Microwave-enhanced solid phase synthesis of *N,N'*-linked aliphatic oligoureas and related hybrids

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SUPPORTING INFORMATION

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1. General techniques **SI-2**
2. Azido building blocks synthesis **SI-3**
3. General procedure of oligourea SPS **SI-10**
4. ^{1}H NMR Spectra **SI-12**
5. HPLC chromatograms **SI-24**
6. Early investigation of oligourea SPS with microwave irradiation using Boc chemistry **SI-25**

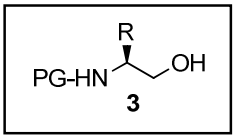
1 General techniques:

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. NovaPEG Rink amide resin and 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HBTU) were purchased from Novabiochem. All organic solvents for solid phase synthesis were of analytical grade. Anhydrous THF was obtained from Sigma Aldrich and anhydrous dichloromethane was distilled over CaH_2. RP-HPLC-quality acetonitrile (CH_3CN) and MilliQ water were used for RP-HPLC analyses and purification. Thin layer chromatography (TLC) was performed on silica gel 60 F254 (Merck) with detection by UV light and charring with 1% ninhydrin in ethanol followed by heating. Flash column chromatography was carried out on silica gel (40-63 μm, Merck). Melting points were measured in open capillary tubes and are uncorrected. Optical rotations were determined on a Jasco P-2000 polarimeter and are given as $[\alpha]_D^{25}$ (concentration in g/100 mL solvent). ^{1}H NMR and ^{13}C NMR spectra were recorded on an Avance II NMR spectrometer (Bruker Biospin) with a vertical 7.05T narrow-bore/ultrashield magnet operating at 300 MHz for ^{1}H observation and 75 MHz for ^{13}C observation by means of a 5-mm direct BBO ^{1}H/^{19}F_XBB_H probe with Z gradient capabilities. Chemical shifts are reported in parts per million (ppm) relative to the ^{1}H residual signal of the deuterated solvent used. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Coupling constants (*J*) are reported in hertz. Analytical RP-HPLC analyses were performed on a Dionex U3000SD using a Macherey-Nagel Nucleodur column (4.6 × 100 mm, 3μm) at a flow rate of 1mL·min^{-1}. The mobile phase was composed of 0.1% (v/v) TFA-H_2O (Solvent A) and 0.1%TFA-CH_3CN (Solvent B). Semi-preparative purification of oligourea **10** and related hybrid **11** were performed on a Dionex U3000SD using a Macherey-Nagel Nucleodur column (10× 250 mm, 5μm). A gradient elution of 30 to 60% of B 15 min at a flow rate of 4 mL.min^{-1}was applied to purify **10** and a gradient elution of 25 to 55% of B 20 min at a flow rate of 4mL·min^{-1} was applied to purify **11**. Column effluent was monitored by UV detection at 200 nm and 254 nm. ESI-MS analyses were carried out on a ThermoElectron LCQ Advantage spectrometer equipped with an ion trap mass analyzer and coupled with a ThermoElectron Surveyor HPLC system.

Solid phase syntheses of oligoureas and hybrid **11** with microwave irradiation were conducted on the Discover® System from CEM (CEM μWaves S.A.S., Orsay, France)

2 Azido Building Block Synthesis

*2.1 General procedure for N-protected amino alcohol (**D**) formation*[1]



The *N*-protected α-amino acid (10 mmol) was dissolved in THF (30 mL) under Ar and cooled to -20 °C. After addition of isobutyl chloroformate (1.368 mL, 10.5 mmol) and NMM (1.209 mL, 11 mmol), the mixture was stirred at -20 °C for 20 min. The resulting white suspension was then filtered off and the filtrate was added at -20°C to a solution of $NaBH_4$ (0.76 g, 20 mmol) in water (15 mL). The reaction mixture was left to react overnight and then a 1M solution of $KHSO_4$ was added (30 mL). The resulting aqueous solution was extracted two times with EtOAc (30 mL). The organic layers were combined, washed two times with 1M $KHSO_4$ (30 mL), two times with saturated solution of $NaHCO_3$ (30mL), one time with brine (30 mL), dried over sodium sulfate and concentrated under vacuum. In most cases, no silica gel purification was required.

***N*-Boc-Phe-ol (3a)**1**:** Solid; yield 92%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 – 7.18 (m, 5H), 4.76 (bp, 1H), 3.90 (bp, 1H), 3.69 (m, 1H), 3.59 (m, 1H), 2.86 (d, *J*= 7.5, 2H), 2.36 (bp, 1H), 1.43 (s, 9H).

***N*-Z-Tyr(O*t*Bu)-ol (3b):**[2] Oil; yield 89%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.29 (m, 5H), 7.08 (d, *J*=8.5, 2H), 6.91 (d, *J*=8.5, 2H), 5.07 (s, 2H), 4.97 (d, *J*= 8.0, 1H), 3.92 (bp, 1H), 3.62 (dd, J= 10.7 and 5.3, 2H), 2.81 (d, *J*= 7.2, 2H), 1.33 (s, 9H).

***N*-Z-Orn(Boc)-ol (3c):** White solid; yield 87% (crude); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40 – 7.32 (m, 5H), 5.13 (s, 2H), 5.07 (d, *J*= 6.3, 1H), 4.63 (bs, 1H), 3.74 – 3.65 (m, 3H), 3.17 (bd, *J*= 3.0, 2H), 2.32 (bs, 1H), 1.68 – 1.52 (m, 4H), 1.47 (s, 9H).

***N*-Boc-Leu-ol (3d):** Oil; yield 89% (crude); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.57 (bs, 1H), 3.75 – 3.68 (m, 2H), 3.54 (dd, *J* = 10.8, 6.0, 1H), 1.70 (sept., *J* = 6.0, 1H), 1.48 (s, 9H), 1.37 – 1.32 (m, 2H), 0.98 (d, *J* = 1.3, 3H), 0.96 (d, *J* = 1.2, 3H).

***N*-Boc-Ala-ol (3e):** Oil; yield 83% (crude); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65 (bs, 1H), 3.85 – 3.77 (m, 1H), 3.68 (dd, *J* = 10.9, 3.7, 1H), 3.54 (dd, *J* = 10.9, 6.2, 1H), 1.48 (s, 9H), 1.18 (d, *J* = 6.8, 3H).

***N*-Boc-Trp-ol (3f):** Creamy solid; yield 92% (crude); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (bs, 1H), 7.69 (d, *J* = 7.8, 1H), 7.43 – 7.39 (m, 1H), 7.21 (dtd, *J* = 14.8, 7.1, 1.2, 2H), 7.10 (d, *J* =

(1) Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Letters* **1991**, *32*, 923−926.
(2) Bianco, A. ; Maggini, M. ; Scorrano, G. ; Toniolo, C. ; Marconi, G. ; Villani, C. ; Prato, M. *J. Amer. Chem. Soc.* **1996**, ***118,*** 4072−4080

2.2, 1H), 4.84 (bs, 1H), 4.08 – 3.98 (m, 1H), 3.74 (dd, *J* = 11.0, 3.8, 1H), 3.65 (dd, *J* = 11.0, 5.5, 1H), 3.04 (d, *J* = 6.8, 2H), 1.46 (s, 9H).

2.2 General procedure for Boc removal

N-Boc protected amino alcohol (10 mmol) was dissolved in pure TFA (8 mL) and left to react without stirring for 30 min. The TFA was removed under reduced pressure and the TFA salt was dried overnight on vacuum line. No purification and no isolation of the TFA salts were done. They were directly engaged in the next step.

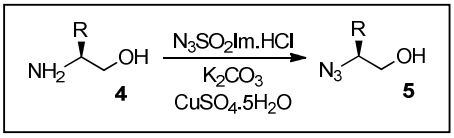
*2.2.1 General procedure for Boc removal of intermediates **8***

N-Boc protected aminophthalimide **8** (7.65 mmol) was dissolved in a mixture of TFA and DCM (18 mL, 1:1, v/v) and was stirred under N_2 for 1.5 h. After that time TFA and DCM were removed under reduced pressure and the resulting TFA salt was used in the next step without any purification. In the case of Trp analogue **8f,** the corresponding TFA salt was precipitated with diethyl ether, filtered and dried.

2.3 General procedure for Z deprotection.

To a solution of *N*-Z protected amino alcohol **3b-c** (10 mmol) in MeOH (80 mL) was gently added 10% of Pd/C and the reaction mixture was stirred overnight under 1 bar H_2 atmosphere (balloon). After filtration over Millipore paper filter, the filtrate was concentrated under reduced pressure to quantitatively furnish corresponding amino derivatives **4b-c** as pale oils. These compounds were not isolated and were directly engaged in the next step.

*2.4 General procedure for amine to azide conversion (compounds **5** and **6**)* [3]



To a solution of amine or corresponding TFA ammonium salt **3** (10 mmol) in MeOH (50 mL) were successively added K_2CO_3 (3.06 g, n + 0.5 mmol),[4] $CuSO_4.5H_2O$ (0.025 g, 0.1 mmol) and imidazole-1-sulfonyl azide hydrochloride (2.525 g, 12 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was then filtered off to remove the remaining K_2CO_3, concentrated under reduced pressure and dissolved in EtOAc (50 mL). The organic layer was then washed two times with 1N HCl aqueous solution (30 mL), one time with brine (30 mL), dried over sodium sulfate and

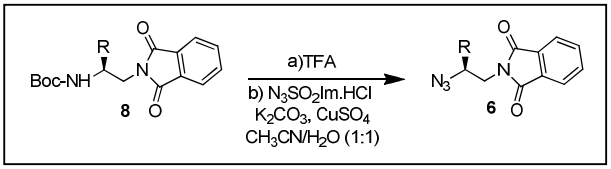
(3) Goddard-Borger, E. D.; Stick, R. V. *Organic Letters* **2007**, *9*, 3797−3800.
(4) Where 'n' is the number of mols of acid in the system. For example: the reaction of **N_3SO_2Im·HCl** (12 mmol) and the TFA,amino alcohol of L-Phe (10 mmol) requires n = 22 mmol.

concentrated under reduced pressure to furnish after silica gel flash chromatography azides **4** as pure compounds.

(*S*)-2-azido-3-phenyl-propan-1-ol (5a): Oil; yield 56% (flash chromatography: cyclohexane/EtOAc (7:3, v/v)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 – 7.20 (m, 5H), 3.72 (m, 2H), 3.56 (m, 1H), 2.87 (ABsyst, *J*= 15.6, 10, 6, 2H), .81 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.21, 128.9, 127.09, 65.5, 64.6, 37.17.

(*S*)-2-azido-3-(4-(tert-butoxy)phenyl)propan-1-ol (5b): Oil; yield 61% (flash chromatography: cyclohexane/EtOAc (7:3, v/v)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.94 (d, *J*=8, 2H), 3.70 (m, 2H), 3.53 (m, 1H), 2.82 (AB_{syst}, *J*= 17, 14, 7, 2H), 1.87 (bp, 1H), 7.12 (d, *J*=8, 2H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.37, 131.79, 129.70, 124.43, 65.80, 64.43, 36.44, 28.83.

(*S*)-2-azido-5-(N-*tert*-butoxycarbonylamino)pentan-1-ol (5c): Oil; yield 85% (flash chromatography: cyclohexane/EtOAc (1/1, v:v)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.61 (bs, 1H), 3.75 (ddd, *J* = 10.3, 6.4, 3.8, 1H), 3.62 (ddd, *J* = 11.7, 8.5, 5.2, 1H), 3.56 – 3.49 (m, 1H), 3.20 – 3.16 (m, 2H), 1.97 (t, *J* = 5.7, 1H), 1.74 – 1.55 (m, 4H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.09, 79.42, 65.18, 63.88, 40.10, 28.42, 27.70, 26.76.



To a solution of the corresponding TFA ammonium salt of **8** (8 mmol) in a mixture of CH_3CN/H_2O (1:1, 20 mL) were successively added K_2CO_3 (2.462 g, n + 0.5 mmol)[4], $CuSO_4{\cdot}5H_2O$ (0.02 g, 0.08 mmol) and imidazole-1-sulfonyl azide hydrochloride (2.012 g, 9.6 mmol). After 10 min, pH was controlled and if necessary some amount of K_2CO_3 was added to adjust the pH to 8-9. After 1 hour, the reaction was complete and CH_3CN was evaporated. To the remaining aqueous layer was added EtOAc (20mL). The layers were separated and the aqueous one was extracted four times with EtOAc (20mL). Combined organic layers were washed three times with 1M $KHSO_4$ (30mL), one time with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to furnish after silica gel flash chromatography in cyclohexane/EtOAc mixture (9:1, v/v), azides **6** as pure compounds.

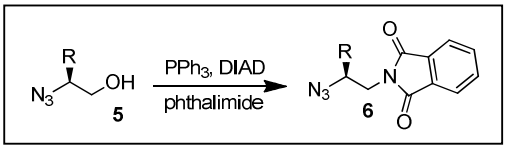
***N*-(2-azido-4-methylpentyl)phthalimide (6d)**: White solid; yield 87%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 – 7.87 (m, 2H), 7.82 – 7.74 (m, 2H), 3.92 – 3.67 (m, 3H), 1.98 – 1.79 (m, 1H), 1.65 – 1.52 (m, 1H), 1.48 – 1.35 (m, 1H), 1.03 (d, *J* = 6.7, 3H), 0.99 (d, *J* = 6.6, 2H); ^{13}C

NMR ($CDCl_3$, 75 MHz) δ 168.29, 134.31, 131.98, 123.62, 58.79, 41.73, 41.03, 25.14, 23.12, 21.97.

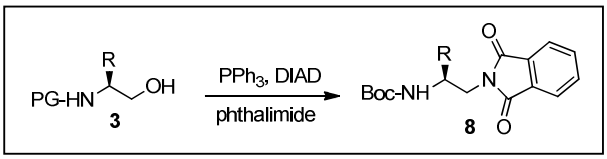
***N*-(2-azidopropyl)phthalimide** (**6e**): White solid; yield 65%;^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.92 – 7.84 (m, 2H), 7.78 – 7.71 (m, 2H), 3.97 – 3.85 (m, 1H), 3.79 (dd, *J* = 13.7, 8.6, 1H), 3.64 (dd, *J* = 13.7, 4.8, 1H), 1.35 (d, *J* = 6.5, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.25, 134.32, 131.97, 123.63, 55.72, 42.54, 17.28.

***N*-(2-azido-3-indolepropyl)phthalimide** (**6f**): Yellow foam; yield 45%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.20 (s, 1H), 7.94 – 7.85 (m, 2H), 7.79 – 7.73 (m, 2H), 7.68 – 7.65 (m, 1H), 7.44 – 7.36 (m, 1H), 7.28 – 7.15 (m, 3H), 4.22 (m, *J* = 8.7, 7.6, 6.2, 4.8, 1H), 3.89 (ddd, *J* = 18.7, 14.0, 6.7, 2H), 3.23 – 3.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.32, 136.31, 134.29, 131.93, 127.35, 123.57, 123.13, 122.39, 119.83, 118.66, 111.40, 110.74, 60.66, 41.43, 28.70.

*2.5 General procedure for conversion of alcohol into amine (compounds **6** and **8**) – the Mitsunobu reaction*



To a solution of triphenylphosphine (2.62 g, 10 mmol) in anhydrous THF (20 mL) at 0°C and under positive N_2 atmosphere pressure, were successively added DIAD (2.02 mL, 10 mmol) and phthalimide (1.47 g, 10 mmol). Azido alcohol **5** (10 mmol) dissolved in anhydrous THF (10 mL) was next added dropwise and the reaction mixture was stirred and allowed to reach the room temperature. After 4 hours the reaction was completed. THF was evaporated under reduced pressure and the crude material was directly engaged in the next step.



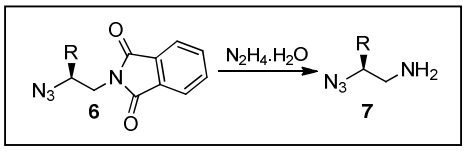
N-Boc protected amino alcohol **3** **(**11 mmol) was dissolved in anhydrous THF (20 mL) under positive N_2 atmosphere pressure. Triphenylphosphine (3.458 g, 13.2 mmol) and phthalimide (1.94 g, 13.2 mmol) were added, followed by dropwise addition of DIAD (2.596 mL, 13.2 mmol). The reaction mixture was stirred for 30 min, at 0°C and was then allowed to reach room temperature. The reaction was completed after 2h or overnight stirring. THF was evaporated under reduced pressure and the crude material was purified by silica gel flash chromatography (cyclohexane/EtOAc).

***N*-(2-*N*-*tert*-butoxycarbonylamino-4-methylpentyl)phthalimide** (**8d**): White solid; yield 72%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 – 7.81 (m, 2H), 7.72 – 7.66 (m, 2H), 4.44 (d, *J* = 9.0, 1H), 4.13 – 4.01 (m, 1H), 3.77 – 3.54 (m, 2H), 1.75 (sept., *J* = 6.0, 1H), 1.34 (t, *J* = 7.2, 2H), 1.19 (s, 9H), 0.96 (d, *J* = 6.7, 3H), 0.93 (d, *J* = 6.6, 3H).

***N*-(2-*N*-*tert*-butoxycarbonylaminopropyl)phthalimide (8e)**: White solid; yield 69%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 – 7.81 (m, 2H), 7.73 – 7.68 (m, 2H), 4.65 (d, *J* = 6.0, 1H), 4.14 – 4.03 (m, 1H), 4.73 – 4.62 (m, 2H), 1.25 (s, 9H), 1.20 (d, *J* = 6.7, 3H).

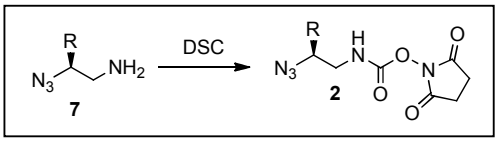
***N*-(2-*N*-*tert*-butoxycarbonylamino-3-indolepropyl)phthalimide (8f)**: Yellowish solid; yield 77%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (s, 1H), 7.85 – 7.79 (m, 2H), 7.70 – 7.67 (m, 2H), 7.63 (d, *J* = 7.7, 1H), 7.37 (d, *J* = 7.9, 1H), 7.24 – 7.08 (m, 3H), 4.75 (d, *J* = 8.6, 1H), 4.41 (bs, 1H), 3.77 (qd, *J* = 13.9, 6.8, 2H), 3.05 (bd, *J* = 5.9, 2H), 1.23 (s, 9H).

2.6 General procedure for azido amine 7 synthesis



To a solution of azido phthalimide derivatives **6a- f** (10 mmol) in MeOH (50 mL) was added hydrazine hydrate (1.453 mL, 30 mmol). The reaction mixture was heated to reflux and heating was maintained for 4 hours with apparition of a white precipitate. The reaction mixture was filtered off, washed with MeOH and the filtrate was concentrated under reduced pressure. The crude material was dissolved in EtOAc (100 mL). The organic layer was washed two times with 1N HCl aqueous solution (30 mL). The combined aqueous phases were again washed with EtOAc (2 × 20 mL) and were neutralized by addition of solid $NaHCO_3$ until pH 8. The aqueous phase was finally extracted with DCM (2 × 30 mL) and the combined organic layers were washed with brine (20 mL), dried on Na_2SO_4, concentrated under reduced pressure to give amines **7** as pale oils. Importantly, in case of amines **7d-e,** the basic aqueous phase was extracted in the same way with EtOAc (4 × 30 mL) and after drying, the solvent was not evaporated to dryness to avoid the loss of azido amines 7**d-e** which are quite volatile. Resulting azido amines 7**d-e** were directly engaged for activation step without further purification.

*2.7 General procedure for the preparation of succinimidyl azido-2-substituted-ethyl-carbamates **2***



To a stirred suspension of disuccinimidyl carbonate (1.537 g, 6 mmol) in freshly distilled DCM (50 mL) was added drop by drop a solution of (*S*)-2-azido-3-X-propan-1-amine **7** (5 mmol) in distilled DCM (50mL). After 3 hours, the reaction mixture was concentrated under reduced pressure and the crude material was dissolved in EtOAc (70 mL). The organic layer was washed with 1M $KHSO_4$ (2 × 30 mL), with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish activated carbamates **2a-f** as white solids.

(*S*)-2,5-dioxopyrrolidin-1-yl (2-azido-3-phenylpropyl)carbamate (2a). White solid; yield 90 %; mp 85-87°C; $[\alpha]^{25}_D$ + 54.2; t_R = 7.25 min. (gradient 10 to 100% of B in 10 min.);^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 – 7.17 (m, 5H), 5.57 (t, *J*= 6, 1H), 3.84 (m, 1H), 3.46 (m, 1H), 3.17 (m, 1H), 2.89 (d, *J*=7, 2H), 2.82 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.82, 151.63, 136.20, 129.32, 128.86, 127.23, 77.49, 77.07, 76.64, 62.94, 44.93, 38.41, 25.48. HRMS (ESI-TOFMS) *m/z* cald for $C_{14}H_{15}N_5O_4Na$ $[M+Na]^+$ 340.1022, found 340.1021.

(*S*)-2,5-dioxopyrrolidin-1-yl (2-azido-3-(4-(tert-butoxy)phenyl)propyl)carbamate (2b). White solid; yield 83 %; mp 106-108 °C; $[\alpha]^{25}_D$ + 52.2; t_R = 8.25 min. (gradient 10 to 100% of B in 10 min.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (d, *J*=8.5, 2H), 6.95 (d, *J*=8.5, 2H), 5.51 (t, *J*= 5, 1H), 3.80 (m, 1H), 3.47 (m, 1H), 3.15 (m, 1H), 2.87 (d, *J*=6, 1H), 2.83 (bp, 5H), 1.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.88, 154.64, 151.68, 131.15, 129.90, 124.71, 78.68, 63.28, 45.06, 38.03, 28.93, 25.58. HRMS (ESI-TOFMS) *m/z* cald for $C_{18}H_{23}N_5O_5Na$ $[M+Na]^+$ 412.1597, found 412.1607.

Carbamates 2c-f

A solution of amine **7c-f** (8 mmol) dissolved in EtOAc (60-80 mL) and cooled at 0°C was added drop by drop to solid disuccinimidyl carbonate (2.459 g, 9.6 mmol). The reaction mixture was stirred under N_2 atmosphere and during the amine addition the temperature was maintained at 0°C. After 30 min. the reaction mixture was allowed to reach room temperature. After 1.5 hour, the remaining solid was filtered off and washed with EtOAc. The organic phase was washed with 1M $KHSO_4$ (5× 20 mL), with brine (20 mL) and dried over $MgSO_4$ to furnish after evaporation of the solvent, the activated carbamates as white to yellowish solids.

(*S*)-2,5-dioxopyrrolidin-1-yl (2-azido-5-N-*tert*-butoxycarbonylaminopentyl)carbamate (2c). White solid; yield 65 % (after 2 steps); mp 81-83°C; $[\alpha]^{25}_{D}$ + 24.2; t_R = 6.88 min. (gradient 10 to 100% of B in 10 min.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.60 (t, *J* = 6.0 Hz, 1H), 4.61 (s, 1H), 3.61 (m, 1H), 3.44 (ddd, *J* = 14.0, 6.5, 4.3, 1H), 3.26 – 3.16 (m, 3H), 2.83 (s, 4H), 1.62 – 1.59 (m, 4H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.00, 156.24, 151.92, 79.49, 61.54, 45.29, 40.06, 28.97, 28.50, 26.55, 25.58; HRMS (ESI-TOFMS) *m/z* cald for $C_{15}H_{24}N_6O_6Na$ $[M+Na]^+$ 407.1655, found 407.1654.

(*S*)-2,5-dioxopyrrolidin-1-yl (2-azido-4-methylpentyl)carbamate (2d). White solid; yield 86% (after 2 steps); mp 92-94°C; $[\alpha]^{25}_{D}$ + 49.3; t_R = 7.25 min. (gradient 10 to 100% of B in 10 min.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ ^{1}H NMR (300 MHz,) δ 5.69 (t, *J* = 6.0, 1H), 3.65 – 3.56 (m, 1H), 3.46 (ddd, J = 13.9, 6.8, 3.7, 1H), 3.14 (ddd, *J* = 13.8, 8.2, 5.4, 1H), 2.83 (s, 4H), 1.87 – 1.70 (m, 1H), 1.51 (ddd, *J* = 14.6, 8.5, 6.2, 1H), 1.35 (ddd, *J* = 13.9, 8.1, 5.6, 1H), 0.96 (d, *J* = 6.6, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.97, 151.77, 77.58, 77.16, 76.74, 60.12, 45.73, 40.74, 25.58, 25.00, 22.92, 22.19; HRMS (ESI-TOFMS) *m/z* cald for $C_{11}H_{17}N_5O_4Cl$ $[M+Cl]^-$ 318.0969, found 318.0978.

(*S*)-2,5-dioxopyrrolidin-1-yl (2-azidopropyl)carbamate (2e). White solid; yield 56% (after 2 steps); mp 83-85°C; $[\alpha]^{25}_{D}$ + 70.8; t_R = 4.83 min. (gradient 10 to 100% of B in 10 min.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.58 (bt, *J* = 6.0, 1H), 3.81 – 3.71 (m, 1H), 3.41 (ddd, *J* = 13.9, 7.0, 4.0, 1H), 3.14 (ddd, *J* = 13.7, 7.9, 5.4, 1H), 2.84 (s, 4H), 1.32 (d, *J* = 6.6, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.90, 151.69, 77.51, 77.29, 77.09, 76.66, 56.96, 46.57, 25.50, 16.66; HRMS (ESI-TOFMS)*m/z* cald for $C_8H_{11}N_5O_4Cl$ $[M+Cl]^-$ 276.0500, found 276.0490.

(*S*)-2,5-dioxopyrrolidin-1-yl (2-azido-3-indolepropyl)carbamate (2f). Creamy foam; yield 90% (after 2 steps); mp 75-78 °C; $[\alpha]^{25}_{D}$ + 32.5; t_R = 7.09 min. (gradient 10 to 100% of B in 10 min.); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (s, 1H), 7.58 (d, *J* = 9.0, 1H), 7.40 – 7.33 (m, 1H), 7.25 – 7.07 (m, 3H), 5.58 (t, *J* = 5.8, 1H), 3.94 (qd, J = 7.1, 3.9, 1H), 3.44 (ddd, *J* = 13.9, 6.2, 3.9, 1H), 3.22 (ddd, *J* = 13.7, 7.3, 6.0, 1H), 3.08 (qd, *J* = 7.2, 14.7, 2H), 2.81 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.05, 151.81, 136.33, 127.21, 123.53, 122.41, 119.87, 118.47, 111.54, 110.20, 61.83, 44.79, 27.85, 25.55; HRMS (ESI-TOFMS)*m/z* cald for $C_{16}H_{16}N_6O_4Na$ $[M+Na]^+$ 379.1131, found 379.1126.

3. General procedure for oligourea solid phase synthesis under microwave irradiation

Oligourea 9. The NovaPEG Rink amide resin (0.05 g, 0.032 mmol) was placed in a polypropylene SPE tube (CEM), suspended in DMF (2 mL) and **2a** (0.015 g, 0.048 mmol, 1.5 equiv relative to resin loading) and DIEA (14 μL, 0.080 mmol) were successively added. The tube was then placed inside the microwave reactor (CEM Discover) and irradiated (25 W maximum power, 70 °C, ramp 5 min, hold 15min). All microwave experiments were conducted at atmospheric pressure. The temperature was maintained by modulation of power and controlled with a fiber optic sensor. Coupling with **2a** was repeated once. The tube was then removed from the microwave reactor and the resin was filtered off, washed four times with DMF (3 mL) and two times with DCM (3 mL). The coupling efficiency was monitored with the chloranil test.[5] Reduction of the azide group was next done with microwave assistance by swelling the resin in a mixture of dioxane/water (70:30, v/v, 2 mL) and adding 1M PMe_3 solution in THF (0.320 mL, 10 equiv relative to the resin loading), irradiating with 25 W power, heating at 70 °C for 30 min. The reaction was repeated once. The resin was then filtered off, washed with the dioxane/water mixture (2 × 3 mL) and DMF (3 × 3 mL). The preceding acylation steps and reduction of azides were repeated. End-capping was carried out once in presence of benzylisocyanate (3 equiv) and DIEA (3 equiv) and under microwave assistance (25 W, 70 °C, 15 min). Resin was filtered off, washed with DMF (2 × 2 mL) and DCM (2 × 2 mL) and dried. The resin was finally swelled in pure TFA and left to react for 120 min. After that time, the resin was filtered off, washed with DCM and the filtrate was evaporated under reduced pressure to give, after *t*-buthyl methyl ether precipitation the expected oligourea **9** in good purity and yield.

HPLC purity of crude product 74%. Yield after cleavage/precipitation 86%; White powder; RP-HPLC t_R 8.24 min (gradient, 50-100% of B in 10 min); ESI-MS *m/z* cald for $C_{48}H_{59}N_{10}O_6[M+H]^+$ 855.46, found 855.2.

Oligourea 10. The same procedure to that described for oligourea **9** was applied by alternatively coupling carbamate **2a** and **2b**. To improve the solubility no end-capping was done on the oligourea **10**.

(5) Vojkovsky, T. *Pept. Res.* **1995**, *8*, 236–237.

HPLC purity of crude product 70%. Yield after cleavage/precipitation, 24 mg, 57%; yield after HPLC purification 4 mg, 10 %; White powder; RP-HPLC t_R 5.73 min (gradient 10 to 100% of B in 10 min); ESI-MS *m/z* cald for $C_{70}H_{88}N_{15}O_{11}$ $[M+H]^+$ 1313.67, found 1314.3.

Hybrid 11. NovaPEG Rink amide resin (0.05 g, 0.032 mmol) was used for the synthesis of hybrid **11**. The same carbamate coupling and azide reduction conditions to those developed for **9** & **10** were applied. Each coupling/reduction step was performed twice. Couplings of *N*-Fmoc-*γ*-amino acids (0.048 mmol, 1.5 equiv. relative to the resin loading) were done under microwave assistance (50 W, 50 °C, 12 min) by employing HBTU (18.2 mg, 0.048 mmol, 1.5 equiv) and HOBt (7.34 mg, 0.048 mmol, 1.5 equiv) as coupling reagents and DIEA (27.9 μL, 0.160 mmol, 5 equiv) as base. The coupling step was performed twice. Fmoc removal was carried out in 20% piperidine in DMF mixture and under microwave assistance (50 W, 50 °C, 4 and 8 min). End-capping acetylation was carried out in the presence of Ac_2O (30μL, 0.32 mmol, 10 equiv) and DIEA (84μL, 0.48 mmol, 15 equiv) and under microwave assistance (50 W, 50 °C, 5 min × 2). The resin was washed (DMF × 5, DCM × 5, MeOH × 5, Et_2O × 5) and dried under vacuum. The cleavage of hybrid **11** was performed without microwave assistance. A mixture of TFA/TIS/H_2O (95:2.5:2.5) was used as a cleavage cocktail. After 3 hours, the resin was filtered off and washed with DCM and MeOH. The solvents were evaporated and the remaining material was redissolved in a mixture of H_2O and ACN and lyophilized to give hybrid **11** in good purity and yield. Hybrid **11** was then purified by semi-preparative HPLC (gradient 75% to 45% of A 15 min).

HPLC purity of crude product 86%. Yield after cleavage/precipitation 17 mg, 50%; yield after purification 4 mg, 11%; White powder; RP-HPLC t_R 5.28min (gradient 10 to 100% of B in 10 min); ESI-MS *m/z* 999 $[M+H]^+$, 1021 $[M+Na]^+$, 500 $[M+2H]^+$

4. 1H NMR spectra

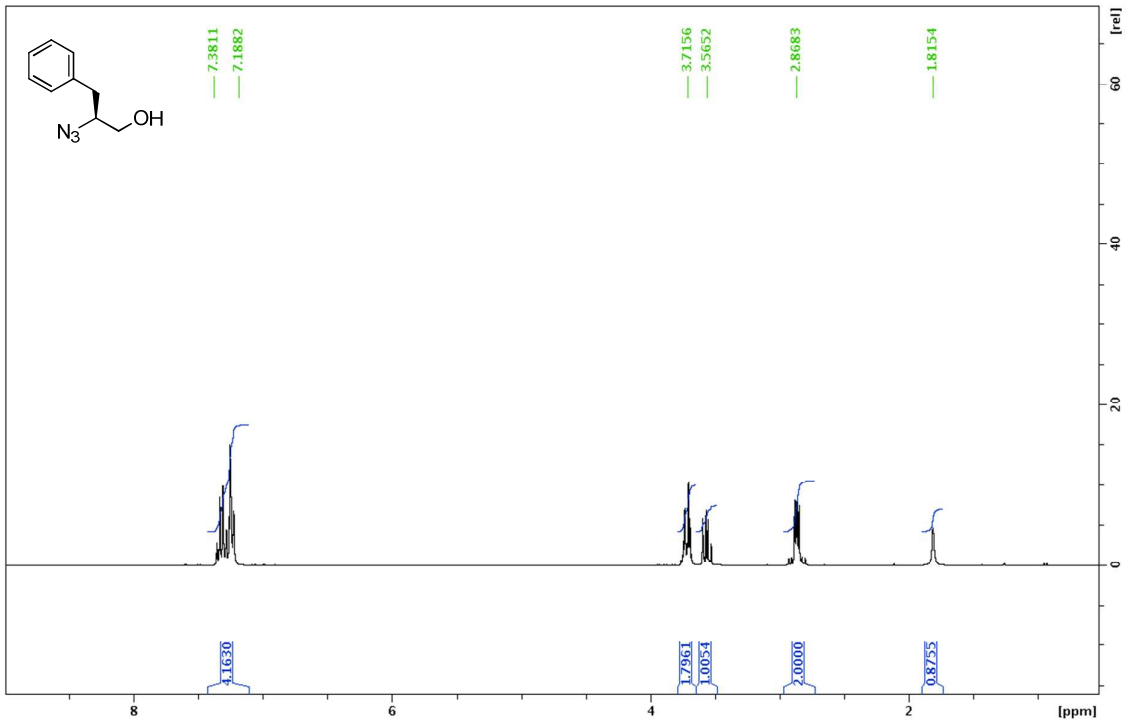


Figure S1. ^{1}H NMR spectrum of compound **5a**, recorded in $CDCl_3$ (300 MHz)

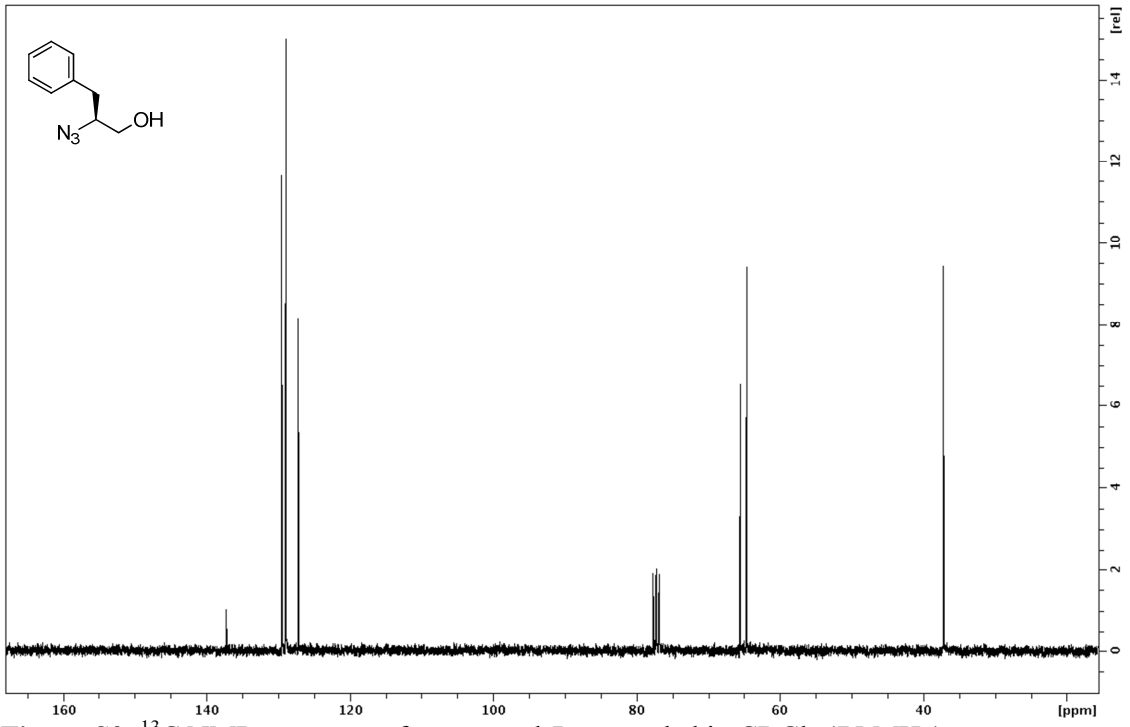


Figure S2. ^{13}C NMR spectrum of compound **5a**, recorded in $CDCl_3$ (75 MHz)

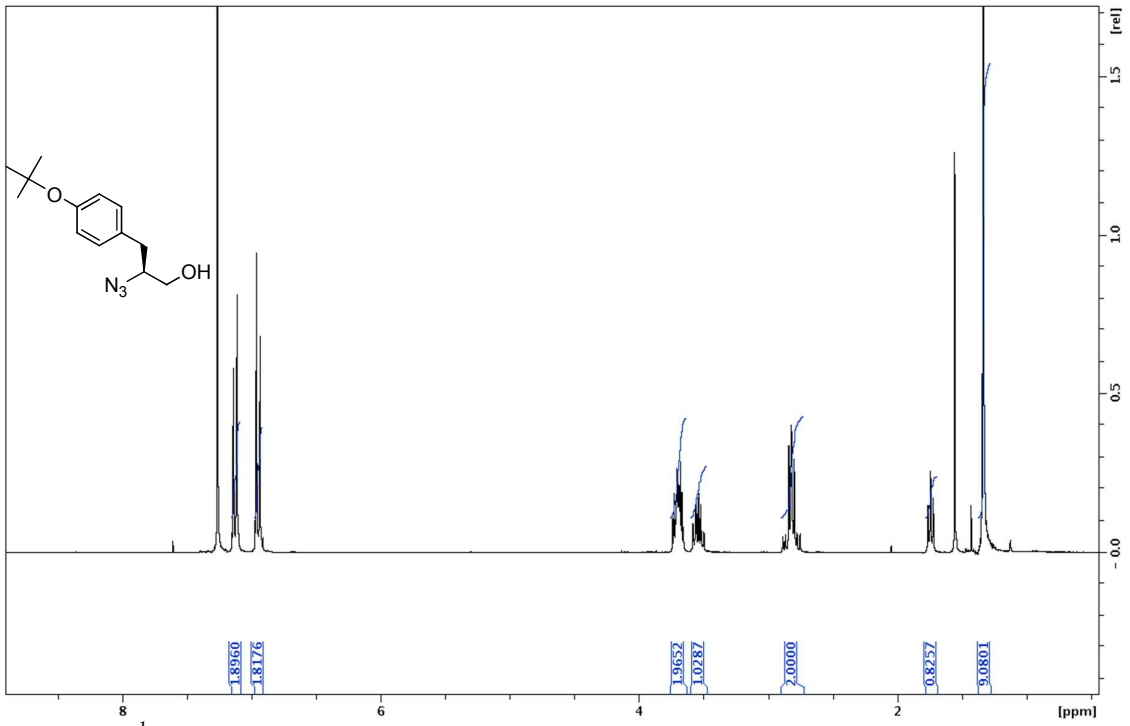


Figure S3. ^{1}H NMR spectrum of compound **5b**, recorded in $CDCl_3$ (300 MHz)

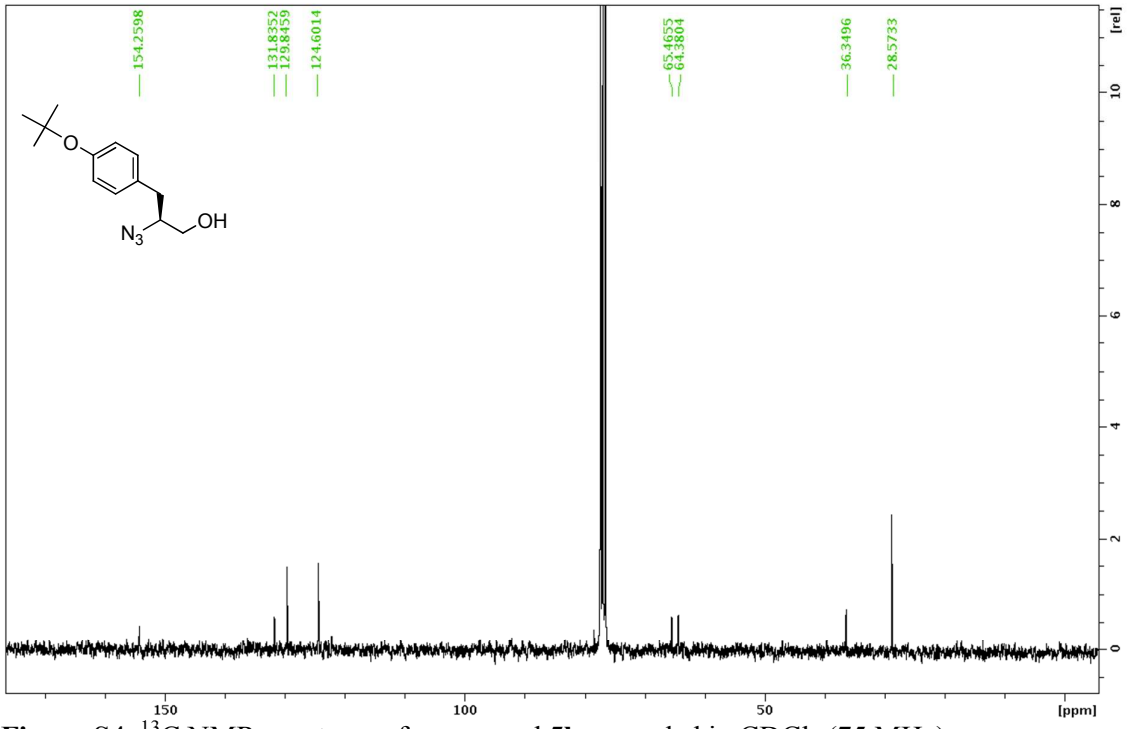


Figure S4. ^{13}C NMR spectrum of compound **5b**, recorded in $CDCl_3$ (75 MHz)

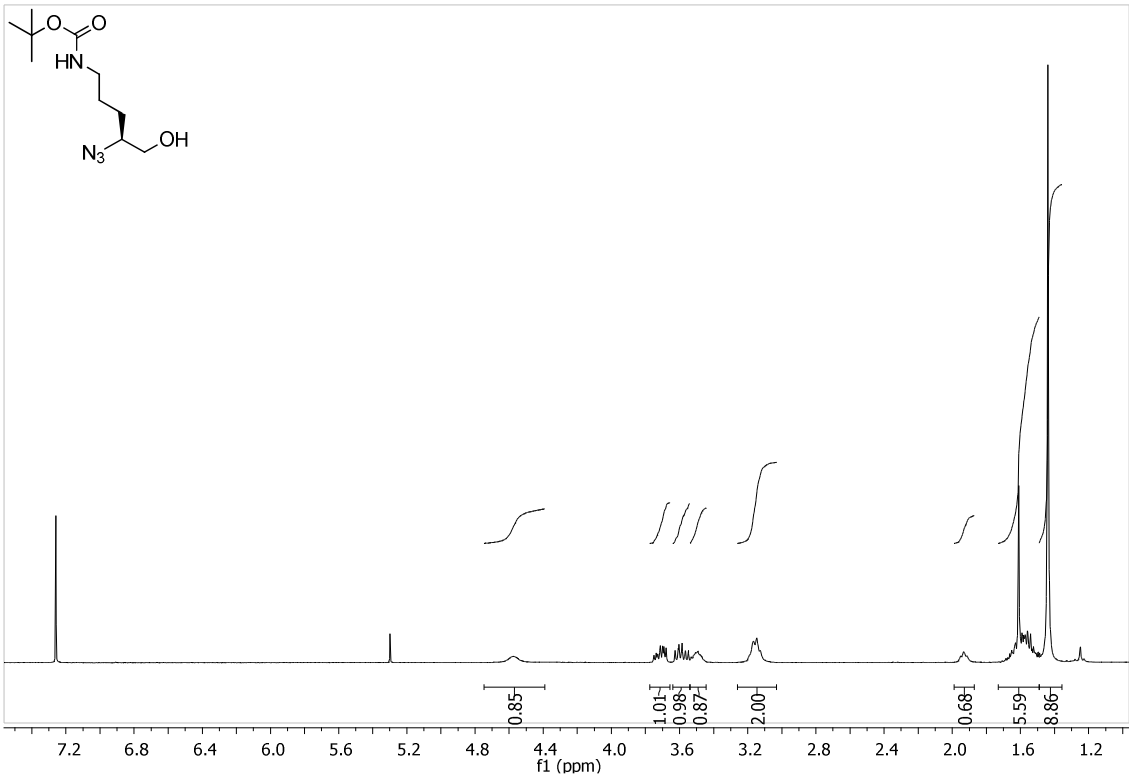


Figure S5. ^{1}H NMR spectrum of compound **5c**, recorded in $CDCl_3$ (300 MHz)

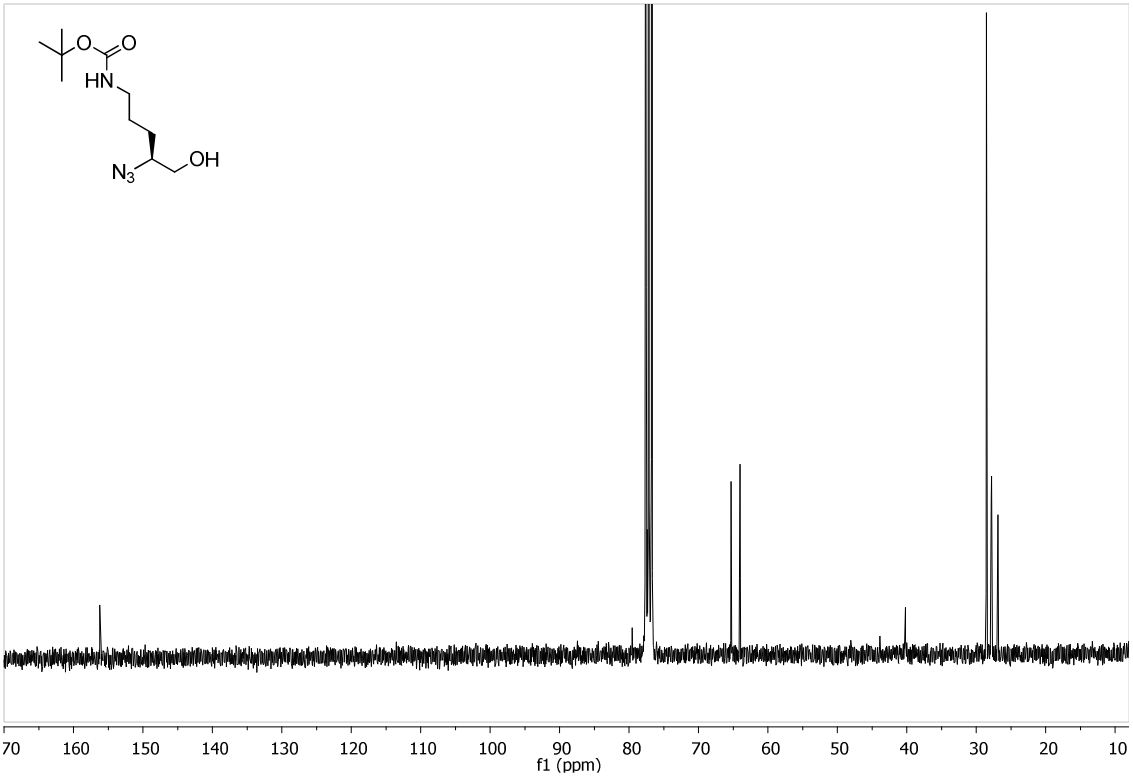


Figure S6. ^{13}C NMR spectrum of compound **5c**, recorded in $CDCl_3$ (75 MHz)

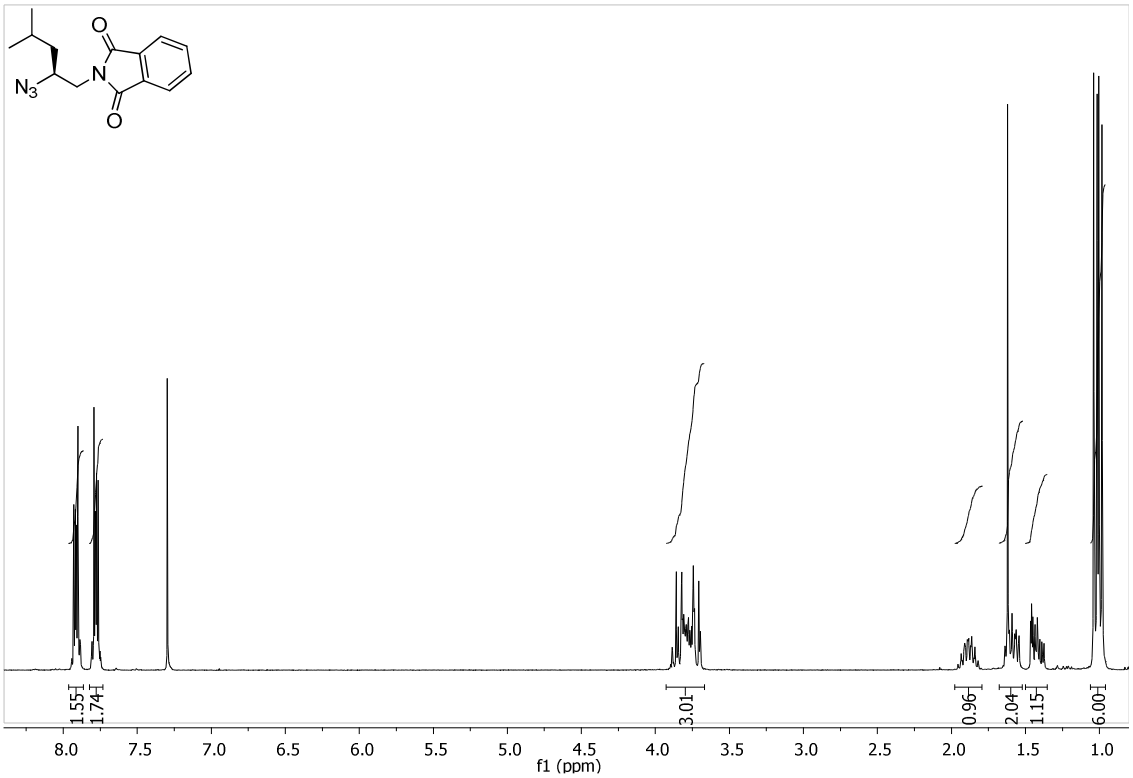


Figure S7. ^{1}H NMR spectrum of compound **6d**, recorded in $CDCl_3$ (300 MHz)

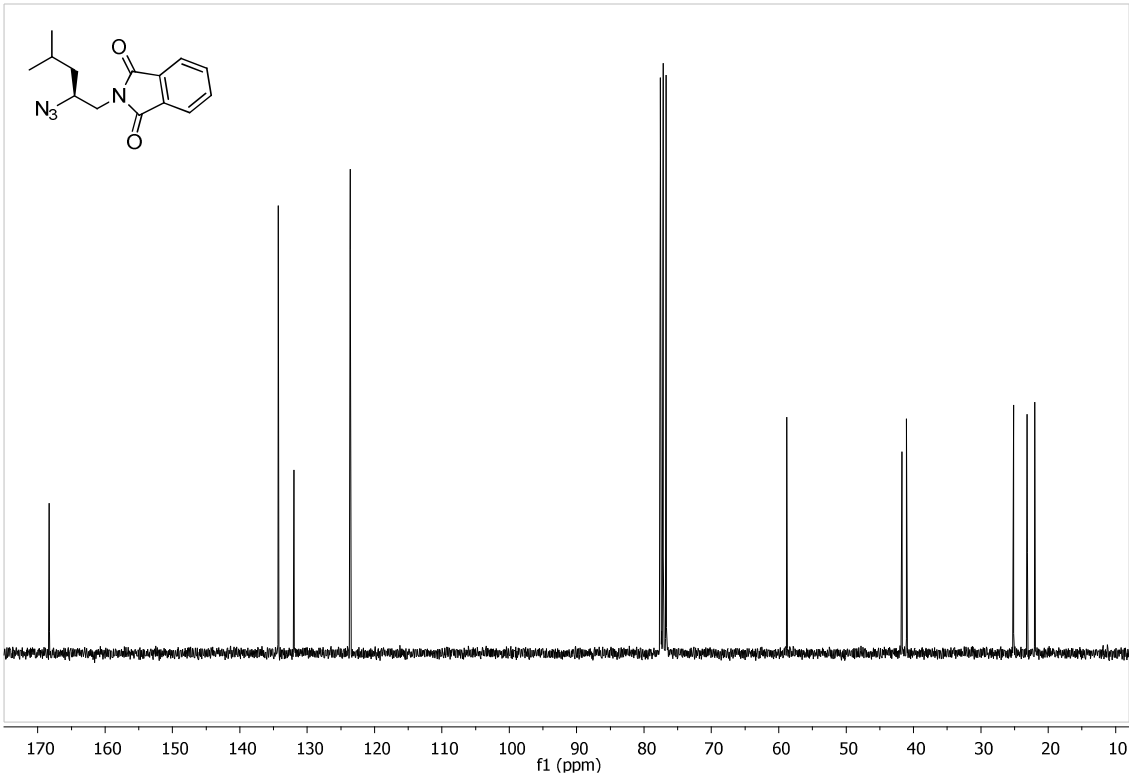


Figure S8. ^{13}C NMR spectrum of compound **6d**, recorded in $CDCl_3$ (75 MHz)

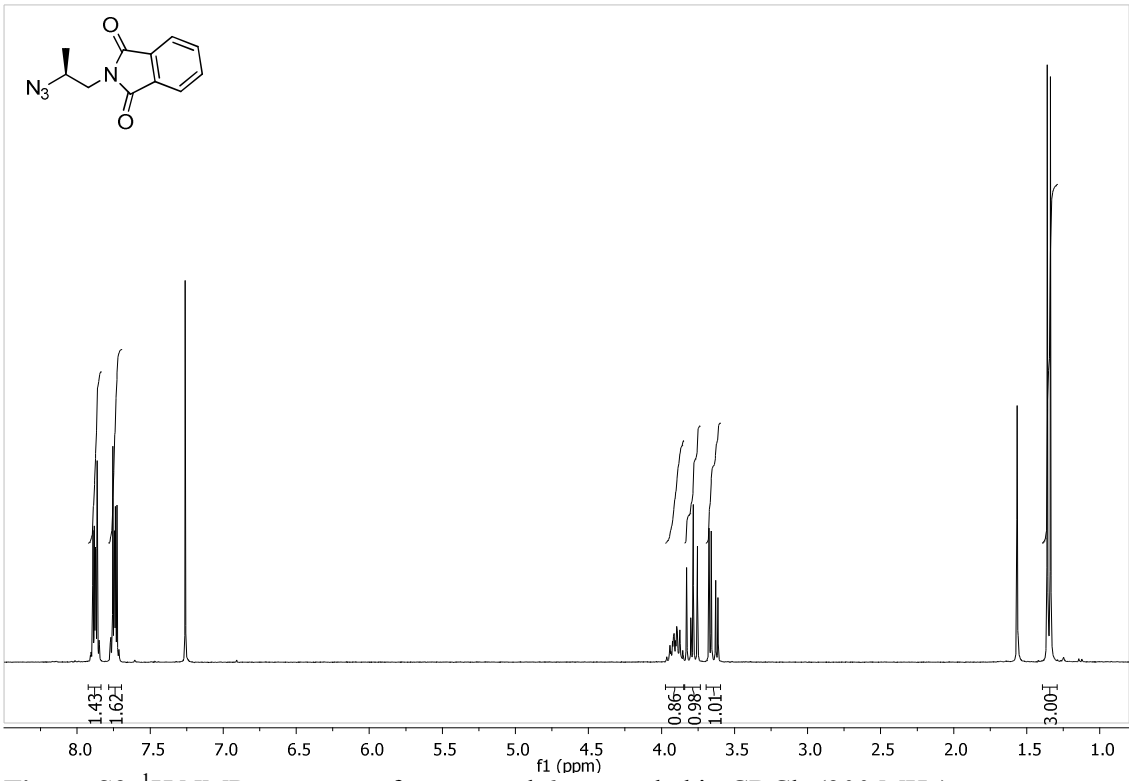


Figure S9. ^{1}H NMR spectrum of compound **6e**, recorded in $CDCl_3$ (300 MHz)

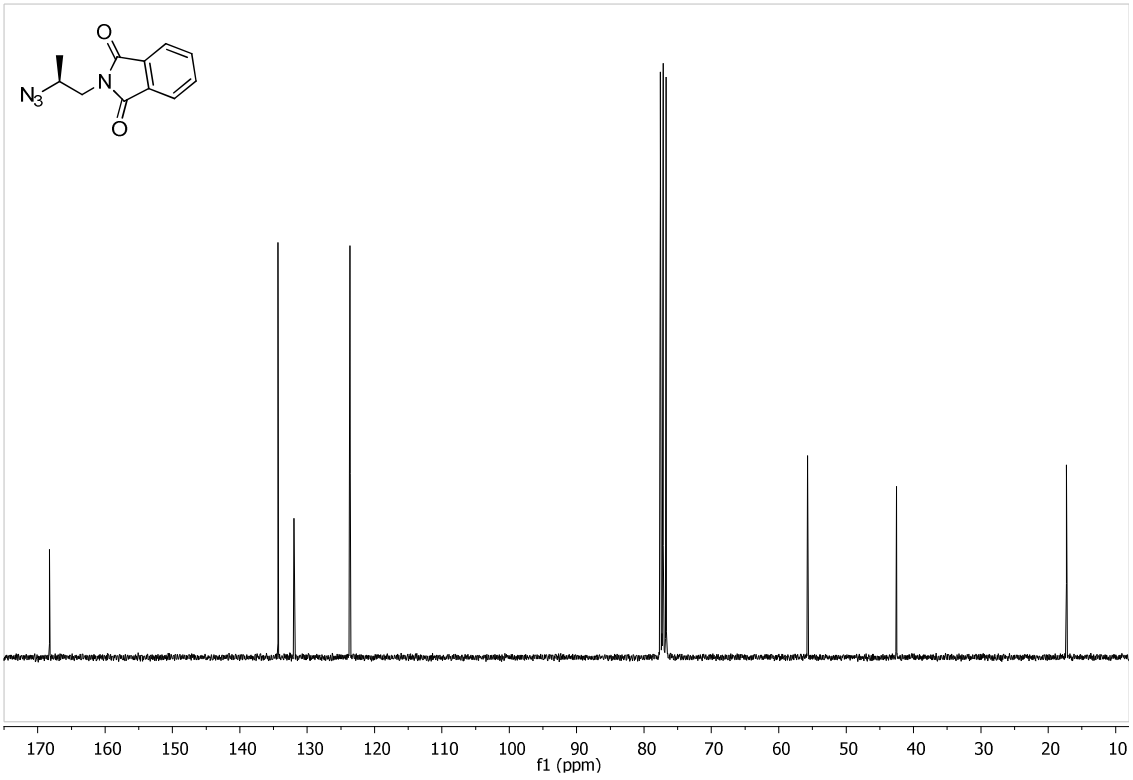


Figure S10. ^{13}C NMR spectrum of compound **6e**, recorded in $CDCl_3$ (75 MHz)

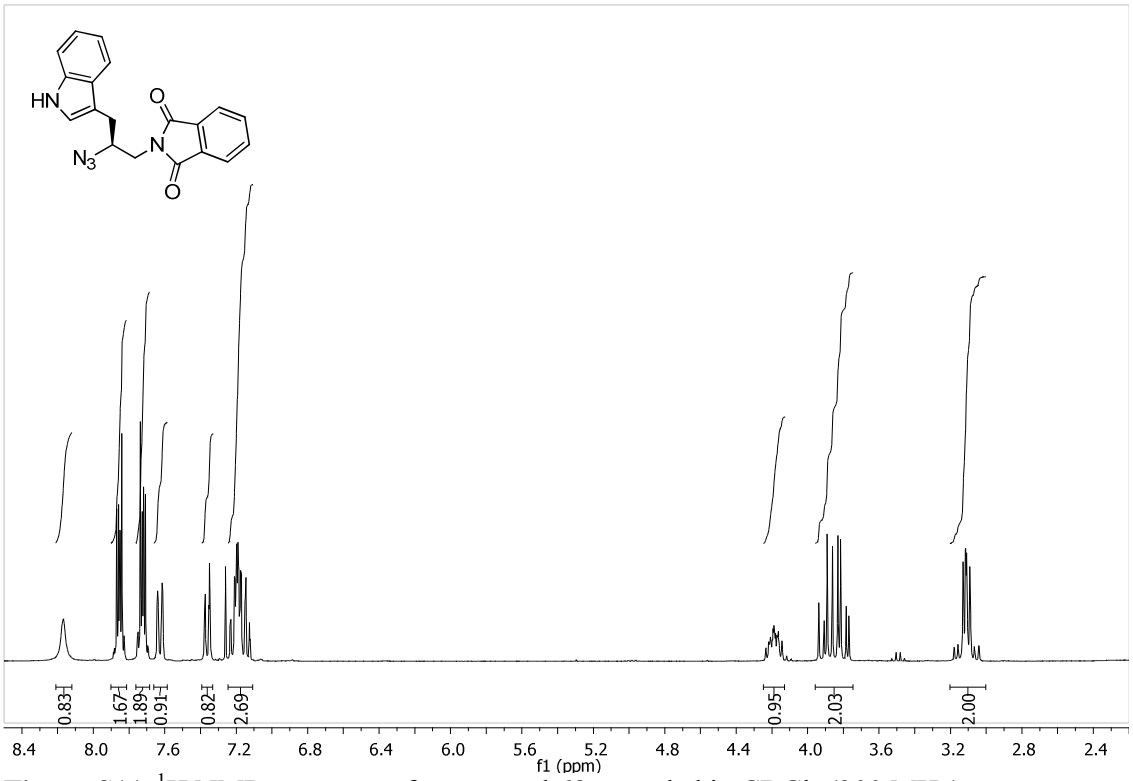


Figure S11. ^{1}H NMR spectrum of compound **6f**, recorded in $CDCl_3$ (300 MHz)

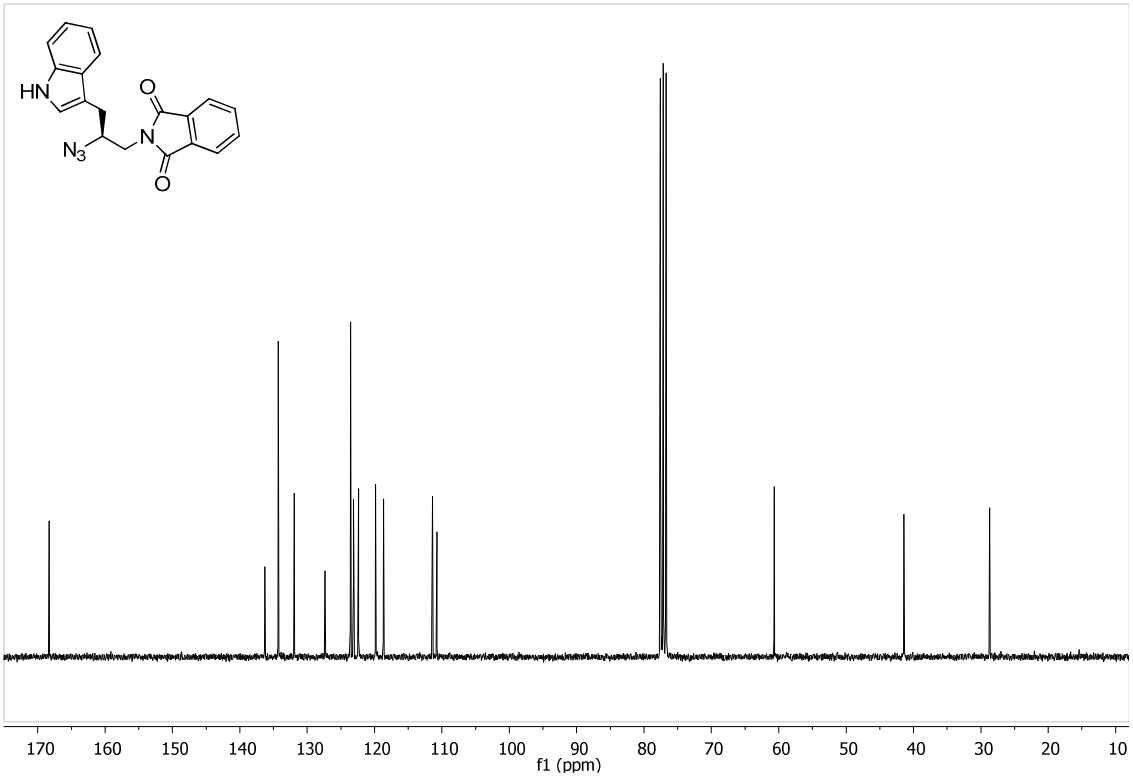


Figure S12. ^{13}C NMR spectrum of compound **6f**, recorded in $CDCl_3$ (75 MHz)

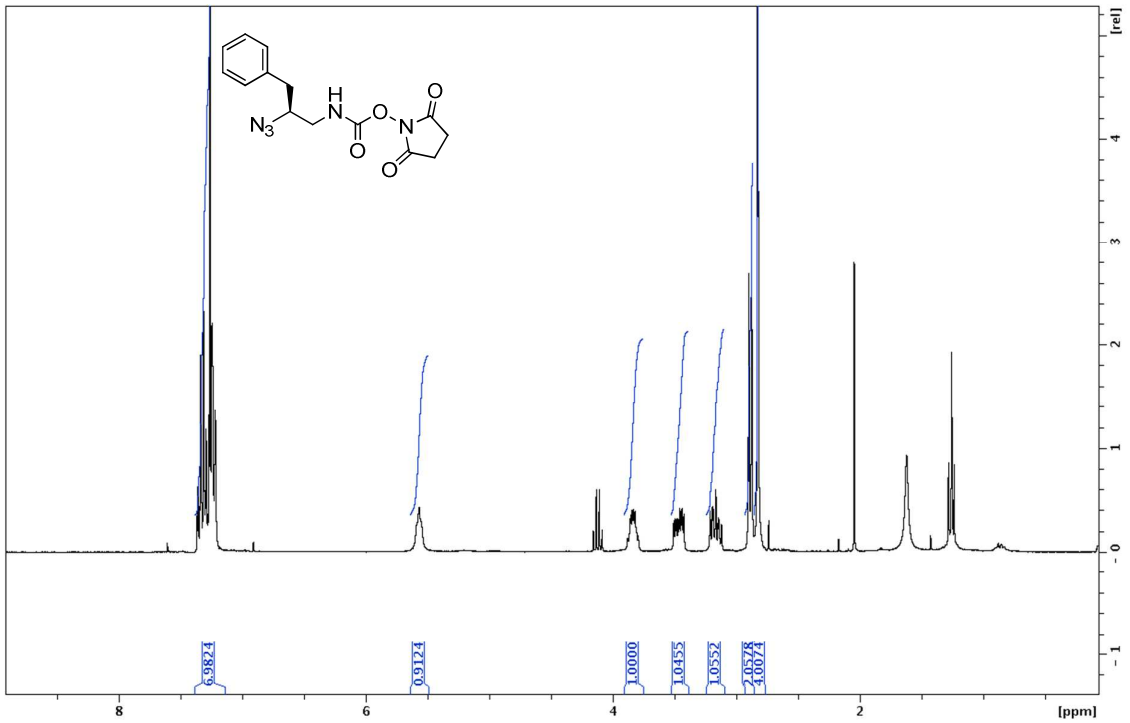


Figure S13. ^{1}H NMR spectrum of compound **2a**, recorded in $CDCl_3$ (300 MHz)

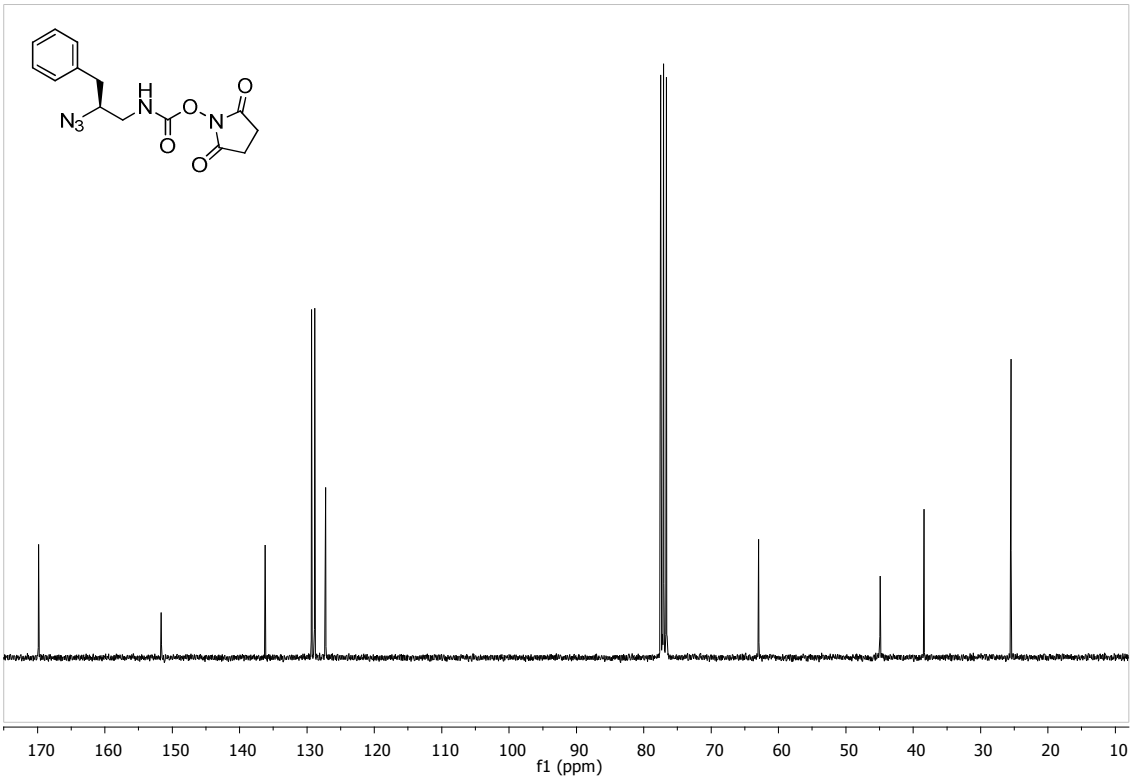


Figure S14. ^{13}C NMR spectrum of compound **2a**, recorded in $CDCl_3$ (75 MHz)

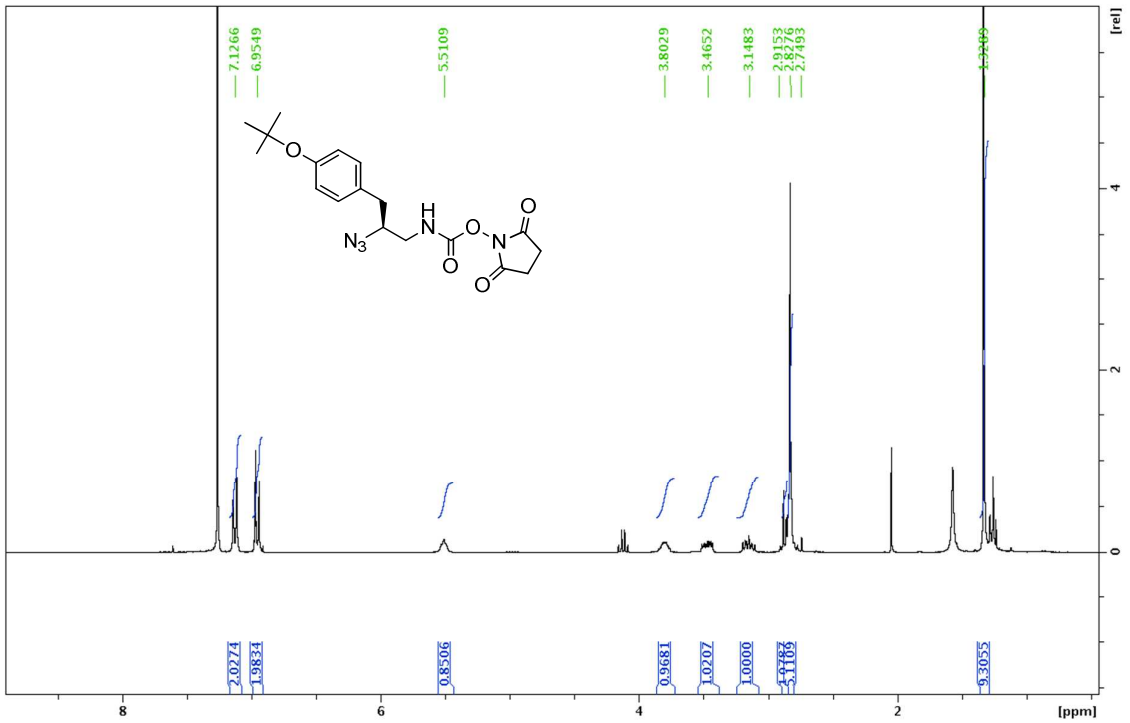


Figure S15. ^{1}H NMR spectrum of compound **2b**, recorded in $CDCl_3$ (300 MHz)

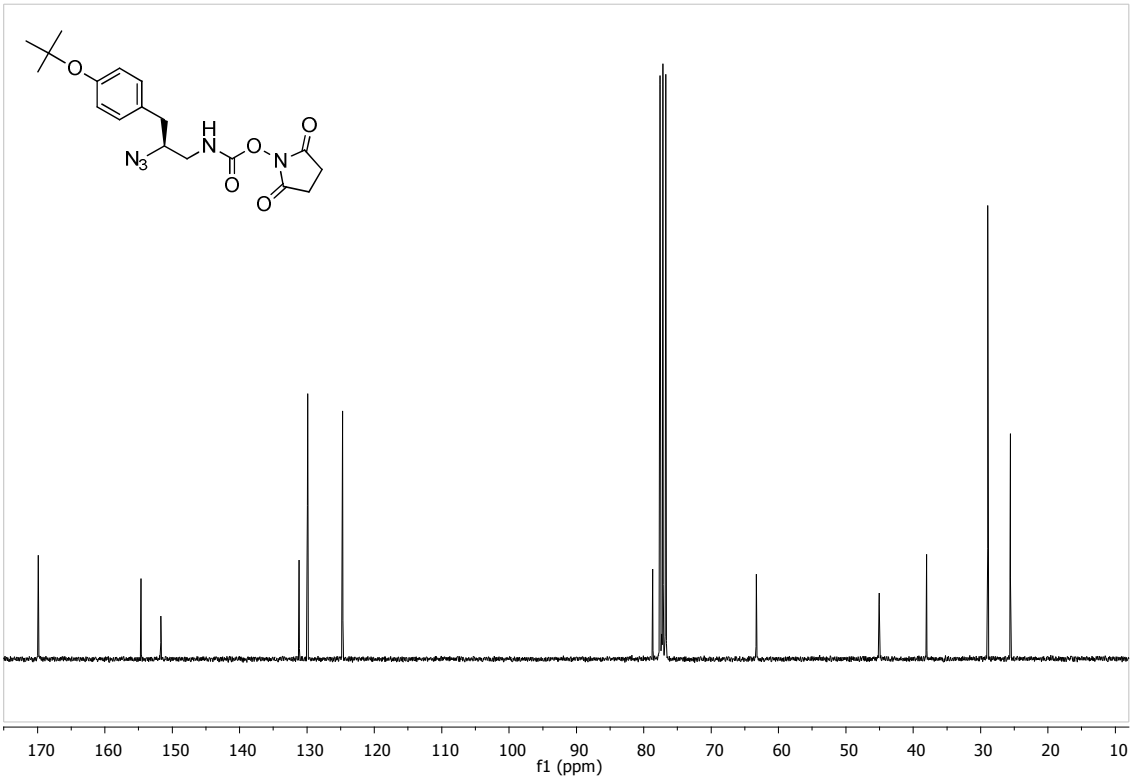


Figure S16. ^{13}C NMR spectrum of compound **2b**, recorded in $CDCl_3$ (75 MHz)

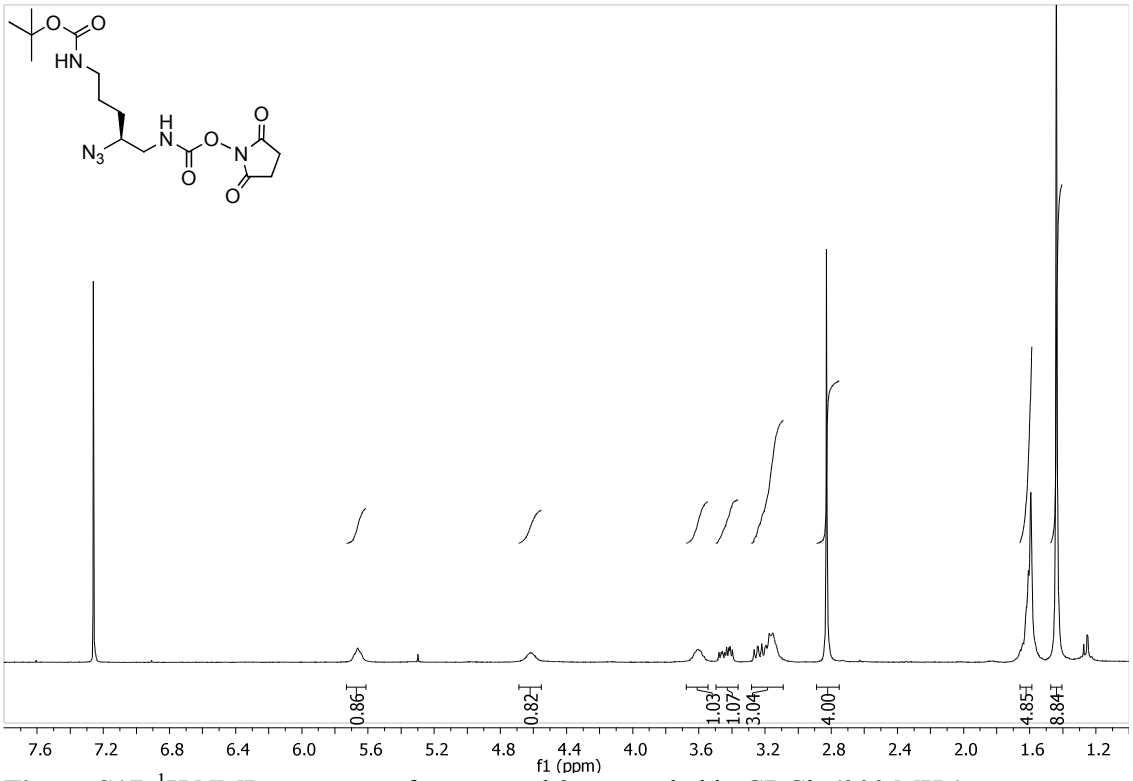


Figure S17. ^{1}H NMR spectrum of compound **2c**, recorded in $CDCl_3$ (300 MHz)

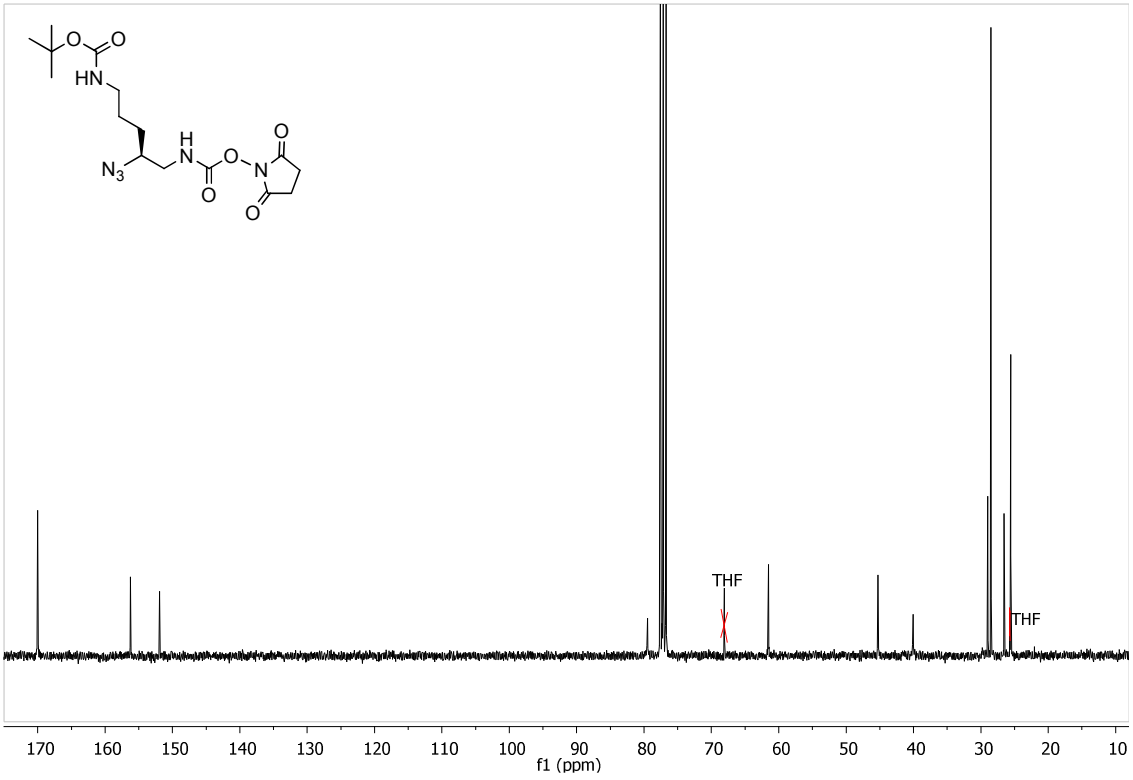


Figure S18. ^{13}C NMR spectrum of compound **2c**, recorded in $CDCl_3$ (75 MHz)

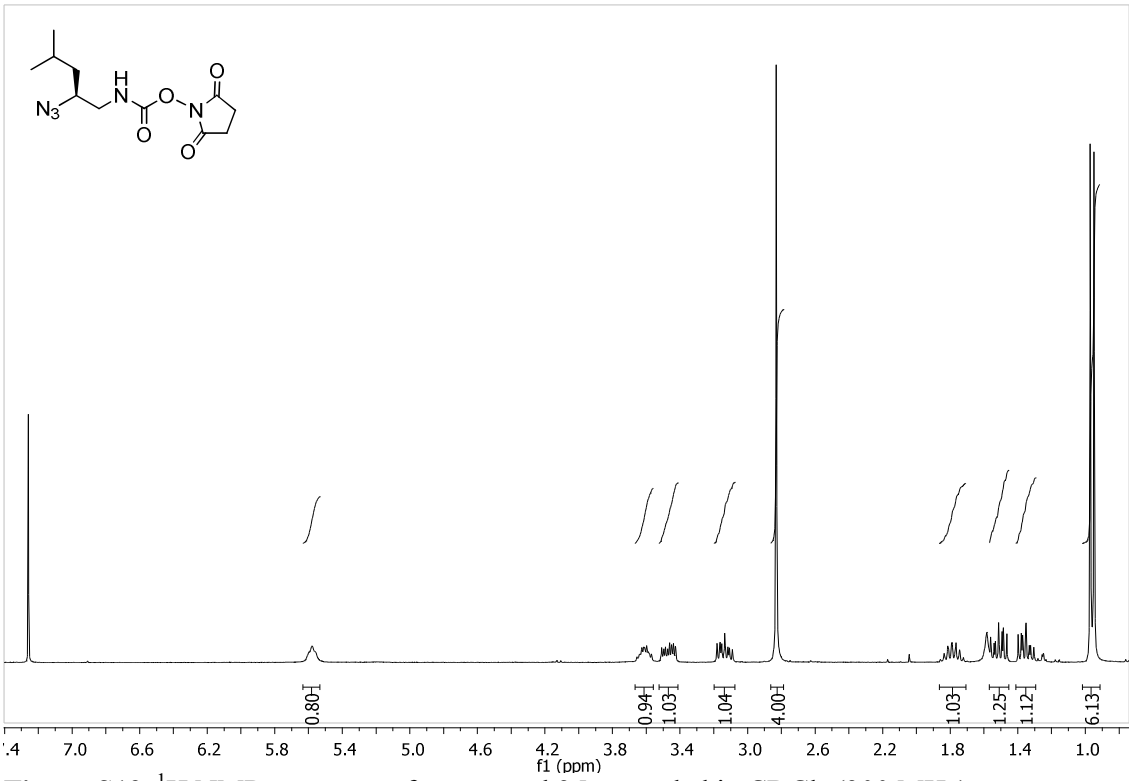


Figure S19. ^{1}H NMR spectrum of compound **2d**, recorded in $CDCl_3$ (300 MHz)

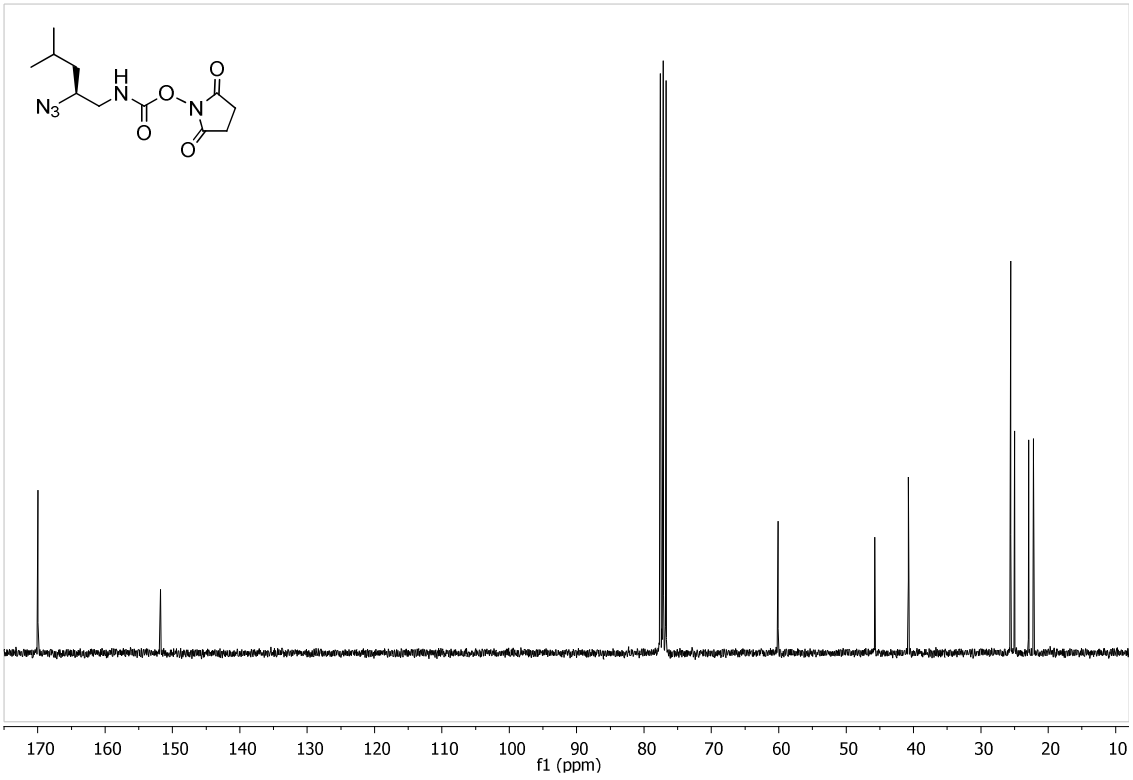


Figure S20. ^{13}C NMR spectrum of compound **2d**, recorded in $CDCl_3$ (75 MHz)

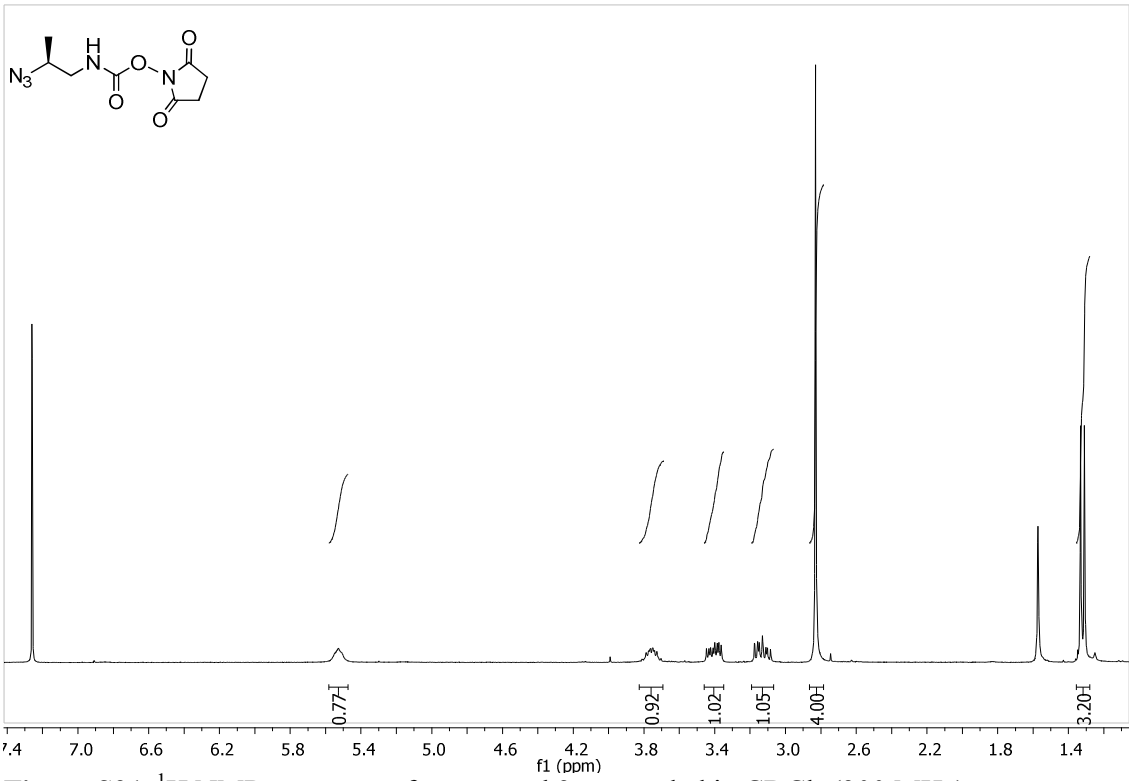


Figure S21. ^{1}H NMR spectrum of compound **2e**, recorded in $CDCl_3$ (300 MHz)

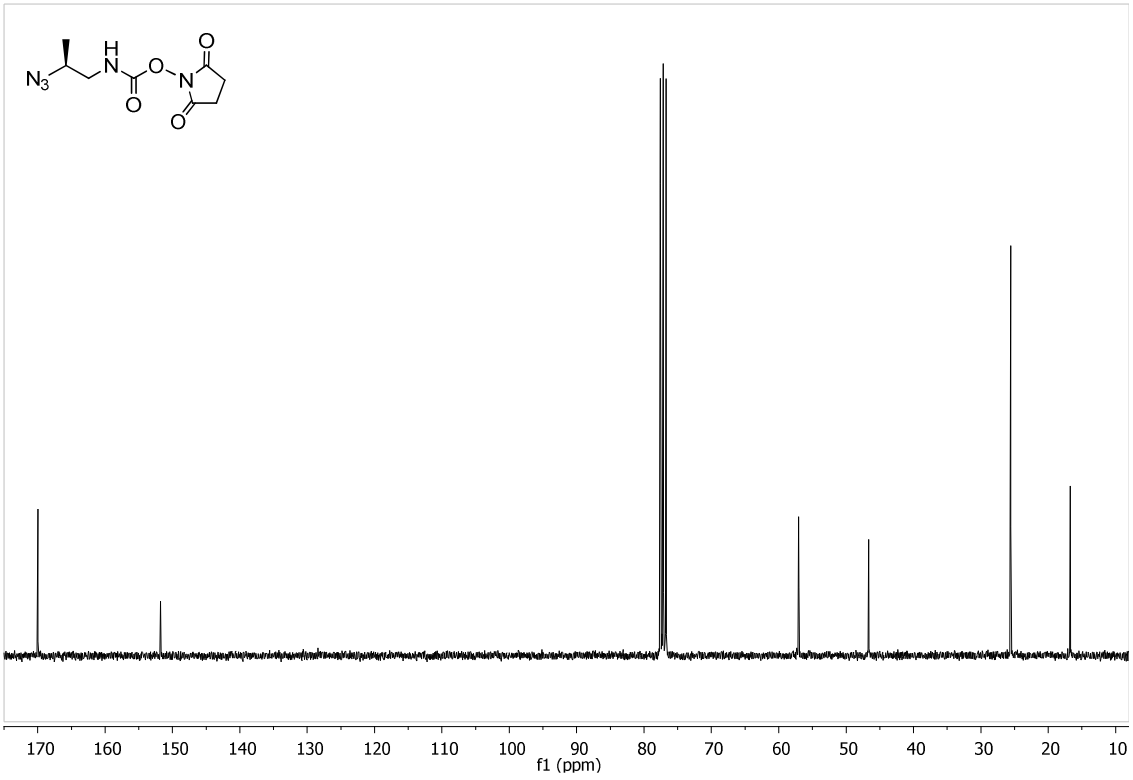


Figure S22. ^{13}C NMR spectrum of compound **2e**, recorded in $CDCl_3$ (75 MHz)

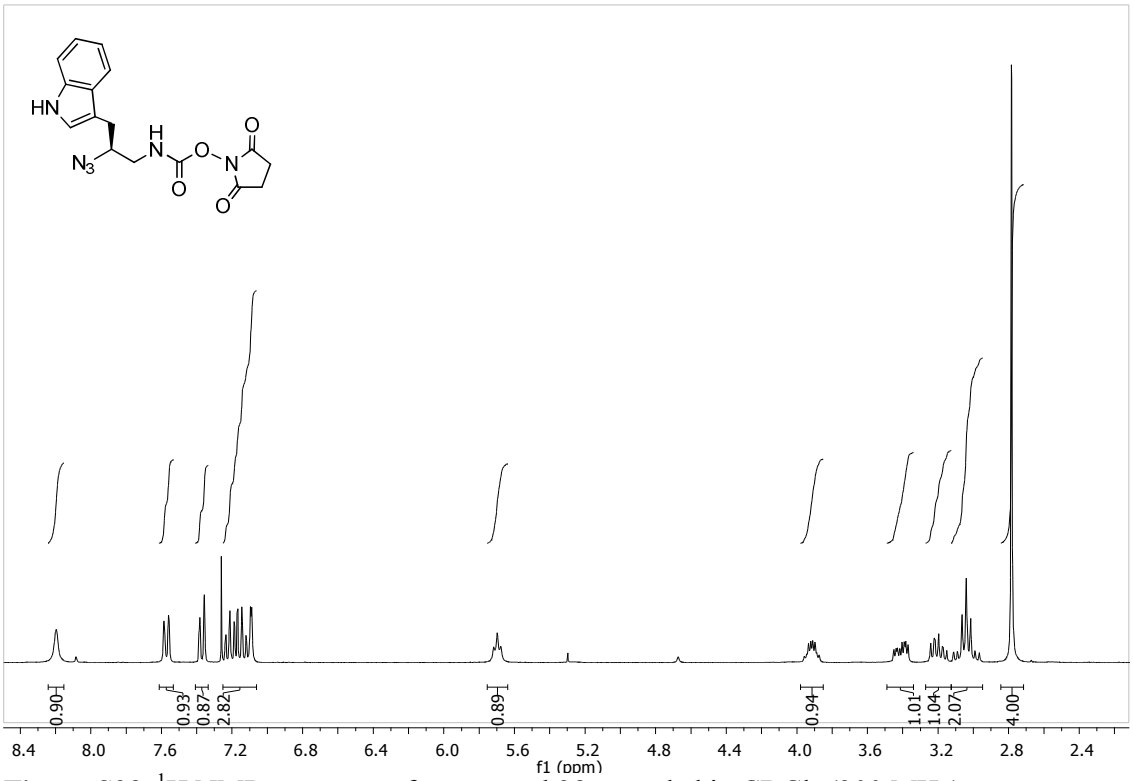


Figure S23. ^{1}H NMR spectrum of compound **2f**, recorded in $CDCl_3$ (300 MHz)

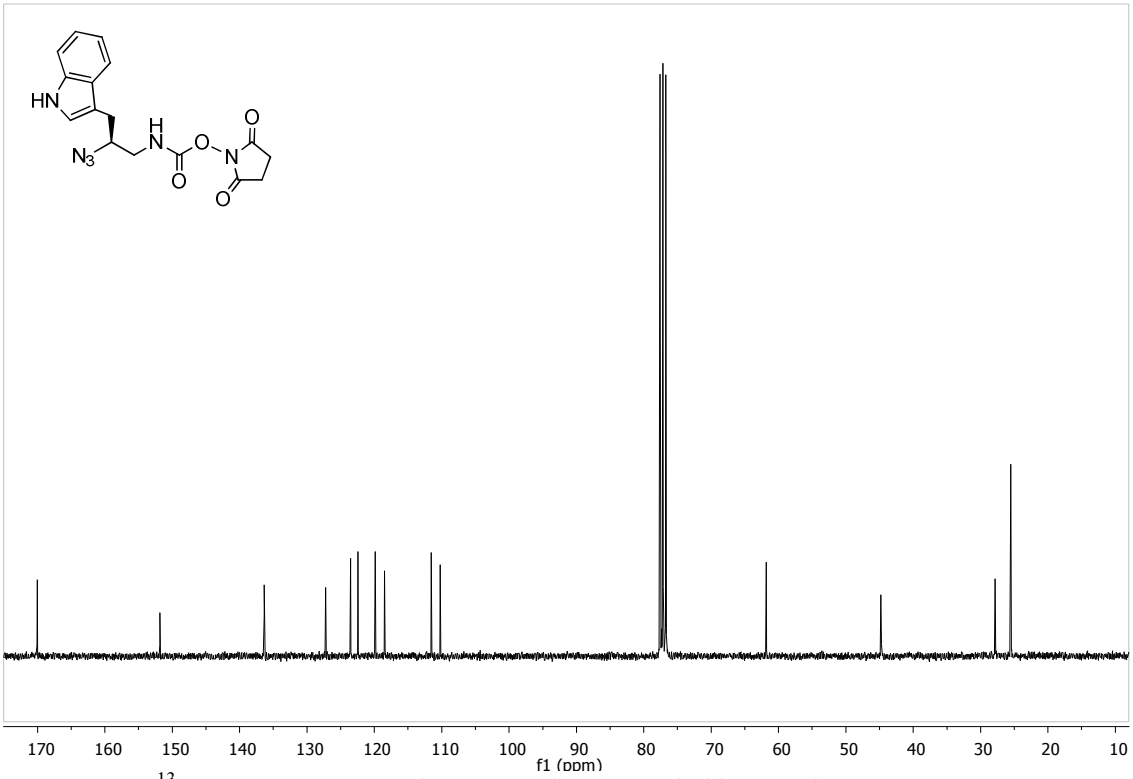


Figure S24. ^{13}C NMR spectrum of compound **2f**, recorded in $CDCl_3$ (75 MHz)

5. HPLC chromatograms

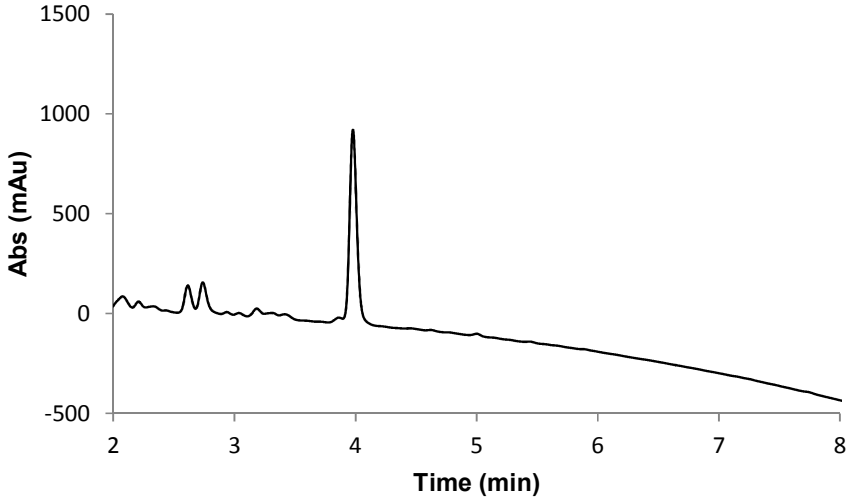


Figure S25. RP-HPLC trace of crude **9** Elution system: solvent A: H_2O, 0.1%TFA, solvent B: acetonitrile, 0.1% TFA. Flow: 1 mL·min^{-1}. Elution gradient 50-100% of B in 10 min.

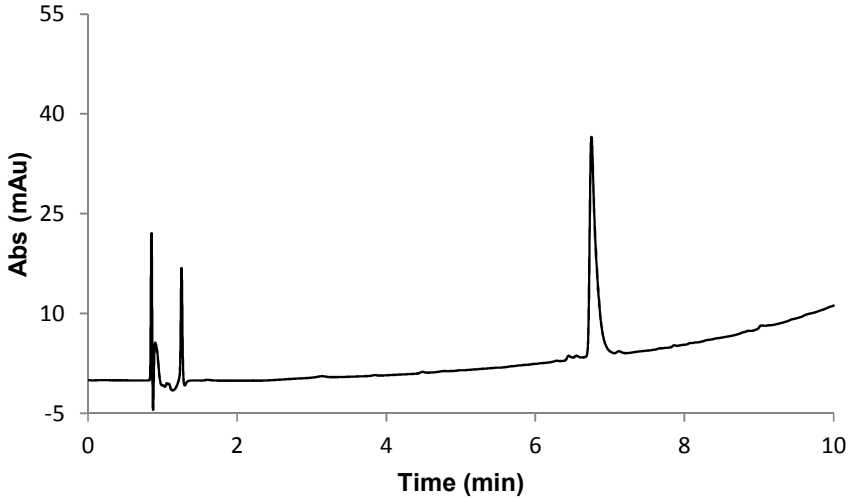


Figure S26. RP-HPLC trace of **10** after semi-preparative purification. Elution system: solvent A: H_2O, 0.1%TFA, solvent B: acetonitrile, 0.1% TFA. Flow: 1 mL·min^{-1}. Elution gradient 10-100% of B in 10 min.

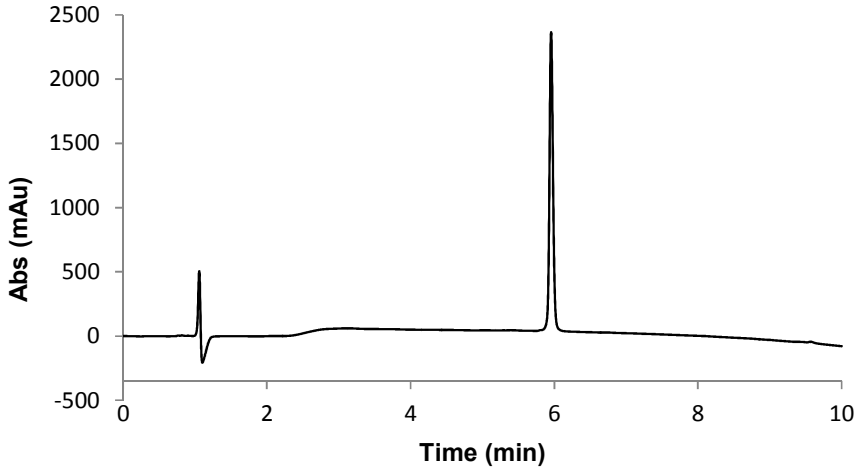


Figure S27. RP-HPLC trace of **11** after semi-preparative purification. Elution system: solvent A: H_2O, 0.1%TFA, solvent B: acetonitrile, 0.1% TFA. Flow: 1 mL·min^{-1}. Elution gradient 10-100% of B in 10 min.

6. Early investigation of oligourea solid-phase synthesis with microwave irradiation using Boc chemistry.

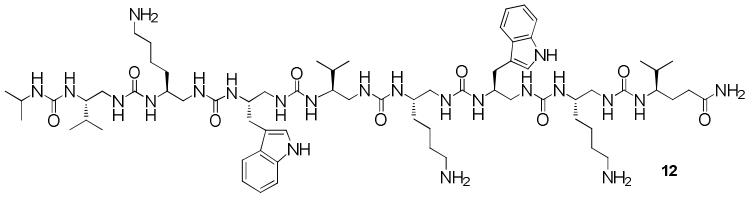
We first evaluated the effect of microwave irradiation on the solid phase synthesis of oligoureas using Boc chemistry. Oligomer **12**, previously shown to exhibit antibacterial properties[6] was selected as a target. Requisite *N*-Boc protected building blocks with side chains of Val, Lys and Trp were synthesized as previously described.6 Synthesis was performed on a 100 or 200 μmol scale starting from 4-methylbenzhydrylamine (MBHA) resin (0.62 mmol/g). The first coupling step was performed with a solution of Boc-protected γ-Val-OH (1.5 eq.) in DMF, with BOP (1.5 eq.), HOBt (1.5 eq.) and DIEA (5 eq.) and the suspension was mixed under periodic nitrogen bubbling for 30 minutes. This step was performed twice and completion of the coupling was monitored by a Kaiser ninhydrin test. The Boc group was removed using TFA (5 and 10 min) under nitrogen bubbling. Subsequent urea formation steps were performed by adding a solution of activated monomer (i.e. succinimidyl {2-{[(*tert*-butoxy)carbonyl]-amino}-2-substituted-ethyl}carbamates **1a**) and DIEA in DMF under microwave irradiation (see Table S1 for conditions tested). A double coupling was performed systematically. At the end of the synthesis, the last Boc group was

(6) Claudon, P.; Violette, A.; Lamour, K.; Decossas, M.; Sylvie Fournel; Heurtault, B.; Godet, J.; Mély, Y.; Jamart-Grégoire, B.; Averlant-Petit, M.-C.; Briand, J.-P.; Duportail, G.; Monteil, H.; Guichard, G. *Angew. Chem. Int. Ed.* **2009**, *48*, 1−5.

removed. Acylation of the terminal amine with isopropyl isocyanate (3 equiv) was performed in DMF, in the presence of DIEA (3 equiv). The resin was finally washed with DCM, Et_2O and dried under nitrogen. Side chain deprotection and cleavage of the oligomers from the resin were performed simultaneously by treatment with HF (containing 10% *p*-cresol as a scavenger) for 60 min at 0°C. The crude oligomers were then precipitated in Et_2O and analyzed by C_{18} RP-HPLC (linear gradient, 5 to 65% or 20 to 80% of B in 30 min).

We found that both coupling times and excess monomers could be considerably reduced under microwave irradiation (compare entries 1 and 4, Table S1). Optimal conditions were the following: *N*-Boc protected monomers **1a** (1.5 equiv), DIEA (3 equiv), DMF, 70 °C, 25 W, 2 × 10 min.

Table S1. Microwave-assisted SPS of urea-based tetramer **12** conditions screened on solid support.



12

Entry	Coupling Time (min)	**1a** equiv	T_{max} (°C)	Power (W)	Purity (%) of the **12** crude
1	120	3	/	/	56
2	30	3	50	40	62
3	10	3	70	25	65
4	10	1.5	70	25	62

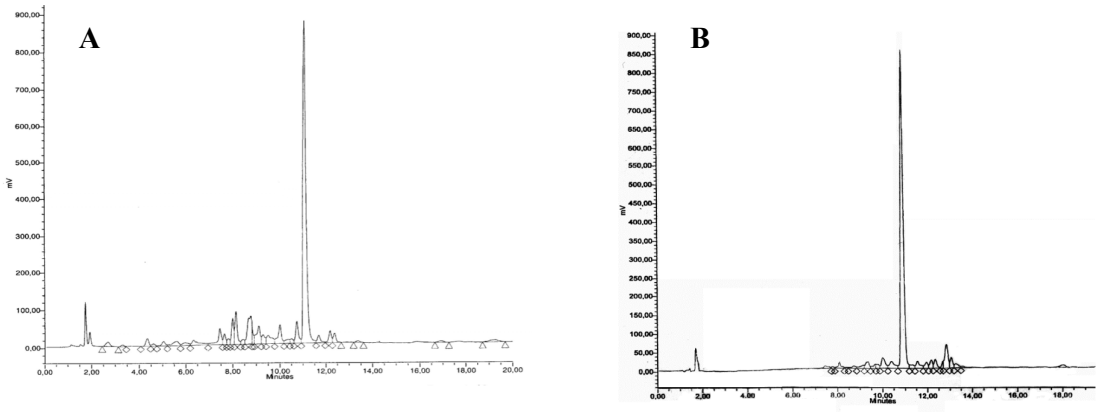


Figure S28. A) RP-HPLC trace of crude **12** after classical SPS with Boc strategy; B) RP-HPLC trace of crude **12** after microwave-assisted SPS under Boc strategy.