid Analogues via Sequential Electrooxidation and Heterodimerization of N-Urea-Protected Cyclic-Amines

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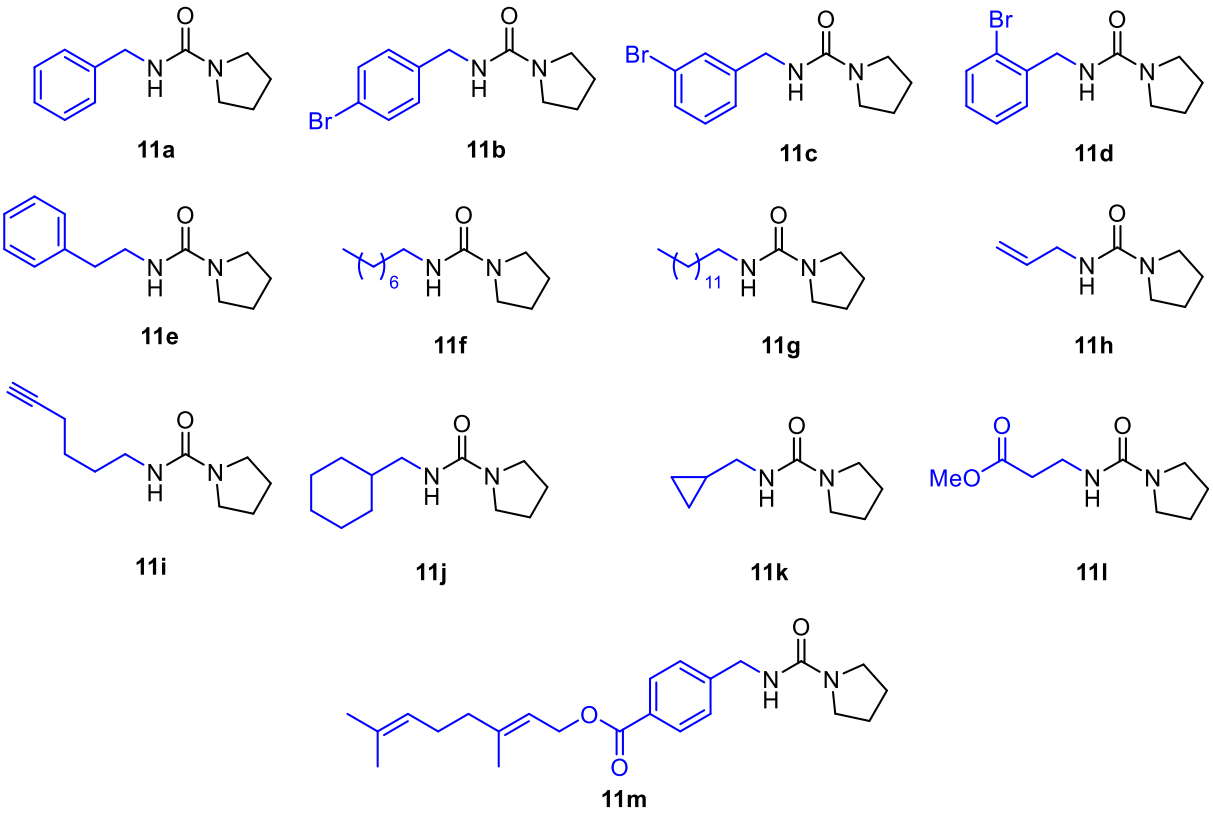
General information

Reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Analytical thin layer chromatography (TLC) was purchased from Merck KGaA (silica gel 60 F254). Visualization was accomplished by irradiation with a UV light at 254 nm. Flash column chromatography was performed on Silica gel 60Å (40-63µ mesh) using a CombiFlash Rf 200. Residual solvent was removed using a static oil pump (< 10 mbar). ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker 500 MHz and 300 MHz instruments. ^{1}H and ^{13}C chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance as the internal standard. The following calibration values have been used for ^{1}H NMR: $CDCl_3$ (7.26 ppm), CD_3CN (1.94 ppm), Acetone-d_6 (2.05 ppm), CD_3OD (3.31 ppm); for ^{13}C NMR: $CDCl_3$ (77.2 ppm), CD_3CN (1.3 and 118.3 ppm), Acetone-d_6 (29.8 and 206.3 ppm), CD_3OD (49.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, *br.* s = broad singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, h = hexuplet, ht = heptuplet, m = multiplet), coupling constants (Hz) and integration. ^{1}H-^{1}H NOESY experiments were recorded using degassed NMR solvents. Infrared spectra were recorded on neat samples, on a Perkin Elmer Spectrum BX FT-IR spectrometer and the characteristic IR absorption frequencies are reported in cm^{-1}. Melting points were recorded using a Büchi melting point apparatus and temperatures are uncorrected. UPLC-MS analysis was run using an Acquity Waters UPLC equipped with a Waters LCT Premier XE (ESI ionization) and a Waters Acquity PDA detector, using a column BEH C18 1.7 µm, 2.1 mm × 50 mm. Gradients were run using water and acetonitrile (1:1) with 0.1% of acetic acid. Temperature: 40°C. UV detection from 210 to 410 nm. ESI+ detection in the 80−1500 m/z range. Chiral HPLC analysis was performed on Hitachi LaChrom-Elite apparatus equipped with diode array UV detector (UV detection monitored at 254 nm), using Daicel Chiralcel OD-H, AD-H, AS-H, IA, IB and IC columns. The enantiomeric excesses were determined by HPLC analysis employing a chiral stationary phase column specified in the individual experiment, by comparing the samples with the appropriate racemic mixture. Optical rotations were performed on an Anton Paar MCP 300 Modular Circular (589 nm) using a 700 µL cell with a path length of 1 dm.

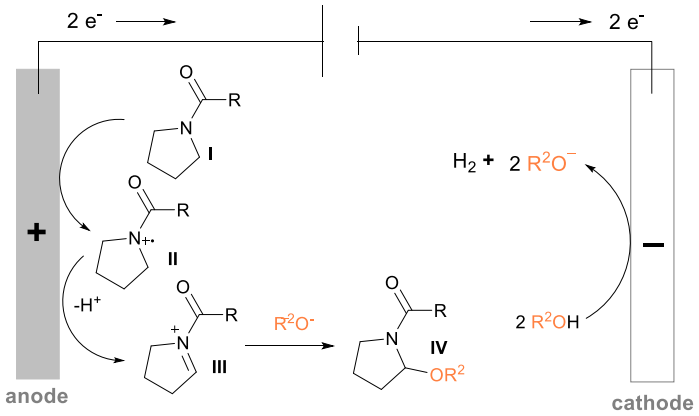
Electrolyses were performed using an IKA Electrasyn 2.0 using carbon-graphite working and counter electrodes in the absence of a reference electrode at constant current (galvanostatic mode).

Urea derivatives used in this study

Urea derivatives were prepared according to procedure **A** except for compound **11d**. Compounds **11a**, **11e**, **11h**, **11l, 11n**, and **11o** were already described in the literature.



Shono electro-oxidation mechanism



Optimization studies

Optimization study for the synthesis of 9c

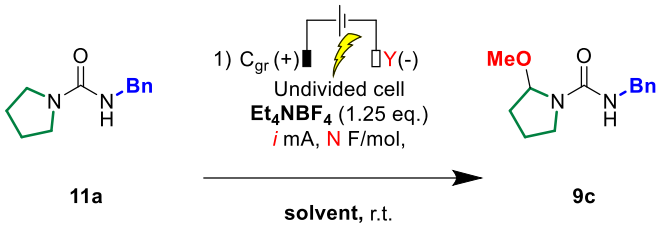
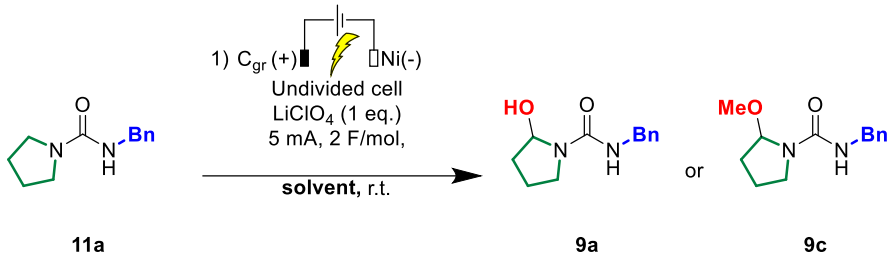


Table 1 : Cathode, intensity and electrons equivalents screening

Entry	Cathode	Intensity (mA.cm^{-1})	N F.mol^{-1}	Yield[c]
1[a]	Ni	10	2.5	63
2[a]	C	10	2.5	63
3[a]	Steel	10	2.5	64
4[a]	Ni foam	10	2.5	63
5[b]	Ni	10	2.5	77
6[b]	Ni	10	8	35
7[b]	Ni	10	2	73
8[b]	Ni	15	2	48
9[b]	**Ni**	**5**	**2**	**90**

[a] Conditions : **11a** (0.2 mmol), Et_4NBF_4 (1.25 eq), MeOH (0.05 M), r.t. ; [b]Conditions : **11a** (0.2 mmol), $LiClO_4$ (1.0 eq), MeOH (0.05 M), r.t. ; [c]^{1}H NMR yield using 1,1,2,2-tetrachloroethane as internal standard.

Table 2 : Solvent screening

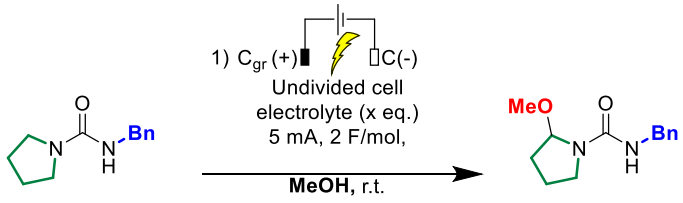


11a 9a 9c

Entry[a]	Solvent	Yield[b]
1	**MeOH**	**90% (9c)**
2	MeCN/H_2O (3 :2)	63% (**9a**)
3	MeCN/H_2O (10 :1)	36% (**9a**)
4	MeCN/H_2O (1 :4)	37% (**9a**)
5	DCM/MeOH (9 :1)	20% (**9c**) + complexe mixture

[a]Conditions : **11a** (0.2 mmol), $LiClO_4$ (1.0 eq), 5 mA, 2 F.mol^{-1}, solvent (0.05 M) r.t. ; [b]^{1}H NMR yield using 1,1,2,2-tetrachloroethane as internal standard.

Table 3 : Electrolyte screening



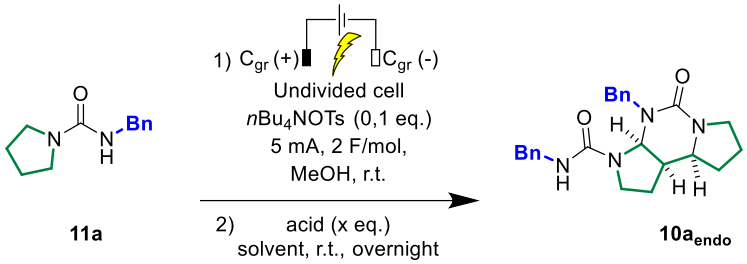
11a 9c

Entry[a]	**Electrolyte (x eq)**	**Yield[b]**
1[c]	$LiClO_4$ (1 eq)	90%
2	$LiClO_4$ (1 eq)	90%
3	Et_4NBF_4 (0.5 eq)	70%
4	Et_4NBF_4 (0.1 eq)	70%
5	*n*Bu_4OTs (1 eq)	91%
6[c]	*n*Bu_4OTs (1 eq)	91%
7	***n*Bu_4OTs (0.1 eq)**	**>99%**
8	No	0%

[a]Conditions : **11a** (0.2 mmol), 5 mA, 2 F.mol^{-1}, MeOH, r.t. ; [b]^{1}H NMR yield using 1,1,2,2-tetrachloroethane as internal standard. [c]Using a Ni counter electrode instead of graphite

Optimization study for the synthesis of endo Dimer $10a_{endo}$ in 2 steps from 11a

Table 4 : Solvent and acid screening



Entry[a]	Solvent	Acid (x eq)	dr(endo/exo)	Conversion[c]
1	MeOH	HCl_{aq} 1eq	/	0%
2	MeOH	HCl_{aq} 1eq	3 :1	100%
3	MeOH	BF_3OEt_2 (1.5 eq.)	/	0%
4	MeOH	TFA (1.5 eq)	2.6 :1	100%
5[b]	MeCN	TFA (1.5 eq)	>98 :2	100% (68%)
6[b]	**MeCN**	**TFAA (1.0 eq.)**	**>98 :2**	**100% (94%)**

[a]Conditions : **11a** (0.2 mmol), *n*BuNOTs (0.1 eq), 5 mA, 2 $F.mol^{-1}$, MeOH (0.05 M), r.t. ; [b]Conditions : **11a** (0.2 mmol), *n*BuNOTs(0.1 eq), 5 mA, 2 $F.mol^{-1}$, MeOH (0.05 M), r.t., followed by evaporation and treatment of the crude with the source of acid in MeCN (0.03 M), r.t., overnight. ; [c]Conversion of hemiaminal ether. Isolated yield of **$10a_{endo}$** in parentheses.

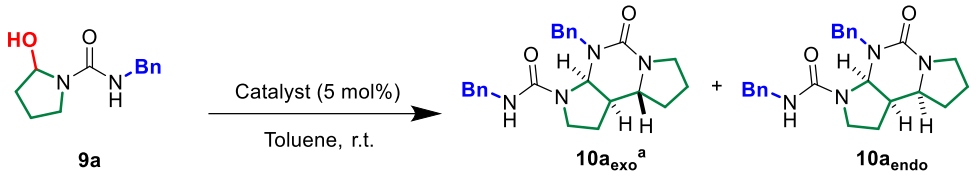
Comment:

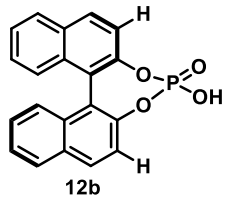
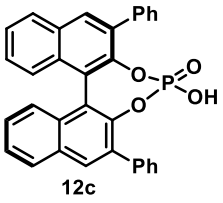
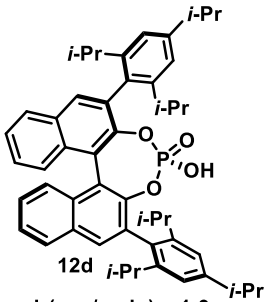
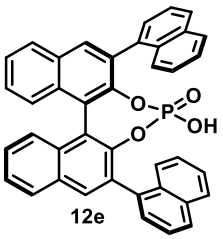
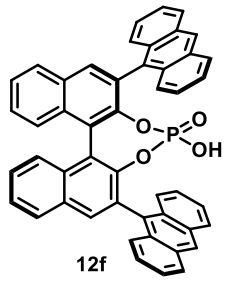
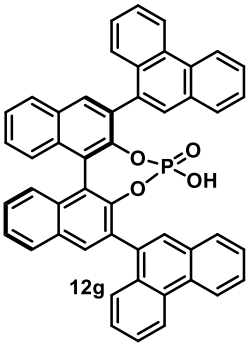
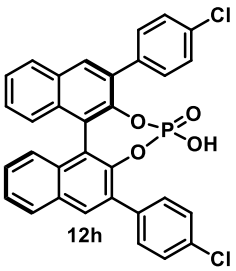
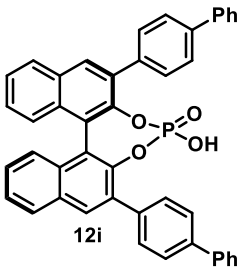
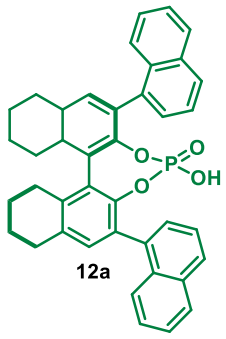
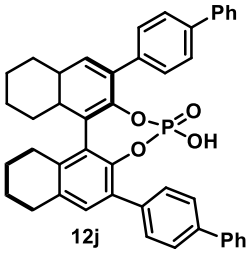
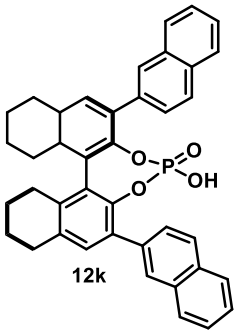
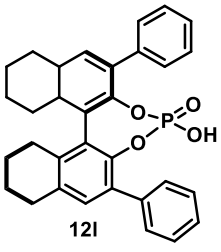
In acetonitrile, both TFA and TFAA were effective, but higher yields were obtained with TFAA. TFAA was chosen based on superior experimental results (entry 6).

Hetero-dimerization involves the transient formation of iminium/eneurea from 2-methoxypyrrolidine-1-carboxamide with concomitant release of methanol; we believe that TFAA is able to quench this methanol through methyl 2,2,2-trifluoroacetate and trifluoroacetic acid formation, thereby driving the reaction.

Optimization study for the synthesis of exo dimer $10a_{exo}$ from 9a

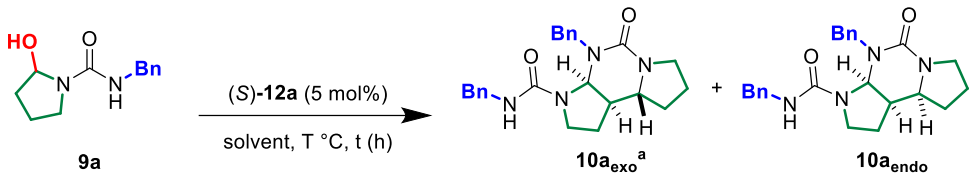
Catalyst screening



 12b	 12c	 12d	 12e
dr(exo/endo) = 1:1.7 -% ee	dr(exo/endo) = 1.3:1 -% ee	dr(exo/endo) = 1:9 -% ee	dr(exo/endo) = 3:1 80% ee
 12f	 12g	 12h	 12i
dr(exo/endo) = 1:3 50% ee	dr(exo/endo) = 1:1 50% ee	dr(exo/endo) = 1.4:1 22% ee	dr(exo/endo) = 1.6:1 22% ee
 12a	 12j	 12k	 12l
dr(exo/endo) = 4.5:1 80% ee (exo)	dr(exo/endo) = 1:1 10% ee	dr(exo/endo) = 3:1 50% ee	dr(exo/endo) = 1:1.3 10% ee

[a]diastereoselectivity determined by crude ^{1}H NMR, before purification**.** Enantiomeric excess refers to **$10a_{exo}$** dimer.

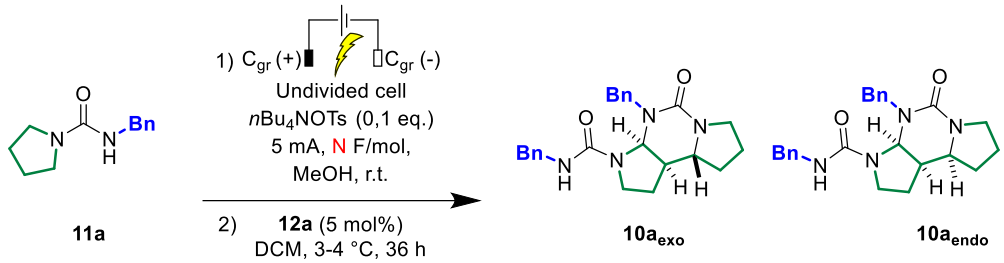
Solvent, temperature and reaction time screening



Entry	Solvent	Temperature (°C)	dr(exo/endo)[a]	%ee[b]	Yield[c]
1	Toluene	r.t. (5 h)	4.5 :1	80	n.d.
2	Toluene	3-4 °C (overnight)	3.4 :1	82	n.d.
3	Toluene	-20 °C (4 days)	-	-	/ (Solubility issue)
4	MeCN	r.t.	1 :1	28	n.d.
5	Hexane	r.t.	/	/	/ (heteogeneous medium)
6	EtOAc	3-4 °C	5 :1	88	n.d.
7	EtOAc	-20 °C	4.3 :1	86	n.d.
8	DCM	r.t. (4 h)	2.5 :1	79	13%
9	**DCM**	**3-4 °C (30 h)**	**4.6 :1**	**92**	**95%**
10	DCM	0 °C (48 h)	3 :1	90	85%
11	DCM	-15 °C (3 days)	4.5 :1	91	5%

[a]diastereoselectivity determined by crude ^{1}H NMR, before purification ; [b]Enantiomeric excess refers to **10a$_{exo}$** dimer ; [c]Isolated yield.

Optimization study for the enantioselective synthesis of exo dimer $10a_{exo}$ in 2 steps from 11a



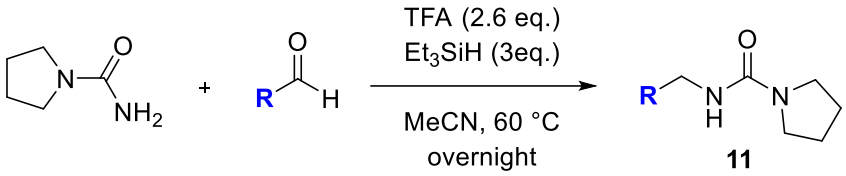
Entry[a]	N (F.mol^{-1})	C_{DCM} (mol.L^{-1})	dr(exo/endo)[b]	%ee[c]	Yield[d]
1	2	0.1	2.2 :1	80	57%
2[e]	2	0.1	0.5 :1	n.d.	n.d.
3	2	0.2	2.1 :1	70	45%
4	1.8	0.1	2.9 :1	86	66%
5[f]	1.8	0.1	4.1 :1	87	52%
6[g]	**1.8**	**0.1**	**3.9 :1**	**90**	**66%**

[a]Conditions : **11a** (0.2 mmol), *n*BuNOTs(0.1 eq), 5 mA, MeOH (0.05 M), r.t., followed by evaporation, filtration on alumina pad and treatment of the crude with **12a** (5 mol%), 3-4 °C, 36 h. ; [b]diastereoselectivity determined by crude ^{1}H NMR, before purification **;** [c]Enantiomeric excess refers to $\mathbf{10a_{exo}}$ dimer ; [d]Isolated yield of combined $\mathbf{10a_{endo}}$ and $\mathbf{10a_{exo}}$. ; [e]second step without filtration on alumina pad ; [f]72 h of stirring instead of 36 h. ; [g]3 Å molecular sieves was added for the second step.

Experimental details and characterization data

Experimental procedures and spectroscopic data for undescribed urea derivatives 11

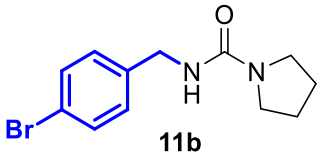
General procedure A for the synthesis of Urea derivatives 11[1]



Pyrrolidine-1-carboxamide (**1 eq.**) and aldehyde (**1 eq.**) were dissolved in acetonitrile. Trifluoacetic acid (TFA, **2.6 eq.**) and Et_3SiH (**3 eq.**) were successively added and the system was stirred at 60 °C overnight. Then, the reaction was cooled to r.t. and $NaHCO_3$ was added. Gaz evolution can be observed. The mixture was diluted in DCM and the aqueous layer was extracted three times with DCM. Finally, the organic layer was dried over $MgSO_4$, concentrated under reduced pressure and the crude was purified by flash chromatography (Petroleum ether/acetone, 9:1 to 1:1) to give the desired urea **11**.

Spectroscopic data for urea derivatives 11

***N*-(4-bromobenzyl)pyrrolidine-1-carboxamide (11b)**



Prepared according to general procedure **A** to provide the title compound **11b** as a white solid (157 mg, 36% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.23 – 7.18 (m, 2H), 4.49 (*br*. s, 1H), 4.39 (d, *J* = 5.7 Hz, 2H), 3.41 – 3.28 (m, 4H), 1.95 – 1.86 (m, 4H).

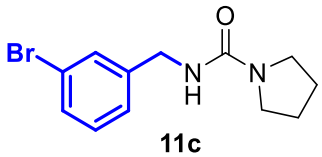
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 139.2, 131.8 (2C), 129.6 (2C), 121.2, 45.8 (2C), 44.2, 25.7(2C).

IR (neat) *v* (cm^{-1}): 3324, 2928, 2868, 2230, 1716, 1627, 1525, 1485, 1390, 1351, 1336, 1069, 1010.

HRMS (ESI+, m/z): calculated for $C_{12}H_{16}BrN_2O$ **[M+H]$^+$**: 283.0446, found 283.0421.

Mp: 118-120 °C.

***N*-(3-bromobenzyl)pyrrolidine-1-carboxamide (11c)**



11c

Prepared according to general procedure **A** to provide the title compound **11c** as a white solid (453 mg, 78% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 1.9 Hz, 1H), 7.38 (ddd, *J* = 7.7, 1.7 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.22 – 7.14 (m, 1H), 4.59 – 4.52 (*br*. s, 1H), 4.41 (d, *J* = 5.8 Hz, 2H), 3.45 – 3.27 (m, 4H), 2.04 – 1.72 (m, 4H).

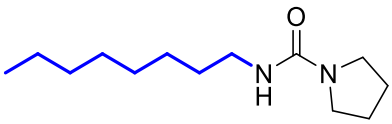
^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 142.6, 130.8, 130.4, 130.3, 126.5, 122.8, 45.8 (2C), 44.2, 25.7 (2C).

IR (neat) *v* (cm^{-1}): 3308, 3072, 2968, 2932, 2869, 1615, 1528, 1424, 1399, 1336, 1294, 1258, 1208, 1068.

HRMS (ESI+, m/z): calculated for $C_{12}H_{16}BrN_2O$ **[M+H]$^+$**: 283.0446, found 283.0442.

Mp: 143-145 °C.

***N*-octylpyrrolidine-1-carboxamide (11f)**



11f

Prepared according to general procedure **A** to provide the title compound **11f** as a white solid (502 mg, 69% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54 – 4.02 (*br*. s, 1H), 3.49 – 3.28 (m, 4H), 3.28 – 3.16 (m, 2H), 1.99 – 1.76 (m, 4H), 1.58 – 1.42 (m, 2H), 1.39 – 1.23 (m, 10H), 1.01 – 0.78 (m, 3H).

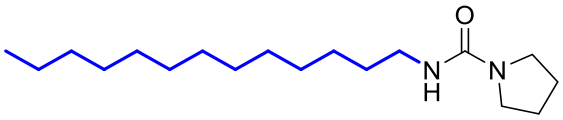
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 45.6 (2C), 40.8, 31.9, 30.7, 29.5, 29.3, 27.1, 25.7 (2C), 22.7, 14.2.

IR (neat) *v* (cm^{-1}): 3346, 2955, 2916, 2869, 2851, 1619, 1531, 1488, 1399, 1357, 1232, 1193.

HRMS (ESI+, m/z): calculated for $C_{13}H_{27}N_2O$ **[M+H]$^+$**: 227.2123, found 227.2113.

Mp: 66-68 °C.

***N*-tridecylpyrrolidine-1-carboxamide (11g)**



11g

Prepared according to general procedure **A** to provide the title compound **11g** as a white solid (254 mg, 57% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (*br*. s, 1H), 3.42 – 3.26 (m, 4H), 3.26 – 3.14 (m, 2H), 2.04 – 1.79 (m, 4H), 1.56 – 1.38 (m, 2H), 1.36 – 1.14 (m, 20H), 0.92 – 0.81 (m, 3H).

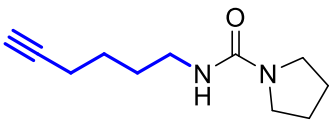
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 45.6 (2C), 40.9, 32.1, 30.7, 29.8 (3C), 29.7 (2C), 29.5, 29.5, 27.1, 25.7 (2C), 22.8, 14.2.

IR (neat) *v* (cm^{-1}): 3345, 2953, 2915, 1869, 1849, 1618, 1541, 1531, 1469, 1402, 1362.

HRMS (ESI+, m/z): calculated for $C_{18}H_{37}N_2O$ **[M+H]$^+$**: 297.2906, found 297.2892.

Mp: 81-83 °C.

***N*-(hex-5-yn-1-yl)pyrrolidine-1-carboxamide (11i)**



11i

Prepared according to general procedure **A** to provide the title compound **11i** as a pale yellow solid (294 mg, 68% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (*br*. s, 1H), 3.37 – 3.20 (m, 6H), 2.22 (td, *J* = 6.8, 2.6 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.93 – 1.85 (m, 4H), 1.67 – 1.52 (m, 4H).

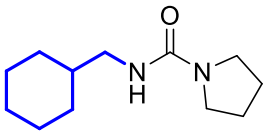
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 84.5, 68.6, 45.7 (2C), 40.2, 29.8, 25.9, 25.7 (2C), 18.3.

IR (neat) *v* (cm^{-1}): 3300, 3229, 2924, 2860, 1616, 1534, 1484, 1452, 1431, 1395, 1369, 1334.

HRMS (ESI+, m/z): calculated for $C_{11}H_{19}N_2O$ **[M+H]$^+$**: 195.1497 found 195.1487.

Mp: 69-71 °C.

***N*-(cyclohexylmethyl)pyrrolidine-1-carboxamide (11j)**



11j

Prepared according to general procedure **A** to provide the title compound **11j** as a white solid (325 mg, 87% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (t, *J* = 6.3 Hz, 1H), 3.45 – 3.16 (m, 4H), 3.05 (dd, *J* = 6.4 Hz, 2H), 2.02 – 1.80 (m, 4H), 1.75 – 1.58 (m, 5H), 1.55 – 1.35 (m, 1H), 1.29 – 1.06 (m, 3H), 0.98 – 0.78 (m, 2H).

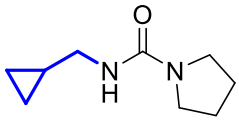
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 47.0, 45.6 (2C), 38.6, 31.0 (2C), 26.7, 26.0 (2C), 25.7 (2C).

IR (neat) *v* (cm^{-1}):3323, 2969, 2920, 2853, 1626, 1530, 1427, 1396, 1353, 1335, 1228, 1195.

HRMS (ESI+, m/z): calculated for $C_{12}H_{23}N_2O$ $[M+H]^+$: 211.1810, found 211.1788.

Mp: 136-138 °C.

***N*-(cyclopropylmethyl)pyrrolidine-1-carboxamide (11k)**



11k

Prepared according to general procedure **A** to provide the title compound **11k** as a white solid (393 mg, 82% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (*br*. s, 1H), 3.38 – 3.22 (m, 4H), 3.08 (dd, *J* = 7.1, 5.4 Hz, 2H), 2.00 – 1.66 (m, 4H), 1.17 – 0.80 (m, 1H), 0.66 – 0.34 (m, 2H), 0.28 – 0.07 (m, 2H).

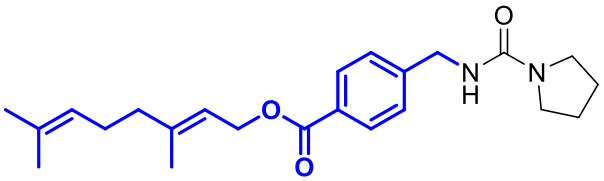
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 45.7, 45.6 (2C), 25.7 (2C), 11.6, 3.4 (2C).

IR (neat) *v* (cm^{-1}): 3303, 3079, 3305, 2961, 2917, 2869, 1617, 1536, 1474, 1405, 1373, 1323, 1255, 1232, 1193, 1154.

HRMS (ESI+, m/z): calculated for $C_9H_{17}N_2O$ **$[M+H]^+$**: 169.1341, found 169.1338.

Mp: 115-117 °C.

(*E*)-3,7-dimethylocta-2,6-dien-1-yl 4-((pyrrolidine-1-carboxamido)methyl)benzoate (11m)



11m

Prepared according to general procedure **A** to provide the title compound **11m** as a colorless oil (41 mg, 25% yield) from the correspondent aldehyde[2].

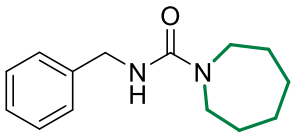
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 2H), 7.48 – 7.29 (m, 2H), 5.52 – 5.38 (m, 1H), 5.18 – 5.04 (m, 1H), 4.82 (d, *J* = 7.1 Hz, 2H), 4.60 – 4.52 (m, 1H), 4.53 – 4.47 (m, 2H), 3.49 – 3.25 (m, 4H), 2.26 – 2.03 (m, 4H), 1.97 – 1.85 (m, 4H), 1.75 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 156.7, 145.3, 142.5, 132.0, 130.1 (2C), 129.7, 127.6 (2C), 123.9, 118.6, 62.0, 45.8 (2C), 44.5, 39.7, 26.5, 25.8, 25.7 (2C), 17.8, 16.7.

IR (neat) *v* (cm^{-1}): 3320, 3028, 2967, 2927, 2870, 1777, 1714, 1630, 1528, 1388, 1267, 1174, 1097, 1018.

HRMS (ESI+, m/z): calculated for $C_{23}H_{33}N_2O_3$ **[M+H]$^+$**: 385.2491, found 385.2501.

***N*-benzylazepane-1-carboxamide (11p)**



11p

Prepared according to the literature procedure to provide the title compound **11p** as a white solid (144 mg, 62% yield)[3].

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.15 (m, 5H), 5.58 (*br*. s, 1H), 4.32 (d, *J* = 5.9 Hz, 2H), 3.41 – 3.31 (m, 1H), 1.72 – 1.60 (m, 4H), 1.58 – 1.49 (m, 4H).

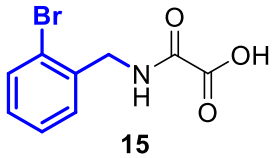
^{13}C NMR (75 MHz, CD_3CN) δ 142.5, 129.4, 129.2 (2C), 128.1 (2C), 127.5, 47.2 (2C), 44.8, 29.5 (2C), 27.9 (2C).

HRMS (ESI+, m/z): calculated for $C_{14}H_{21}N_2O$ **[M+H]$^+$**: 233.1654, found 233.1625.

Mp: 104-106 °C.

Experimental procedure and spectroscopic data for 2-((2-bromobenzyl)amino)-2-oxoacetic acid

2-((2-bromobenzyl)amino)-2-oxoacetic acid (15)



15

Prepared according to the literature procedure to provide the title compound **15** as a white solid (334 mg, 72% yield over 2 steps)[4].

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.60 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.41 – 7.29 (m, 2H), 7.25 – 7.13 (m, 2H), 4.63 (d, *J* = 6.3 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.4, 160.3, 135.9, 133.3, 130.4, 129.9, 128.2, 123.9, 44.7.

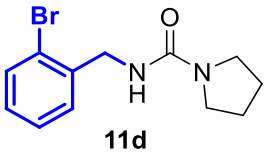
IR (neat) *v* (cm^{-1}): 3261, 1756, 1684, 1554, 1435, 1360, 1344, 1277, 1179.

HRMS (ESI+, m/z): calculated for $C_9H_9BrNO_3$ **[M+H]$^+$**: 257.9766, found 257.9777.

Mp: 148-150 °C.

Experimental procedure and spectroscopic data for urea derivatives 11d

***N*-(2-bromobenzyl)pyrrolidine-1-carboxamide (11d)**



11d

Prepared from 2-((2-bromobenzyl)amino)-2-oxoacetic acid **15** according to the literature procedure to provide the title compound **11d** as a white solid (34 mg, 52% yield)[4].

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.27 (td, *J* = 8.0, 7.5, 1.4 Hz, 1H), 7.12 (td, *J* = 7.6, 1.8 Hz, 1H), 4.89 – 4.75 (m, 1H), 4.48 (d, *J* = 6.1 Hz, 2H), 3.41 – 3.28 (m, 4H), 1.96 – 1.84 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 138.9, 132.8, 130.8, 129.0, 127.8, 123.9, 45.7 (2C), 45.0, 25.7 (2C).

IR (neat) *v* (cm^{-1}): 3310, 3066, 2969, 2947, 2867, 1628, 1527, 1461, 1412, 1394, 1343, 1261, 1227, 1208, 1027.

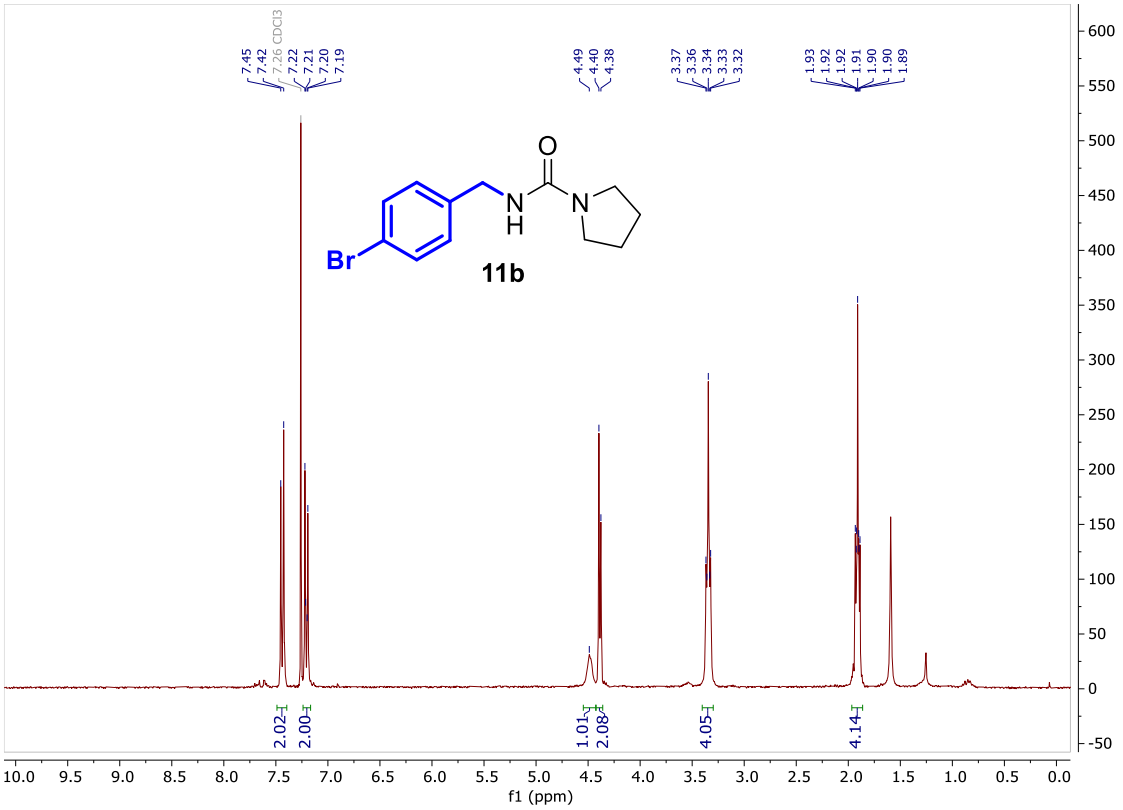
HRMS (ESI+, m/z): calculated for $C_{12}H_{16}BrN_2O$ **[M+H]$^+$**: 283.0446, found 283.0443.

Mp: 124-126 °C.

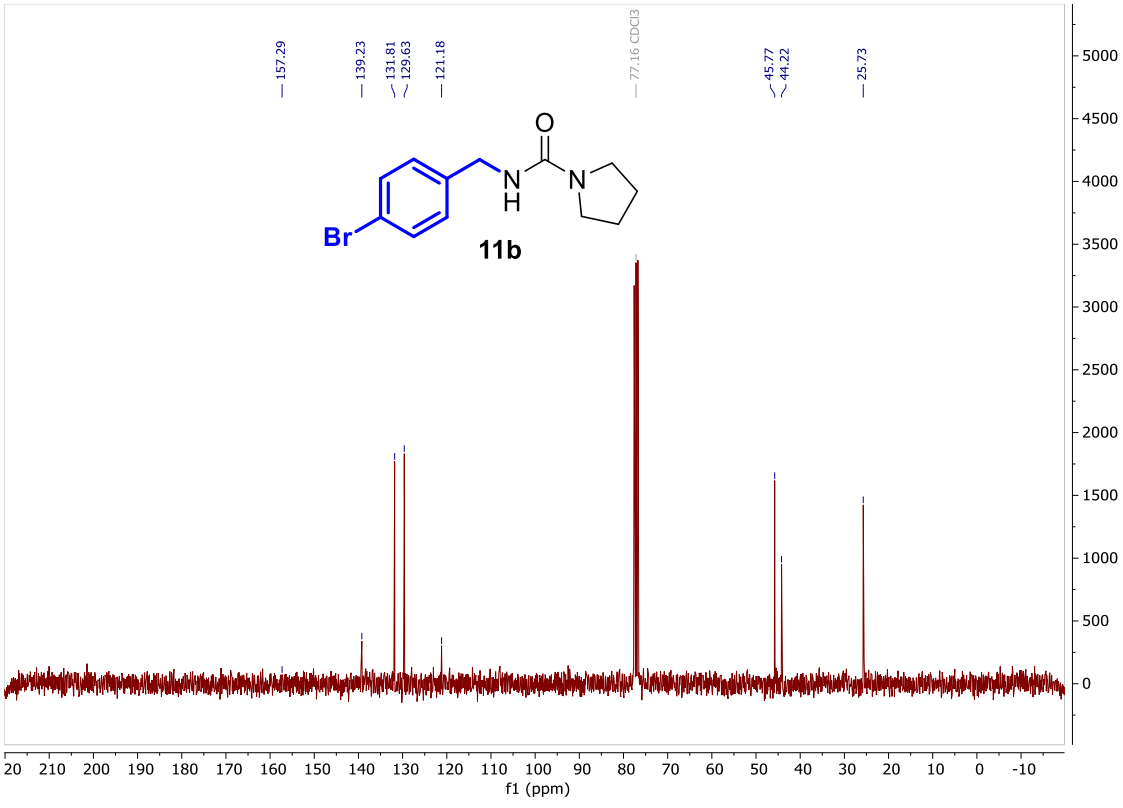
^{1}H and ^{13}C NMR spectra of undescribed urea derivatives 11

N-(4-bromobenzyl)pyrrolidine-1-carboxamide (11b)

^{1}H NMR, 300 MHz, $CDCl_3$

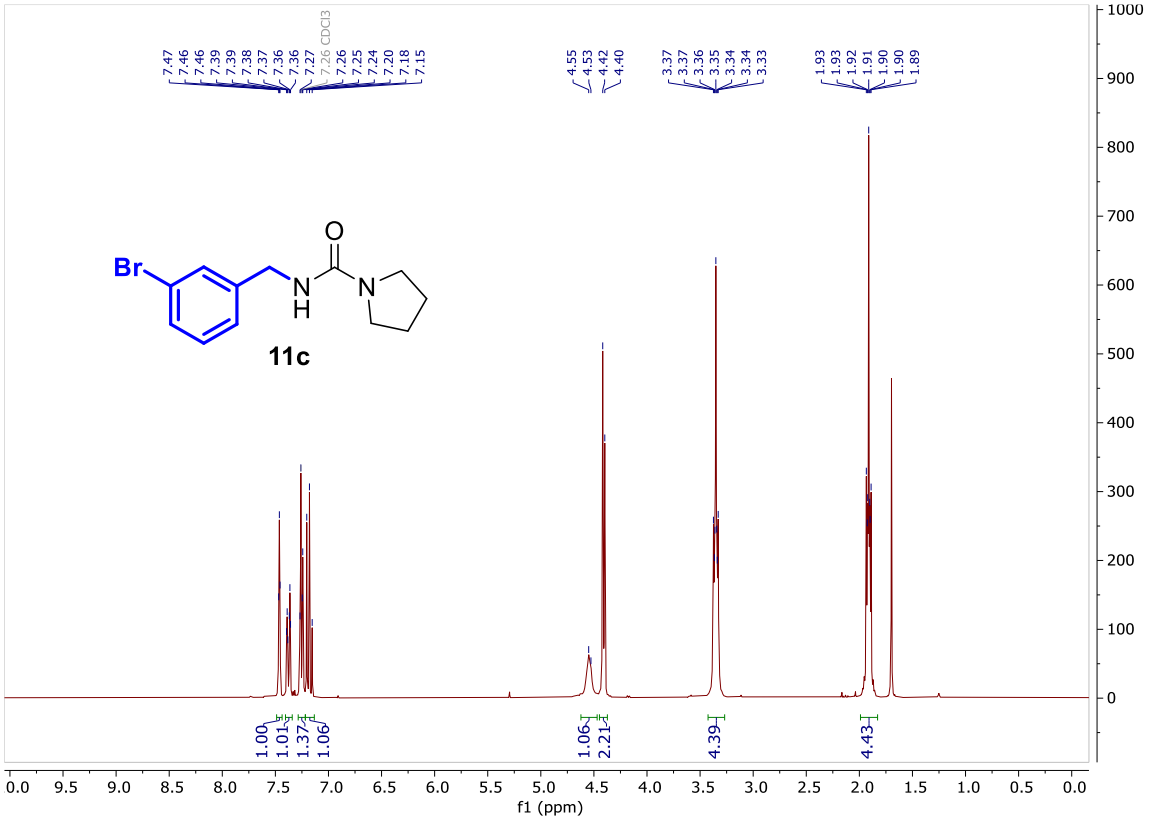


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$

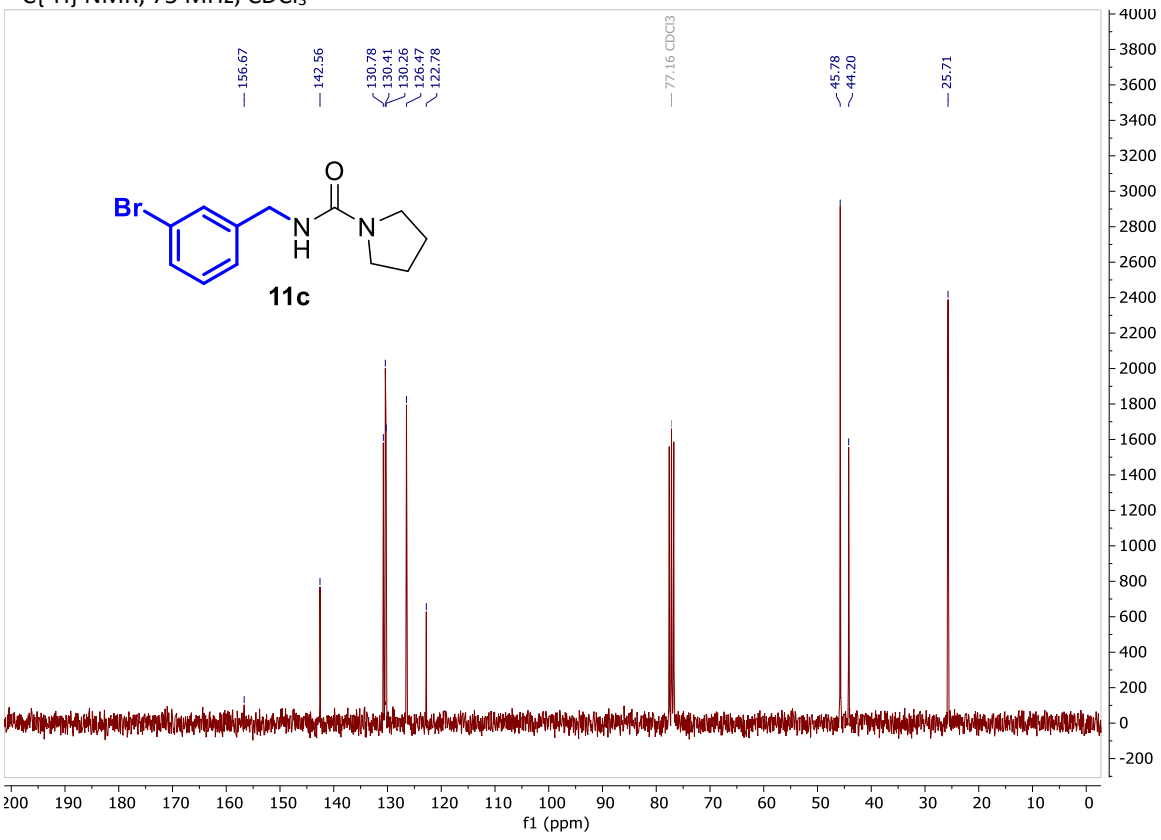


N-(3-bromobenzyl)pyrrolidine-1-carboxamide (11c)

^{1}H NMR, 300 MHz, $CDCl_3$

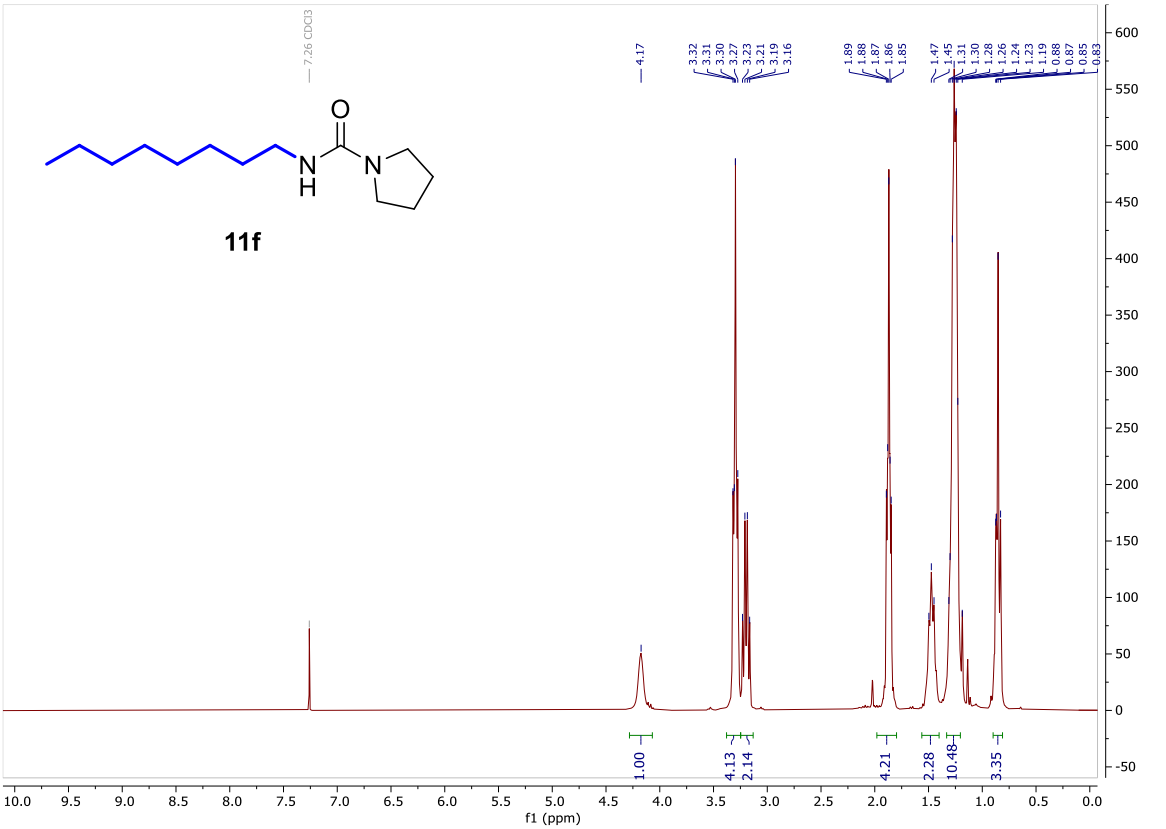


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$

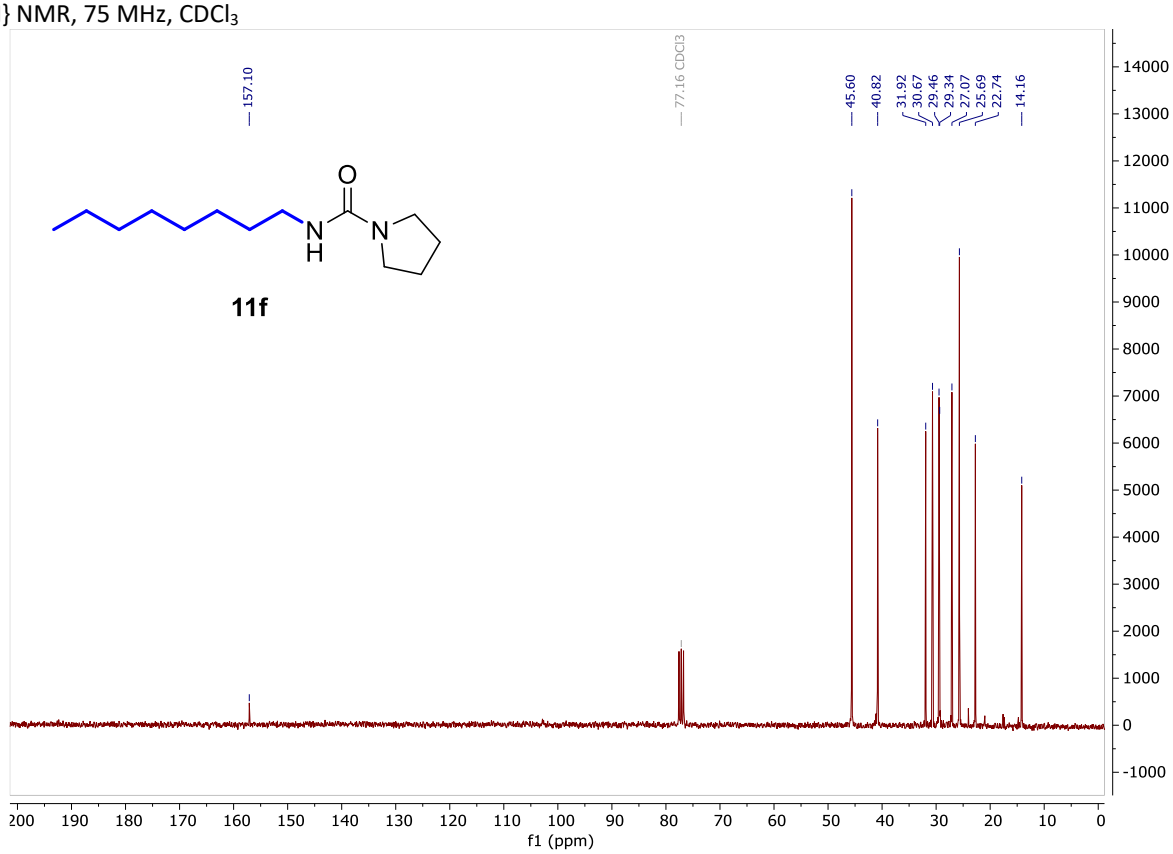


N-octylpyrrolidine-1-carboxamide (11f)

^{1}H NMR, 300 MHz, $CDCl_3$

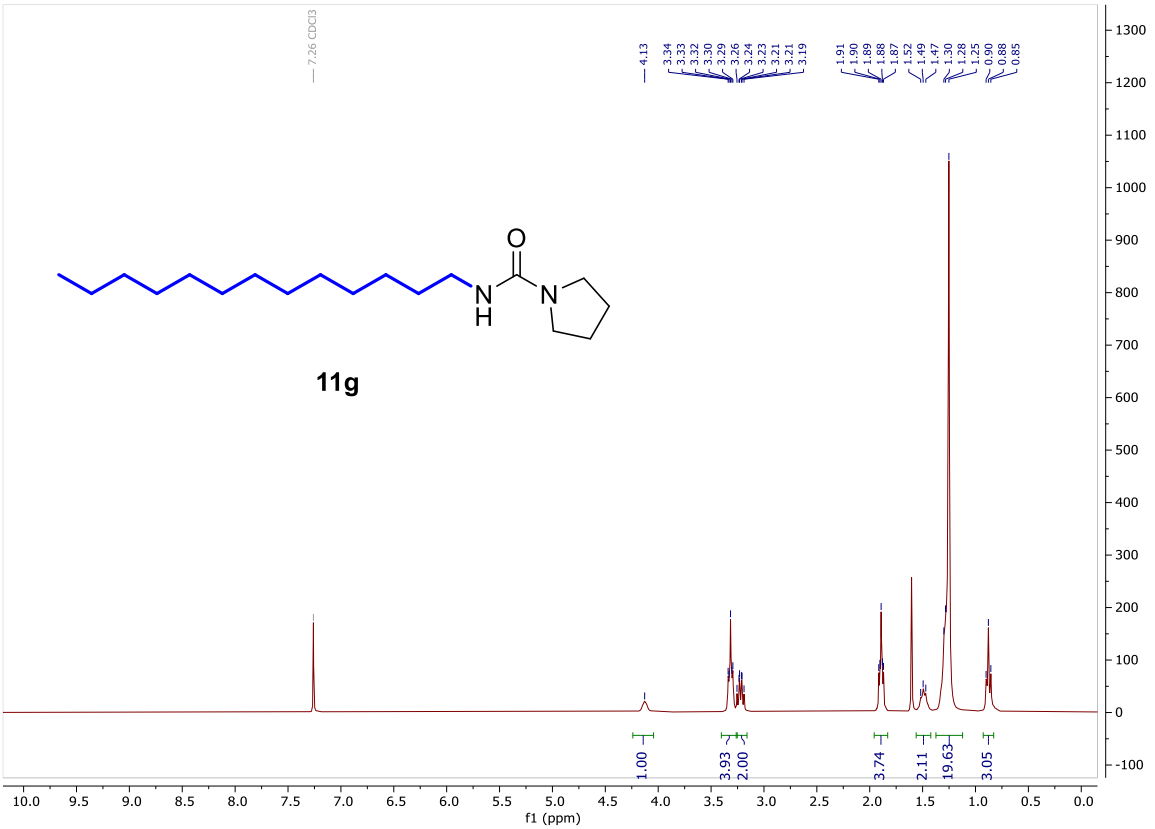


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$

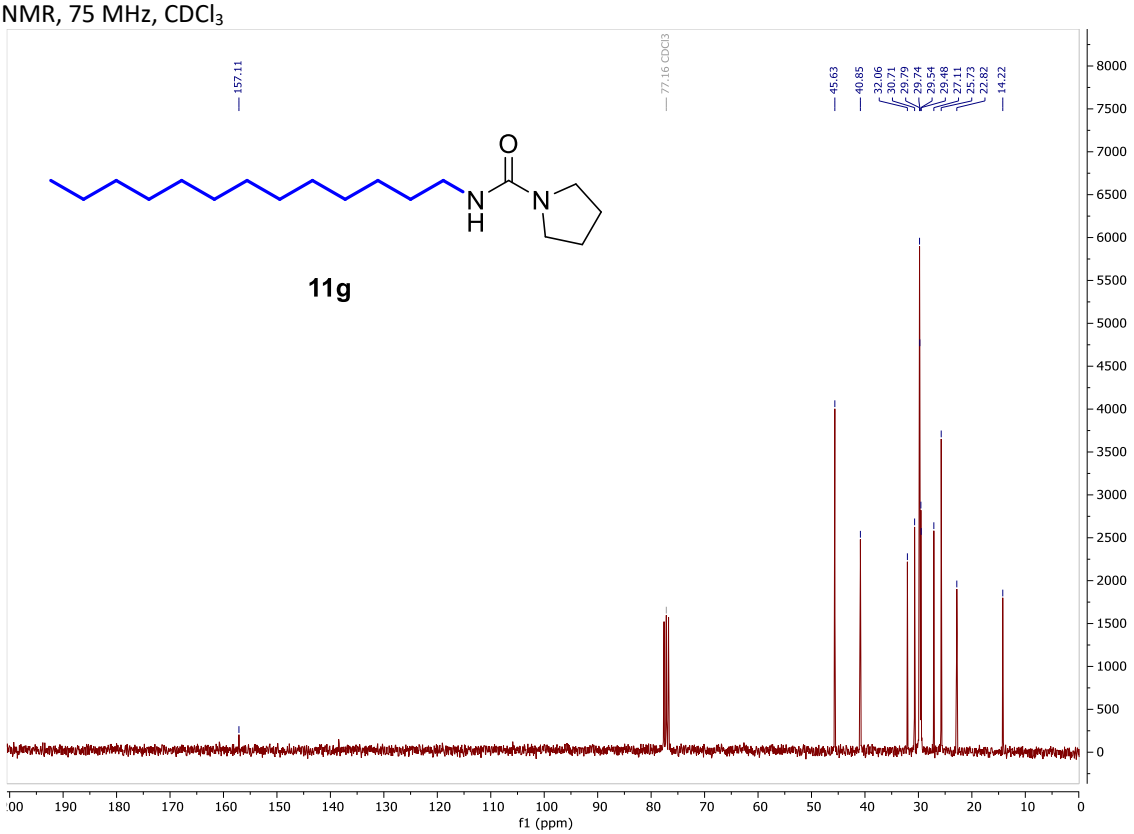


N-tridecylpyrrolidine-1-carboxamide (11g)

^{1}H NMR, 300 MHz, $CDCl_3$

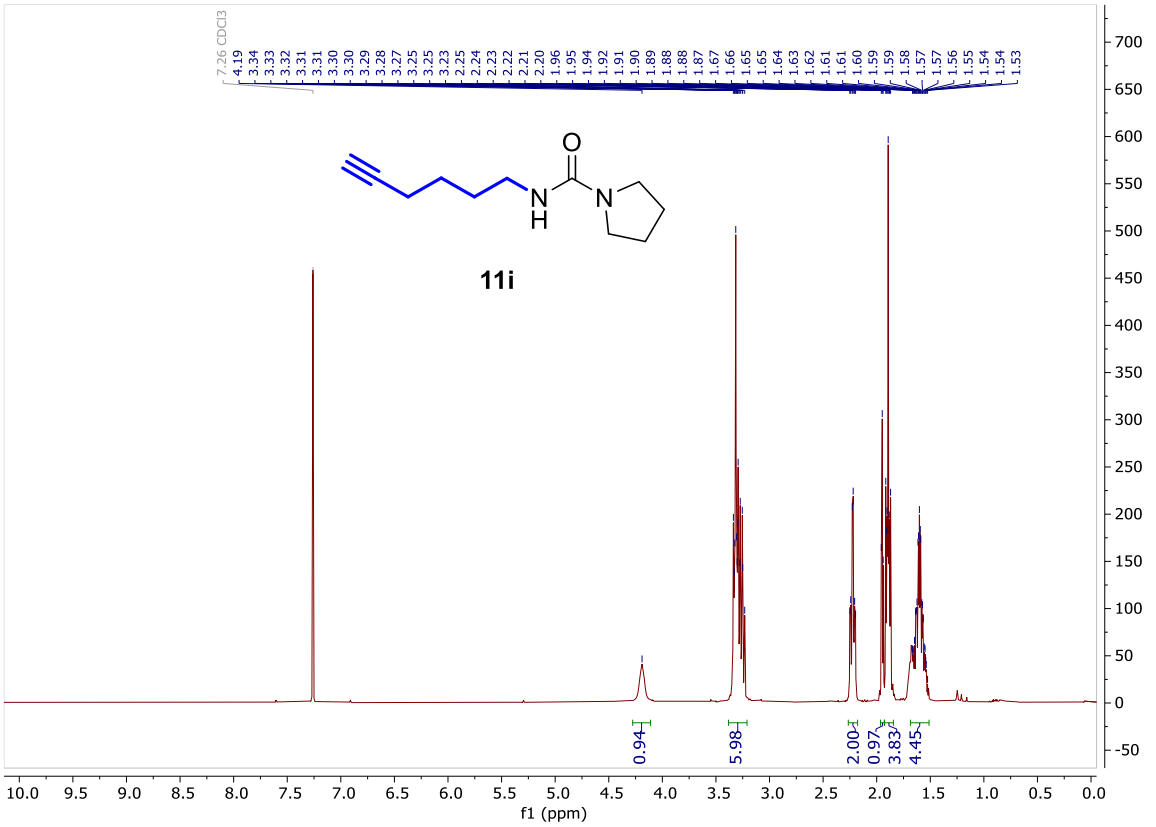


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$

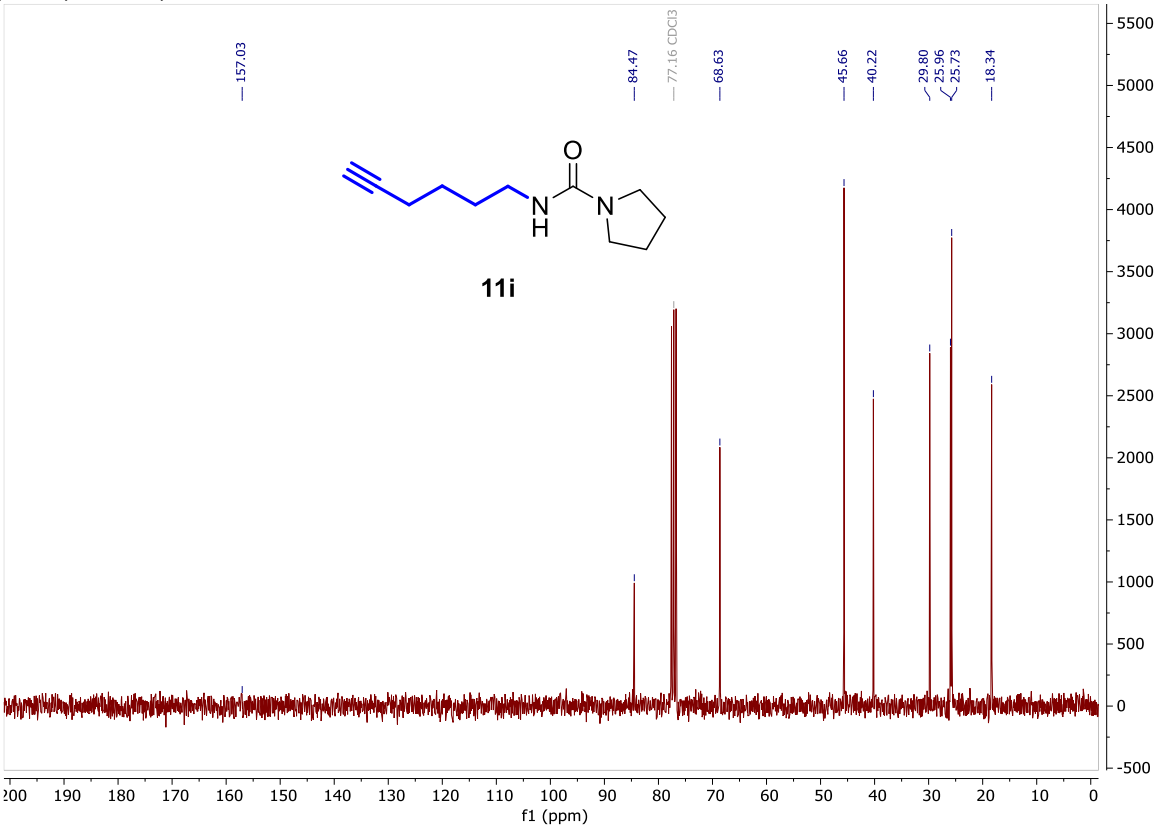


N-(hex-5-yn-1-yl)pyrrolidine-1-carboxamide (11i)

^{1}H NMR, 300 MHz, $CDCl_3$

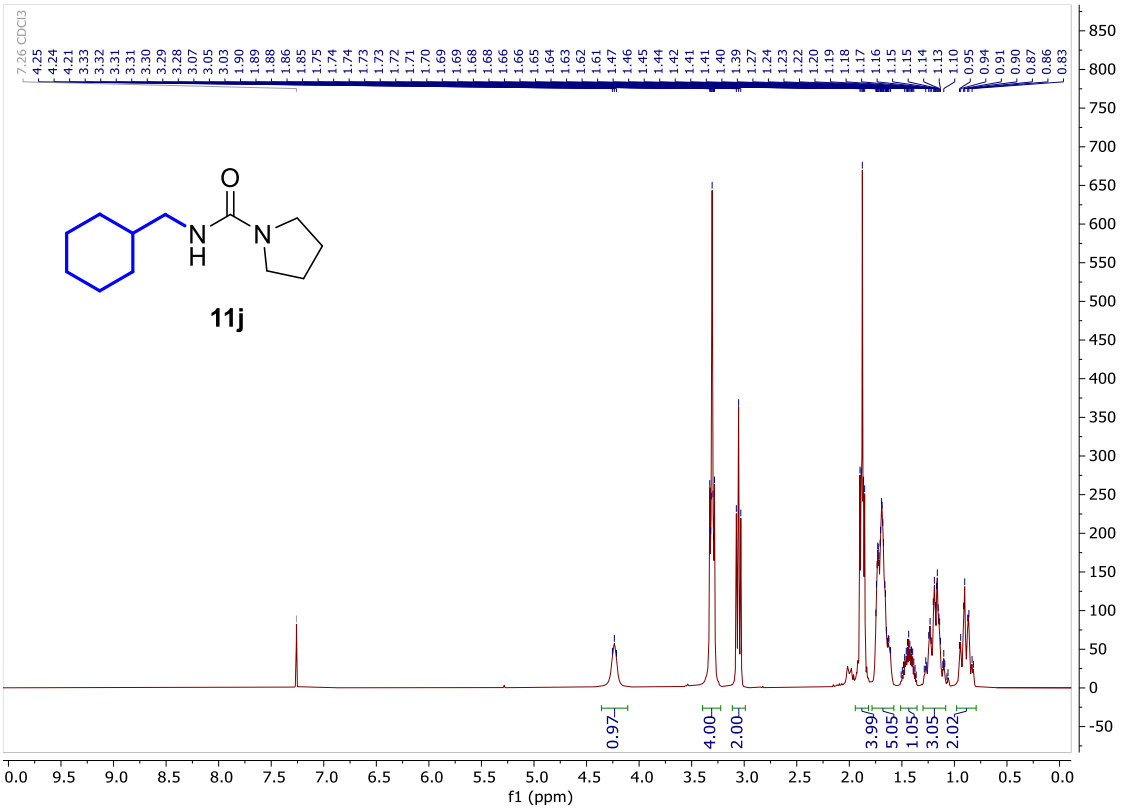


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$

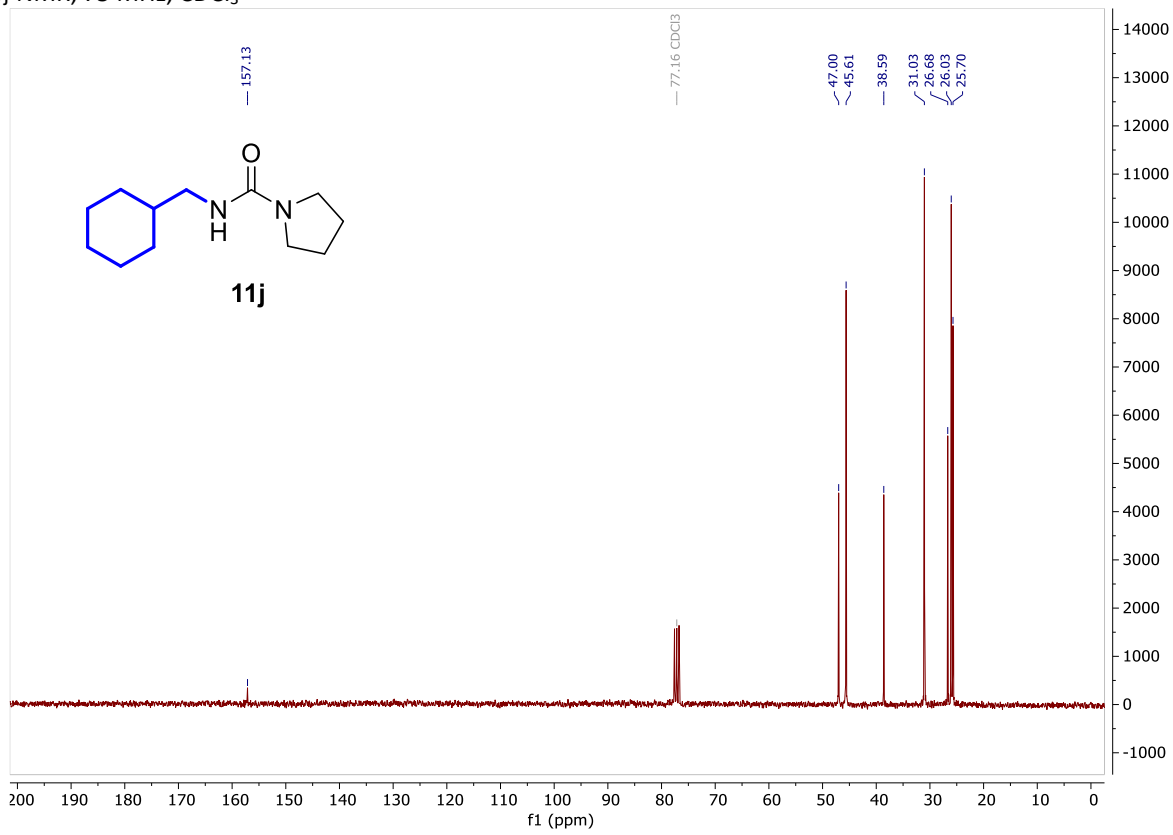


N-benzylazepane-1-carboxamide (11j)

^{1}H NMR, 300 MHz, $CDCl_3$

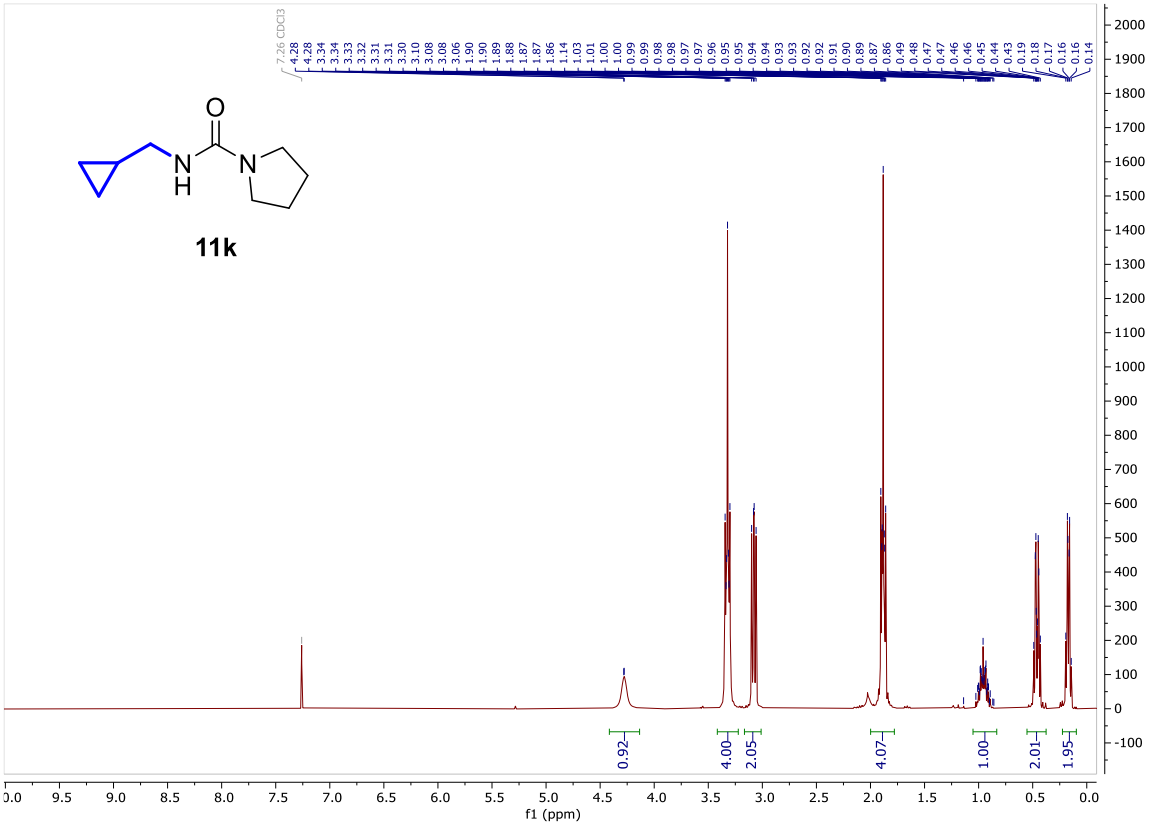


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

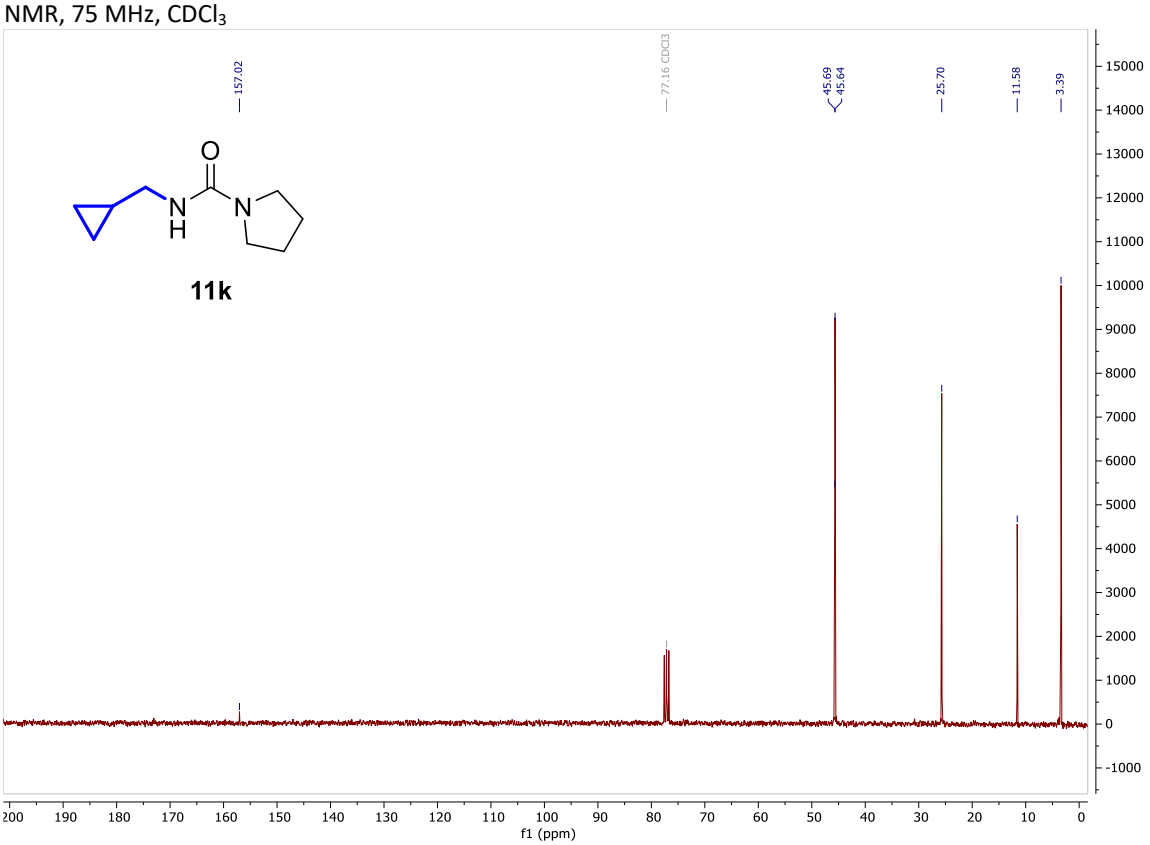


N-(cyclopropylmethyl)pyrrolidine-1-carboxamide (11k)

^{1}H NMR, 300 MHz, $CDCl_3$

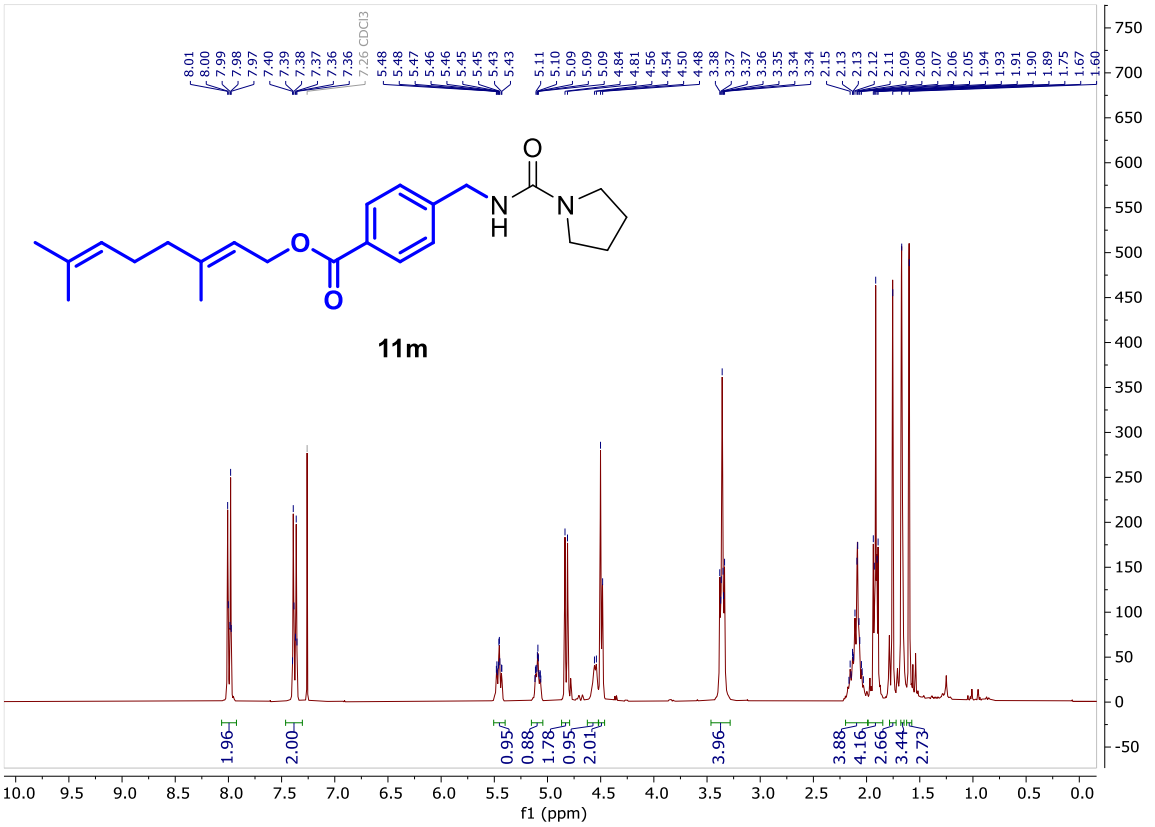


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$

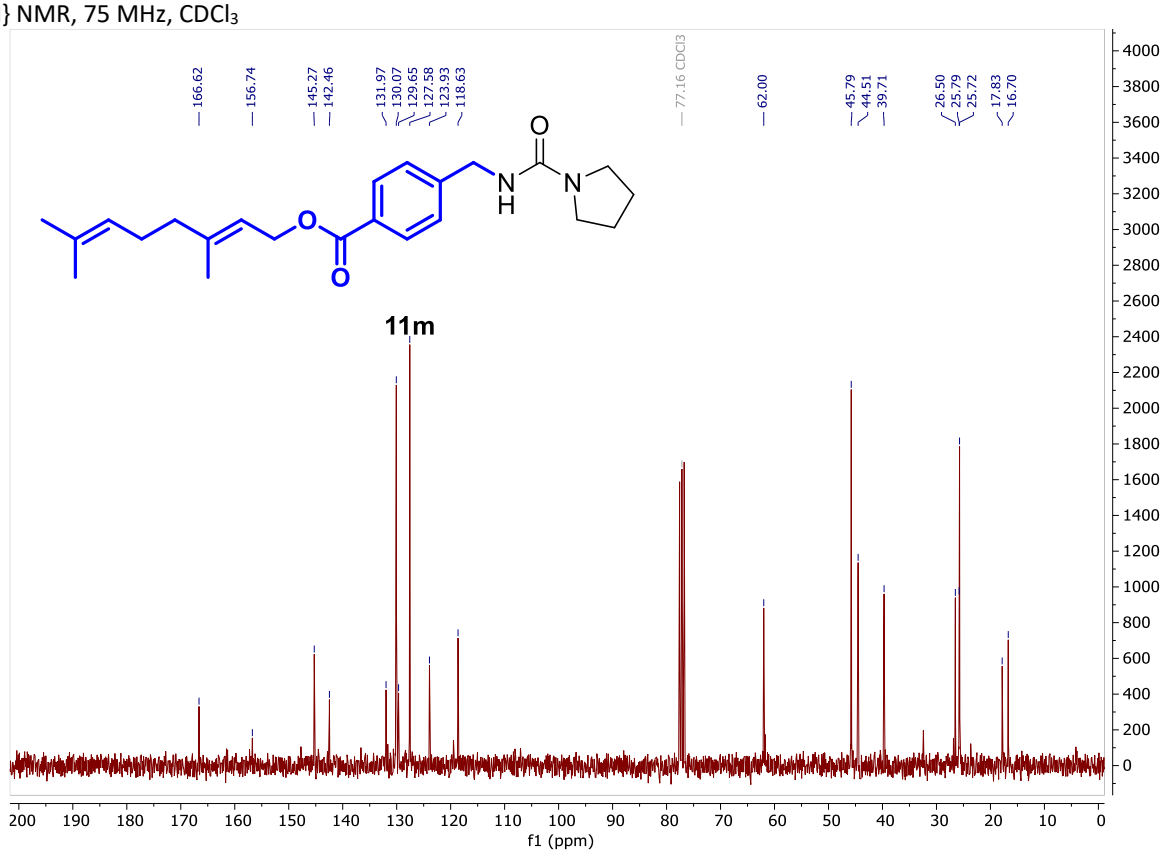


(*E*)-3,7-dimethylocta-2,6-dien-1-yl 4-((pyrrolidine-1-carboxamido)methyl)benzoate (11m)

^{1}H NMR, 300 MHz, $CDCl_3$

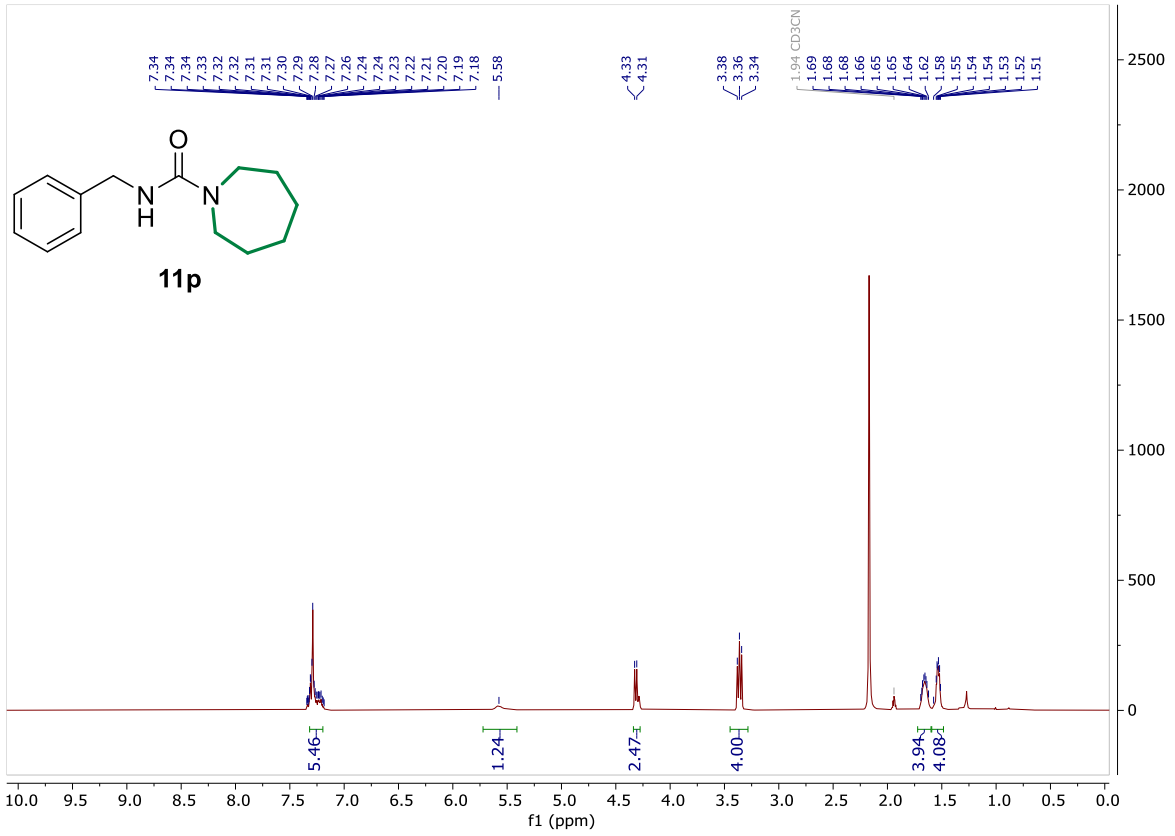


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

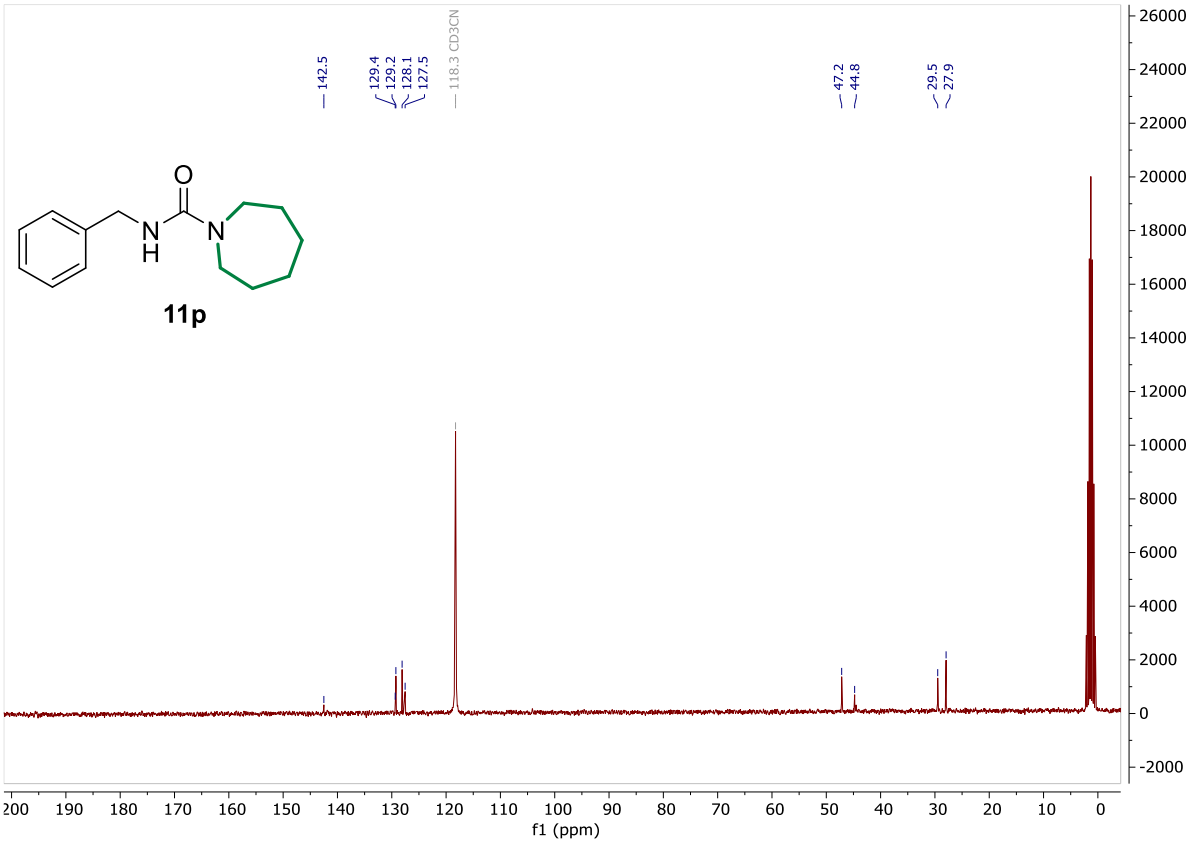


N-benzylazepane-1-carboxamide (11p)

^{1}H NMR, 300 MHz, $CDCl_3$

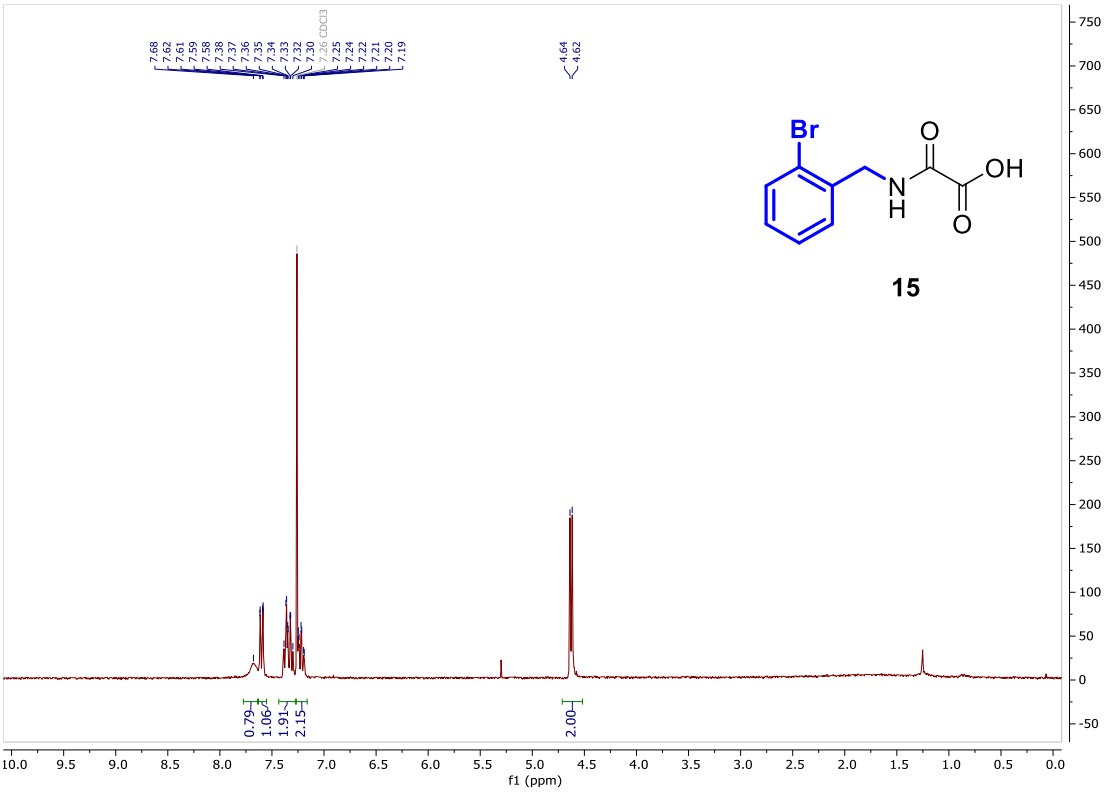


$^{13}C\{^{1}H\}$ NMR, 75 MHz, CD_3CN

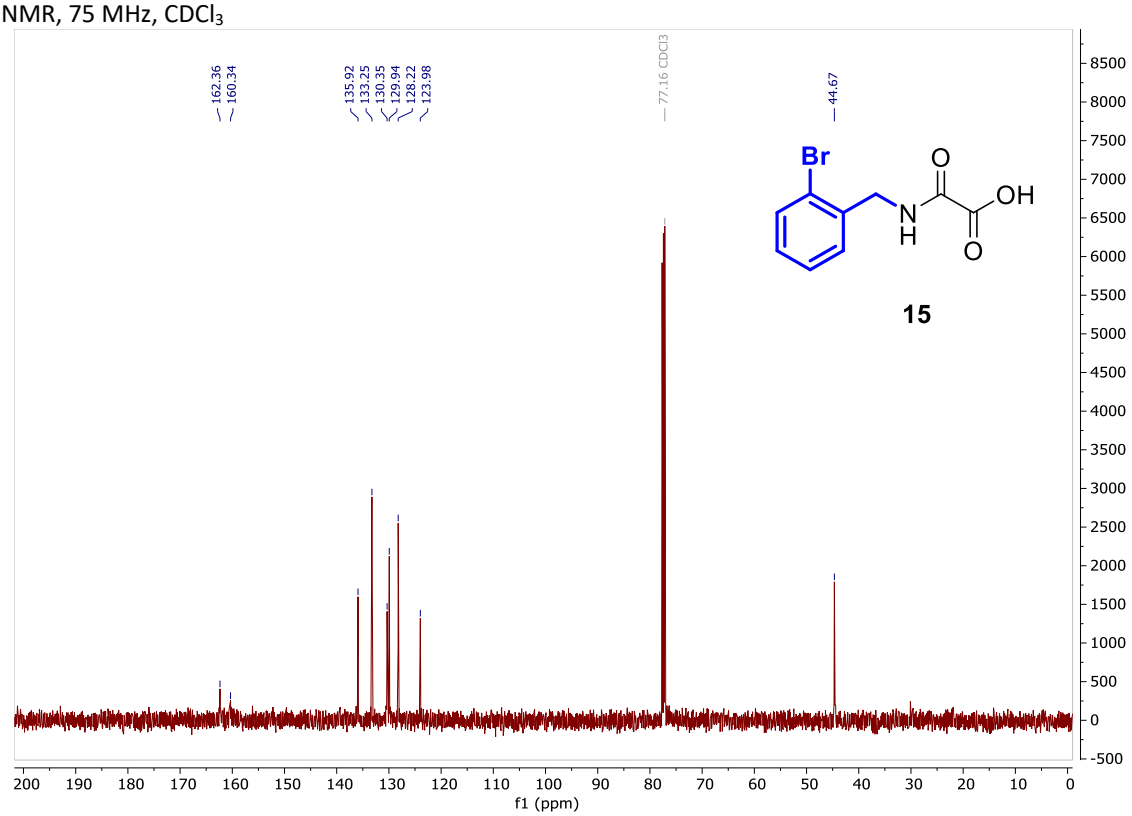


2-((2-bromobenzyl)amino)-2-oxoacetic acid (15)

^{1}H NMR, 300 MHz, $CDCl_3$

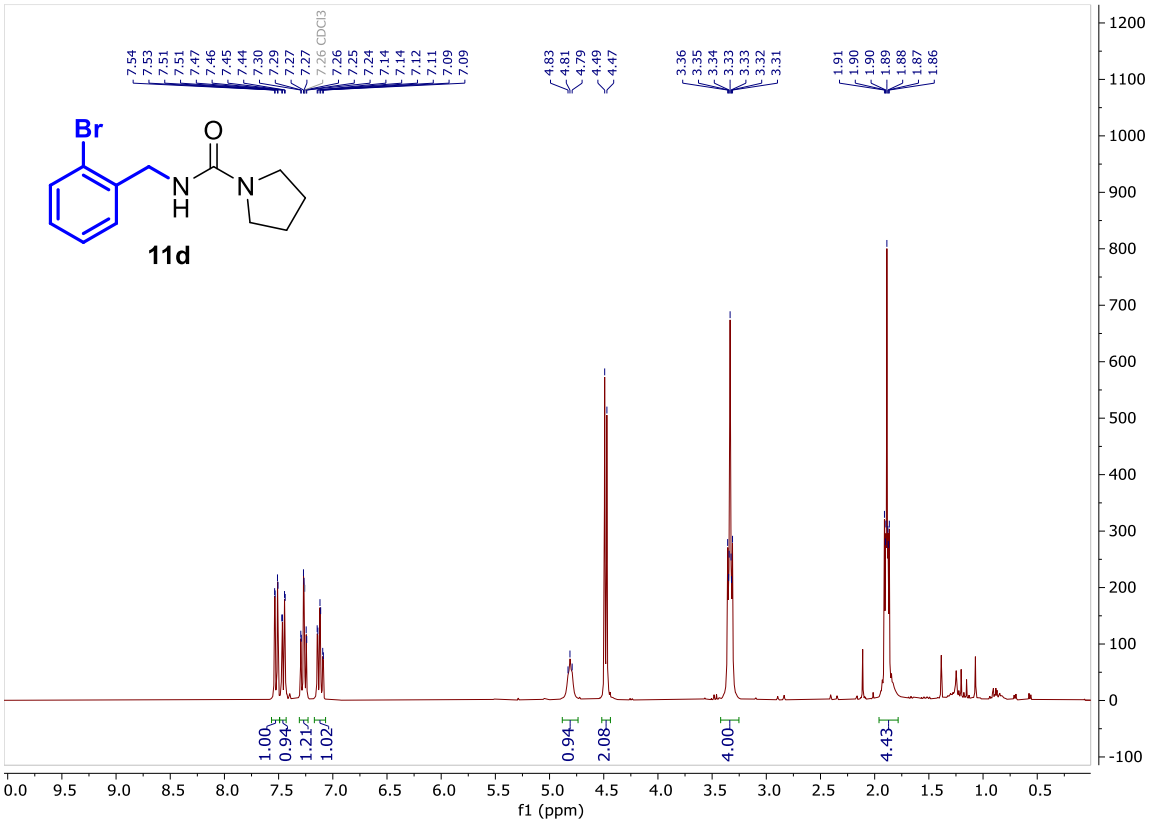


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$

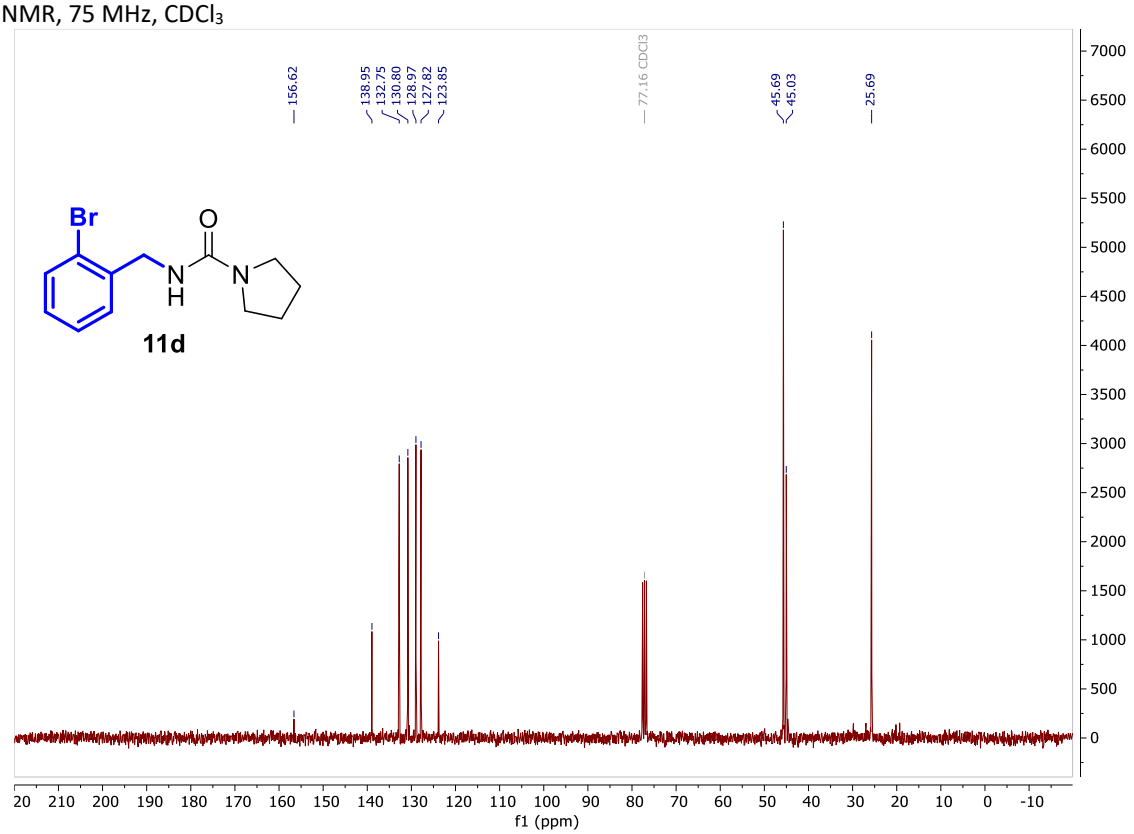


N-(2-bromobenzyl)pyrrolidine-1-carboxamide (11d)

^{1}H NMR, 300 MHz, $CDCl_3$

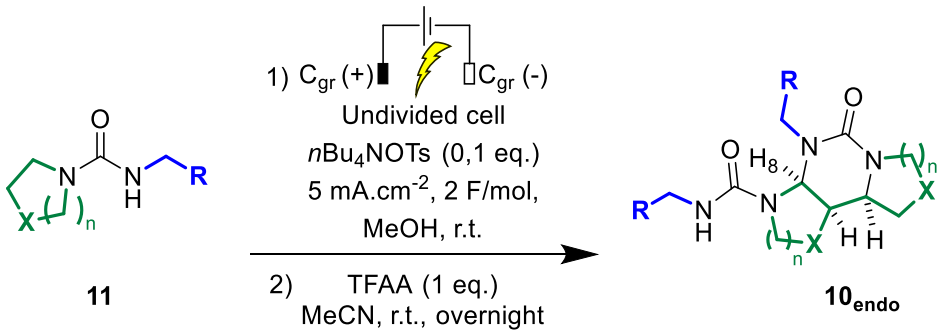


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$



Experimental procedure and spectroscopic data for endo dimers 10_{endo}

General procedure B for the synthesis of Endo dimers 10_{endo}



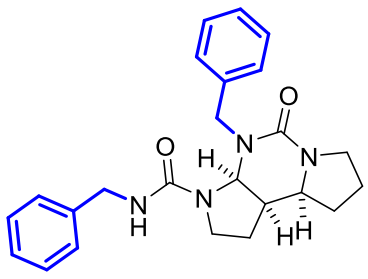
A 5 mL IKA Electrasyn electrochemical cell was charged with urea derivative (0.1-0.2 mmol, **1 eq.**), nBu$_4$NOTs (**0.1 eq.**) and MeOH (0.06 M), and the resulting solution was electrolyzed (constant current, 5 mA.cm^{-2}, 2.00 F mol^{-1}, 600 rpm) using an isostatic graphite electrode both as cathode and anode. The crude was concentrated under reduced pressure and re-dissolved in acetonitrile (0.03 M). Trifluoroacetic anhydride (TFAA, **1 eq.**) was added and the mixture was stirred overnight. After evaporation of the solvent, the crude was purified by flash chromatography (Petroleum ether/acetone, 9:1 to 1:1) to give the desired Endo dimer 10_{endo}. If necessary, the product can be extracted in a system *n*-Heptane/acetonitrile to remove the residual grease.

Diastereoisomeric ratio was established by ^{1}H NMR on crude reaction integrating H_8 and found to be >98:2 unless otherwise mentioned. Yields were given for the purified Endo adduct 10_{endo}.

Some Dimers are presenting a high lipophilicity. Complete removal of grease was not achieved in selected cases.

Spectroscopic data for endo dimers 10_{endo}

(3aS,9aS,9bR)-N,4-dibenzyl-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10a_{endo}$)



$10a_{endo}$

Prepared according to general procedure **B** to provide the title compound **$10a_{endo}$** as a white foam (27.8 mg, 94% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.08 (m, 10H), 5.76 (d, *J* = 5.7 Hz, 1H), 4.86 (d, *J* = 15.9 Hz, 1H), 4.47 (d, *J* = 15.5 Hz, 1H), 4.32 (dd, *J* = 14.6, 5.9 Hz, 1H), 4.17 (dd, *J* = 14.3, 5.1 Hz, 1H), 3.91 (t, *J* = 5.7 Hz, 1H), 3.87 – 3.74 (m,

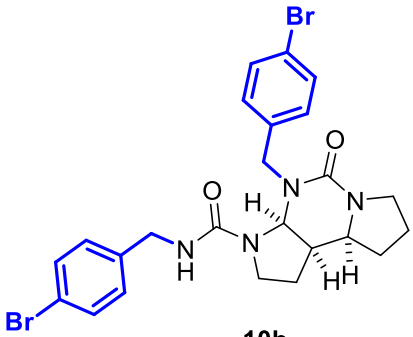
1H), 3.72 – 3.59 (m, 1H), 3.59 – 3.44 (m, 1H), 3.26 – 3.11 (m, 1H), 2.92 – 2.79 (m, 1H), 2.63 – 2.48 (m, 1H), 2.10 – 1.90 (m, 4H), 1.88 – 1.71 (m, 1H), 1.70 – 1.49 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 154.6, 140.8, 139.0, 128.7 (2C), 128.1 (2C), 128.0 (2C), 127.5, 127.0 (2C), 126.3, 71.2, 53.4, 47.0, 46.1, 44.8, 44.0, 40.6, 30.7, 23.4, 23.0.

IR (neat) *v* (cm^{-1}): 3334, 3029, 2927, 2878, 1626, 1534, 1494, 1474, 1451, 1374, 1340, 1271.

HRMS (ESI+, m/z): calculated for $C_{24}H_{29}N_4O_2$ **[M+H]$^+$**: 405.2291, found 405.2307.

(3aS,9aS,9bR)-N,4-bis(4-bromobenzyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10b$_{endo}$)



10b$_{endo}$

Prepared according to general procedure **B** to provide the title compound **10b$_{endo}$** as a pale yellow foam (8.8 mg, 51% yield).

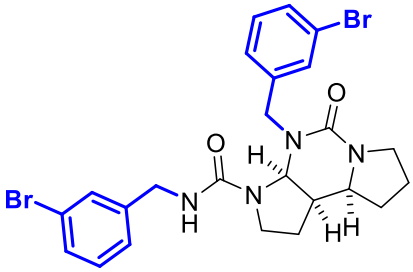
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 5.74 (d, *J* = 5.7 Hz, 1H), 4.81 (d, *J* = 15.7 Hz, 1H), 4.38 (d, *J* = 15.8 Hz, 1H), 4.30 – 4.07 (m, 2H), 4.06 – 3.96 (m, 1H), 3.85 – 3.72 (m, 1H), 3.72 – 3.58 (m, 1H), 3.57 – 3.41 (m, 1H), 3.25 – 2.98 (m, 1H), 3.10 – 2.76 (m, 1H), 2.68 – 2.43 (m, 1H), 2.15 – 1.90 (m, 4H), 1.92 – 1.74 (m, 1H), 1.69 – 1.51 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 156.2, 140.1, 138.0, 131.9 (2C), 131.1 (2C), 129.7 (2C), 128.9 (2C), 121.5, 120.0, 71.4, 53.5, 46.9, 46.1, 44.2, 44.1, 40.6, 30.6, 23.4, 23.1.

IR (neat) *v* (cm^{-1}): 3326, 3028, 2924, 2853, 1627, 1537, 1487, 1475, 1374, 1272.

HRMS (ESI+, m/z): calculated for $C_{24}H_{27}N_4O_2Br_2$ **[M+H]$^+$**: 561.0501, found 561.0468.

(3aS,9aS,9bR)-N,4-bis(3-bromobenzyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10c$_{endo}$)



10c$_{endo}$

Prepared according to general procedure **B** to provide the title compound **10c$_{endo}$** as a pale yellow foam (19.6 mg, 73% yield).

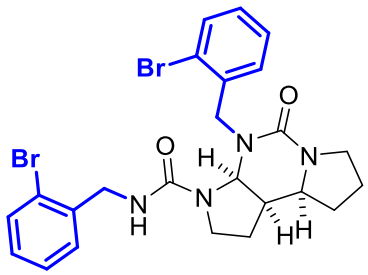
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 3H), 7.31 – 7.03 (m, 5H), 5.75 (d, *J* = 5.8 Hz, 1H), 4.91 (d, *J* = 15.5 Hz, 1H), 4.43 – 4.29 (m, 2H), 4.16 – 4.00 (m, 2H), 3.90 – 3.76 (m, 1H), 3.71 – 3.57 (m, 1H), 3.57 – 3.43 (m, 1H), 3.33 – 3.11 (m, 1H), 3.00 – 2.81 (m, 1H), 2.65 – 2.49 (m, 1H), 2.17 – 1.93 (m, 4H), 1.91 – 1.76 (m, 1H), 1.62 – 1.52 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 154.4, 143.6, 141.5, 130.8, 130.6, 130.3, 129.8, 129.7, 129.4, 126.5, 125.8, 122.8, 122.1, 71.4, 53.5, 46.9, 46.1, 44.2, 44.0, 40.5, 30.7, 23.4, 23.1.

IR (neat) *v* (cm^{-1}): 3333, 3061, 2928, 2879, 2235, 1626, 1569, 1535, 1473, 1373, 1336.

HRMS (ESI+, m/z): calculated for $C_{24}H_{27}Br_2N_4O_2$ **[M+H]$^{+}$**: 561.0501, found 561.0486.

(3aS,9aS,9bR)-N,4-bis(2-bromobenzyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10d$_{endo}$)



10d$_{endo}$

Prepared according to general procedure **B** to provide the pure isolated title compound **10d$_{endo}$** as a pale yellow foam (13.2 mg, 48% yield).

dr(Endo/Exo) of reaction was found to be 9:1 as determined by ^{1}H NMR on the crude reaction mixture.

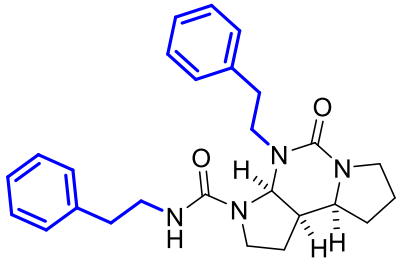
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.37 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.24 – 6.92 (m, 6H), 5.74 (d, *J* = 6.0 Hz, 1H), 4.83 – 4.59 (m, 2H), 4.42 (t, *J* = 6.1 Hz, 1H), 4.36 – 4.19 (m, 2H), 3.87 (ddd, *J* = 9.6, 5.8, 3.2 Hz, 1H), 3.64 (ddd, *J* = 9.7, 8.9, 2.6 Hz, 1H), 3.48 (ddd, *J* = 10.5, 9.9, 7.1 Hz, 1H), 3.38 – 3.26 (m, 1H), 3.19 (ddd, *J* = 8.7, 2.8 Hz, 1H), 2.69 – 2.53 (m, 1H), 2.16 – 1.93 (m, 4H), 1.93 – 1.74 (m, 1H), 1.71 – 1.57 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 154.4, 138.8, 138.1, 132.7, 132.7, 130.7, 129.1, 127.9, 127.6, 126.9, 126.8, 123.8, 122.7, 71.7, 53.6, 47.8, 46.1, 44.9, 44.6, 40.8, 30.7, 23.4, 23.2.

IR (neat) *v* (cm^{-1}): 3328, 3058, 2924, 2854, 1630, 1533, 1491, 1474, 1439, 1474, 1371, 1337, 1295, 1271.

HRMS (ESI+, m/z): calculated for $C_{24}H_{27}Br_2N_4O_2$ **[M+H]$^+$**: 561.0501, found 561.0485.

(3aS,9aS,9bR)-5-oxo-N,4-diphenethyldecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10e$_{endo}$)



10e$_{endo}$

Prepared according to general procedure **B** to provide the title compound **10e$_{endo}$** as a white foam (28.5 mg, 90% yield).

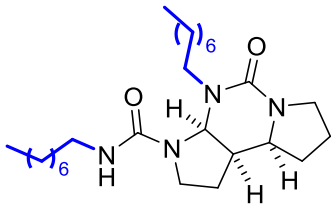
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.12 (m, 10H), 5.63 (d, *J* = 6.1 Hz, 1H), 4.31 (t, *J* = 5.8 Hz, 1H), 3.85 (ddd, *J* = 13.8, 10.3, 5.7 Hz, 1H), 3.70 (ddt, *J* = 8.9, 6.3, 3.1 Hz, 1H), 3.67 – 3.28 (m, 5H), 3.25 – 3.01 (m, 3H), 2.92 – 2.82 (m, 2H), 2.76 (ddd, *J* = 12.4, 10.1, 5.7 Hz, 1H), 2.62 – 2.38 (m, 1H), 2.13 – 1.88 (m, 4H), 1.87 – 1.76 (m, 1H), 1.66 – 1.48 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 154.3, 140.3, 139.3, 129.4 (2C), 128.9 (2C), 128.8 (2C), 128.3 (2C), 126.6, 126.0, 70.7, 53.3, 45.8, 45.2, 44.2, 42.0, 40.7, 36.5, 35.1, 30.5, 23.3, 23.2.

IR (neat) *v* (cm^{-1}): 3331, 3061, 3026, 2946, 2877, 2229, 1622, 1533, 1494, 1477, 1454, 1431, 1349, 1272, 1248.

HRMS (ESI+, m/z): calculated for $C_{26}H_{33}N_4O_2$ **[M+H]$^+$**: 433.2604, found 433.2598.

(3aS,9aS,9bR)-N,4-dioctyl-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10f_{endo}$)



$10f_{endo}$

Prepared according to general procedure **B** to provide the title compound **$10f_{endo}$** as a white foam (20 mg, 69% yield).

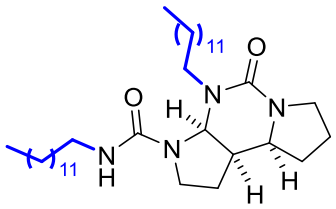
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (d, *J* = 6.1 Hz, 1H), 4.34 – 4.01 (m, 1H), 3.77 – 3.67 (m, 1H), 3.63 – 3.17 (m, 7H), 3.10 (ddd, *J* = 14.1, 9.5, 5.1 Hz, 1H), 2.66 – 2.45 (m, 1H), 2.13 – 1.84 (m, 4H), 1.82 – 1.62 (m, 4H), 1.58 – 1.43 (m, 2H), 1.36 – 1.17 (m, 20H), 1.02 – 0.80 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 154.2, 70.4, 53.2, 45.7, 44.2, 43.4, 40.8, 40.6, 31.9, 31.8, 30.5, 30.4, 29.6, 29.4, 29.3, 29.2, 28.9, 27.3, 26.9, 23.2, 23.0, 22.7, 22.6, 14.1, 14.1.

IR (neat) *v* (cm^{-1}): 3340, 2954, 2924, 2853, 1649, 1620, 1531, 1487, 1362, 1337.

HRMS (ESI+, m/z): calculated for $C_{26}H_{49}N_4O_2$ **[M+H]$^+$**: 449.3856, found 449.3877.

(3aS,9aS,9bR)-5-oxo-N,4-ditridecyldecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10g_{endo}$)



$10g_{endo}$

Prepared according to general procedure **B** to provide the title compound **$10g_{endo}$** as a white foam (34.2 mg, 77% yield).

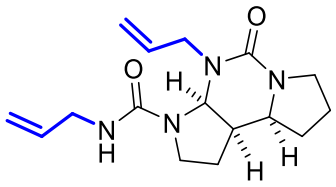
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (d, *J* = 6.0 Hz, 1H), 4.29 (t, *J* = 5.7 Hz, 1H), 3.73 (ddd, *J* = 5.9, 3.2 Hz, 1H), 3.66 – 3.06 (m, 8H), 2.55 (ddd, *J* = 9.3, 6.2, 3.3 Hz, 1H), 2.14 – 1.87 (m, 4H), 1.87 – 1.75 (m, 1H), 1.60 – 1.46 (m, 3H), 1.41 – 1.09 (m, 42H), 0.98 – 0.81 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 154.3, 70.5, 53.3, 45.8, 44.3, 43.5, 40.9, 40.7, 32.1, 30.6, 30.6, 29.9, 29.9 (3C), 29.8 (3C), 29.8 (3C), 29.8 (3C), 29.7, 29.5 (2C), 29.5, 29.0, 27.4, 27.1, 23.4, 23.2, 22.8, 14.3.

IR (neat) *v* (cm^{-1}): 3321, 2954, 2918, 2850, 1621, 1532, 1479, 1467, 1428, 1387, 1362, 1272.

HRMS (ESI+, m/z): calculated for $C_{36}H_{69}N_4O_2$ **[M+H]$^+$**: 589.5421, found 589.5466.

(3aS,9aS,9bR)-N,4-diallyl-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10h_{endo}$)



$10h_{endo}$

Prepared according to general procedure **B** to provide the title compound **$10h_{endo}$** as a white foam (42.6 mg, 96% yield).

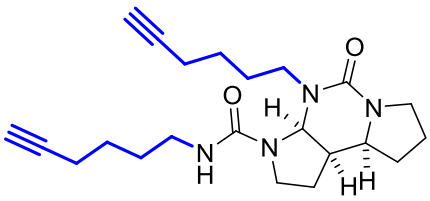
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 – 5.77 (m, 2H), 5.64 (d, *J* = 6.0 Hz, 1H), 5.36 – 4.97 (m, 4H), 4.56 – 4.26 (m, 1H), 4.20 – 4.06 (m, 1H), 4.05 – 3.81 (m, 3H), 3.76 (ddd, *J* = 9.2, 5.8, 3.2 Hz, 1H), 3.61 (ddd, *J* = 11.0, 8.7, 2.6 Hz, 1H), 3.50 – 3.25 (m, 3H), 2.66 – 2.46 (m, 1H), 2.09 – 1.86 (m, 4H), 1.87 – 1.72 (m, 1H), 1.63 – 1.44 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 154.1, 135.8, 135.4, 116.0, 114.5, 70.8, 53.4, 45.9, 45.6, 44.2, 43.2, 40.7, 30.6, 23.3, 23.0.

IR (neat) *v* (cm^{-1}): 3324, 3075, 2923, 2878, 1620, 1532, 1491, 1474, 1370, 1332, 1293, 1271.

HRMS (ESI+, m/z): calculated for $C_{16}H_{25}N_4O_2$ **$[M+H]^+$**: 305.1978, found 305.1988.

(3aS,9aS,9bR)-N,4-di(hex-5-yn-1-yl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10i_{endo}$)



$10i_{endo}$

Prepared according to general procedure **B** to provide the title compound **$10i_{endo}$** as a white foam (23.8 mg, 80% yield).

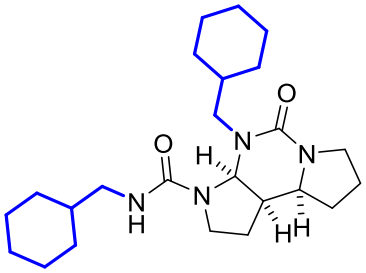
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 6.1 Hz, 1H), 4.37 (t, *J* = 5.6 Hz, 1H), 3.72 (ddd, *J* = 9.1, 5.8, 3.1 Hz, 1H), 3.65 – 3.49 (m, 2H), 3.46 – 3.19 (m, 5H), 3.12 (ddd, *J* = 13.9, 8.6, 5.3 Hz, 1H), 2.61 – 2.47 (m, 1H), 2.28 – 2.15 (m, 4H), 2.07 – 1.87 (m, 6H), 1.88 – 1.70 (m, 2H), 1.68 – 1.43 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 154.3, 85.1, 84.3, 70.6, 68.8, 68.1, 53.3, 45.9, 44.4, 42.8, 40.7, 40.3, 30.6, 29.5, 28.2, 26.4, 25.9, 23.4, 23.2, 18.5, 18.3.

IR (neat) *v* (cm^{-1}): 3297, 2940, 2869, 1619, 1535, 1493, 1476, 1433, 1360.

HRMS (ESI+, m/z): calculated for $C_{22}H_{33}N_4O_2$ **[M+H]**$^+$: 385.2604, found 385.2589.

(3aS,9aS,9bR)-N,4-bis(cyclohexylmethyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10j$_{endo}$)



10j$_{endo}$

Prepared according to general procedure **B** to provide the title compound **10j$_{endo}$** as a white foam (29.8 mg, quantitative yield).

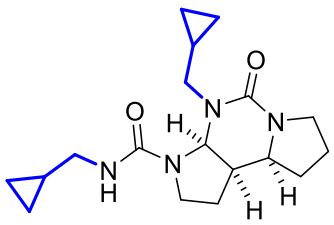
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (d, *J* = 6.3 Hz, 1H), 4.33 (t, *J* = 6.0 Hz, 1H), 3.75 (ddd, *J* = 9.4, 6.0, 3.1 Hz, 1H), 3.61 (ddd, *J* = 11.0, 8.5, 2.7 Hz, 1H), 3.50 (dd, *J* = 13.9, 7.6 Hz, 1H), 3.45 – 3.29 (m, 3H), 3.12 – 2.99 (m, 2H), 2.84 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.66 – 2.50 (m, 1H), 2.09 – 1.87 (m, 4H), 1.84 – 1.54 (m, 14H), 1.53 – 1.38 (m, 1H), 1.30 – 1.10 (m, 5H), 1.02 – 0.76 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 154.9, 71.1, 53.3, 48.5, 47.0, 46.0, 44.5, 41.0, 38.5, 36.7, 31.0, 30.9, 30.9 (2C), 30.6, 26.7, 26.6, 26.3, 26.2, 26.0 (2C), 23.4, 23.2.

IR (neat) *v* (cm^{-1}): 3332, 2921, 2850, 2230, 1623, 1536, 1491, 1474, 1447, 1432, 1355, 1335, 1270.

HRMS (ESI+, m/z): calculated for $C_{24}H_{41}N_4O_2$ **[M+H]**$^+$: 417.3230, found 417.3232.

(3aS,9aS,9bR)-N,4-bis(cyclopropylmethyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10k$_{endo}$)



10k$_{endo}$

Prepared according to general procedure **B** to provide the title compound **10k$_{endo}$** as a white foam (24.5 mg, 83% yield).

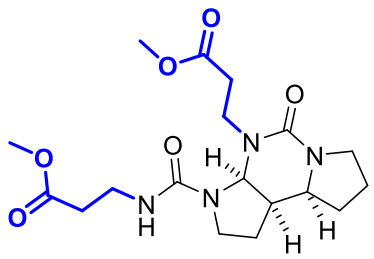
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (d, *J* = 6.0 Hz, 1H), 4.42 (t, *J* = 5.5 Hz, 1H), 3.81 – 3.74 (m, 1H), 3.64 – 3.56 (m, 1H), 3.53 – 3.27 (m, 4H), 3.10 (t, *J* = 6.3 Hz, 2H), 3.01 (dd, *J* = 14.3, 6.6 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.11 – 1.98 (m, 3H), 1.97 – 1.88 (m, 1H), 1.87 – 1.73 (m, 1H), 1.67 – 1.45 (m, 1H), 1.39 – 1.08 (m, 1H), 1.00 – 0.91 (m, 1H), 0.69 – 0.26 (m, 5H), 0.27 – 0.15 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 154.4, 70.5, 53.2, 47.0, 45.8, 45.6, 44.3, 40.6, 30.5, 23.2, 23.1, 11.3, 10.6, 3.7, 3.4, 3.3, 3.3.

IR (neat) *v* (cm^{-1}): 3321, 3078, 2925, 2877, 1619, 1531, 1491, 1473, 1359, 1323, 1294, 1269, 1235, 1196.

HRMS (ESI+, m/z): calculated for $C_{18}H_{29}N_4O_2$ **[M+H]$^+$**: 333.2291, found 333.2293.

Methyl 3-((3aS,9aS,9bR)-4-(3-methoxy-3-oxopropyl)-5-oxodecahydro-1H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamido)propanoate (10l$_{endo}$)



10l$_{endo}$

Prepared according to general procedure **B** to provide the title compound **10l$_{endo}$** as a pale yellow oil (45.4 mg, 92% yield).

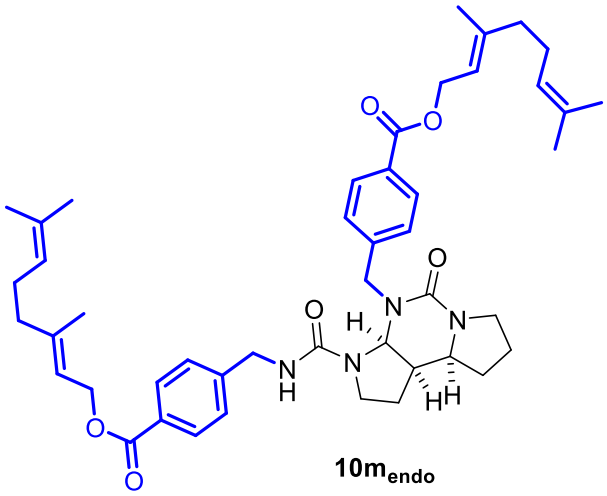
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 – 5.61 (m, 1H), 5.57 (d, *J* = 6.0 Hz, 1H), 3.91 – 3.77 (m, 1H), 3.76 – 3.63 (m, 1H), 3.67 (s, 3H), 3.65 (s, 3H), 3.58 – 3.31 (m, 7H), 2.92 – 2.75 (m, 1H), 2.62 – 2.40 (m, 4H), 2.07 – 1.84 (m, 4H), 1.83 – 1.70 (m, 1H), 1.56 (qd, *J* = 11.5, 7.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 173.5, 157.2, 153.9, 71.3, 53.2, 51.8, 51.8, 45.9, 44.4, 41.0, 38.7, 36.4, 34.4, 33.5, 30.5, 23.3, 22.5.

IR (neat) *v* (cm^{-1}): 3347, 2952, 2881, 1731, 1619, 1533, 1494, 1478, 1436, 1361, 1273, 1195, 1171.

HRMS (ESI+, m/z): calculated for $C_{18}H_{29}N_4O_2$ **[M+H]$^+$**: 397.2087, found 397.2063.

(E)-3,7-dimethylocta-2,6-dien-1-yl 4-(((3aS,9aS,9bR)-4-(4-((((E)-3,7-dimethylocta-2,6-dien-1-yl)oxy)carbonyl)benzyl)-5-oxodecahydro-1H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamido)methyl)benzoate (10m$_{endo}$)



10m$_{endo}$

Prepared according to general procedure **B** to provide the title compound **10m$_{endo}$** as a colorless oil (13.2 mg, 52% yield).

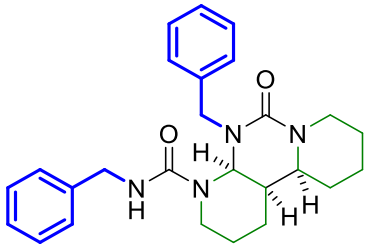
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 17.1, 8.1 Hz, 4H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.76 (d, *J* = 5.8 Hz, 1H), 5.56 – 5.36 (m, 2H), 5.17 – 5.05 (m, 1H), 5.00 – 4.92 (m, 1H), 4.91 – 4.66 (m, 5H), 4.54 – 4.32 (m, 2H), 4.31 – 4.05 (m, 1H), 3.97 (s, 1H), 3.86 – 3.77 (m, 1H), 3.68 – 3.60 (m, 1H), 3.61 – 3.40 (m, 1H), 3.31 – 3.08 (m, 2H), 2.90 – 2.74 (m, 1H), 2.61 – 2.53 (m, 1H), 2.20 – 1.96 (m, 11H), 1.90 – 1.54 (m, 20H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 166.5, 156.2, 154.4, 146.5, 144.0, 142.4, 132.0, 130.1 (2C), 129.4 (2C), 128.6, 127.6 (2C), 126.9, 126.8 (2C), 123.9, 123.9, 118.6, 118.5, 114.0, 110.2, 86.9, 85.3, 71.4, 62.1, 62.0, 56.2, 53.5, 47.3, 46.1, 44.4, 44.1, 40.5, 39.7, 30.6, 29.9, 26.5, 26.5, 25.8, 23.4, 23.1, 17.9, 16.7.

IR (neat) *v* (cm^{-1}): 3324, 3028, 2954, 2924, 2854, 1713, 1630, 1533, 1475, 1376.

HRMS (ESI+, m/z): calculated for $C_{46}H_{61}N_4O_6$ **[M+H]$^{+}$**: 765.4591, found 765.4597.

(4aS,11aS,11bR)-N,5-dibenzyl-6-oxodecahydro-1H-dipyrido[1,2-c:3',2'-e]pyrimidine-4(4aH)-carboxamide (10n$_{endo}$)



10n$_{endo}$

Prepared according to general procedure **B** to provide the pure isolated the title compound **10n$_{endo}$** as a pale yellow foam (12.3 mg, 44% yield).

dr(Endo/Exo) of reaction was found to be 6:4 as determined by ^{1}H NMR on the crude reaction mixture.

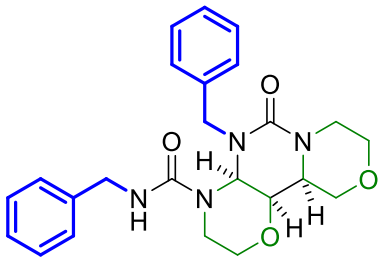
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 3H), 7.25 – 7.09 (m, 7H), 5.69 (d, *J* = 3.8 Hz, 1H), 4.71 – 4.29 (m, 4H), 4.28 – 4.11 (m, 2H), 3.27 (d, *J* = 13.1 Hz, 1H), 2.98 (d, *J* = 10.1 Hz, 1H), 2.68 – 2.51 (m, 1H), 2.44 (td, *J* = 13.7, 13.1, 3.1 Hz, 1H), 2.08 – 1.72 (m, 3H), 1.64 – 1.39 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 156.6, 139.5, 139.3, 128.8 (2C), 128.4 (2C), 128.1 (2C), 128.0 (2C), 127.6, 127.0, 63.1, 60.4, 47.2, 47.1, 45.3, 39.4, 37.2, 32.1, 25.8, 25.7, 25.6, 24.6.

IR (neat) *v* (cm^{-1}): 3347, 3030, 2926, 2854, 1615, 1533, 1470, 1439, 1412, 1341, 1257, 1193, 1161.

HRMS (ESI+, m/z): calculated for $C_{26}H_{33}N_4O_2$ **[M+H]$^+$**: 433.2604, found 433.2597.

(4aS,11aS,11bR)-N,5-dibenzyl-6-oxodecahydro-4H-pyrimido[5,4-b:6,1-c']bis([1,4]oxazine)-4-carboxamide (10o$_{endo}$)



10o$_{endo}$

Prepared according to general procedure **B** to provide the pure isolated the title compound **10o$_{endo}$** as a pale yellow foam (25 mg, 84% yield).

dr(Endo/Exo) of reaction was found to be 9:1 as determined by ^{1}H NMR on the crude reaction mixture.

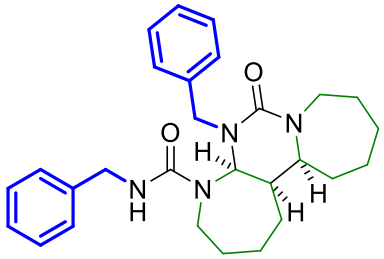
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.07 (m, 10H), 5.61 (d, *J* = 2.7 Hz, 1H), 4.83 (d, *J* = 15.4 Hz, 1H), 4.46 – 4.22 (m, 3H), 4.14 (dd, *J* = 13.3, 1.9 Hz, 1H), 4.11 – 3.94 (m, 1H), 3.96 (dd, *J* = 11.7, 3.8 Hz, 1H), 3.85 – 3.44 (m, 7H), 3.07 – 2.87 (m, 2H), 2.73 – 2.57 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5, 156.5, 139.1, 138.6, 128.8 (2C), 128.4 (2C), 128.2 (2C), 127.8, 127.7 (2C), 127.1, 69.6, 66.9, 66.9, 65.9, 63.1, 53.5, 47.9, 45.3, 42.8, 38.9.

IR (neat) *v* (cm^{-1}): 3353, 3029, 2924, 2855, 1622, 1536, 1495, 1467, 1444, 1341, 1261, 1239, 1121.

HRMS (ESI+, m/z): calculated for $C_{24}H_{29}N_4O_4$ **[M+H]$^+$**: 436.2111, found 436.2186.

(5aS,13aS,13bR)-N,6-dibenzyl-7-oxotetradecahydro-5H-pyrimido[1,6-a:4,5-b']bis(azepine)-5-carboxamide (10p$_{endo}$)



10p$_{endo}$

Prepared according to general procedure **B** to provide the title compound **10p$_{endo}$** as a pale yellow oil (11.1 mg, 37% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.11 (m, 10H), 5.65 – 5.51 (m, 1H), 4.77 – 4.62 (m, 2H), 4.40 (d, *J* = 15.5 Hz, 1H), 4.37 – 4.32 (m, 1H), 4.27 (d, *J* = 5.7 Hz, 2H), 4.18 (ddd, *J* = 14.1, 6.7, 4.0 Hz, 1H), 3.61 – 3.45 (m, 1H), 3.17 – 3.02 (m, 2H), 2.65 (ddd, *J* = 14.1, 9.2, 5.6 Hz, 1H), 2.09 – 1.97 (m, 1H), 1.94 – 1.77 (m, 2H), 1.80 – 1.60 (m, 3H), 1.53 – 1.16 (m, 8H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 154.4, 139.4, 138.9, 128.8 (2C), 128.7 (2C), 127.6 (2C), 127.5 (2C), 127.5, 127.3, 123.1, 116.5, 61.4, 50.0, 47.5, 44.7, 40.3, 36.0, 30.5, 30.0, 27.6, 26.2, 26.1, 25.0.

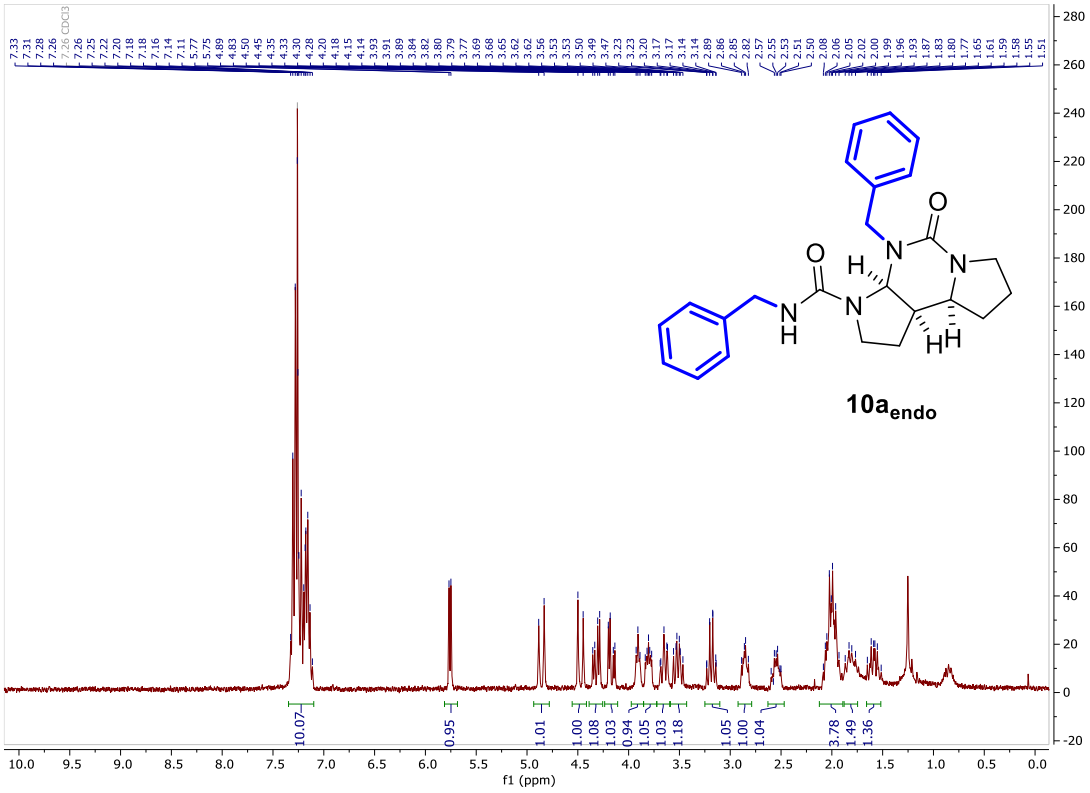
IR (neat) *v* (cm^{-1}): 3353, 3029, 2925, 2856, 1622, 1565, 1472, 1453, 1373, 1253.

HRMS (ESI+, m/z): calculated for $C_{28}H_{37}N_4O_2$ **[M+H]$^+$**: 461.2917, found 461.2914.

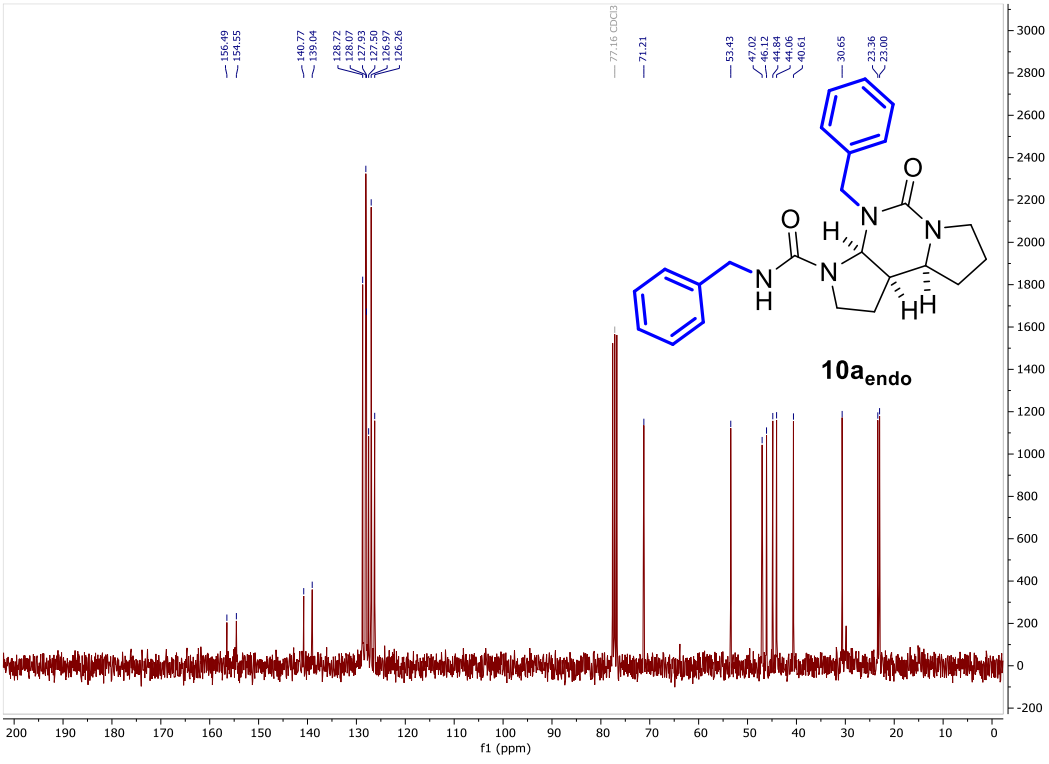
^{1}H and ^{13}C NMR spectra of endo dimers 10$_{endo}$

(3aS,9aS,9bR)-N,4-dibenzyl-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10a$_{endo}$)

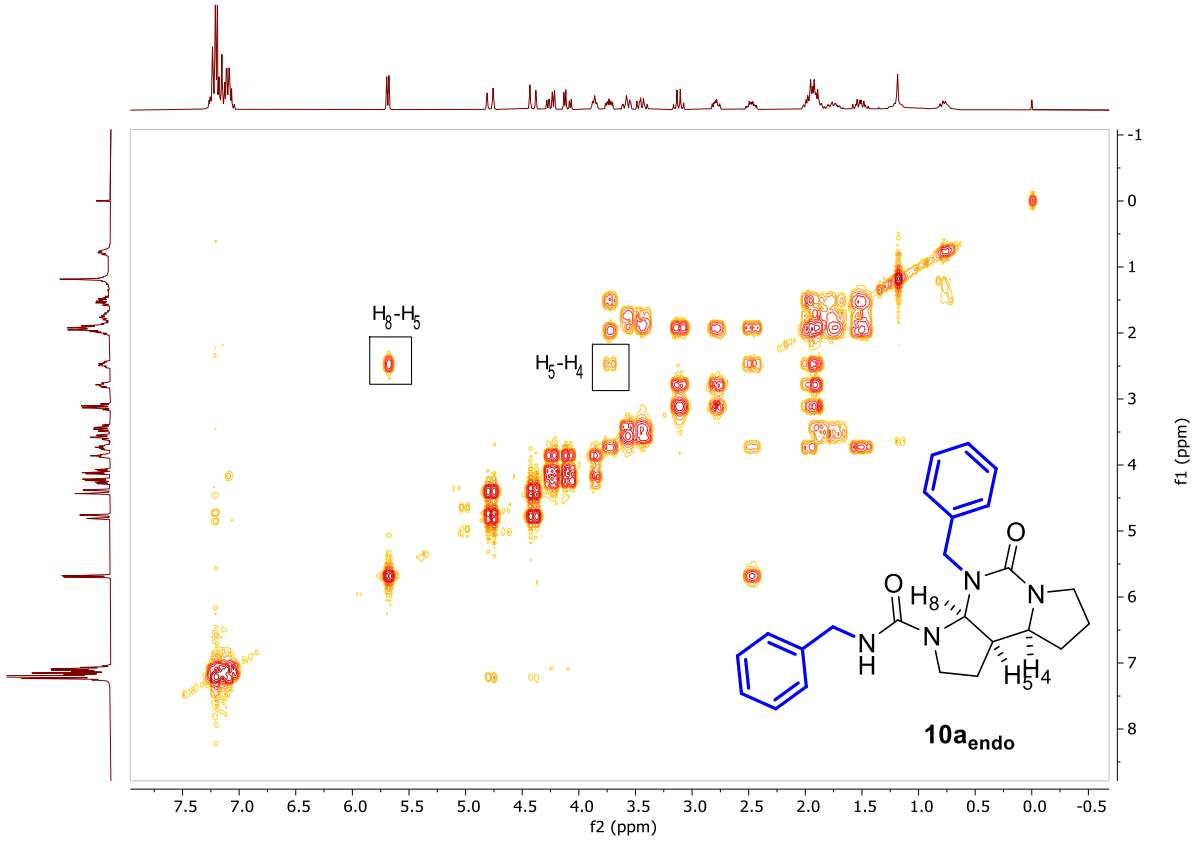
^{1}H NMR, 300 MHz, $CDCl_3$



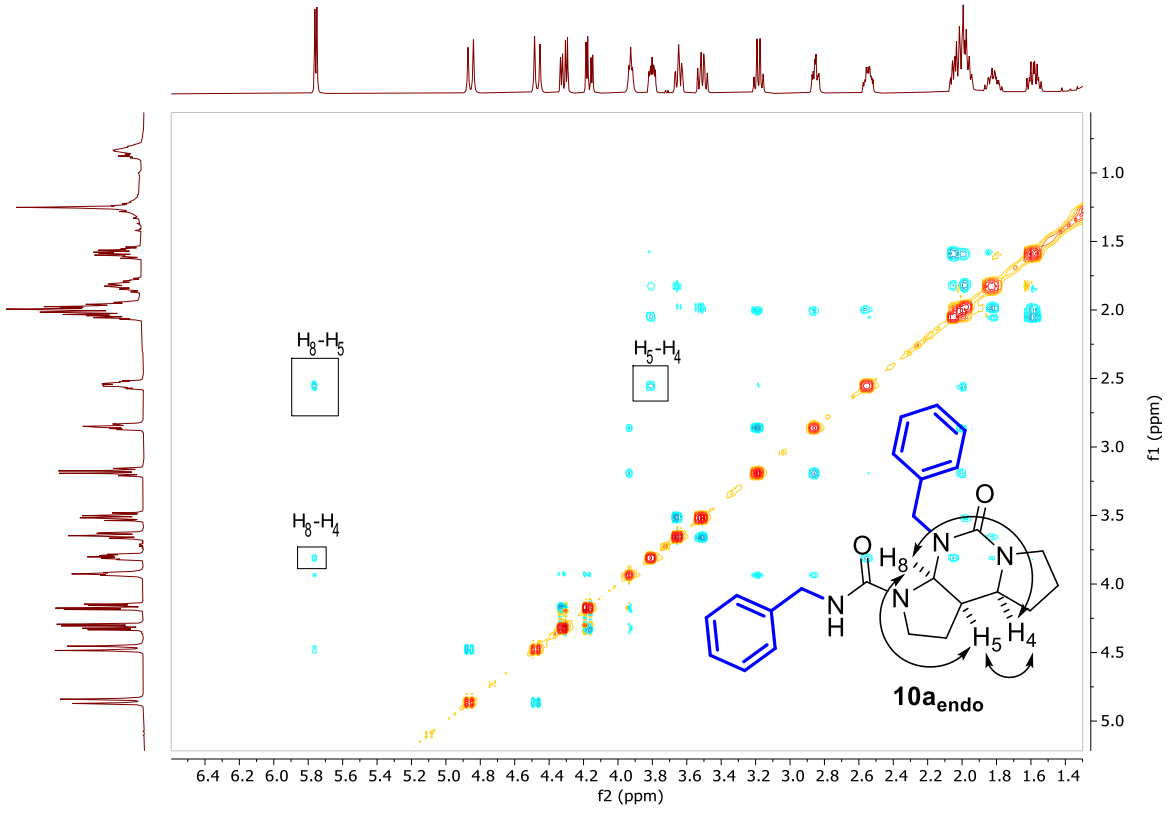
^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$



2D-COSY, 300 MHz, $CDCl_3$

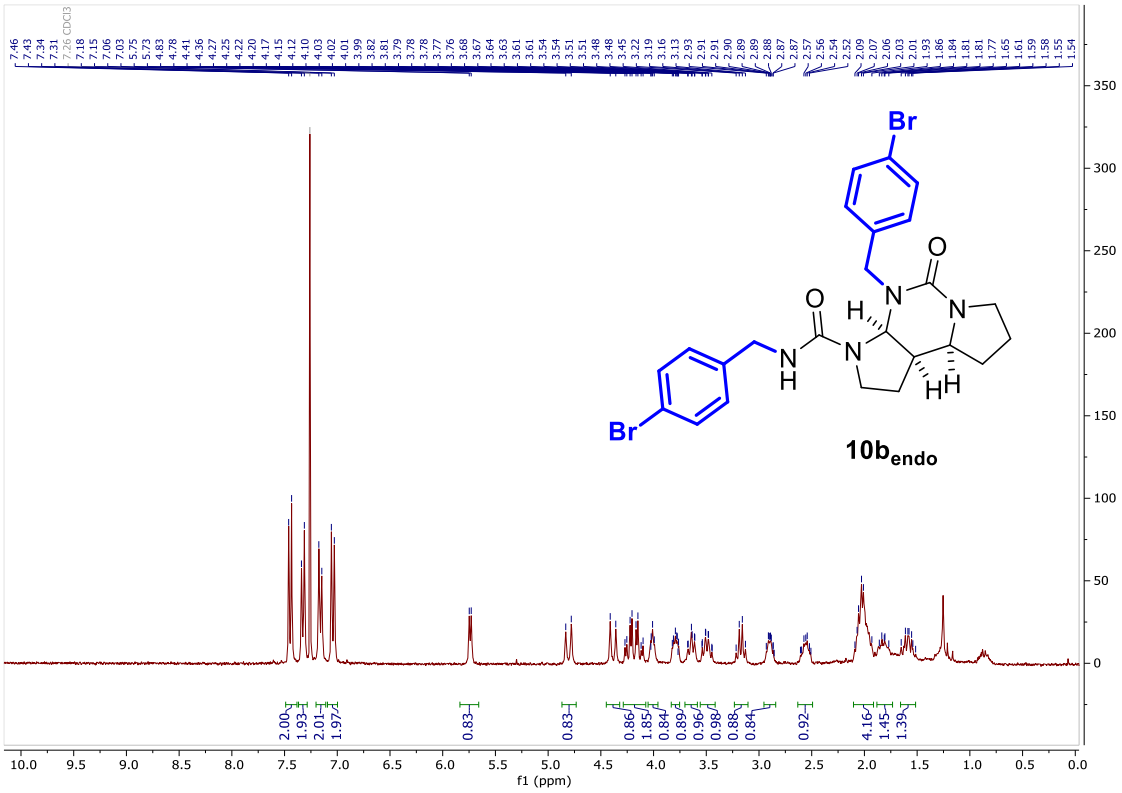


2D ROESY spectrum , 500 MHz, $CDCl_3$

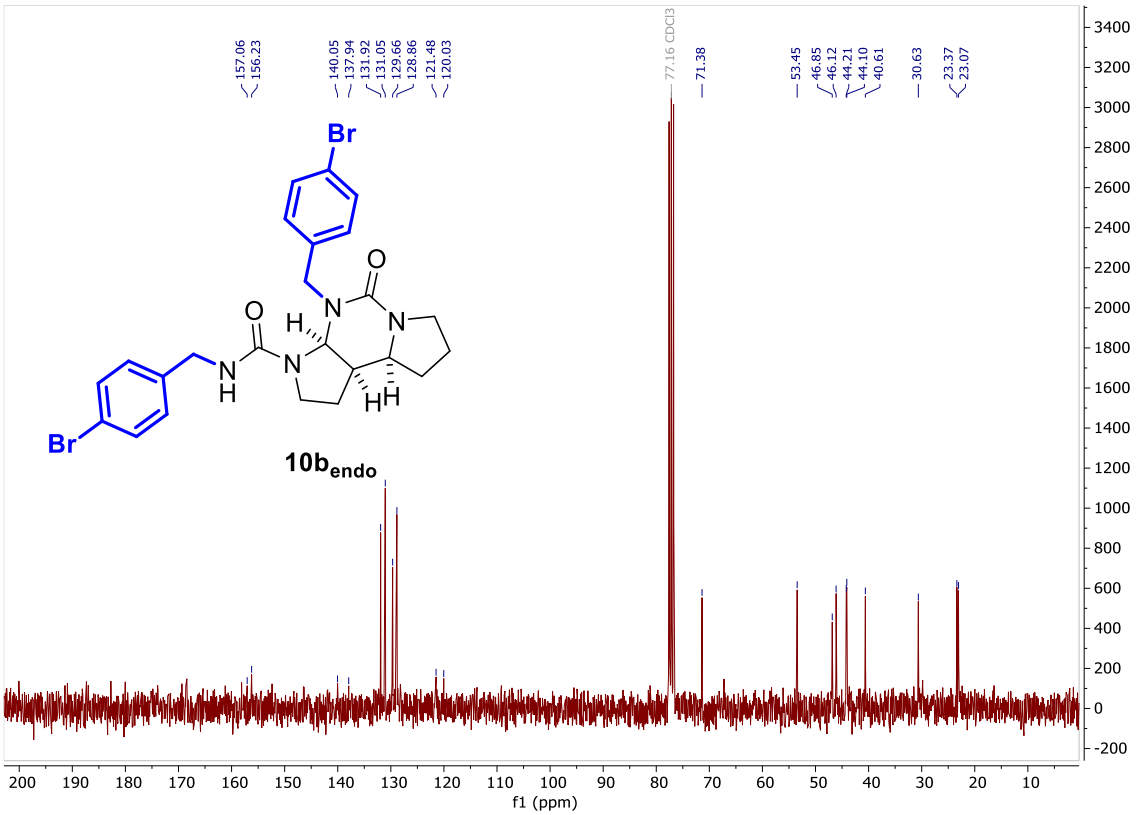


(3aS,9aS,9bR)-N,4-bis(4-bromobenzyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10b_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

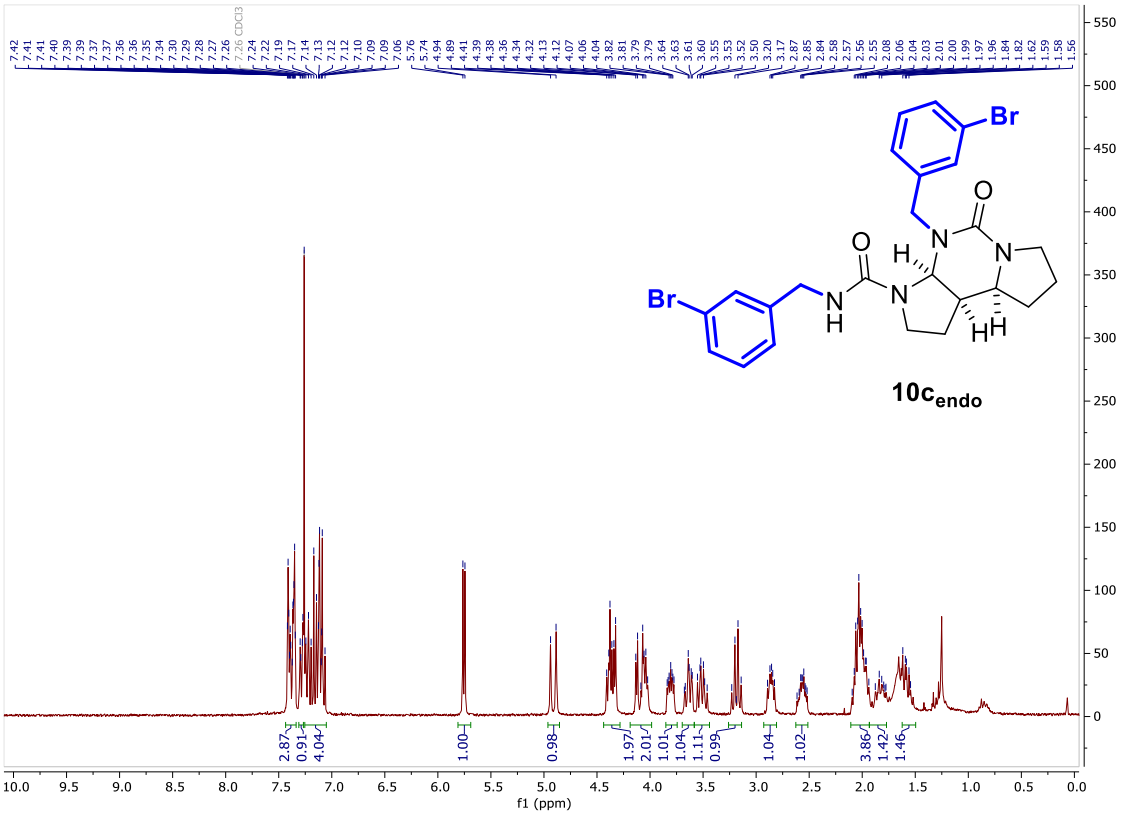


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

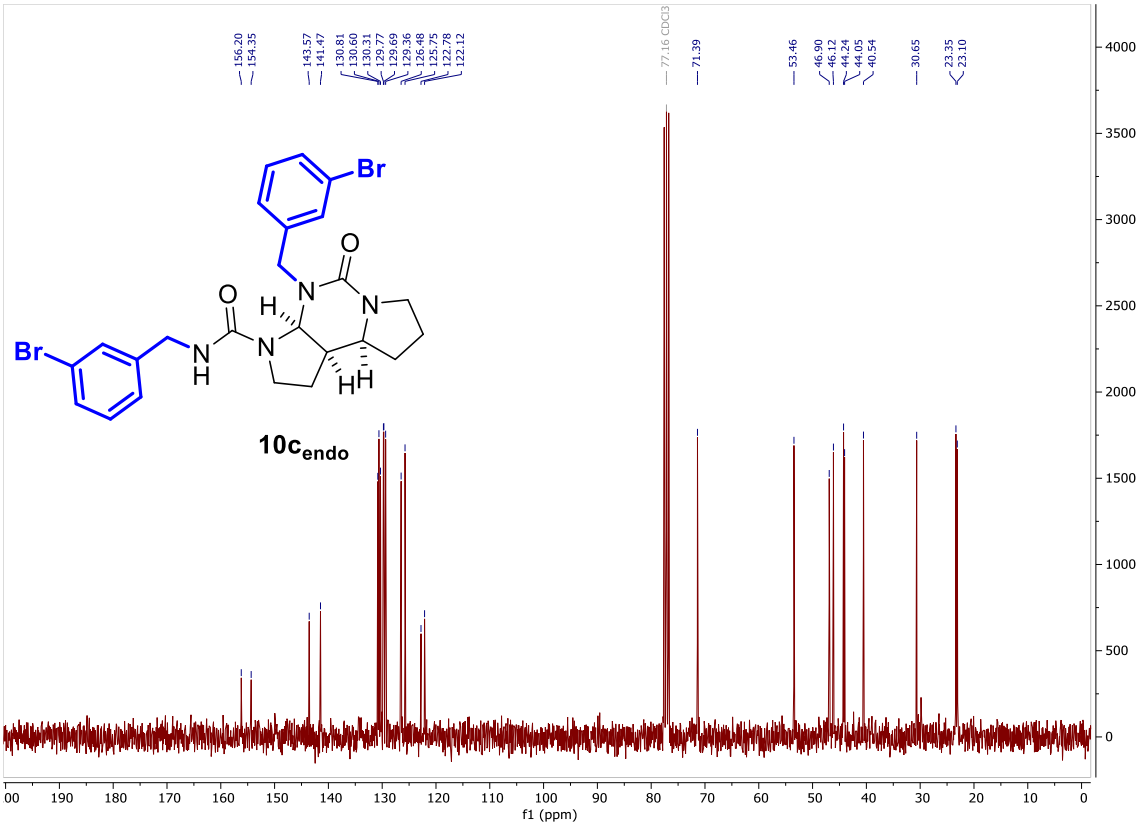


(3aS,9aS,9bR)-N,4-bis(3-bromobenzyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10c$_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

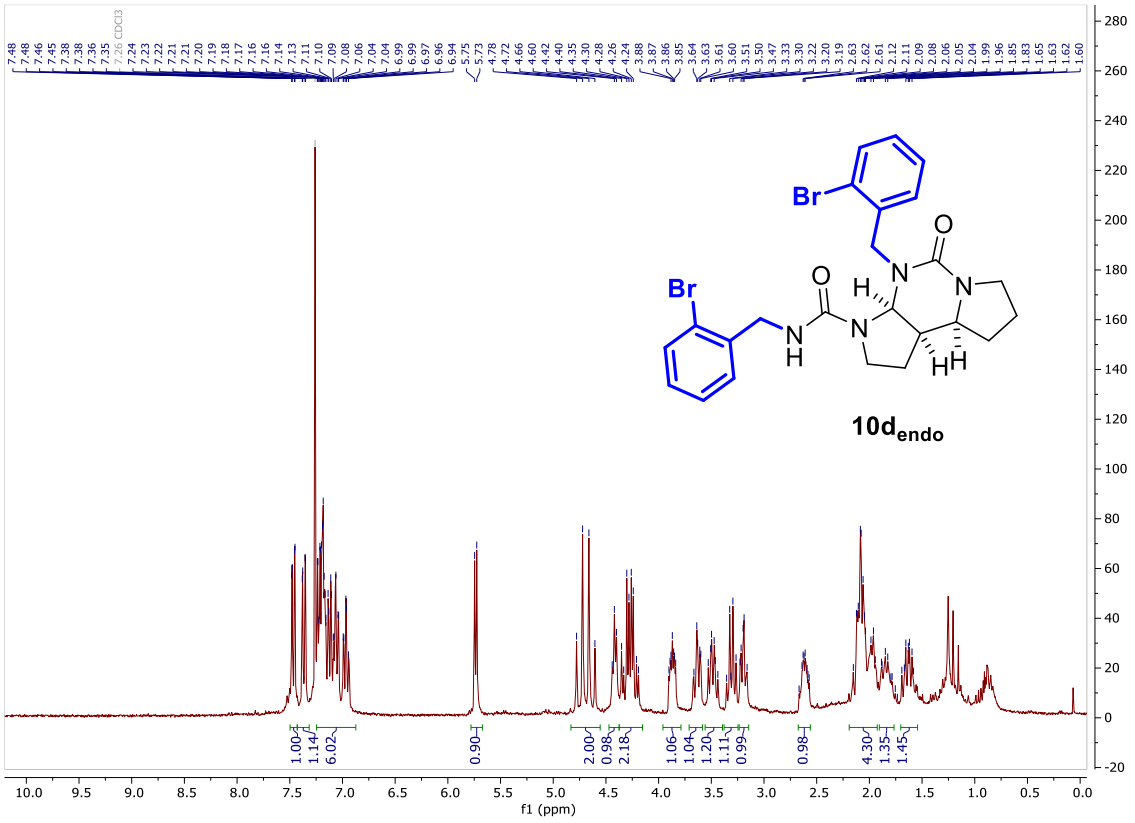


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$

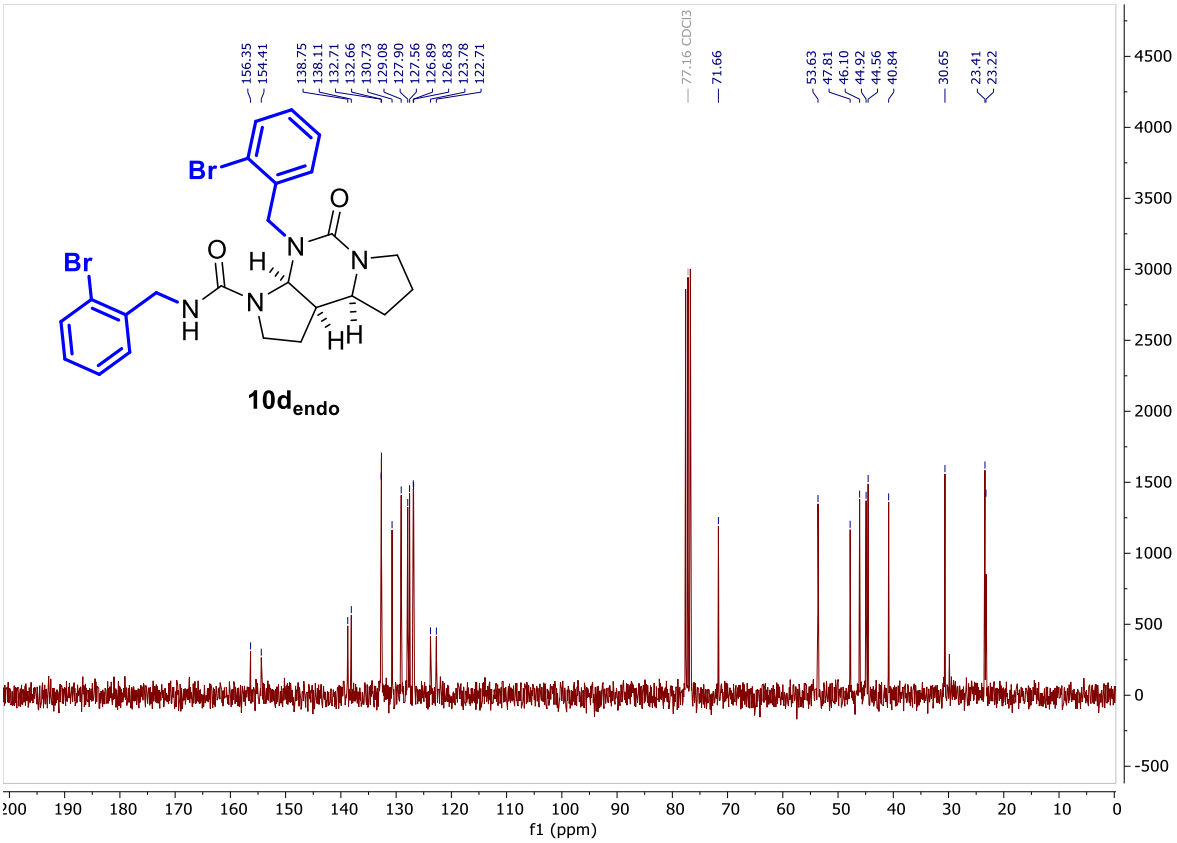


(3aS,9aS,9bR)-N,4-bis(2-bromobenzyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10d_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

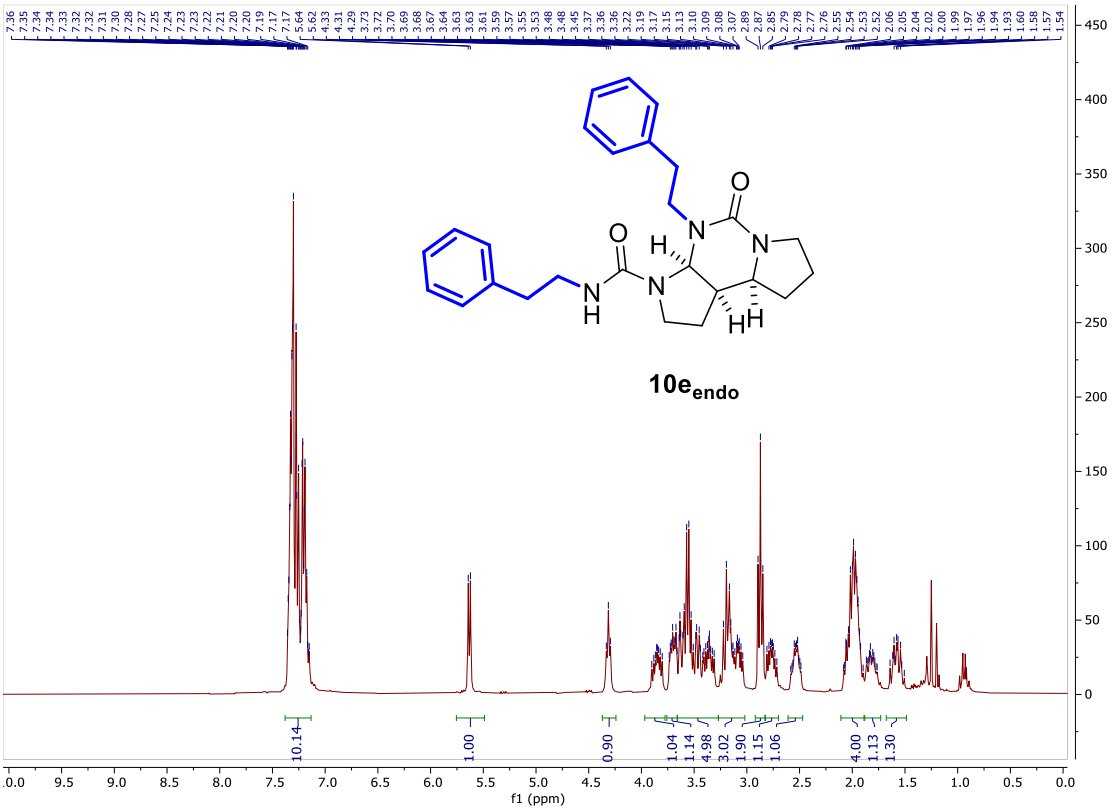


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

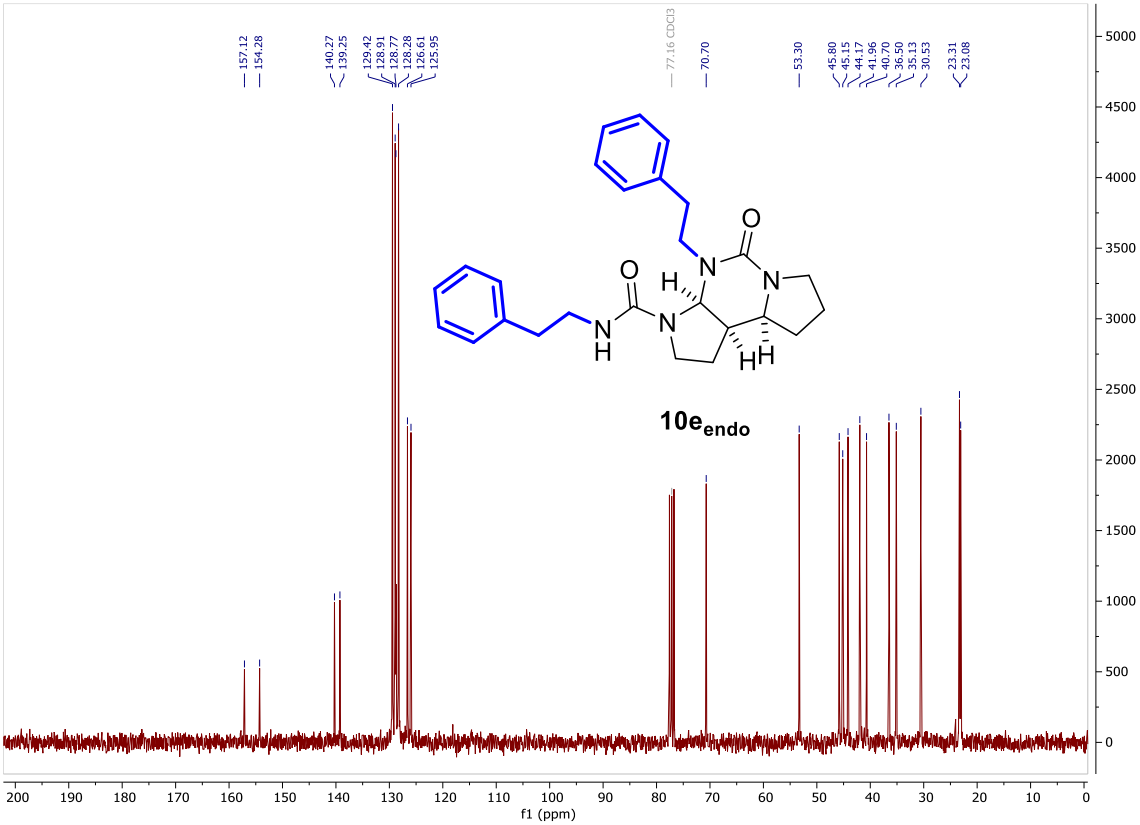


(3aS,9aS,9bR)-5-oxo-N,4-diphenethyldecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10e_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

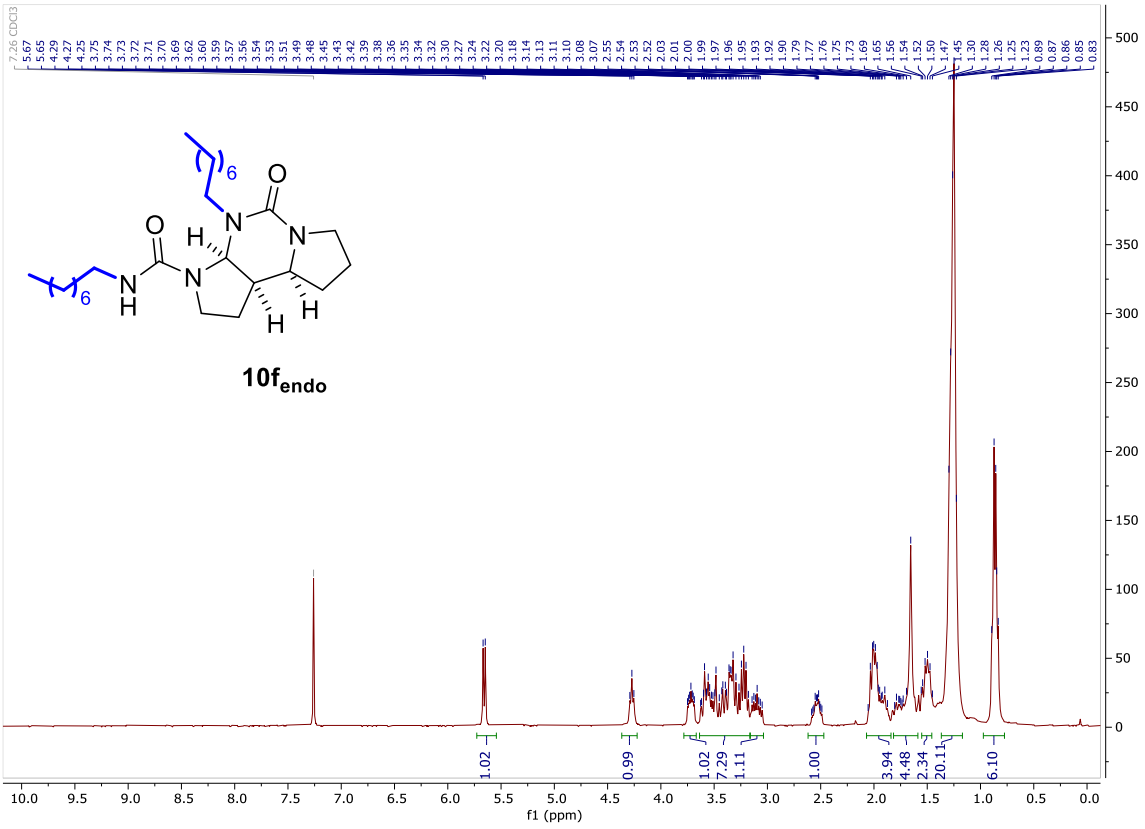


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

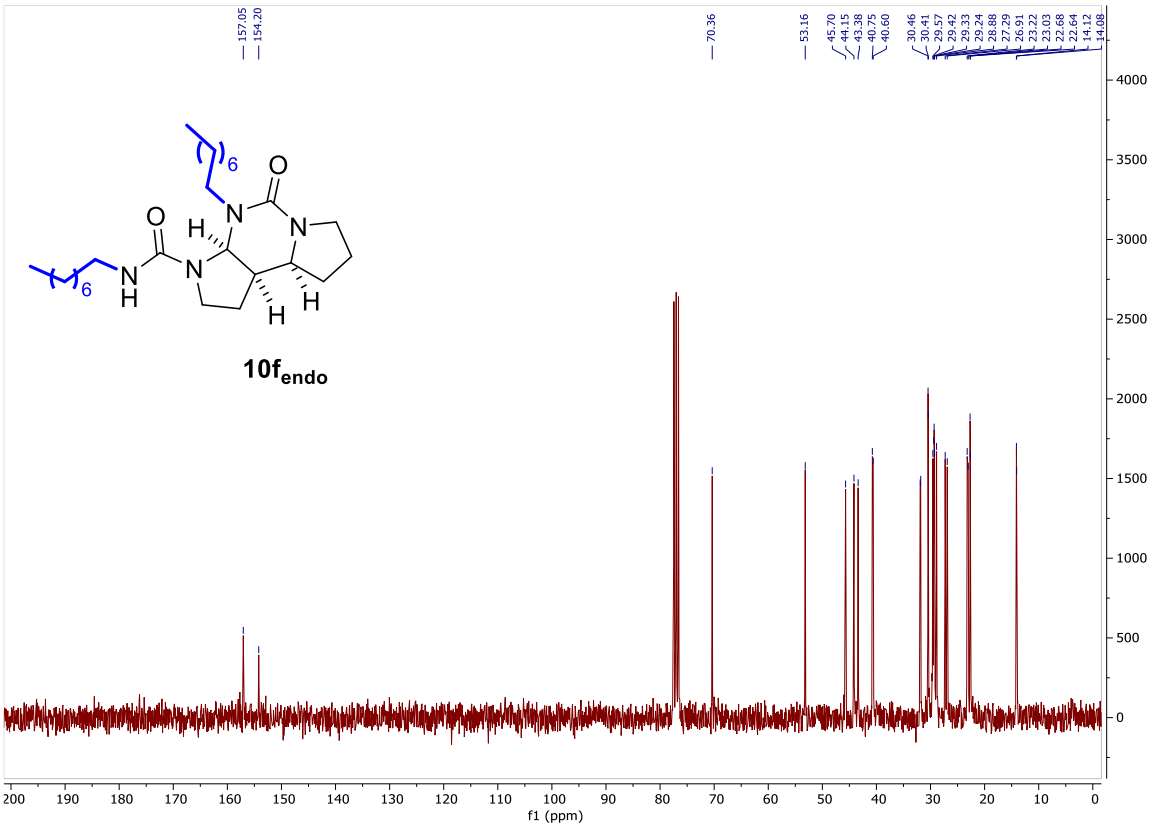


(3aS,9aS,9bR)-N,4-dioctyl-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10f$_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

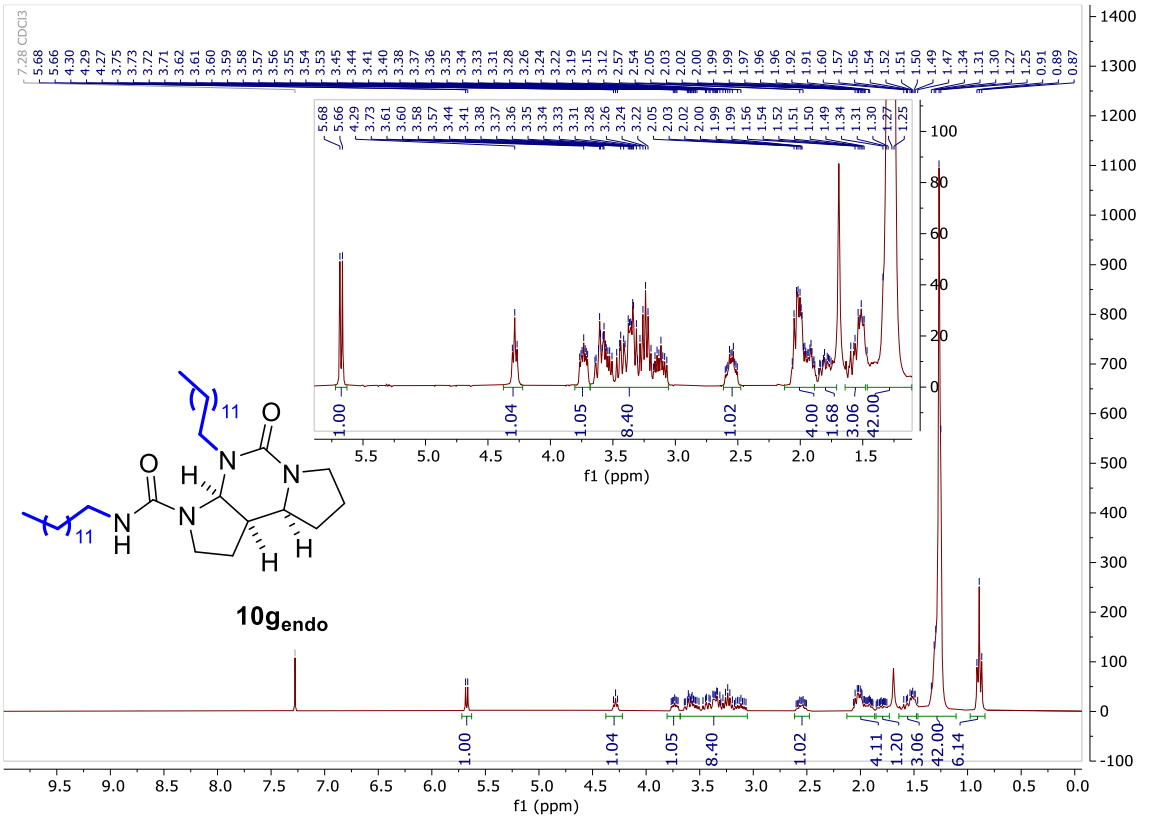


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

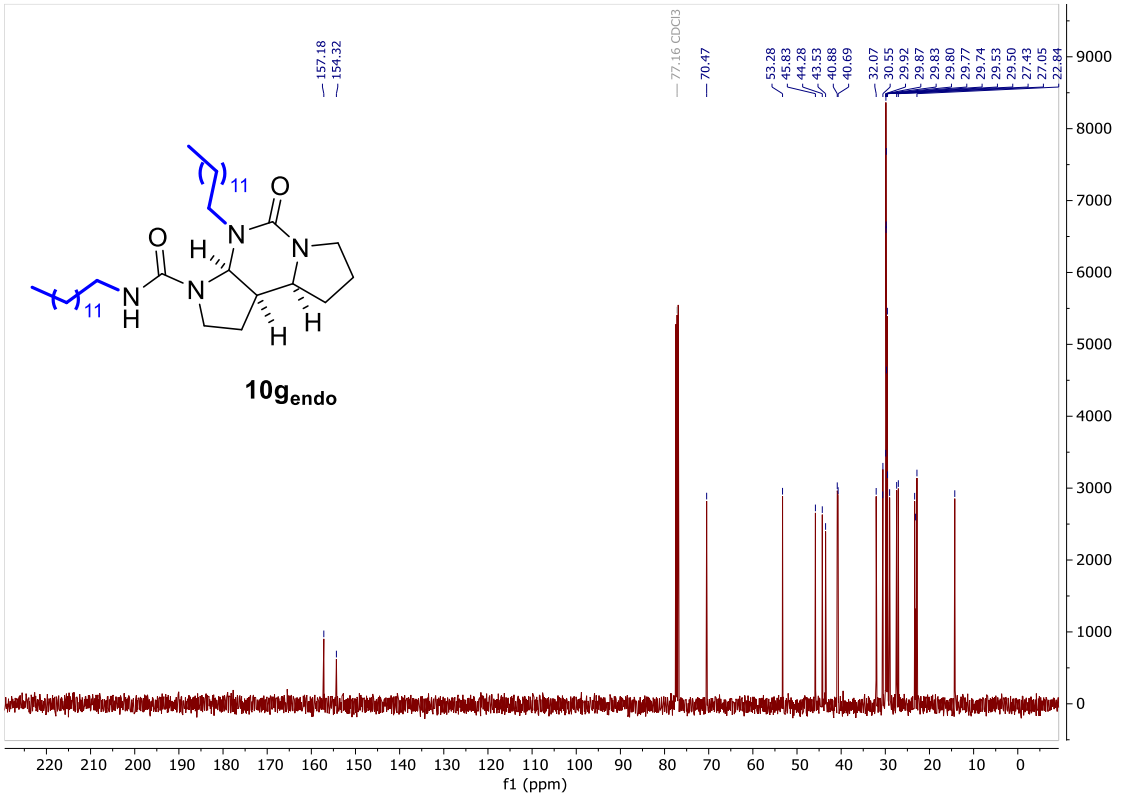


(3aS,9aS,9bR)-5-oxo-N,4-ditridecyldecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10g_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

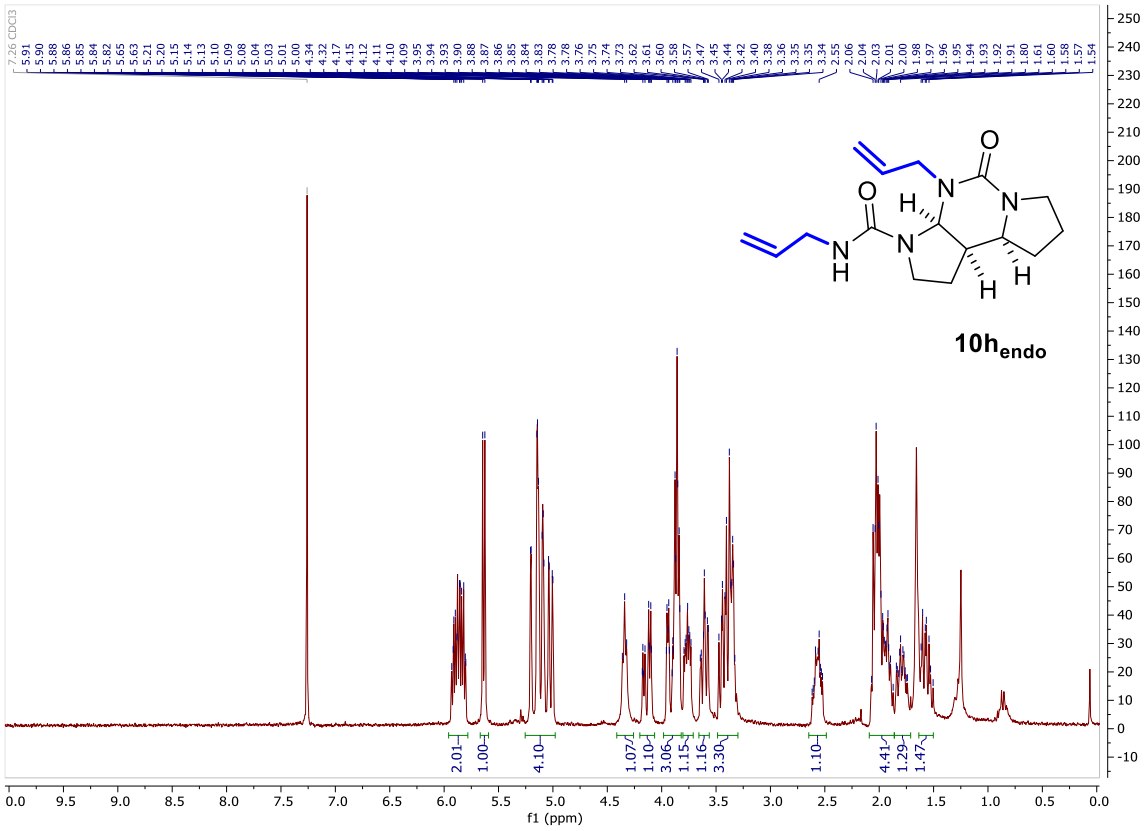


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

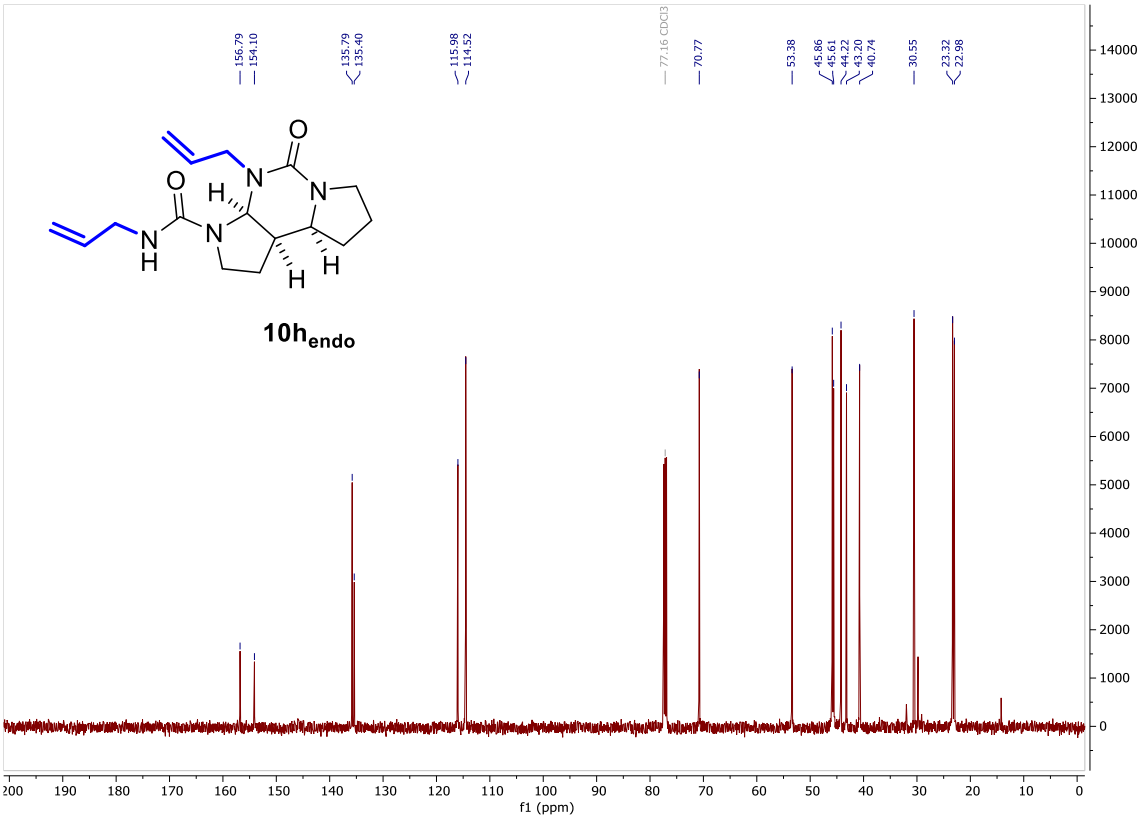


(3aS,9aS,9bR)-N,4-diallyl-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10h_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

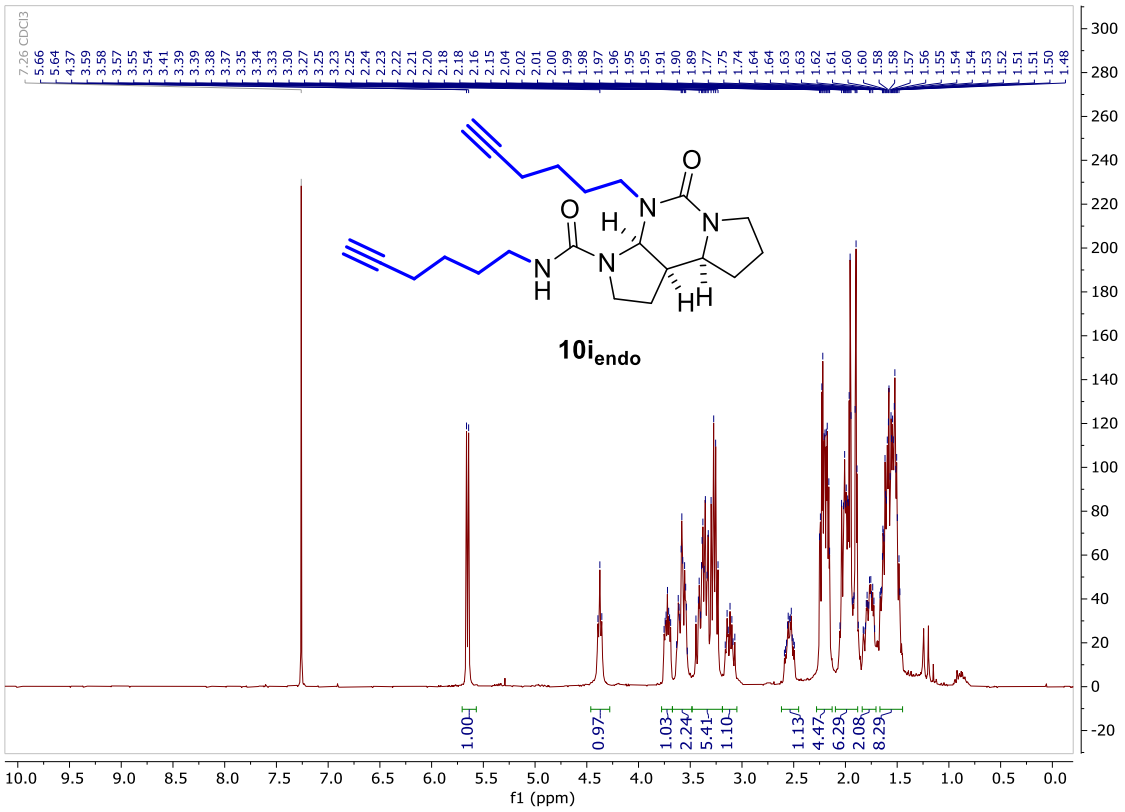


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

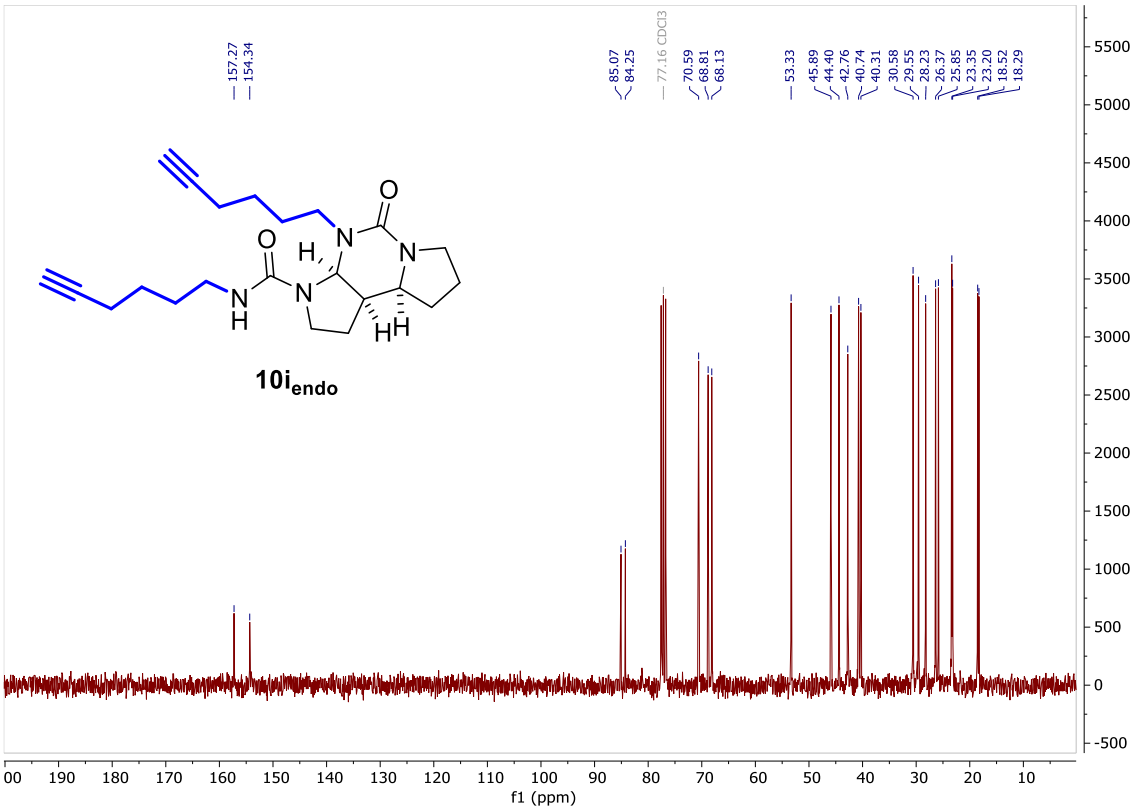


(3aS,9aS,9bR)-N,4-di(hex-5-yn-1-yl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide ($10i_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

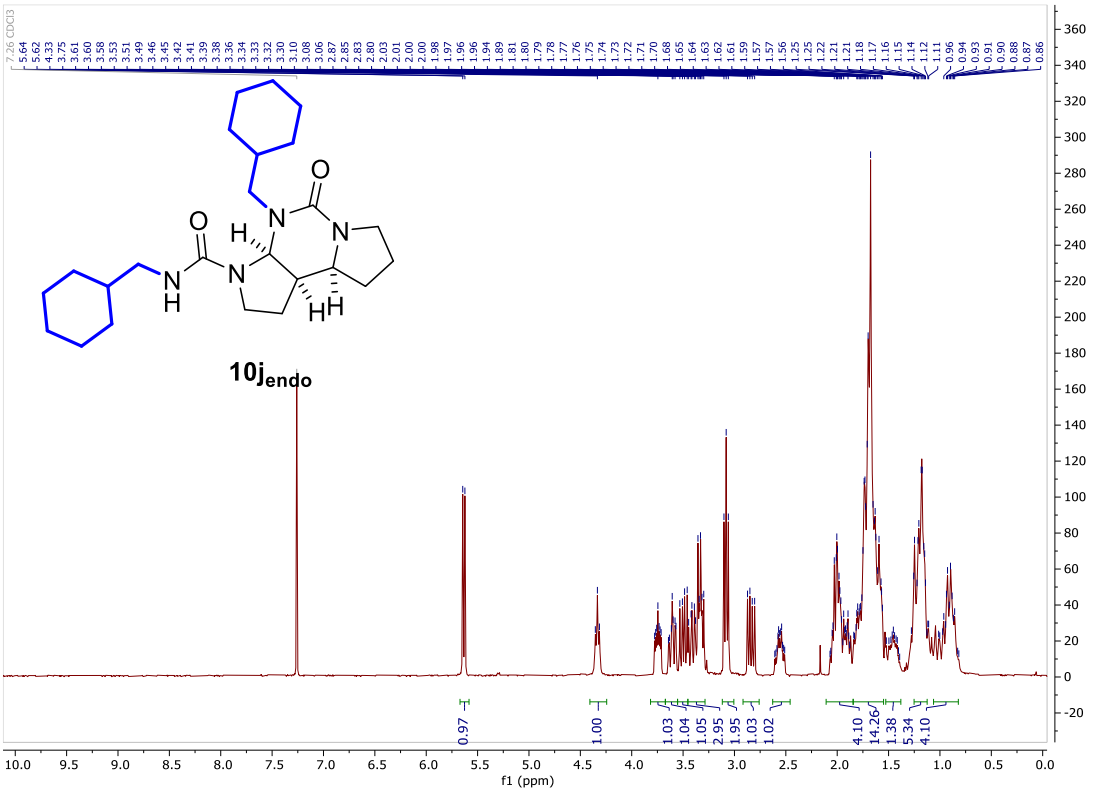


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

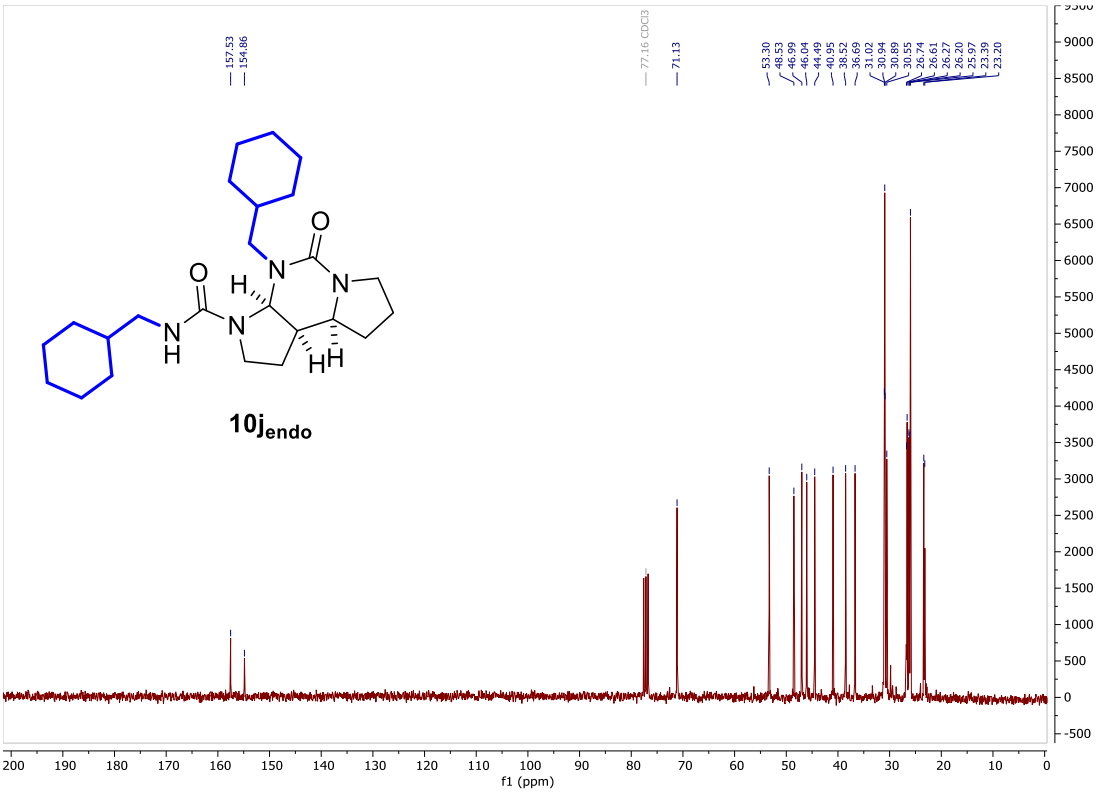


(3aS,9aS,9bR)-N,4-bis(cyclohexylmethyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10j$_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

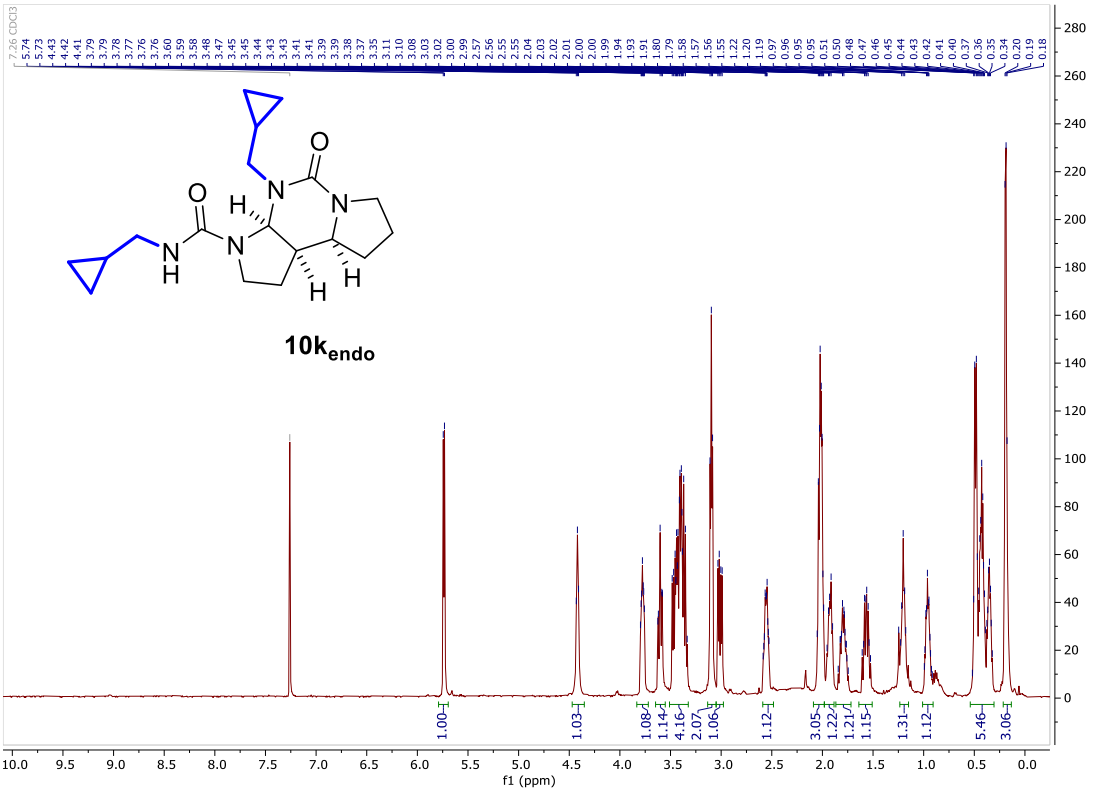


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

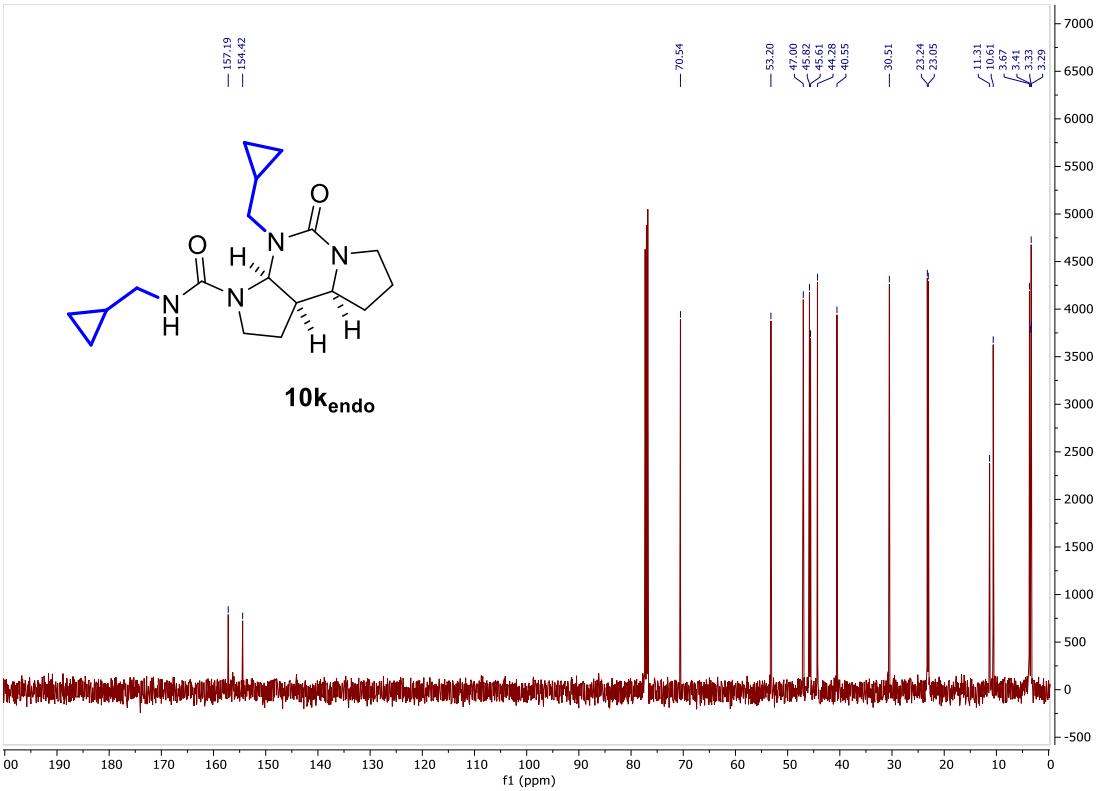


(3aS,9aS,9bR)-N,4-bis(cyclopropylmethyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10k$_{endo}$)

^{1}H NMR, 500 MHz, $CDCl_3$

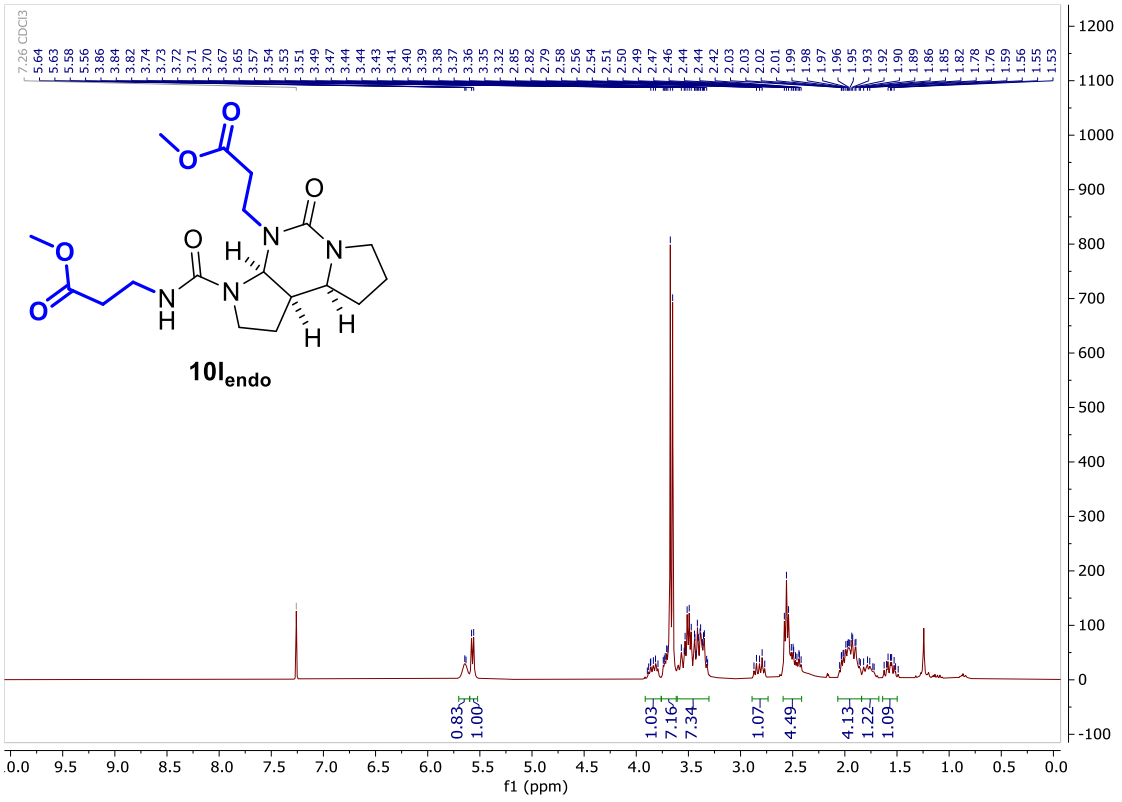


$^{13}C\{^{1}H\}$ NMR, 126 MHz, $CDCl_3$

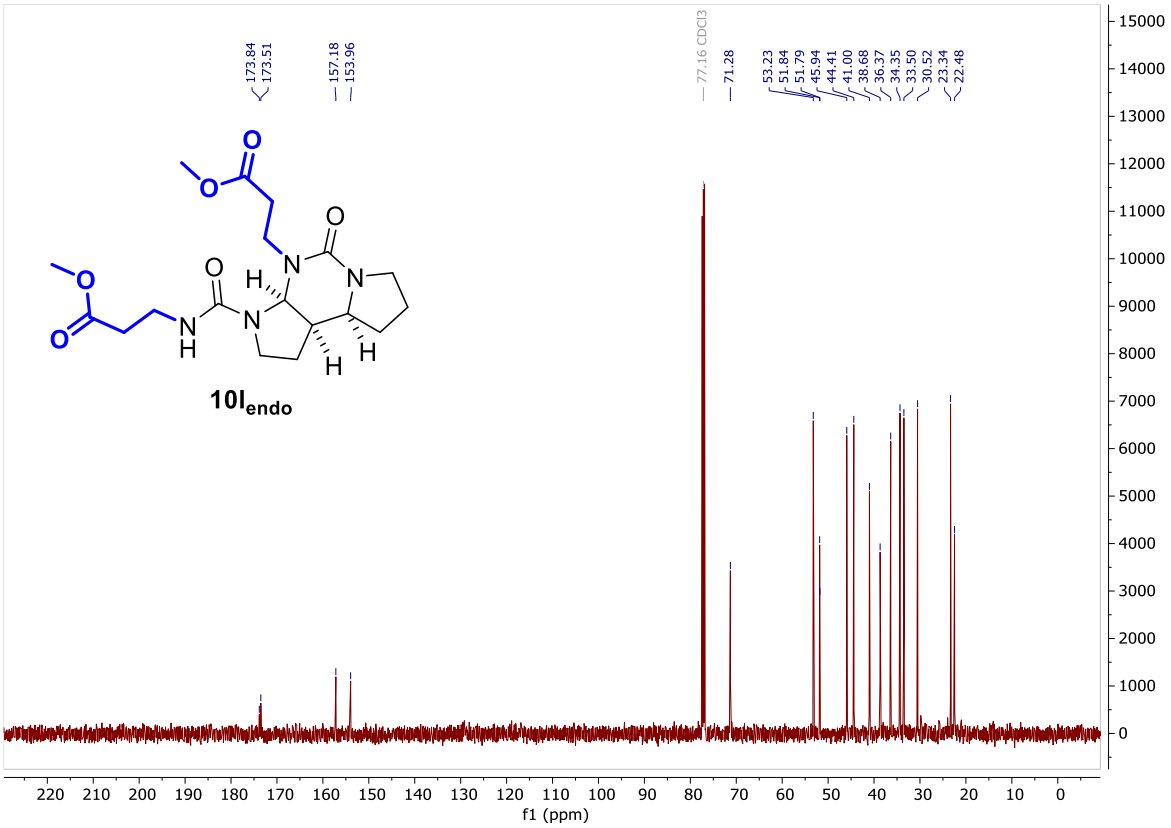


Methyl 3-((3aS,9aS,9bR)-4-(3-methoxy-3-oxopropyl)-5-oxodecahydro-1H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamido)propanoate ($10l_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

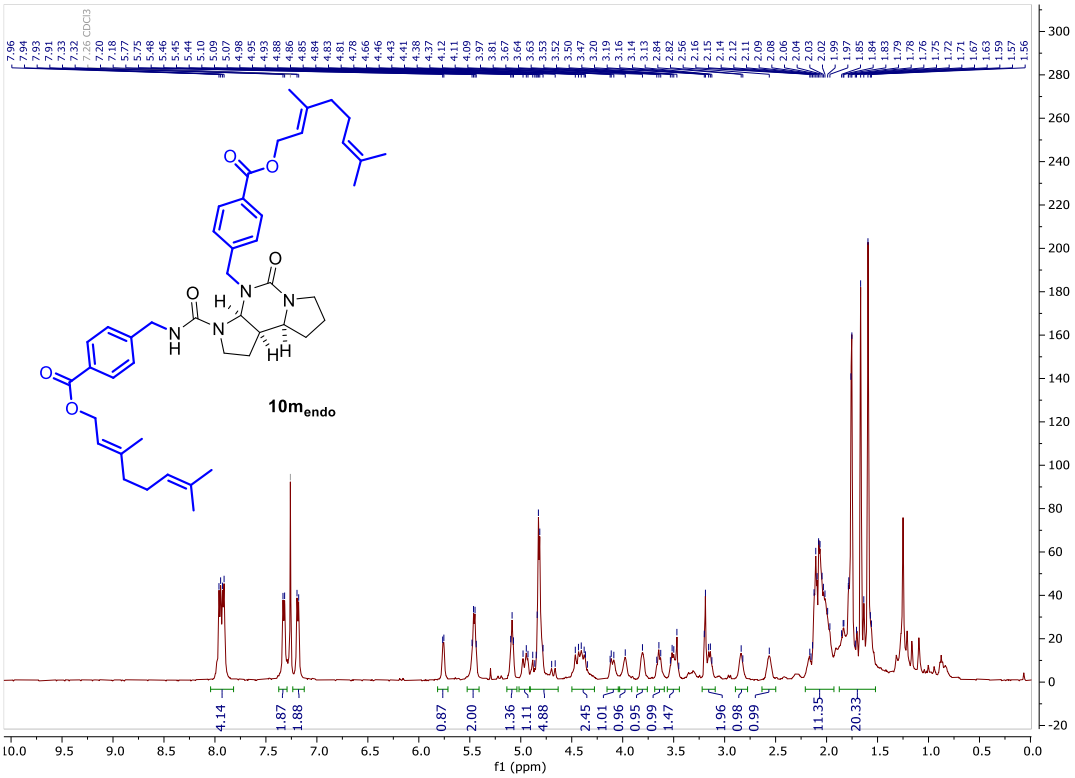


$^{13}C\{^{1}H\}$ NMR, 126 MHz, $CDCl_3$

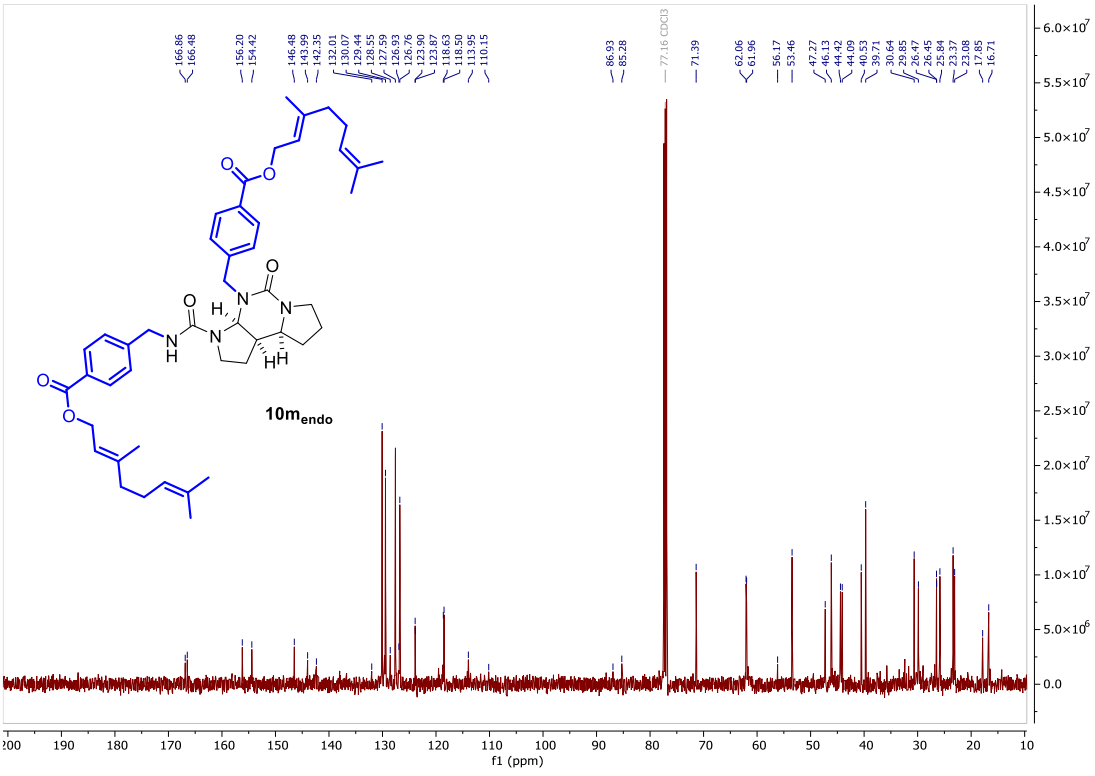


(3aS,9aS,9bR)-N,4-di(hex-5-yn-1-yl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (E)-3,7-dimethylocta-2,6-dien-1-yl 4-(((3aS,9aS,9bR)-4-(4-((((E)-3,7-dimethylocta-2,6-dien-1-yl)oxy)carbonyl)benzyl)-5-oxodecahydro-1H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamido)methyl)benzoate (10m$_{endo}$)

^{1}H NMR, 500 MHz, $CDCl_3$

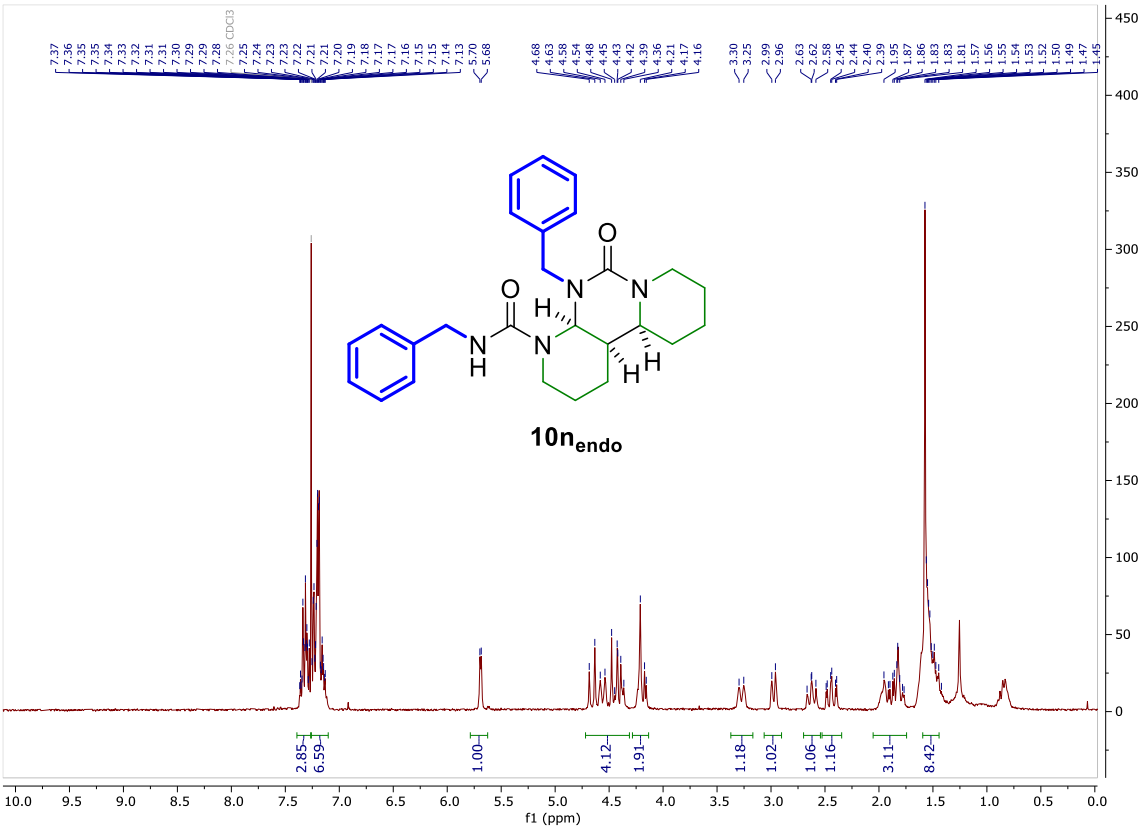


$^{13}C\{^{1}H\}$ NMR, 126 MHz, $CDCl_3$

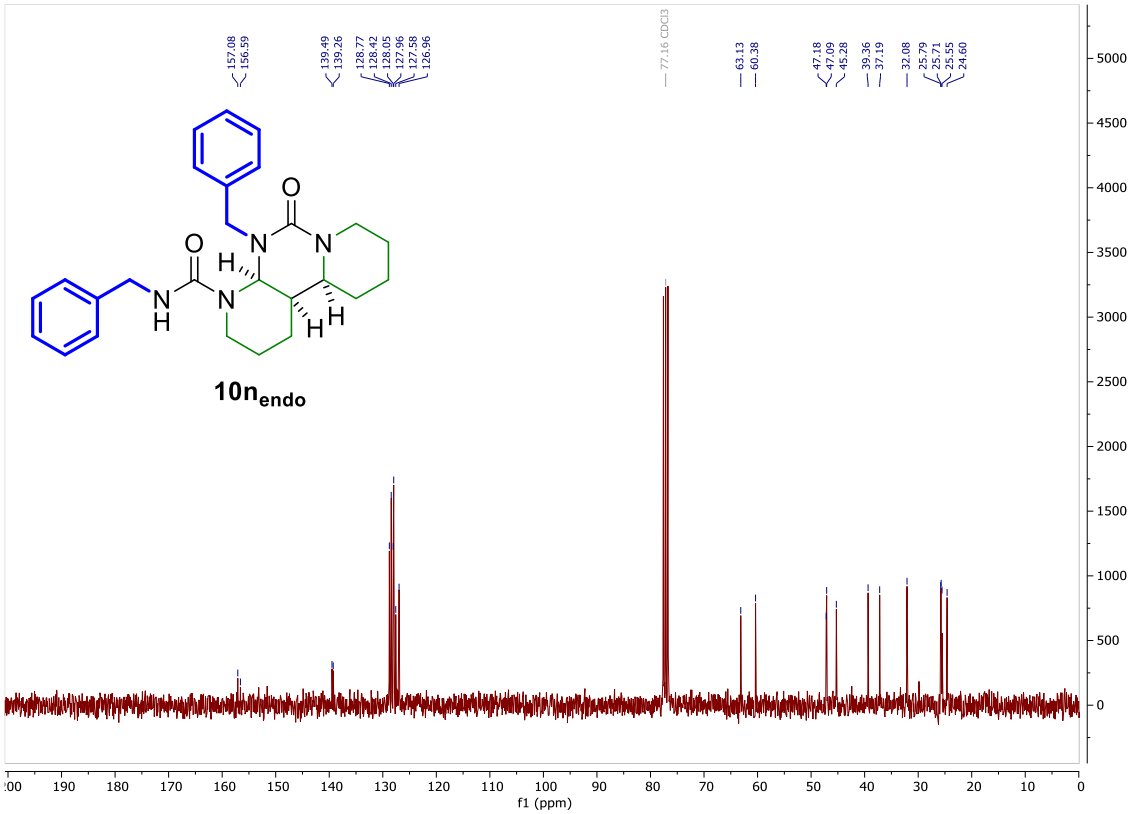


(4aS,11aS,11bR)-N,5-dibenzyl-6-oxodecahydro-1H-dipyrido[1,2-c:3',2'-e]pyrimidine-4(4aH)-carboxamide ($10n_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

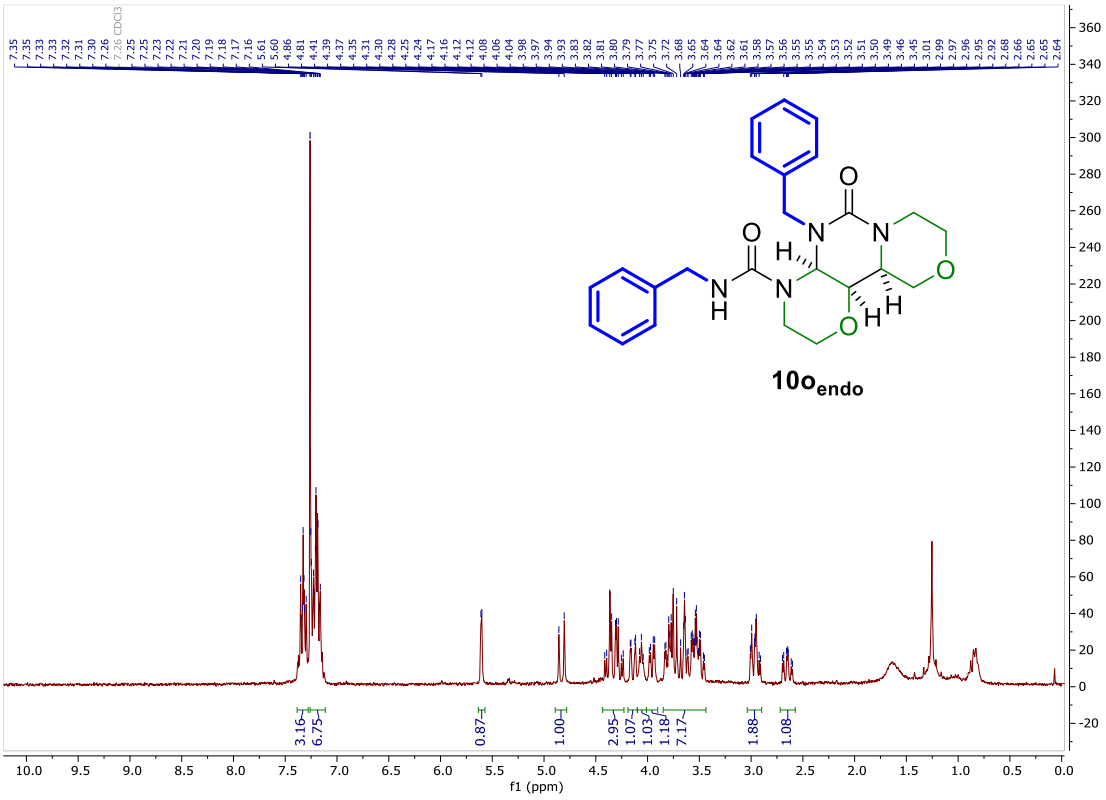


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

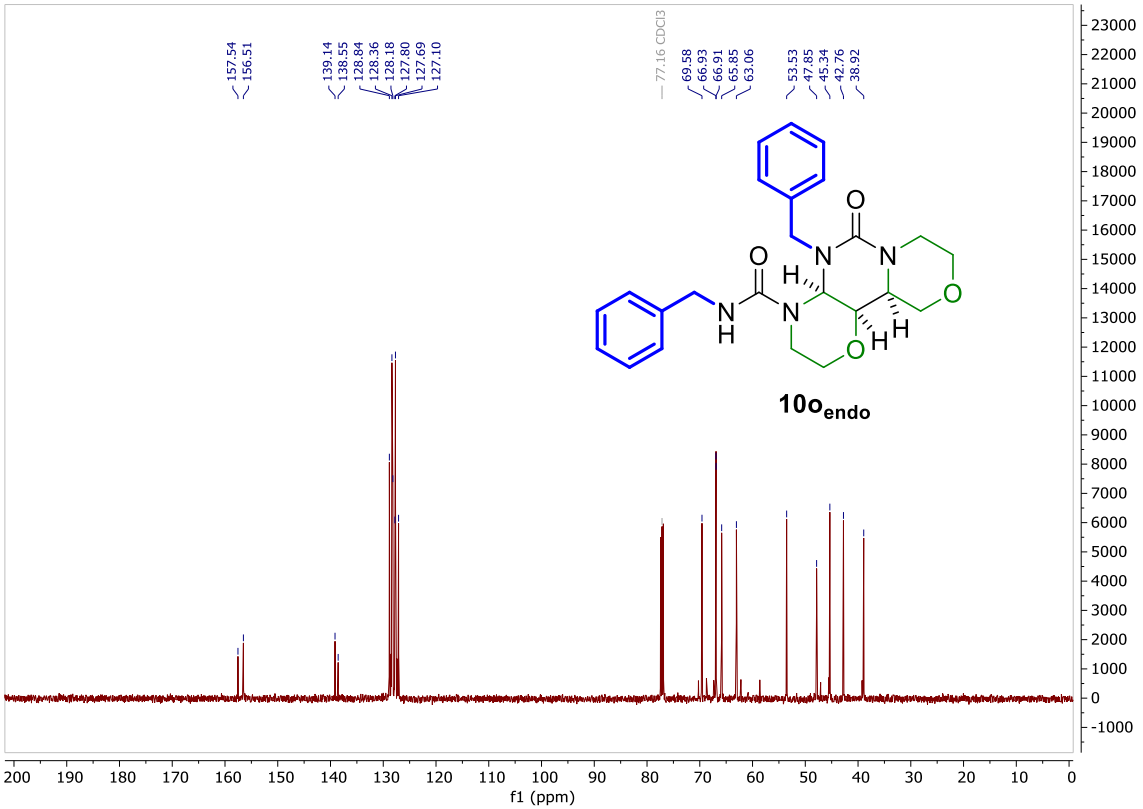


(4aS,11aS,11bR)-N,5-dibenzyl-6-oxodecahydro-4H-pyrimido[5,4-b:6,1-c']bis([1,4]oxazine)-4-carboxamide (10o$_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

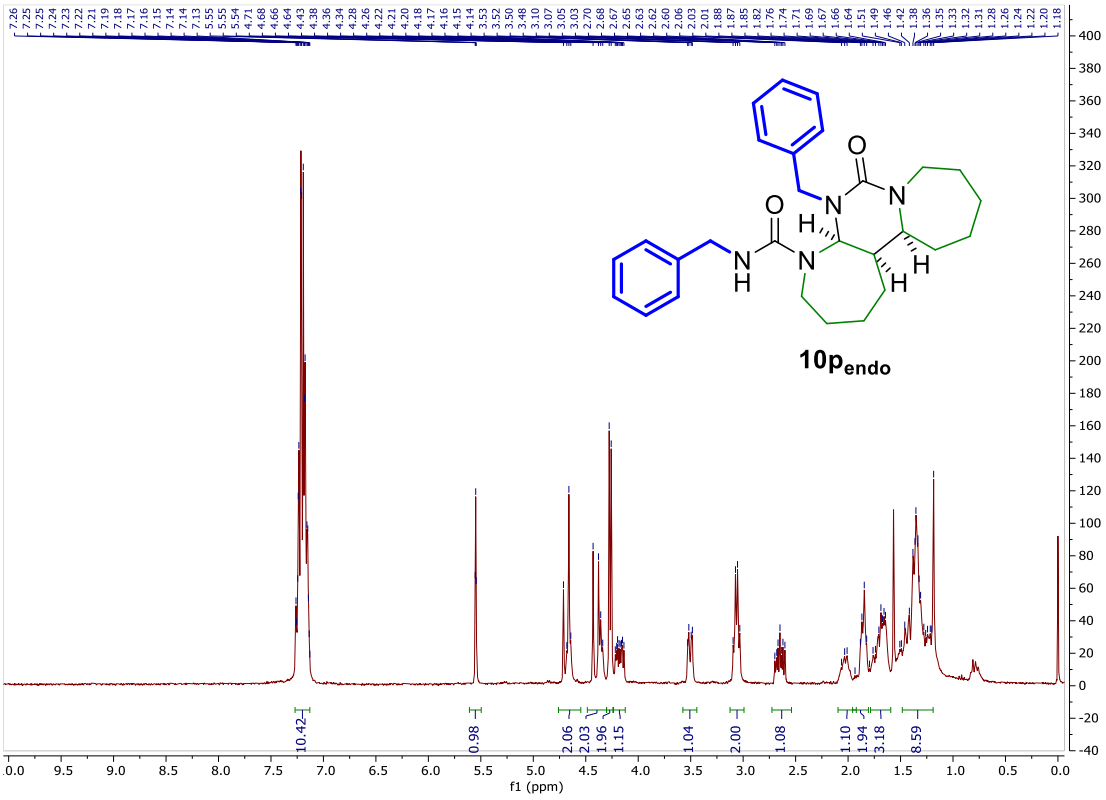


$^{13}C\{^{1}H\}$ NMR, 75 MHz, $CDCl_3$

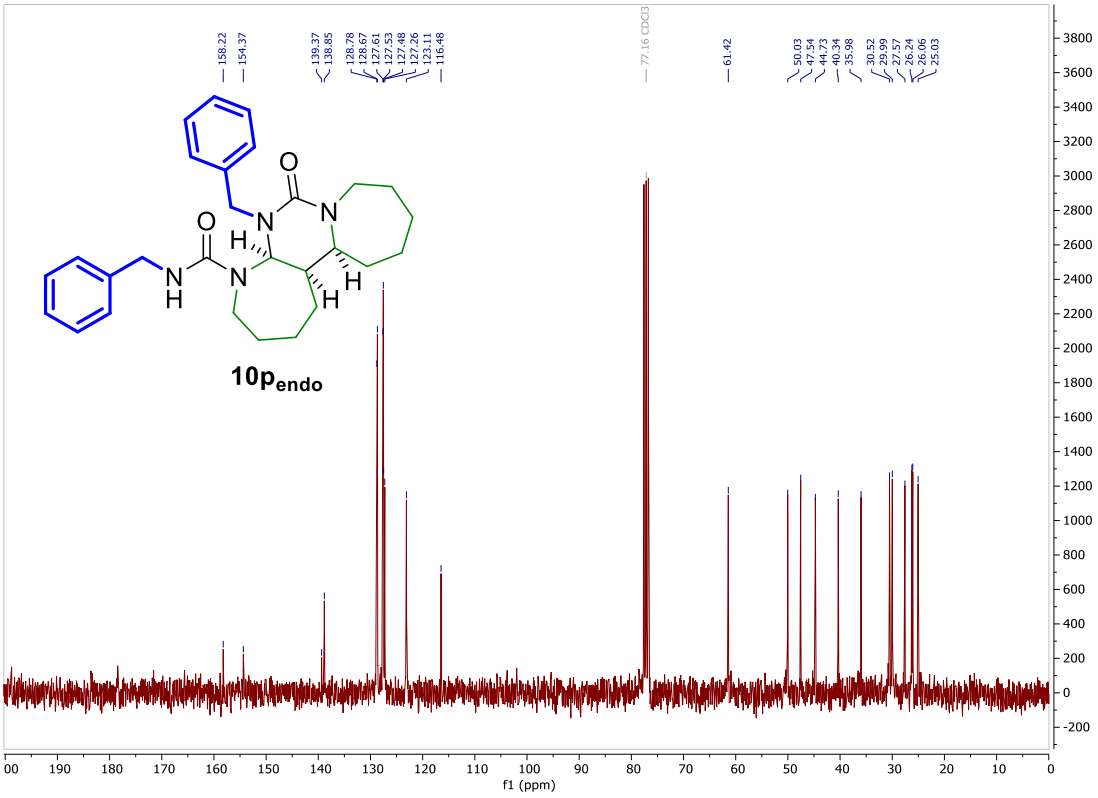


(5aS,13aS,13bR)-N,6-dibenzyl-7-oxotetradecahydro-5H-pyrimido[1,6-a:4,5-b']bis(azepine)-5-carboxamide ($10p_{endo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

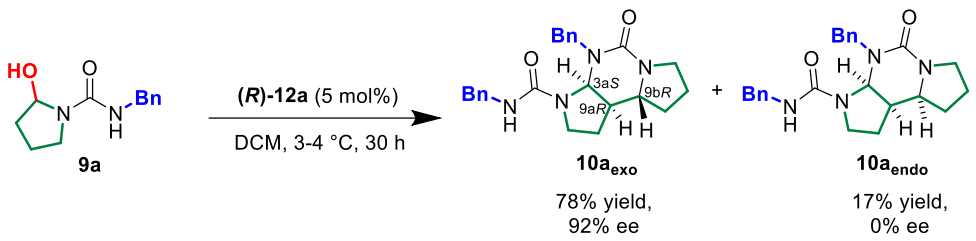


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$



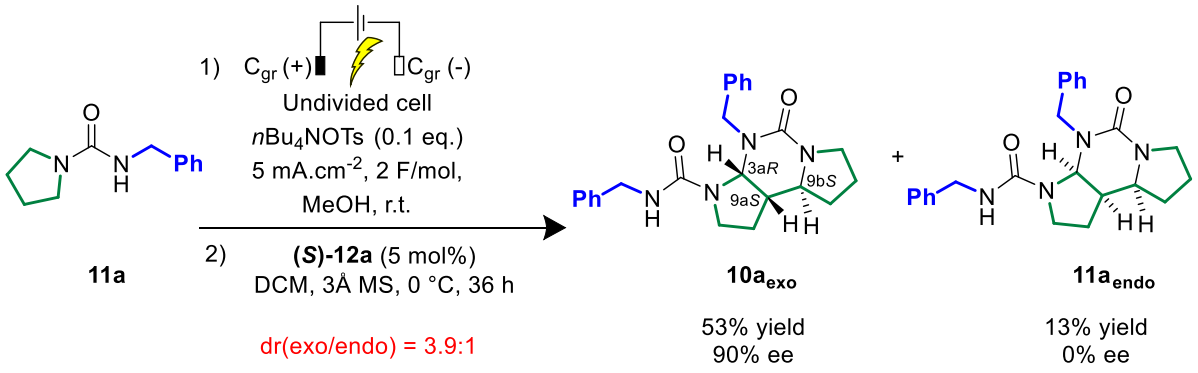
Experimental procedures and spectroscopic data for the asymmetric synthesis of the exo dimer 10_{exo}

Procedure C for the asymmetric synthesis of Exo dimer $10a_{exo}$ from urea 9a



N-benzyl-2-hydroxypyrrolidine-1-carboxamide **9a** (20 mg, 0.09 mmol) was dissolved in DCM (2 mL, 0.1 M) and the system was cooled to 0 °C. (*R*)-3,3'-Bis(1-naphthyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-diol **12a** (2.7 mg, 0.0045 mmol, **5 mol%**) was added. The mixture was stirred for 30 and concentrated under reduced pressure. The crude was purified by preparative TLC (EtOAc/MeOH, 95:5) to give **$10a_{exo}$** (15.4 mg, 0.04 mmol, 78% yield, 92% ee) and **$10a_{endo}$** (3.4 mg, 0.01 mmol, 17% yield, 0% ee). dr(Exo/Endo)$_{procedure\ C}$ = 4.6:1.

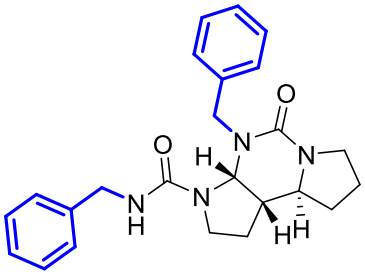
Procedure D for the asymmetric synthesis of exo dimer $10a_{exo}$ from urea 11a



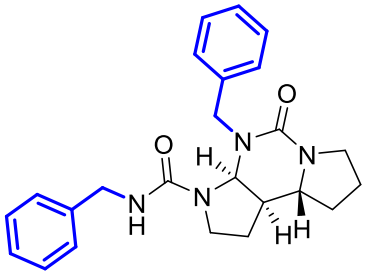
A 5 mL IKA Electrasyn electrochemical cell was charged with urea derivative (41 mg, 0.2 mmol), *n*Bu_4NOTs (8.3 mg, 0.02 mmol, **0.1 eq.**) and MeOH (4 mL, 0.05 M), and the resulting solution was electrolyzed (constant current, 5 mA.cm^{-2}, 2 F mol^{-1}, 600 rpm) using an isostatic graphite electrode both as cathode and anode. The crude was concentrated under reduced pressure and filtrated on a pad of alumina with a mixture of petroleum ether and acetone (8:2) to remove the electrolyte. After evaporation of the solvent, the crude was dissolved in DCM (2 mL, 0.1 M) in a flame-dried tube containing 3 Å molecular sieves. The system was cooled to 0 °C and (*S*)-3,3'-Bis(1-naphthyl)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-diol (6.1 mg, 0.01 mmol, **5 mol%**) was added. The mixture was stirred for 36 h. After evaporation of the solvent, the crude was purified by flash chromatography

(Petroleum ether/acetone, 9:1 to 1:1) to give **10a$_{exo}$** (21.4 mg, 0.05 mmol, 53% yield, 90% ee) and **10a$_{endo}$** (5.3 mg, 0.01 mmol, 13% yield). dr(Exo/Endo)= 3.9:1. Diastereoisomeric ratio was determined before purification.

(3aS,9aR,9bR) or (3aR,9aS,9bS)-N,4-dibenzyl-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (±10a$_{exo}$)



(-)10a$_{exo}$



(+)10a$_{exo}$

(+)10a$_{exo}$ was prepared according to procedure **C** and **(-)10a$_{exo}$** was prepared according to procedure D.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 10H), 5.42 (d, *J* = 5.8 Hz, 1H), 5.08 (d, *J* = 15.7 Hz, 1H), 4.72 (d, *J* = 15.7 Hz, 1H), 4.46 – 4.27 (m, 3H), 3.68 – 3.58 (m, 1H), 3.51 (ddd, *J* = 11.1, 9.2, 3.6 Hz, 1H), 3.37 – 3.24 (m, 2H), 3.03 (dt, *J* = 9.8, 7.3 Hz, 1H), 2.30 – 2.11 (m, 2H), 2.08 – 1.92 (m, 2H), 1.87 – 1.74 (m, 2H), 1.60 – 1.51 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 156.3, 140.6, 138.9, 128.6 (2C), 128.1 (2C), 127.8 (2C), 127.4, 127.1 (2C), 126.3, 71.7, 56.3, 47.9, 45.8, 45.1, 44.8, 42.9, 33.3, 28.7, 22.8.

IR (neat) ν (cm^{-1}): 3314, 3030, 2927, 1713, 1620, 1538, 1495, 1478, 1453, 1340, 1223, 1136, 1078, 1029, 976, 921.

HRMS (ESI+, m/z): calculated for $C_{24}H_{29}N_4O_2$ **[M+H]$^{+}$**: 405.2291, found 405.2277.

HPLC analysis (Daicel Chiralpak IA, Heptane/iPrOH = 80:20, flow rate 1.0 mL/min, 214 nm):

Tr_1: 20 min Tr_2 : 26 min.

Enantiomeric excess of (+)**10a$_{exo}$ from procedure C**: 92%.

Enantiomeric excess of (-)**10a$_{exo}$ from procedure D**: -90%.

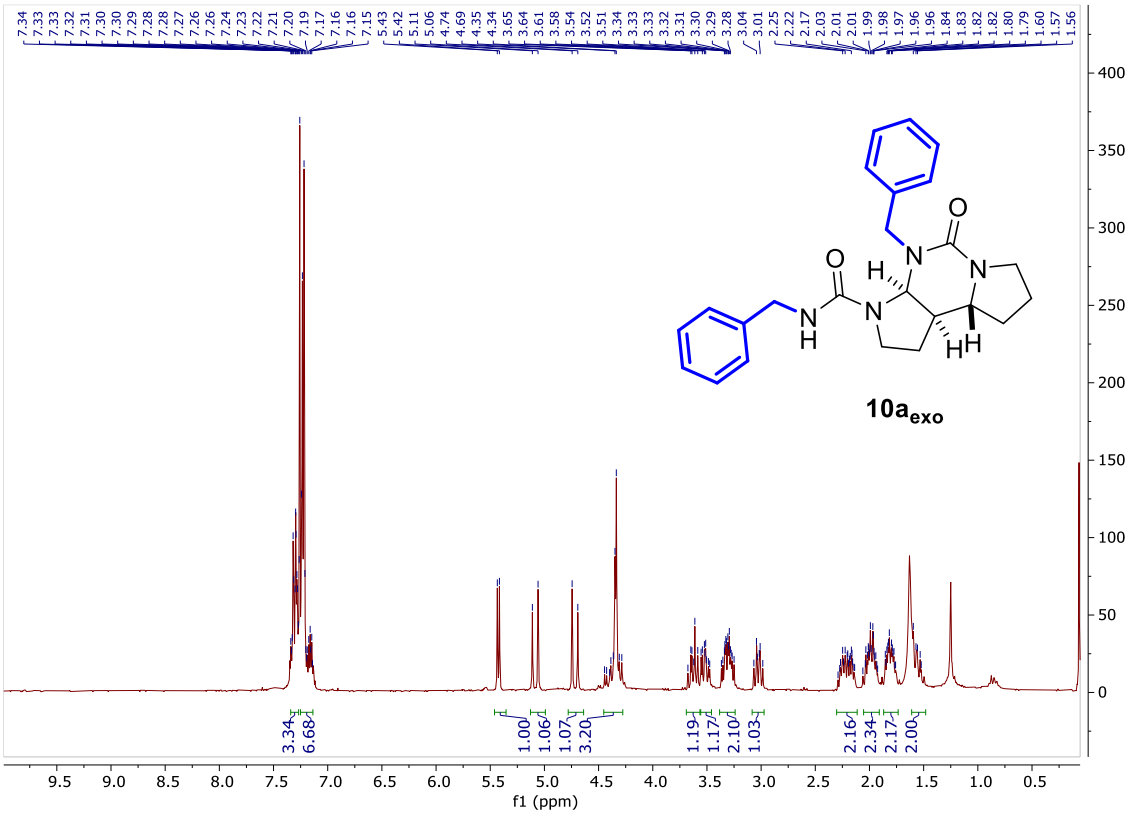
[a]$_D^{25}$ ([c] = 1g/L, $CHCl_3$) of (+)**10a$_{exo}$** from procedure **C**: +67°.

[a]$_D^{25}$ ([c] = 1g/L, $CHCl_3$) of (-)**10a$_{exo}$** from procedure **D**: --67°.

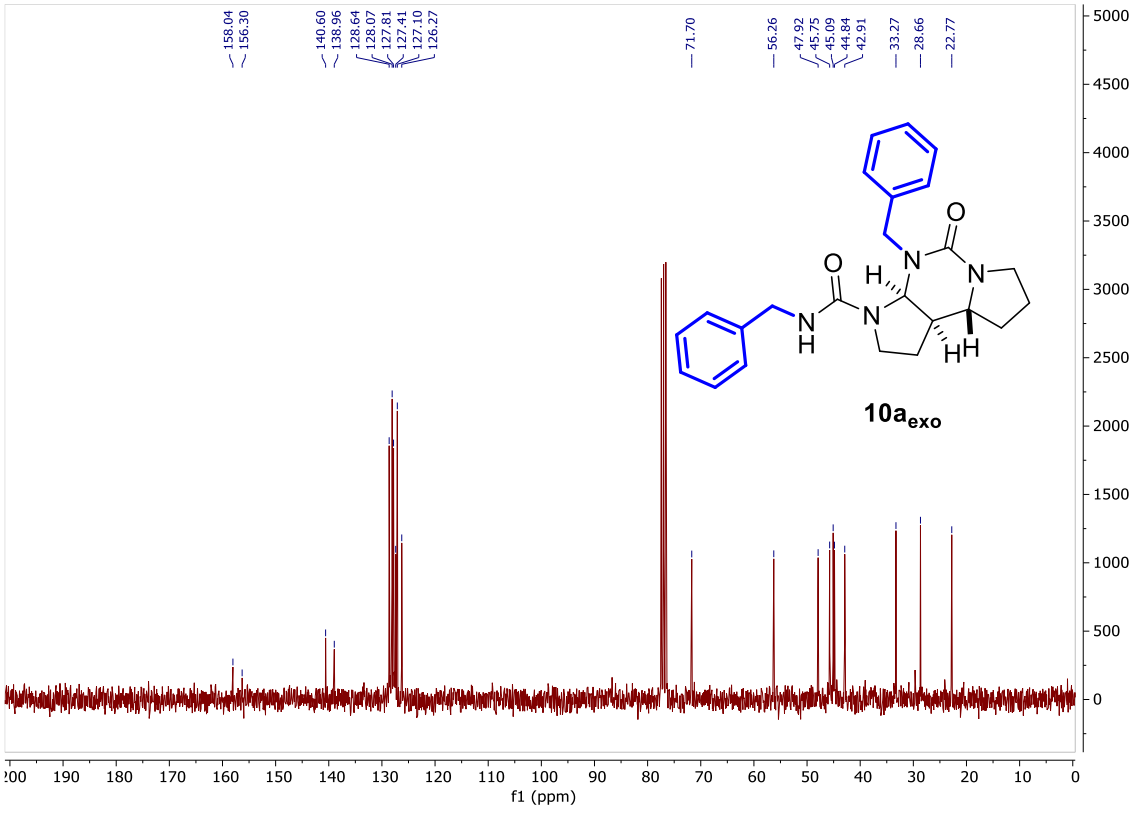
^{1}H and ^{13}C NMR spectra of Exo dimer 10a$_{exo}$

(3aS,9aR,9bR)-N,4-dibenzyl-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (10a$_{exo}$)

^{1}H NMR, 300 MHz, $CDCl_3$

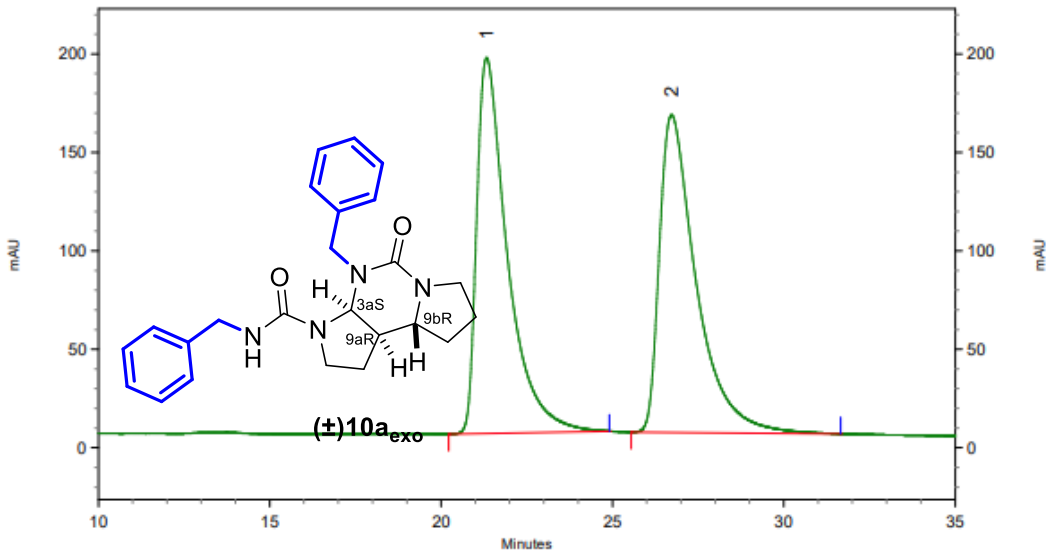


^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$



HPLC data for dimer $10a_{exo}$ and $10a_{endo}$

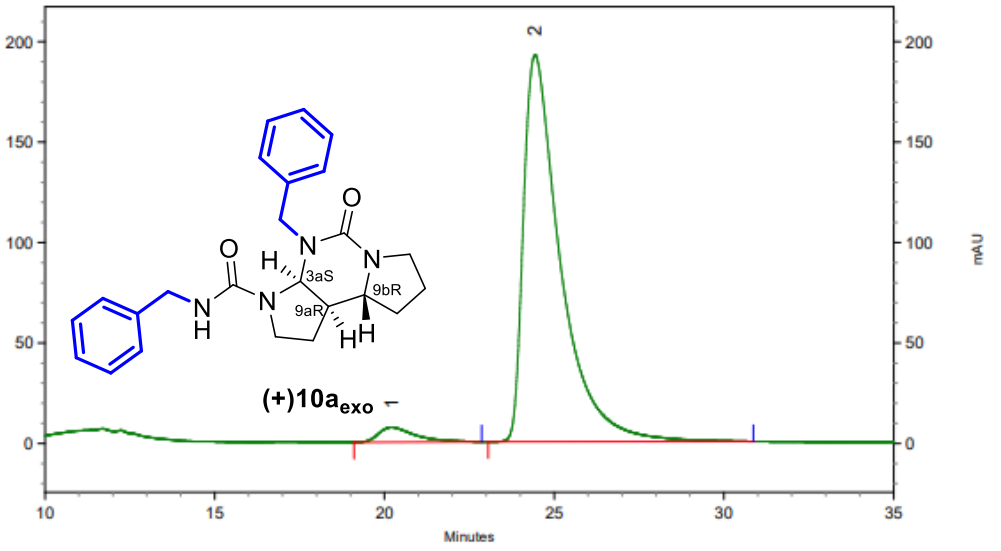
HPLC data for Exo dimer $10a_{exo}$ from procedure C



DAD-CH3 214 nm

Results

Pk #	Retention Time	Area	Area %
1	21,33	47618834	49,71
2	26,73	48174649	50,29

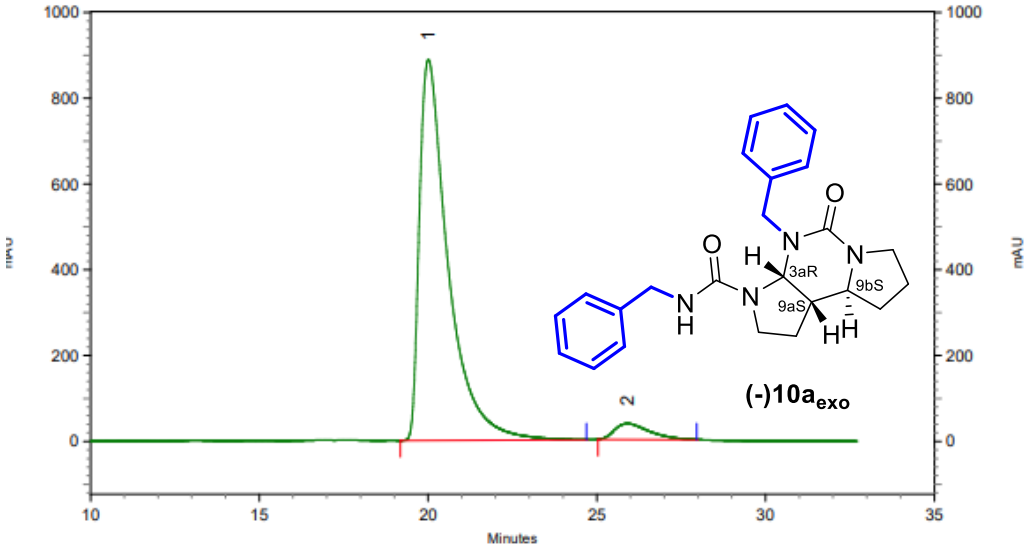


DAD-CH3 214 nm

Results

Pk #	Retention Time	Area	Area %
1	20,20	2191206	3,62
2	24,43	58399526	96,38

HPLC data for Exo dimer 10a$_{exo}$ from procedure D

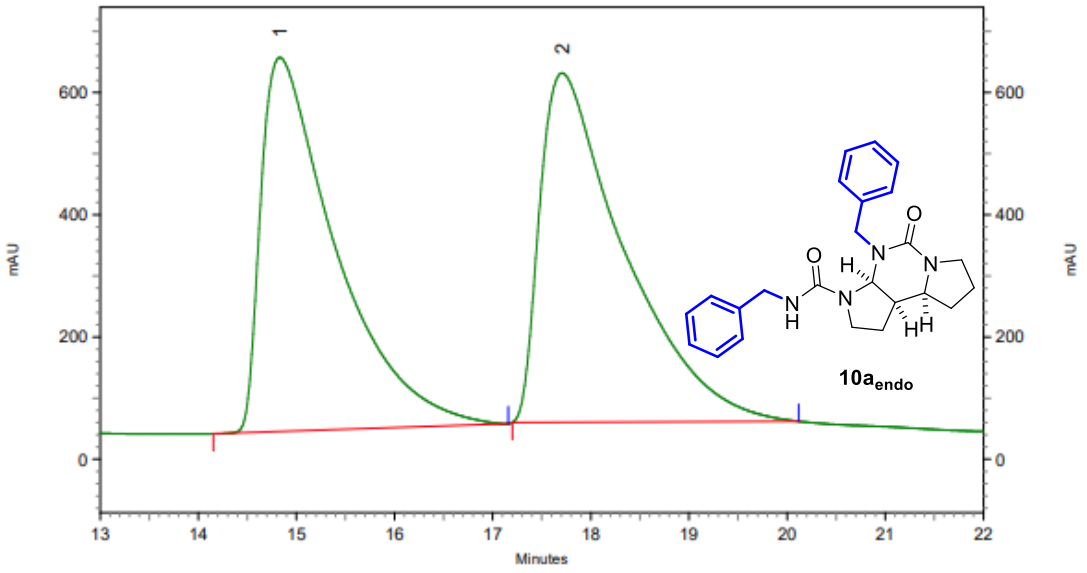


DAD-CH3 214 nm

Results

Pk #	Retention Time	Area	Area %
1	20,01	210303570	95,20
2	25,90	10605424	4,80

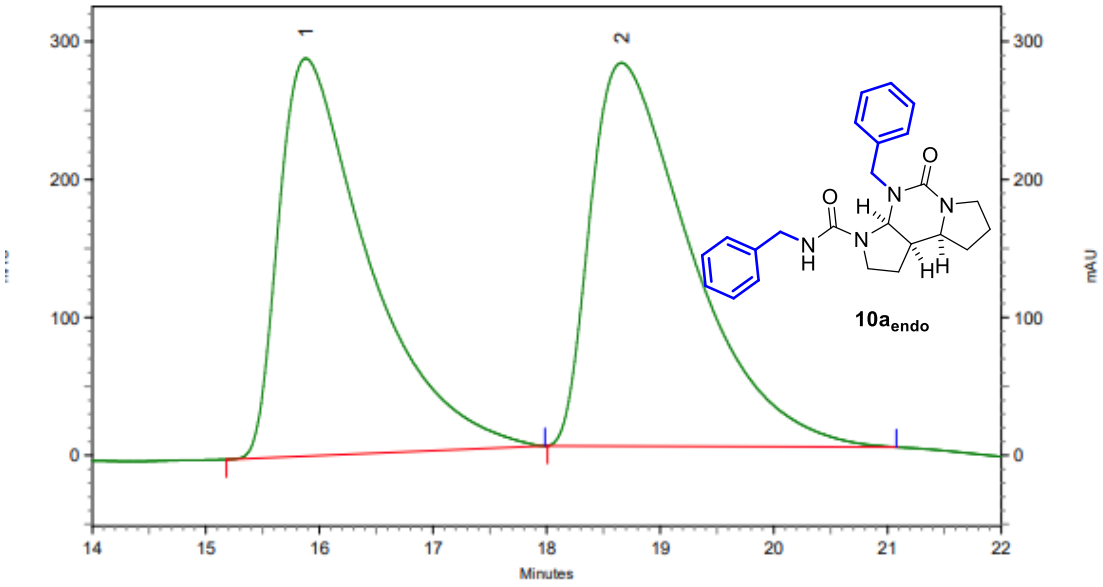
HPLC data for endo dimer 10a$_{endo}$



DAD-CH3 214 nm

Results

Pk #	Retention Time	Area	Area %
1	14,83	129575549	48,71
2	17,71	136434727	51,29



DAD-CH3 214 nm

Results

Pk #	Retention Time	Area	Area %
1	15,88	63347943	48,04
2	18,66	68524891	51,96

Determination of the absolute configuration of (-)10a$_{exo}$.

VCD spectrum acquisition.

The acquisition of the VCD spectrum was realised using the JASCO FVS-6000 spectrometer. All spectra were recorded in $CHCl_3$ using a 50 µm BaF_2 cell at a resolution of 4 cm^{-1} at ambient temperature (20 °C) at a concentration of 0.4 M.

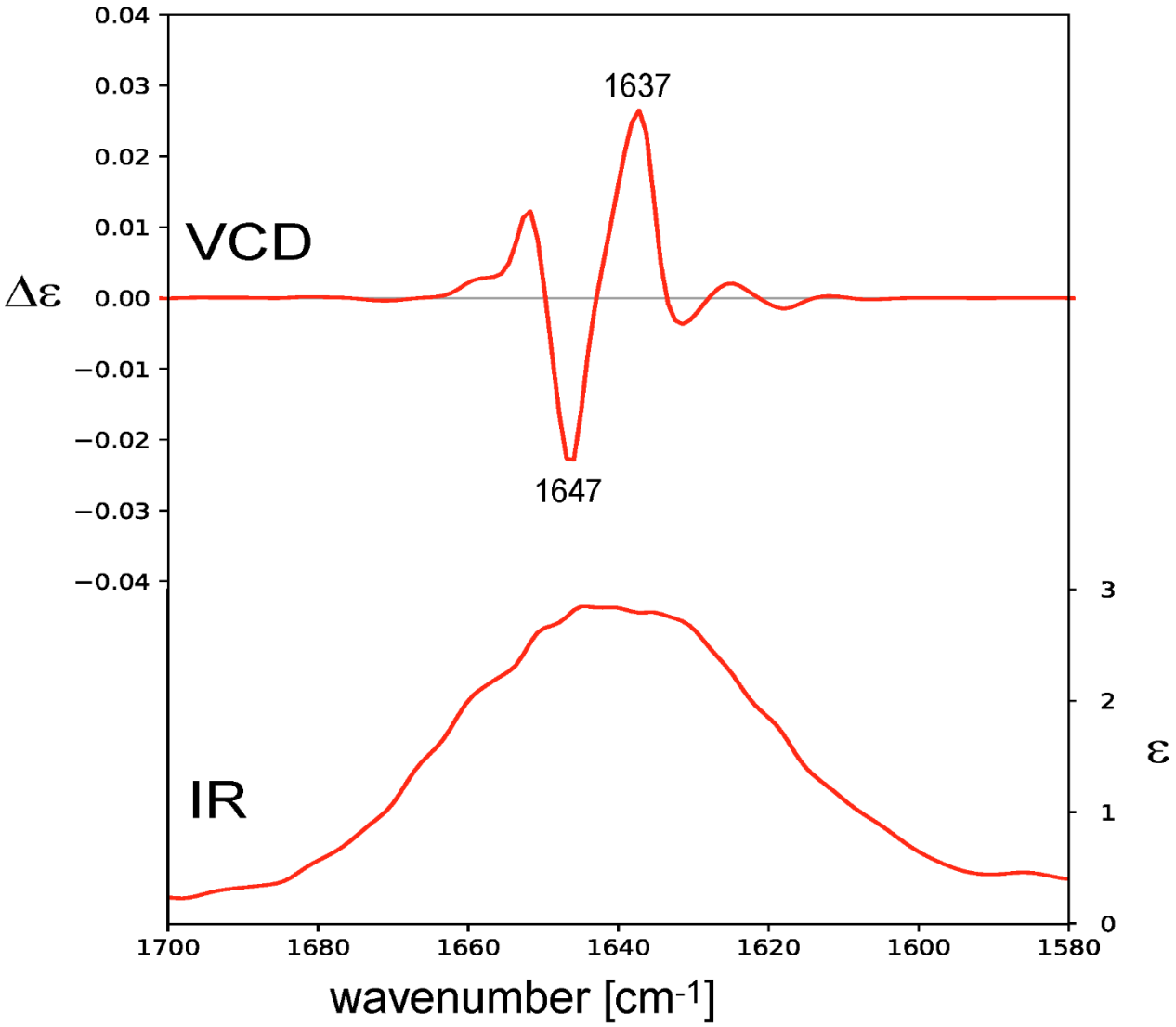


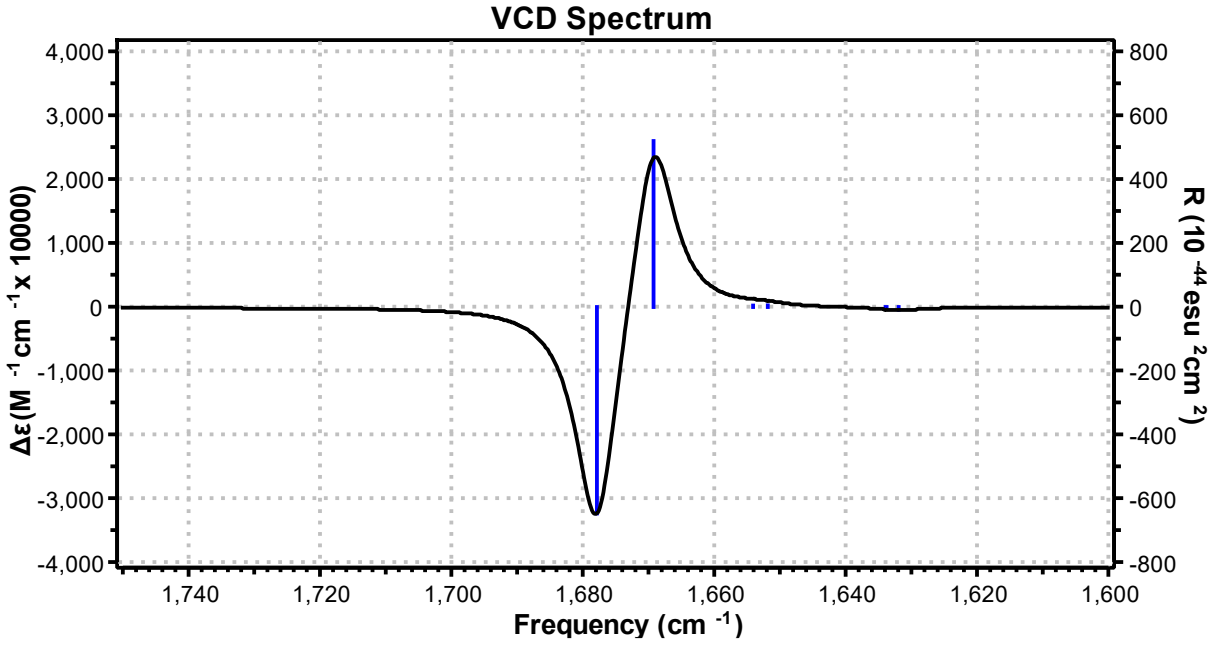
*Figure 1: VCD spectrum of **10a**$_{exo}$ in $CHCl_3$.*

Calculations :

All calculations were performed using the Gaussian 16 package[5]. The conformational analysis using the MMFF94 forcefield led to one major conformer ($\Delta E < 2$ kcal.mol^{-1}) on which all calculations were conducted.

Optimisation of the tridimensional structure was achieved using B3LYP method at the 6-31+g(d) level followed by frequency calculations. To take into account the influence of the chloroform, the IEFPCM solvation model was used for the calculations. IR and VCD spectra were simulated with Lorentzian line shapes of 10 and 4 cm^{-1} width respectively using the Gaussview6 package.

As depicted in the figure below, two alternate Cotton effects are visible on the simulated VCD spectrum (at ν = 1669 and 1677 cm^{-1}) confirming the positive exciton coupling and the **3a*R*, 9a*S*, 9b*S*** configuration.



Cartesian coordinates of **10a**$_{exo}$

Symbol	X	Y	Z
O	-1.164399	-2.992951	2.266773
C	-0.82102	-2.072533	1.506744
N	-1.710031	-1.457463	0.653945
C	-3.047845	-2.023067	0.459207
C	-3.992325	-0.995583	-0.131256
C	-4.434729	-1.106509	-1.455589
C	-5.307313	-0.15754	-2.001537
C	-5.747405	0.916371	-1.224161
C	-5.312485	1.035945	0.101722
C	-4.442538	0.086762	0.641678
N	0.484851	-1.629423	1.484289
C	1.435817	-2.266032	2.416477
C	2.743938	-1.459141	2.252367
C	2.558957	-0.690075	0.936437
C	2.848871	-1.560512	-0.286543

C	4.318876	-1.709404	-0.704868
C	4.207504	-2.087016	-2.193379
C	3.030054	-1.237502	-2.707579
N	2.233061	-0.985971	-1.49412
C	1.182954	-0.127737	-1.521002
O	0.799862	0.403489	-2.576435
N	0.535141	0.132548	-0.302174
C	-0.303239	1.356124	-0.246168
C	0.446697	2.617231	0.151663
C	1.386922	3.204445	-0.712263
C	2.067573	4.365649	-0.339383
C	1.816455	4.963546	0.90151
C	0.877394	4.393651	1.764651
C	0.198775	3.228572	1.389038
C	1.058293	-0.35478	0.965783
H	-1.299584	-0.989025	-0.146354
H	-3.007331	-2.909875	-0.189275
H	-3.401613	-2.35753	1.437323
H	-4.096248	-1.941768	-2.065344
H	-5.640132	-0.259204	-3.031439
H	-6.425742	1.654351	-1.644757
H	-5.655402	1.866115	0.714416
H	-4.10904	0.181723	1.672918
H	1.058158	-2.231897	3.443655
H	1.557206	-3.321421	2.151195
H	2.86611	-0.751269	3.078937
H	3.625382	-2.107543	2.243123
H	3.149503	0.231492	0.890958
H	2.425496	-2.561957	-0.11738
H	4.849773	-2.459789	-0.111416
H	4.837211	-0.748428	-0.588768
H	3.97749	-3.154591	-2.291852
H	5.126836	-1.891445	-2.75293
H	3.362271	-0.283444	-3.133284
H	2.43294	-1.750539	-3.468266
H	-0.749084	1.470167	-1.23495
H	-1.11072	1.170718	0.467017
H	1.575044	2.751715	-1.681992
H	2.788583	4.810064	-1.021193
H	2.344443	5.869357	1.188621
H	0.67016	4.853093	2.727955
H	-0.536984	2.794682	2.063571
H	0.879348	0.438914	1.70194

Applications and derivatization

Large scale syntheses

Synthesis of 10a$_{endo}$ on 1 mmol scale

A 25 mL IKA Electrasyn electrochemical cell was charged with urea derivative (**1 mmol**), *n*Bu$_4$NOTs (38 mg, **0.1 eq.**) and MeOH (17 mL, 0.06M), and the resulting solution was electrolyzed (constant current, 5 mA.cm^{-2}, 3.00 F mol^{-1}). The solvent was subsequently removed and acetonitrile (20 mL, 0.05M) was added. Trifluoroacetic anhydride (TFAA, 139 µL, **1 eq.**) was added and the mixture was stirred overnight. After evaporation of the solvent, the crude was purified by flash chromatography (Petroleum ether/acetone, 9:1 to 1:1) to give the desired endo dimer **10a$_{endo}$** in 81% yield as a white foam (162.9 mg, 0.40 mmol). The starting material **11a** was recovered in 19% yield (39 mg, 0.19 mmol).

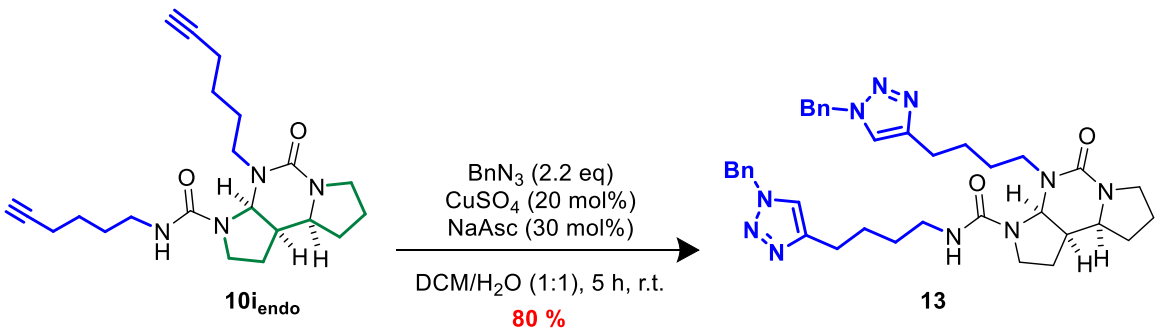
Synthesis of 10i$_{endo}$ on 1 mmol scale

A 25 mL IKA Electrasyn electrochemical cell was charged with urea derivative (**1 mmol**), *n*Bu$_4$NOTs (40.5 mg, **0.1 eq.**) and MeOH (16 mL, 0.06M), and the resulting solution was electrolyzed (constant current, 5 mA.cm^{-2}, 3.00 F mol^{-1}). The solvent was subsequently removed and acetonitrile (20 mL, 0.05M) was added. Trifluoroacetic anhydride (TFAA, 136 µL, **1 eq.**) was added and the mixture was stirred overnight. After evaporation of the solvent, the crude was purified by flash chromatography (Petroleum ether/acetone, 9:1 to 1:1) to give the desired endo dimer **10i$_{endo}$** in 55% yield as a white foam (103 mg, 0.27 mmol).

Post transformations on 10a$_{endo}$ 10i$_{endo}$

Alkyne/azide Click chemistry transformation:

N,4-bis(4-(1-benzyl-1H-1,2,3-triazol-4-yl)butyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (13)



To a solution of **10i$_{endo}$** (20 mg, 0.05 mmol) and NaN_3 (0.22 mL, 0.12 mmol, **2.2 eq**) in DCM/H_2O (1:1, 0.6 mL) were subsequently added $CuSO_4$ (1.7 mg, 0.01 mmol, **20 mol%**) and sodium ascorbate (3.1 mg, 0.02 mmol, **30 mol%**). The mixture was stirred for 5 h at room temperature. Then, the solution was diluted with DCM and H_2O and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography (DCM/MeOH, 100:0 to 95:5) to give the desired product **13** in 80% yield as a colorless oil (27 mg, 0.04 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 6H), 7.29 – 7.20 (m, 6H), 5.62 (d, *J* = 6.1 Hz, 1H), 5.47 (d, *J* = 6.6 Hz, 4H), 4.71 (t, *J* = 5.6 Hz, 1H), 3.73 – 3.67 (m, 1H), 3.58 – 3.45 (m, 2H), 3.42 – 3.27 (m, 3H), 3.26 – 3.10 (m, 3H), 2.71 – 2.61 (m, 4H), 2.54 – 2.46 (m, 1H), 2.04 – 1.83 (m, 5H), 1.80 – 1.65 (m, 4H), 1.61 – 1.43 (m, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 154.3, 135.2, 135.0, 129.2 (2C), 129.1(2C), 128.8 (2C), 128.7 (2C), 128.1 (4C), 121.1 (2C) 70.5, 54.2, 54.1, 53.3, 45.8, 44.4, 42.9, 40.5, 40.4, 30.6, 29.6, 28.5, 26.9, 26.6, 25.6, 25.3, 23.3, 23.1.

IR (neat) ν (cm^{-1}): 3341, 3126, 3068, 2933, 2860, 2225, 1622, 1534, 1495, 1476, 1457, 1360, 1337, 1271, 1216, 1130, 1048.

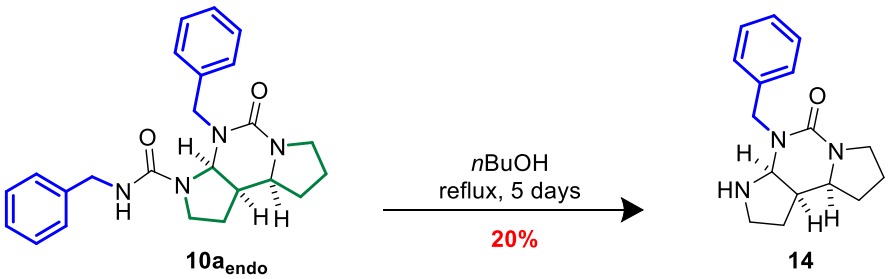
HRMS (ESI+, m/z): calculated for $C_{36}H_{47}N_{10}O_2$ **[M+H]$^+$**: 651.3883, found 651.3878.

Selective (partial) hydrolysis of acyclic urea group:

Selected cases of solvolysis of urea have been reported to take place under neutral condition simply by heating precursor in alcoholic solvents (see Clayden[6] and Booker-Milburn's[7] work).

As such we investigated the possibility to selectively cleave one of the urea bonds in compound **10a$_{endo}$**. Reaction proved to be very slow and we stopped it after 5 days even if conversion was below only 50%. Result is described below:

(3aS,9aS,9bR)-4-benzyldecahydro-5H-dipyrrolo[1,2-c:3',2'-e]pyrimidin-5-one (14)



10a$_{endo}$ (38 mg, 0.09 mmol) was dissolved in *n*BuOH (0.03 M) and was refluxed for 5 days. The solvent was removed under reduced pressure and the crude was purified by preparative TLC (DCM/MeOH, 95/5) to give the desired product **14** in 20% yield as a colorless oil (5.1 mg, 0.02 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.26 – 7.22 (m, 1H), 5.01 (d, *J* = 15.4 Hz, 1H), 4.55 (d, *J* = 6.7 Hz, 1H), 4.26 (d, *J* = 15.4 Hz, 1H), 3.74 – 3.62 (m, 2H), 3.55 – 3.39 (m, 1H), 3.03 – 2.88 (m, 2H), 2.67 – 2.53 (m, 1H), 2.11 – 1.88 (m, 2H), 1.89 – 1.76 (m, 2H), 1.75 – 1.69 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 139.3, 128.6 (2C), 128.2 (2C), 127.1, 73.1, 54.4, 46.1, 46.1, 44.0, 42.9, 30.9, 23.7, 23.5.

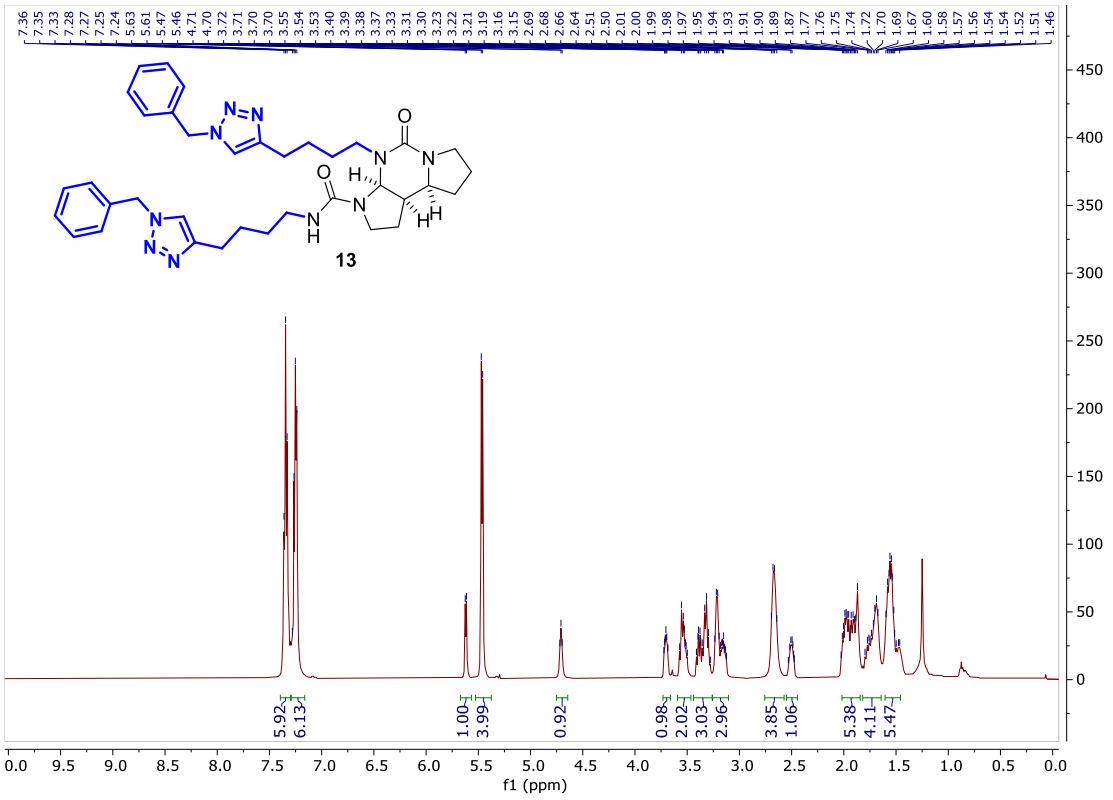
IR (neat) ν (cm^{-1}): 3327, 3025, 2966, 2925, 2873, 1623, 1494, 1474, 1452, 1357.

HRMS (ESI+, m/z): calculated for $C_{16}H_{22}N_3O$ **[M+H]$^+$**: 272.1763, found 272.1748

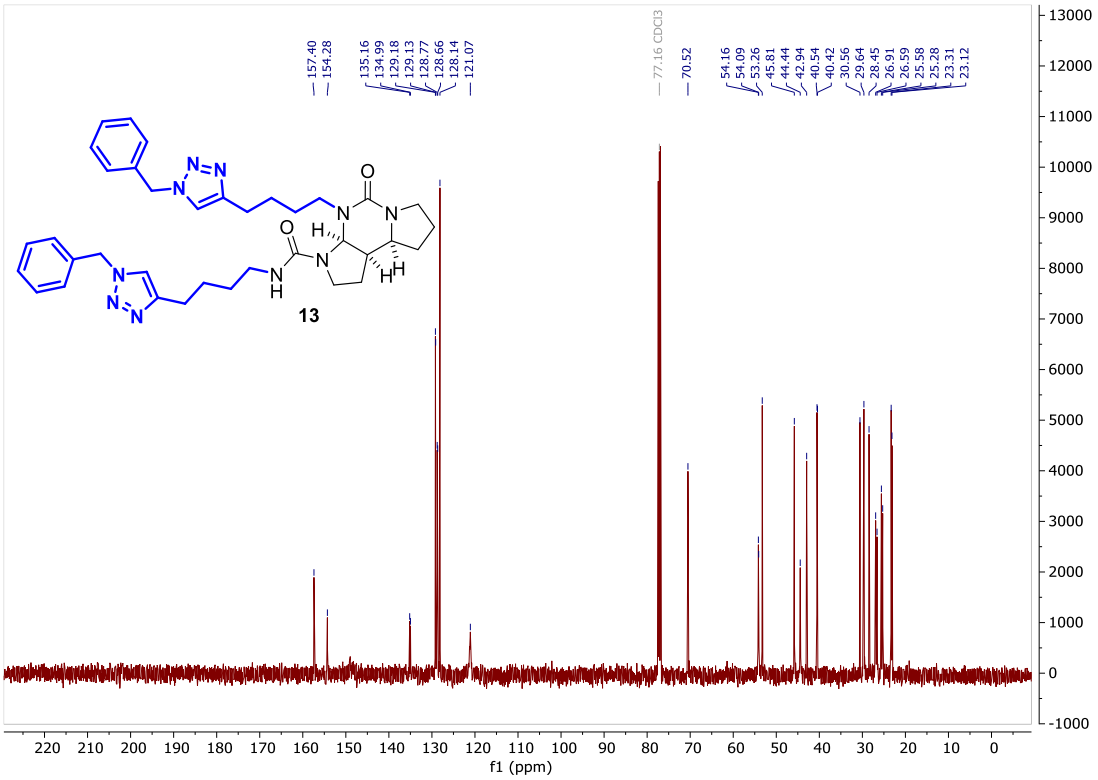
^{1}H and ^{13}C NMR spectra of compound 13 and 14

N,4-bis(4-(1-benzyl-1H-1,2,3-triazol-4-yl)butyl)-5-oxodecahydro-3H-dipyrrolo[1,2-c:3',2'-e]pyrimidine-3-carboxamide (13)

^{1}H NMR, 500 MHz, $CDCl_3$

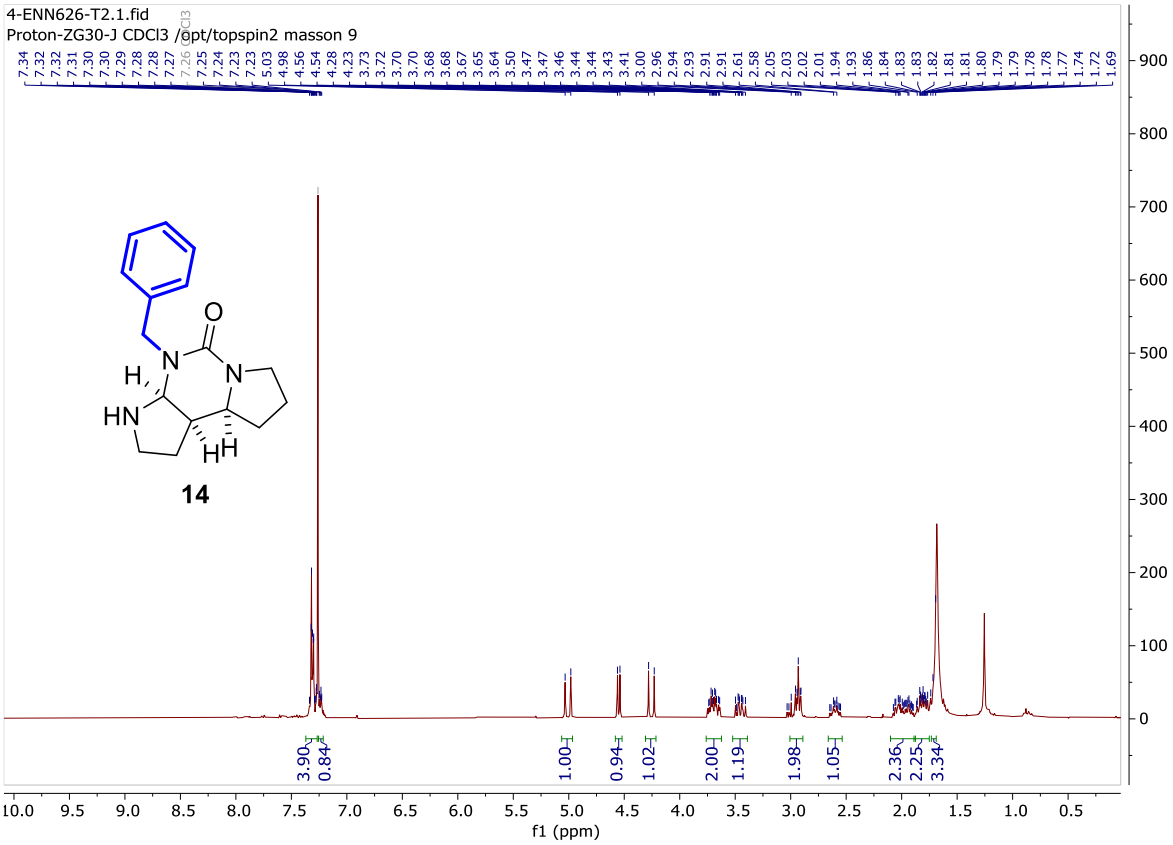


$^{13}C\{^{1}H\}$ NMR, 126 MHz, $CDCl_3$

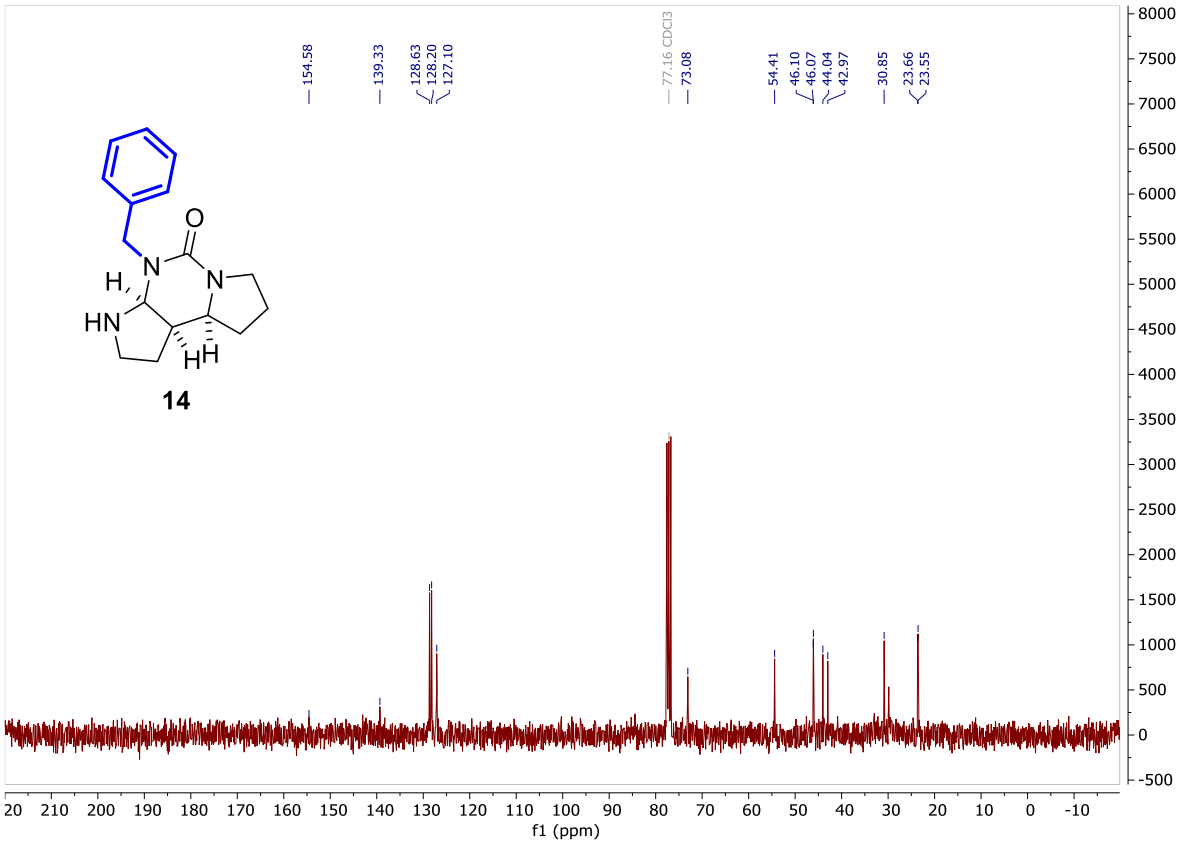


(3aS,9aS,9bR)-4-benzyldecahydro-5H-dipyrrolo[1,2-c:3',2'-e]pyrimidin-5-one (14)

^{1}H NMR, 300 MHz, $CDCl_3$



^{13}C{^{1}H} NMR, 75 MHz, $CDCl_3$



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