SUPPORTING INFORMATION

Helix Forming Propensity of Aliphatic Urea Oligomers Incorporating Non-canonical Residue Substitution Patterns

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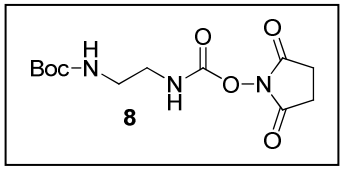
General methods

Commercially available reagents were used throughout without 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). ^{1}H NMR and ^{13}C NMR spectra were recorded on four different NMR spectrometers: (1) 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; (2) a DPX-400 NMR spectrometer (Bruker Biospin) with avertical 9.4T narrow-bore/ultrashield magnet operating at 400 MHz for ^{1}H observation by means of a 5-mm direct QNP $^{1}H/^{13}C/^{31}P/^{19}F$ probe with gradient capabilities; (3) an Avance III NMR spectrometer (BrukerBiospin) with a vertical 16.45T narrow-bore/ultrashield magnet operating at 700 MHz for ^{1}H observation by means of a 5-mm TXI $^{1}H/^{13}C/^{15}N$ probe with Z gradient capabilities and (4) a standard bore Bruker Avance III spectrometer operating at 800.23 MHz for proton detection. Chemical shifts are reported in parts per million (ppm, δ) relative to the ^{1}H or ^{13}C residual signal of the deuterated solvent used. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), broad singlet (brs), doublet (d), triplet (t), or quartet (q). Coupling constants (*J*) are reported in hertz. ESI-MS analyses were carried out on a Thermo Electron LCQ Advantage spectrometer equipped with an ion trap mass analyzer and coupled with a ThermoElectron Surveyor HPLC system.

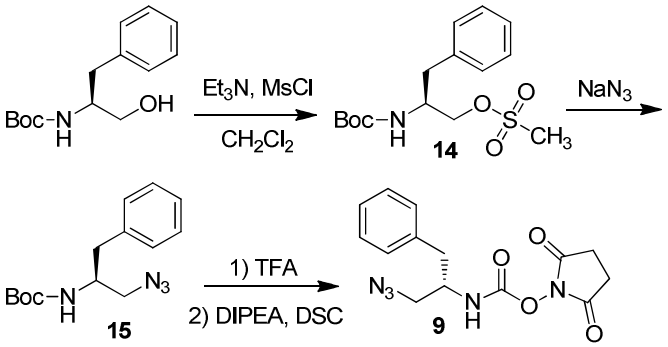
1 Experimental Section

1.1 Synthesis of activated monomers 8-12



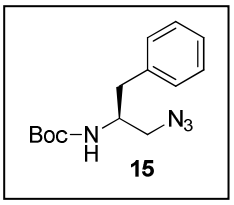
***O*−Succinidimyl−2−(*tert*-butoxycarbonylamino)ethylcarbamate (8).** 3-(*tert*-butoxycarbonylamino) propionic acid (1.5 g, 7.94 mmol) was dissolved in THF (15 mL) under Ar and the reaction mixture was cooled down to -15° C before the addition of EtOCOCl (1.08 mL, 8.34 mmol) and NMM (0.92 mL, 8.34 mmol). The reaction mixture was gently stirred for 20 minutes. The resulting white suspension was allowed to warm at -5° C and was treated with an aqueous (5 mL) solution of NaN_3 (1.3 g, 19.85 mmol). The reaction mixture was next stirred for 5 min, diluted with EtOAc, washed with on time brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the corresponding acyl azide intermediate, which was then diluted in toluene under Ar. The resulting reaction mixture was heated to 65° C. Once gas evolution has stopped, *N*-hydroxysuccinimide (1.04 g, 8.73 mmol) and pyridine (0.7

mL, 8.73 mmol) were added. The mixture was stirred for 10 min. at 65° C and then cooled down to room temperature. The precipitate was filtered off and washed with toluene to afford **8** (1.3 g, 54.4%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.27 (t, J = 5.0 Hz, 1NH), 6.88 (t, J = 5.1 Hz, 1NH), 3.13−3.05 (m, 2H), 3.04−2.97 (m, 2H), 2.76 (s, 4H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$/ DMSO-d_6) δ 169.28, 115.84, 151.26, 41.62, 39.33, 27.53, 24.74; ESIMS: *m/z* 324.4 $[M+Na]^+$, 302.4 $[M+H]^+$, 202.1 $[M+H\text{-}Boc]^+$; HRMS calcd for $C_{12}H_{19}N_3O_6$ $(M + H)^+$: 324.1172, Found: 324.1165.

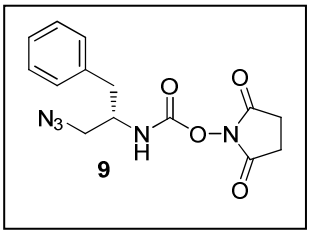


Methanesulphonic acid 2-*tert*-butoxycarbonylamino-3-phenyl-propyl ester (14). To a stirred solution of Boc-Phe-ol[1] (6.0 g, 23.9 mmol) in CH_2Cl_2 (60 mL) at 0° C, Et_3N (6.7 mL, 47.8 mmol) was added and after 10 min, MsCl (2.03 mL, 26.3 mmol) was added dropwise; Stirring was maintained for 2 hours. The reaction mixture was then diluted with brine and the organic layer was dried over Na_2SO_4. Solvent was removed under reduced pressure and the resulting solid was triturated with cyclohexane to give after filtration compound **14** (7.2 g, 92%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.34−7.20 (m, 5H), 4.75 (d, J = 4.92 Hz, 1NH), 4.28−4.20 (m, 1H), 4.13−4.09 (m, 2H), 3.01 (s, 3H), 2.91−2.81 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 136.6, 129.3, 128.8, 127.0, 80.0, 69.8, 50.8, 37.3, 37.2, 28.3; ESIMS: *m/z* 352.2 $[M+Na]^+$, 330.13 $[M+H]^+$.

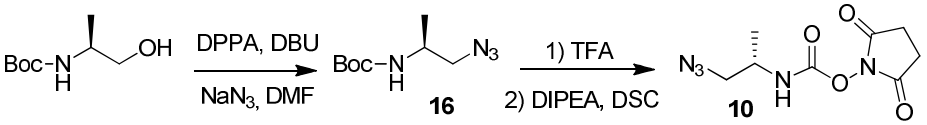
1 Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.*, **1991**, *32*, 923−926.



(2-Azido-1-benzyl-ethyl)-carbamic acid *tert*-butyl ester (15). Compound **14** (7.0 g, 21.3 mmol) was dissolved in DMF (70 mL) and NaN_3 (6.91 g, 106.34 mmol) was added. The reaction mixture was heated to 80 °C and stirring was maintained overnight. The reaction mixture was then cooled down to room temperature diluted with water and extracted several times with diethyl ether. The combined organic layers were then dried over Na_2SO_4 and solvent was removed under reduced pressure to furnish azide **15** (5.2 g, 89%) as a yellow syrup. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.37−7.2 (m, 5H), 4.74 (brs, 1NH), 4.06−3.9 (m, 1H), 3.48−3.29 (dd, J = 4.3, 12.4 Hz, 2H), 2.97−2.76 (m, 2H), 1.31 (s, 9H); ESIMS: *m/z* 299.16 $[M+Na]^+$, 277.2 $[M+H]^+$.

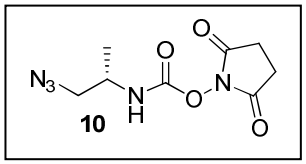


(2-Azido-1-benzyl-ethyl)-carbamic acid 2, 5-dioxo-pyrrolidin-1-yl ester: ***N*-**Boc-protected azide **15** (4.0 g, 14.5 mmol) was treated with TFA (25 mL) at 0° C for 30 min. TFA was then removed under reduced pressure and co evaporated with diethylether. The resulting TFA salt was then dissolved in CH_2Cl_2 (60 mL) at 0° C and DIPEA (4.92 mL, 29 mmol) was added drop wise. After 5 min, DSC (4.45 g, 17.4 mmol) was added and the reaction mixture was stirred for 4 hours, and a precipitate was observed. The reaction mixture was filleted off and the filtrate was washed with 1N $KHSO_4$ then dried over Na_2SO_4. After evaporation under reduced pressure the activated azide carbamate (4.18 g, 91%) was isolated as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41−7.10 (m, 5H), 5.51 (d, 1H), 3.98 (m, 1H), 3.55−3.27 (m, 2H), 3.05−2.67 (m, 2H), 1.31 (s, 9H), 2.83 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.71; 129.35, 128.99, 128.78, 127.21, 126.94, 53.60, 52.87, 52.32, 51.65, 37.54, 25.46. HRMS calcd for $C_{14}H_{15}N_5O_4Cl$ $(M + Cl)^+$: 352.0813, Found: 352.0820.

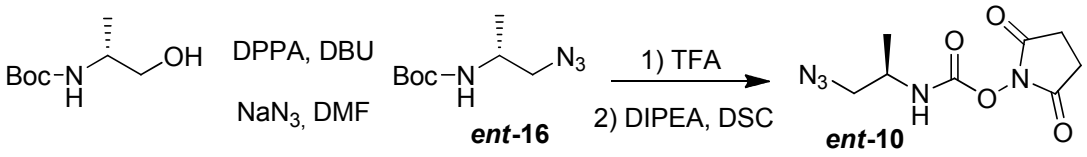


***tert*-butyl (*S*)-1-azidopropan-2-ylcarbamate (16).** To a stirred solution of Boc-Ala-ol1 (6.0 g, 34.3 mmol) in DMF (30 mL) at 70^o C were added DPPA (11.0 mL, 51.4 mmol) and DBU (7.2 mL, 51.4 mmol). After disappearance of the starting alcohol, NaN_3 (1.1 g, 17.2 mmol) was added and the reaction mixture was allowed to stir overnight. The reaction mixture was then diluted with EtOAc and successively washed with $NaHCO_3$, $KHSO_4$, brine and dried over $MgSO_4$. After solvent evaporation under reduced pressure and purification by silica gel column chromatography eluted with 10% EtOAc in cy-

clohexane), compound **16** (6.1 g, 89%) was isolated as yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.58 (brs, 1NH), 3.91−3.82 (m, 1H), 3.45−3.29 (m, 2H), 1.46 (s, 9H), 1.19 (d, *J* = 6.8 Hz, 3H).



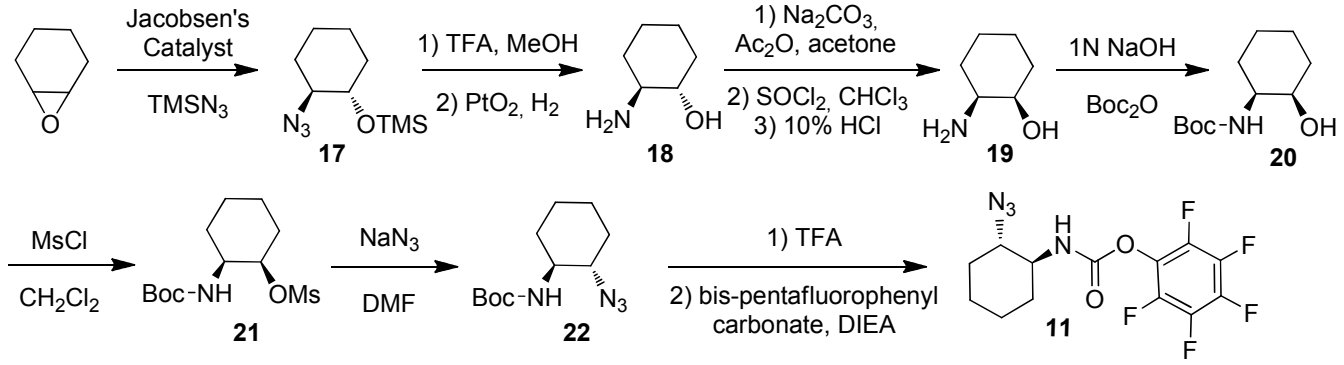
Carbamate-Azide (10). Boc-protected azide **16** (2.5 g, 12.5 mmol) was treated with TFA (25 mL) at 0° C for 30 min. TFA was the removed under reduced pressure by successive coevaporations with cyclohexane and diethyl ether. Then, the resulting TFA salt was dissolved in CH_2Cl_2 (30 mL) at 0° C and DIPEA (4.24 mL, 25.0 mmol) was added drop wise. After 5 min, DSC (3.84 g, 15.0 mmol) was added and stirring was maintained overnight. The crude mixture was then washed with 1N $KHSO_4$ and dried over Na_2SO_4. After concentration under reduced pressure and purification by silica gel column chromatography eluting with 20% EtOAc in cyclohexane, carbamate **10** (1.2 g, 40%) was obtained as yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.83 (m, 1NH), 3.89 (m, 1H), 3.45 (dq, 2H), 2.82 (s, 4H), 1.28 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.00, 150.80, 55.32, 47.96, 25.45, 17.88. HRMS calcd for $C_8H_{11}N_5O_4Cl$ $(M+Cl)^+$: 276.0500, Found: 276.0502.

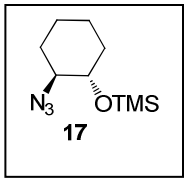


***tert*-butyl (*R*)-1-azidopropan-2-ylcarbamate (*ent*-16):** To a stirred solution of Boc-(*R*)-Ala-ol (4.5 g, 25.7 mmol) in DMF (25 mL) at 70^o C, were added DPPA (8.26 mL, 38.5 mmol) and DBU (5.4 mL, 38.5 mmol). After disappearance of the starting material, NaN_3 (0.84 g, 12.9 mmol) was added and stirring was maintained overnight. The reaction mixture was then diluted with EtOAc and washed with $NaHCO_3$, $KHSO_4$, brine and dried over $MgSO_4$. After evaporation under reduced pressure and purification by silica gel column chromatography eluting with 10% EtOAc in cyclohexane), azide **16** (4.9 g, 95.3%) was isolated as yellow syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.58 (brs, 1NH), 3.91−3.82 (m, 1H), 3.45−3.29 (m, 2H), 1.46 (s, 9H), 1.19 (d, *J* = 6.8 Hz, 3H).

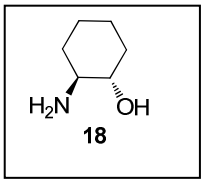
Azide carbamate (*ent*-10). Azide ***ent*-16** (4.8 g, 24.0 mmol) was treated with TFA (20 mL) at 0° C for 30 min. TFA was then removed under reduced pressure by successive coevaporations with cyclohexane and diethyl ether. Then the resulting TFA salt was dissolved in CH_2Cl_2 (30 mL) and DIPEA (8.2 mL,

48.0 mmol) was added drop wise at 0° C. After 5 min, DSC (6.8 g, 26.4 mmol) was added and the reaction mixture was stirred for 2 hours. The reaction mixture was then washed with 1N $KHSO_4$ solution and dried over Na_2SO_4. Solvent evaporation under reduced pressure afforded ***ent*-10** (4.8 g, 83%) as yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.40−5.28 (m, 1NH), 3.99−3.91 (m, 1H), 3.58−3.43 (m, 2H), 2.85 (s, 4H), 1.32 (d, *J* = 6.8 Hz, 3H).



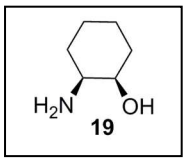


(1*S*,2*S*)-2-azidocyclohexyloxytrimethylsilane (17). A 50 mL flask, preliminary dried under high vacuum, was charged with (*R*,*R*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino chromium(III) chloride (0,13g, 0.204 mmol), flushed several times with N_2 and sealed. Cyclohexene oxide (1.03mL, 10.2 mmol) was then slowly added at room temperature followed by $TMSN_3$ (1.6 mL, 1.05 equiv), so that the temperature inside the flask remains constant. The reaction mixture was allowed to stir at room temperature for 12 h, after which time the excess of $TMSN_3$ was removed under reduced pressure. Compound **17** was isolated by vacuum distillation to afford a clear white oil (1,9 g, 8,9 mmol, 88%) which was shown to be more than 98% pure by HPLC analysis (t_R = 4,45 min) and in 80% ee by chiral GC analysis. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.47−3.34 (m, 1H), 3.25−3.07 (m, 1H), 1.94−1.76 (m, 2H), 1.73−1.55 (m, 2H), 1.37−1.09 (m, 4H), 0.19−0.06 (s, 9H).



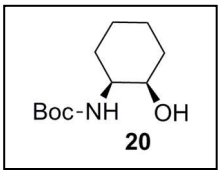
(*1S*,*2S*)-2-aminocyclohexanol (18). Compound **17** (1.62 g, 7.64 mmol) was dissolved in pure MeOH (25 mL) and TFA (0.012 mL, 0.15 mmol) was added. The reaction mixture was stirred for 30 min, after which time PtO_2 (0.162g) was added, and the mixture was placed under H_2 atmosphere (balloon pressure). The mixture was allowed to stir for 40 h at room temperature then filtered off on Milipore filter and concentrated under reduce pressure to furnish a clear tan colored solid. The material obtained was dissolved in 3mL of hot freshly distilled toluene and cooled down overnight at 4°C. The resulting crystals were separated from mother liquor by

filtration. The procedure was repeated until an enantiomeric excess superior to 99% was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.10 (m, 1H), 2.42 (ddd, J = 10.85, 9.20, 4.06 Hz, 1H), 1.91 (m, 1H), 1.86−1.75 (m, 1H), 1.74−1.54 (m, 2H), 1.30−1.02 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 75.70, 56.97, 34.32, 33.84, 25.0, 24.73; HRMS calcd for $C_6H_{14}NO$ $(M + H)^+$: 116.1075, Found: 116.1079.



19

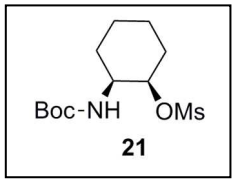
(1*R*,2*S*)-2-aminocyclohexanol (19). Compound **18** (1.0 g, 8.68 mmol) was dissolved in acetone (20mL) and the reaction mixture was cooled down to 0°C. The reaction mixture, vigorously stirred, was treated with 10 mL of 10% aqueous Na_2CO_3 solution, followed by a slow addition of acetic anhydride (0.82 mL, 8.68 mmol). The reaction mixture was allowed to warm to room temperature over 1 hour and was stirred for 2 more hours, after which time it was treated with 10 mL of saturated solution of aqueous $NaHCO_3$ and then 10mL of brine. The resulting solution was then extracted 3 times with a solution mixture of isopropanol in $CHCl_3$ (9:1, v/v). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to furnish a pale yellow solid. This crude material was dissolved in $CHCl_3$ (15 mL) and cooled down to 0°C. $SOCl_2$ (2.27 mL, 31.2 mmol) was added slowly, and the reaction mixture was allowed to warm up to room temperature over a period of 1 hour and stirred for 2 more hours. The solution was then concentrated under reduced pressure to give a brown viscous oil. ^{1}H NMR spectrum on the crude material showed a clean conversion to the oxazoline salt, so that the product was directly engaged without further purification. The material was dissolved in 10% aqueous HCl (30 mL) and heated to reflux for 1 hour. The cooled down solution was filtered off and the filtrate was concentrated under reduced pressure. The solid obtained was recristallized in EtOH/Et_2O solution mixture to afford **19** (0.98 g, 75% over the two steps) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.01 (s, 3H), 5.23 (s, 1H), 3.90 (s, 1H), 2.99 (s, 1H), 1.80−0.90 (m, 8H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 65.05, 52.44, 31.28, 25.10, 23.23, 19.44; HRMS calcd for $C_6H_{14}NO$ $(M + H)^+$: 116.1075, Found: 116.1079.



20

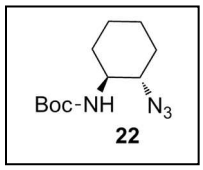
***tert*-butyl (1*S*,2*R*)-2-hydroxycyclohexylcarbamate (20).** Compound **19** (0.66g, 4.4 mmol) was dissolved in 4.4 mL of a 1N NaOH aqueous solution. The solution was cooled down to 0°C and the pH was adjusted to 8-9 before the drop by drop addition of a solution of Boc_2O (1.14 g, 5.2 mmol) in dioxane (5 mL). The reaction mixture was stirred overnight then acidified with 10 mL of 1N $KHSO_4$ aqueous solution then extracted with cyclohexane (1 × 20 mL) and EtOAc (2 × 20 mL). The combined organic layers were washed with H_2O (1 × 30 mL) and brine (1 × 30mL), dried over Na_2SO_4 and evaporated under reduced pressure. The result-

ing yellow oil was purified on silica gel column chromatography eluted with cyclohexane/EtOAc (3:1, v/v) to furnish **20** (0.92 g, 98%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.54 (s, 1H), 2.52 (s, 1H), 3.89 (d, *J* = 2.25 Hz, 1H), 4.99 (d, *J* = 7.92 Hz, 1H), 1.76−1.26 (m, 17H)



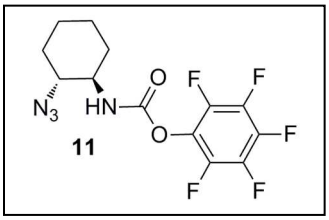
21

(1*R*,2*S*)-2-(*tert*-butoxycarbonylamino)cyclohexyl methanesulfonate (21). To a solution of **20** (0.9 g, 4.2 mmol) dissolved in DCM (30 mL) and placed under Ar atmosphere was added Et_3N (0.86 mL, 6.27 mmol). The reaction mixture was cooled down to 0°C, and MsCl (0.48 mL, 6.27 mmol) was slowly added. The reaction mixture was allowed to stir for 2 hours. The reaction mixture was then washed one time with pure H_2O (20 mL), one time with 1N $KHSO_4$ solution (20mL), one time with saturated aqueous $NaHCO_3$ solution (20mL) and finally one time with brine (20mL). The organic layer was dried over Na_2SO_4, filtered off and concentrated under reduced pressure to afford **21** (1.14g , 93%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.97 (s, 1H), 3.81−3.51 (s, 1H), 3.01 (s, 3H), 2.20−2.03 (m, 1H), 1.83−1.44 (m, 8H), 1.44−1.27 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 80.70, 50.98, 38.11, 30.08, 28.37, 27.12, 24.05, 19.20.

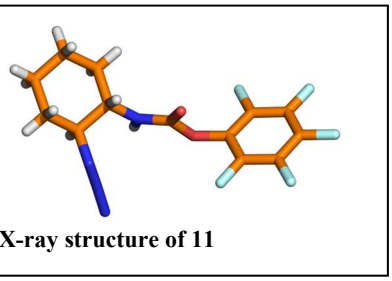


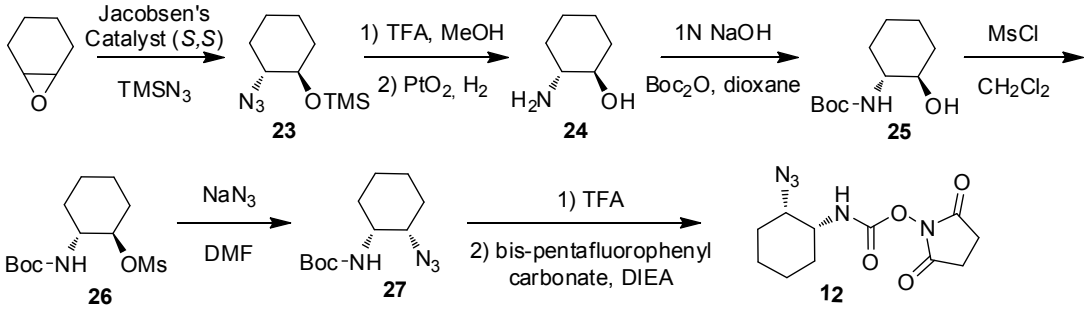
22

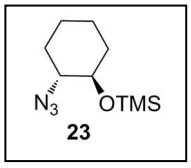
***tert*-butyl (1*S*,2*S*)-2-azidocyclohexylcarbamate (22):** To a solution of **21** (1.14 g , 3.89 mmol) in DMF under Ar atmosphere was added NaN_3 (280 mg, 4.28 mmol). The solution was heated at 55°C overnight, after which time water (100 mL) was added and the resulting solution was extracted twice with Et_2O (2 × 50 mL). The combined organic layers were then washed one time with saturated $NaHCO_3$ aqueous solution (20 mL), one time with 1N $KHSO_4$ aqueous solution (20 mL), on time with brine (20 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **22** (0.93g, 99%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.57 (d, *J* = 8.24 Hz, 1H), 3.40 (m, 1H), 3.09 (m, 1H), 2.09−1.93 (m, 2H), 1.83−1.67 (m, 2H), 1.47−1.18 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 64.36, 3.89, 32.28, 30.67, 28.61, 24.29, 24.05.



Pentafluorophenyl (1*S*,2*S*)-2-azidocyclohexylcarbamate (11): compound **21** (1.47g, 6.12 mmol) was dissolved in pure TFA (10mL). The reaction mixture was stirred for 30 min under Ar atmosphere after which time it was concentrated under reduced pressure then co-evaporated 3 times with cyclohexane before to be dissolved in CH_2Cl_2 (20 mL) and cooled down to 0°C. DIPEA (2.53 mL, 15.3 mmol) and bis-pentafluorophenyl carbonate (2.41 g, 6.12 mmol) were then successively added. The reaction mixture was allowed to warm up over a period of 1 hour and again stirred for one more hour, after which time the solution was concentrated under reduced pressure. The crude material was dissolved in EtOAc and washed successively one time with H_2O (20 mL), with 1N $KHSO_4$ aqueous solution (20 mL) and with brine (20 mL). The organic layer was next dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material such obtained was taken up in 20 mL heptane and cooled to 4° C overnight. The resulting crystals were separated from mother liquor by filtration, rinsed with heptane and dried under high vacuum. The mother liquor was concentrated to about 10 mL and the crystallization operation was repeated until no more crystallization in heptane was observed. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.37 (d, J = 7.61 Hz, 1H), 3.66−3.35 (m, 1H), 3.32−3.05 (m, 1H), 2.28−2.00 (m, 2H), 1.93−1.63 (m, 2H), 1.58−1.18 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 151.16, 63.84, 55.40, 31.71, 30.57, 24.14, 23.96; HRMS calcd for $C_{13}H_{12}N_4O_2F_5$ $(M + H)^+$: 351.0880, Found: 351.0872.

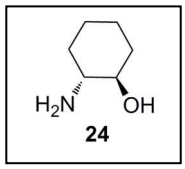

X-ray structure of 11





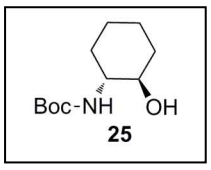
(1*R*,2*R*)-2-azidocyclohexyloxytrimethylsilane (23). A 50 mL dried flask was charged with (0.708 g, 1.12 mmol) of (*S*,*S*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino chromium(III) chloride (Salen catalyst), flushed several time with

N_2 and sealed. Cyclohexene oxide (5.7 mL, 56.04 mmol) was slowly added at room temperature followed by $TMSN_3$ (7.8 mL, 58.84 mmol), so that the inside temperature of the flask remains constant. The reaction mixture was stirred 12 h, after which time the excess of $TMSN_3$ was removed under reduced pressure. Product **23** (10.2 g, 85.4%) was isolated after vacuum distillation as a clear white oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.5−3.41 (m, 1H), 3.25−3.17 (m, 1H), 2.0−1.92 (m, 2H), 1.90−1.85 (m, 2H), 1.42−1.15 (m, 4H), 0.19 (s, 9H).



24

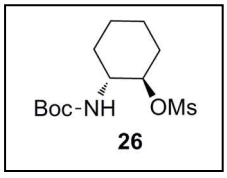
(1*R*,2*R*)-2-aminocyclohexanol (24): Compound **23** (7.5 g, 35.2 mmol) was dissolved in MeOH (117.3 mL) and TFA (0.054 mL, 0.7 mmol) was added. The reaction mixture was stirred for 30 min, after which time PtO_2 (0.16 g, 0.7 mmol) was added, and the mixture was placed under H_2 atmosphere (balloon pressure). The mixture was allowed to stir for 40 hours at room temperature before to be filtered off on a Milipore filter and the filtrate was concentrated under vacuum to produce a clear tan colored solid. The crude material obtained was dissolved in 3mL of hot freshly distilled toluene and cooled overnight at 4°C. The resulting crystals were separated from mother liquor by filtration. This procedure was repeated until an enantiomeric excess > 99% was obtained and compound 24 was obtained as a crystalline solid in 96.3% yield (2.9 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.10 (m, 1H), 2.42 (ddd, J = 10.85, 9.20, 4.06 Hz, 1H), 1.91 (m, 1H), 1.86−1.75 (m, 1H), 1.74−1.54 (m, 2H), 1.30−1.02 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 75.70, 56.97, 34.32, 33.84, 25.0, 24.73; HRMS calcd for $C_6H_{14}NO$ $(M + H)^+$: 116.1075, Found: 116.1079.



25

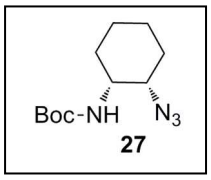
***tert*-butyl (1*R*,2*R*)-2-hydroxycyclohexylcarbamate (25):** Compound **25** (1.76 g, 15.3 mmol) was dissolved in 1N NaOH aqueous solution (15 mL). The solution was cooled down to 0°C and the pH was adjusted to 8-9 before the addition of a solution of Boc_2O (4.21 mL, 18.4 mmol) in dioxane (15 mL). The reaction mixture was stirred for 3 hours then acidified with 1N $KHSO_4$ aqueous solution (10 mL) and extracted with cyclohexane (1 × 20 mL) and EtOAc (2 × 20 mL). The combined organic layers were washed one time with H_2O (30 mL), one time with brine (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The resulting yellow oil was purified on silica gel column chromatography eluted with cyclohexane/EtOAc (3:1, v/v) solvent mixture to furnish **24** (2.8 g, 85%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm

4.53 (brs, 1NH), 3.38−3.27 (m, 2H), 2.10−1.95 (m, 2H), 1.77−1.68 (m, 2H), 1.47 (s, 9H), 1.40−1.09 (m, 4H).



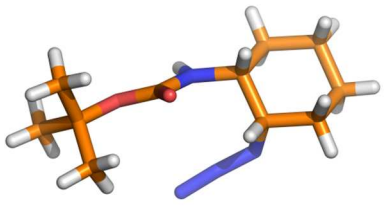
26

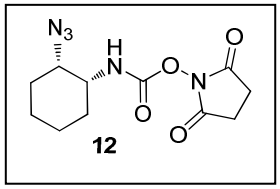
(1*R*,2*R*)-2-(*tert*-butoxycarbonylamino)cyclohexyl methanesulfonate (26): To a solution of compound **25** (2.5 g, 11.62 mmol) in CH_2Cl_2 (25 mL) under Ar atmosphere was added Et_3N (2.45 mL, 17.43 mmol). The solution was cooled down to 0 °C, and MsCl (1.35 mL, 17.43 mmol) was slowly added. The reaction mixture was stirred for 2 hours at 0 °C, then washed one time with H_2O (20 mL), one time with 1N $KHSO_4$ aqueous solution (20mL), one time with a saturated $NaHCO_3$ aqueous solution (20 mL) and finally one time with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **26** (3.25 g, 96%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 4.70 (br.s, 1NH), 4.50-4.41(m, 1H), 3.66-3.54 (m, 1H), 3.04 (s, 3H), 2.25-2.16 (m, 1H), 2.14-2.06 (m, 1H), 1.84-1.60 (m, 4H), 1.46 (s, 9H), 1.39-1.24 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 80.70, 50.98, 38.11, 30.08, 28.37, 27.12, 24.05, 19.20.



27

***tert*-butyl-(1*R*,2*S*)-2-azidocyclohexylcarbamate (27):** Compound **26** (3.2 g, 11 mmol) was dissolved in DMF (25 mL) under Ar atmosphere and NaN_3 (1.78 g, 27.3 mmol) was added. The reaction mixture was heated at 55 °C for 72 hours. After complete conversion, water (100 mL) was added and the resulting solution was extracted twice with Et_2O (50 mL). The combined organic layers were successively washed one time with saturated $NaHCO_3$ aqueous solution (20 mL), 1N $KHSO_4$ aqueous solution (20 mL) and with brine (20 mL), before being dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **27** (1.6 g, 61.06%) as a white solid. 1H NMR (300 MHz, $CDCl_3$) δ ppm 4.73 (d, J = 6.3 Hz, 1NH), 3.99−3.95 (m, 1H), 3.67−3.58 (m, 1H), 2.04−1.52 (m, 1H), 1.76−1.56 (m, 4H), 1.53−1.48 (m, 1H), 1.46 (s, 9H), 1.44−1.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 155.05, 79.52, 61.59, 51.16, 28.75, 28.39, 27.69, 24.37, 19.72.


X-ray structure of 27



Succinimidyl (1*R*,2*S*)-2-azidocyclohexylcarbamate (12): Compound **27** (1.03 g, 4.28 mmol) was dissolved in pure TFA (10mL). The reaction mixture was stirred for 30 min under inert atmosphere (Ar), after which time it was concentrated under reduced pressure and coevaporated 3 times with cyclohexane, before to be basified with saturated $NaHCO_3$ aqueous solution. The aqueous phase was then extracted with CH_2Cl_2 (5 × 25 mL) and the combined organic layers were dried over Na_2SO_4. After removal of solvent under reduced pressure, the crude material was directly engaged in the next step without any purification. To a stirred solution of *N,N'*-Disuccinimidyl carbonate (1.2 g, 4.71 mmol) in CH_2Cl_2 (20 mL), the freshly prepared free amine in CH_2Cl_2 (10 mL) was slowly added, and the reaction mixture was stirred for 1 hour. The reaction mixture was then filtered through the cindered funnel. The filtrate was washed with 1N $KHSO_4$ aqueous solution (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford **12** (0.9 g, 75%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 5.43 (d, *J* = 8.3 Hz, 1NH), 4.04−3.9 (m, 1H), 3.73−3.63 (m, 1H), 2.84 (s, 4H), 2.13−2.02 (m, 1H), 1.83−1.74 (m, 2H), 1.72−1.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.81, 150.64, 60.63, 52.77, 28.50, 27.48, 25.54, 24.08, 19.52; HRMS calcd for $C_{13}H_{18}N_6O_4Na$ $(M + Na)^+$: 345.1287, Found: 345.1291.

1.2 ^{1}H and ^{13}C NMR characterization of compounds 8-13.

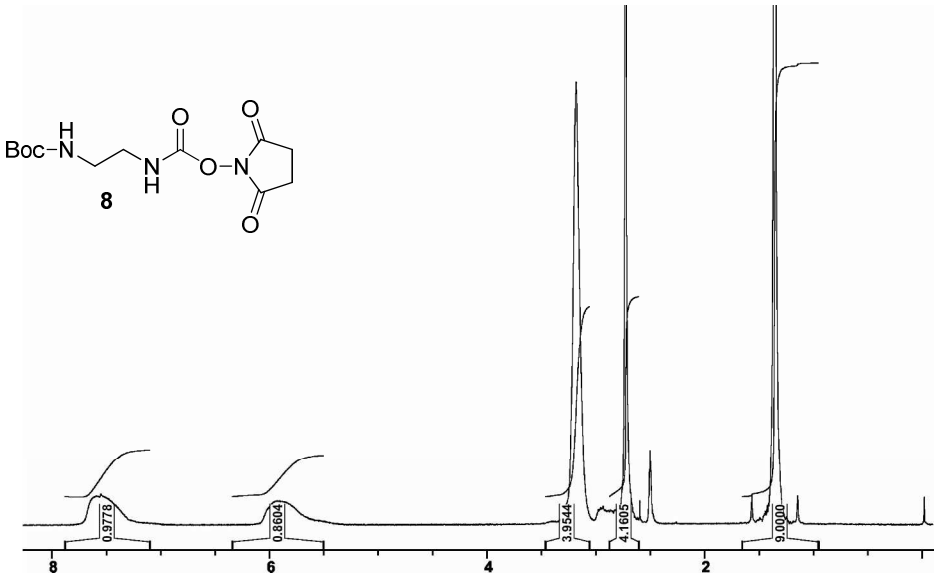


Figure S1. ^{1}H-NMR spectrum of monomer **8** recorded in DMSO-d_6 (300 MHz)

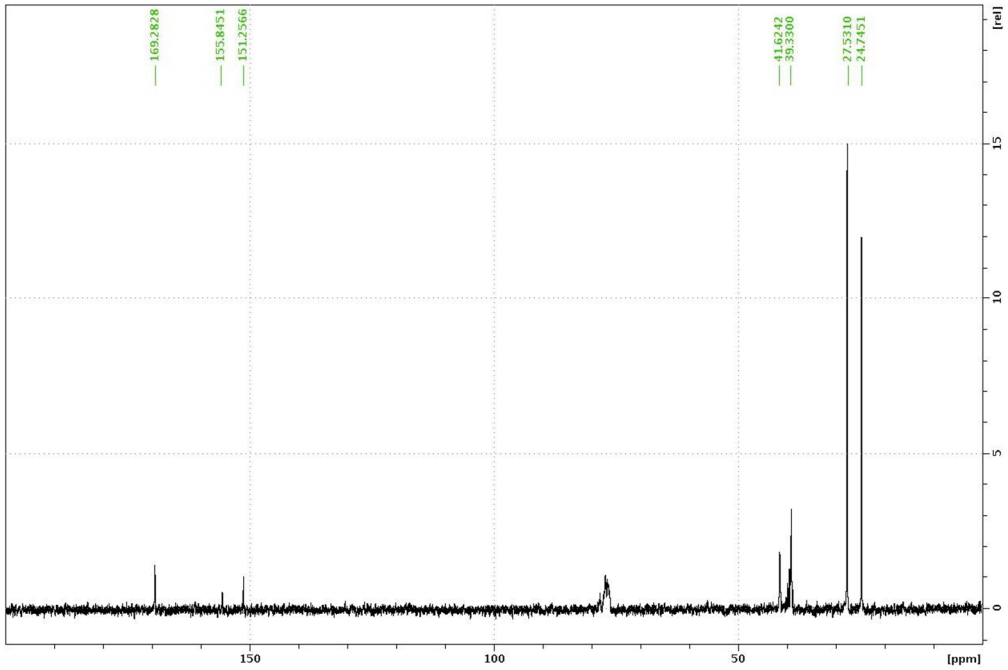


Figure S2. ^{13}C-NMR spectrum of monomer **8** recorded in $CDCl_3$/DMSO-d_6 (75 MHz)

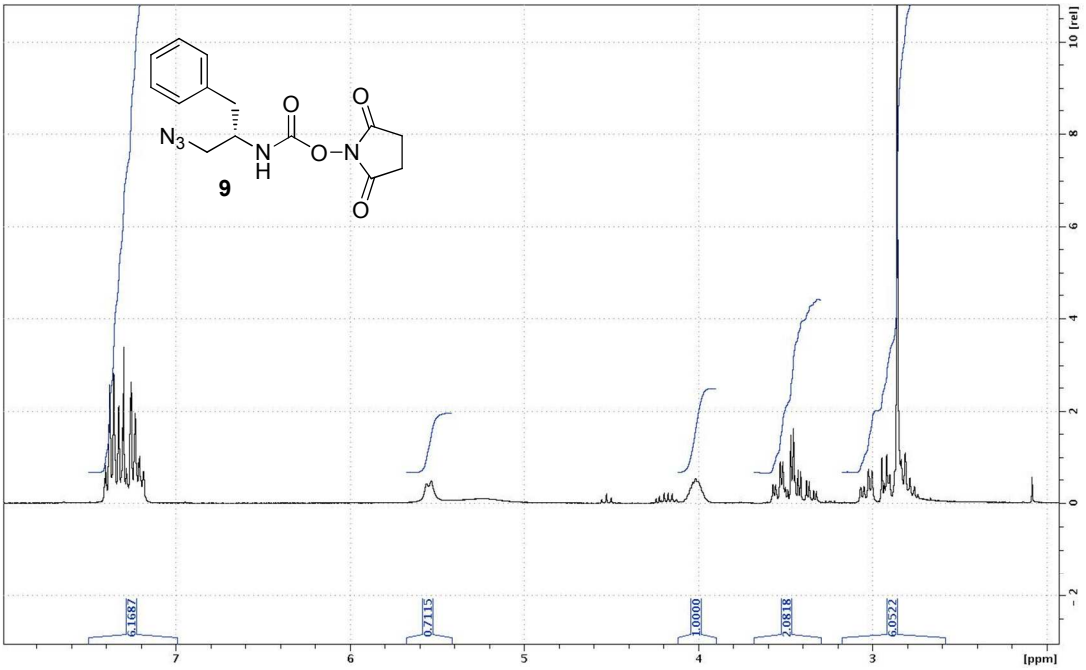


Figure S3. ^{1}H-NMR spectrum of monomer **9** recorded in $CDCl_3$ (300 MHz)

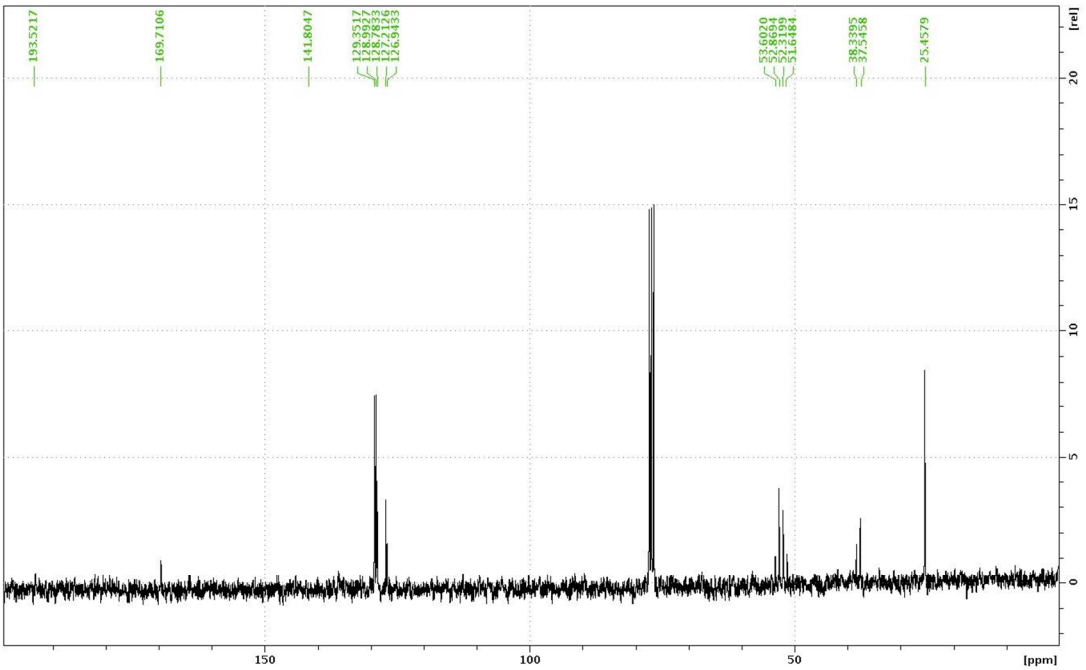


Figure S4. ^{13}C-NMR spectrum of monomer **9** recorded in $CDCl_3$ (75 MHz)

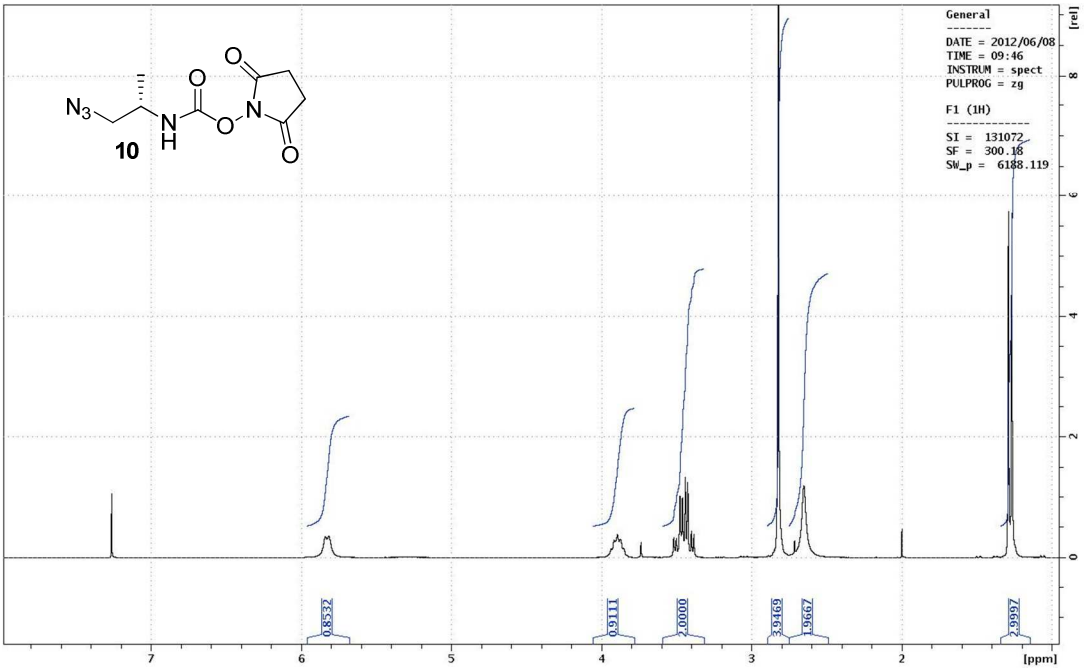


Figure S5. ^{1}H-NMR spectrum of monomer **10** recorded in $CDCl_3$ (300 MHz)

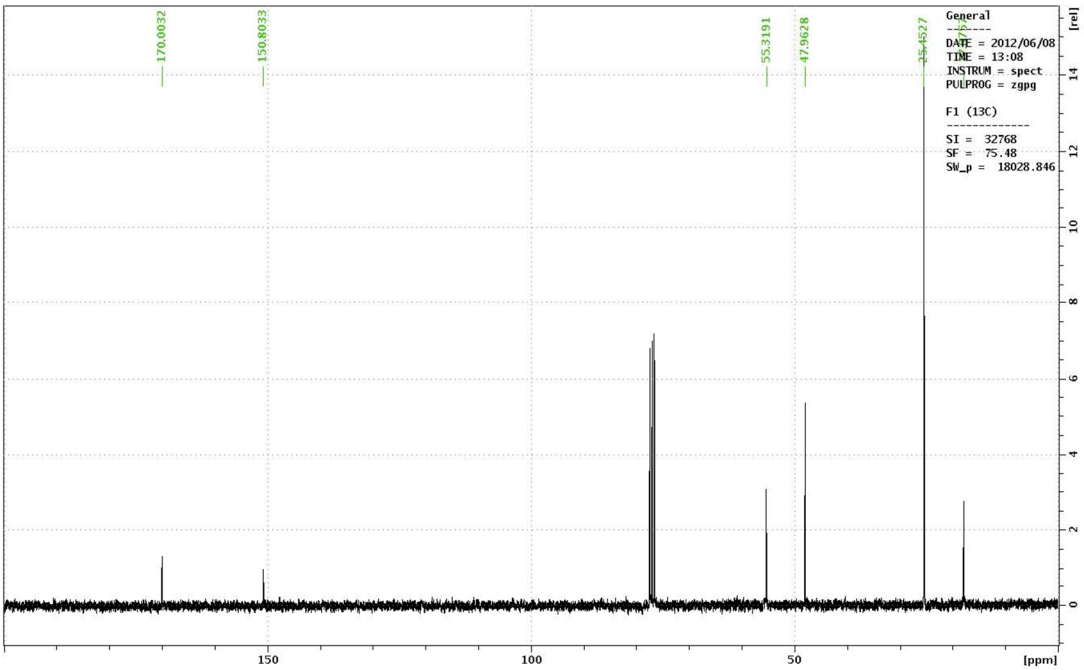


Figure S6. ^{13}C-NMR spectrum of monomer **10** recorded in $CDCl_3$ (75 MHz)

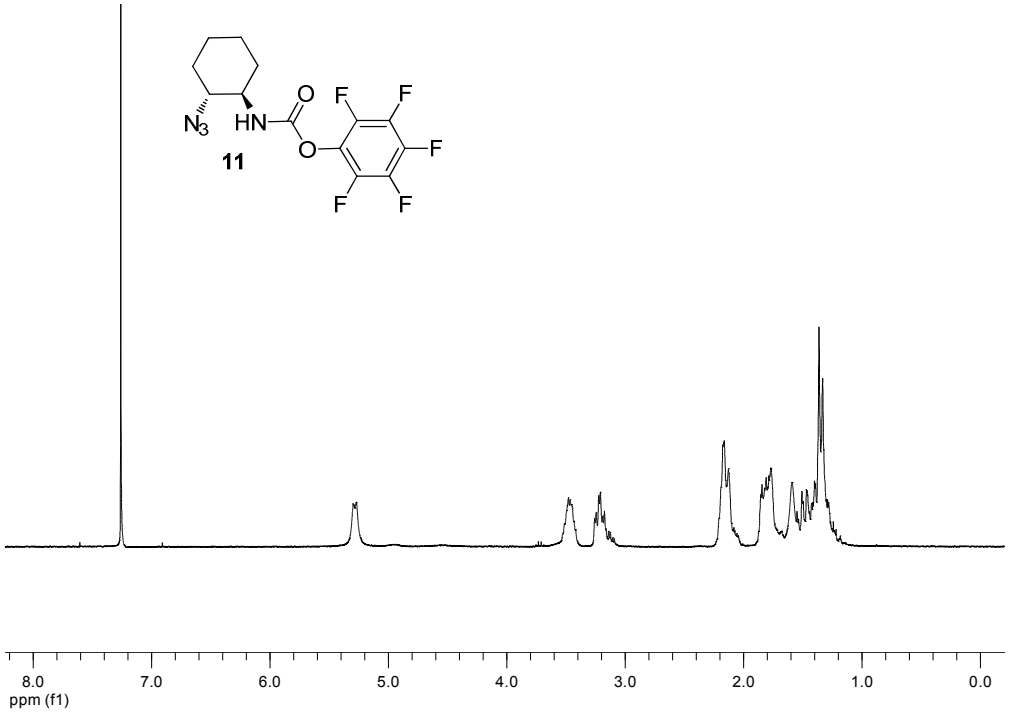


Figure S7: ^{1}H-NMR spectrum of monomer **11** recorded in $CDCl_3$ (300 MHz)

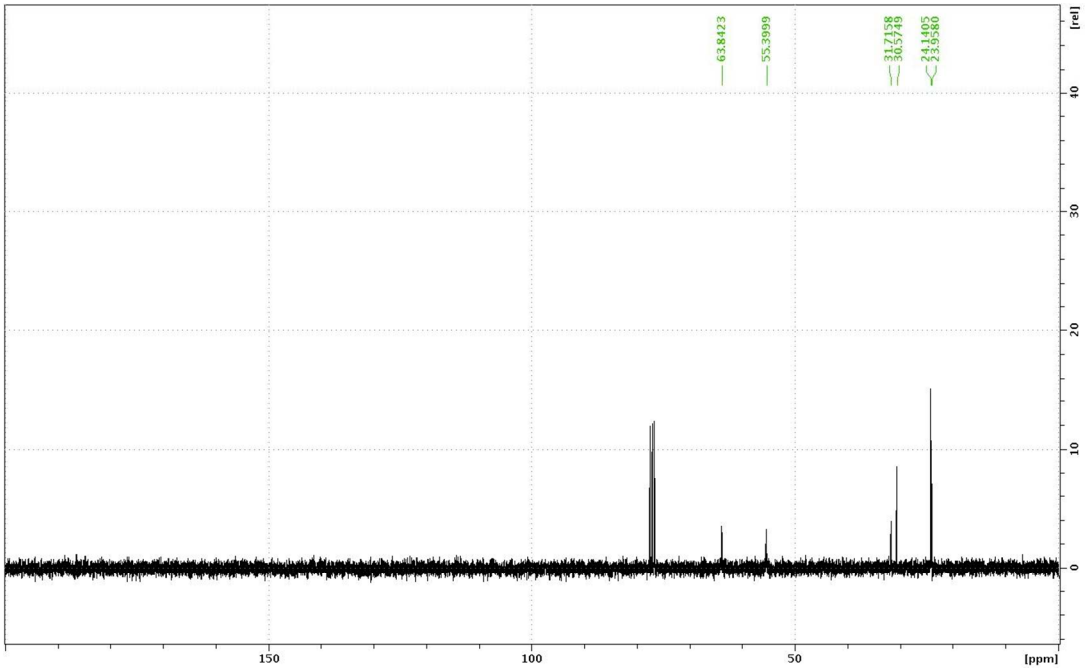


Figure S8. ^{13}C-NMR spectrum of monomer **11** recorded in $CDCl_3$ (75 MHz)

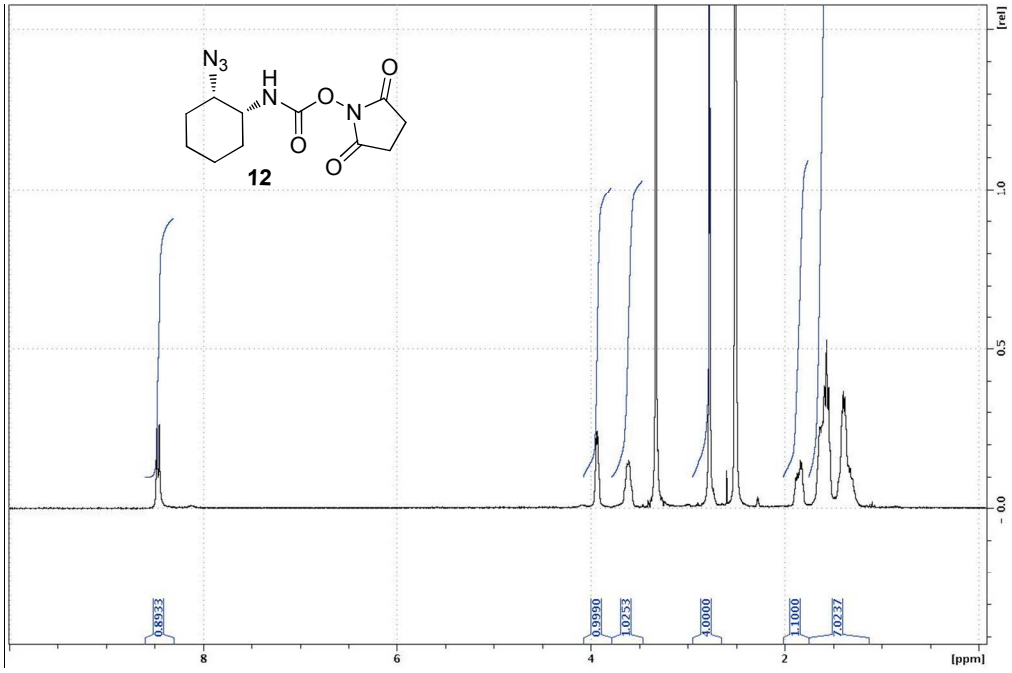


Figure S9: ^{1}H-NMR spectrum of monomer **12** recorded in $CDCl_3$ (300 MHz)

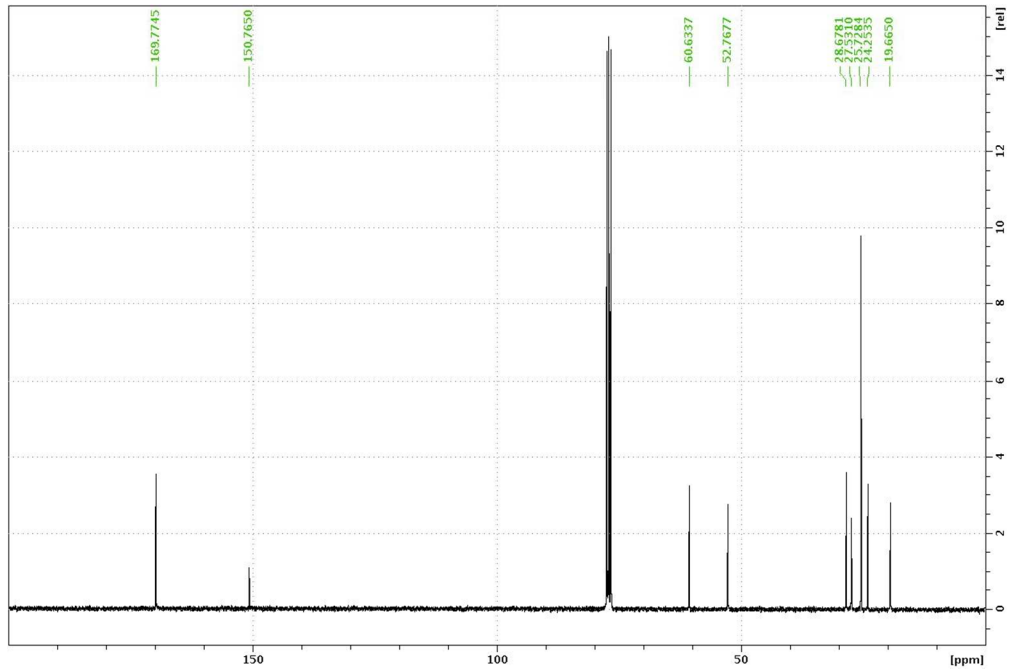
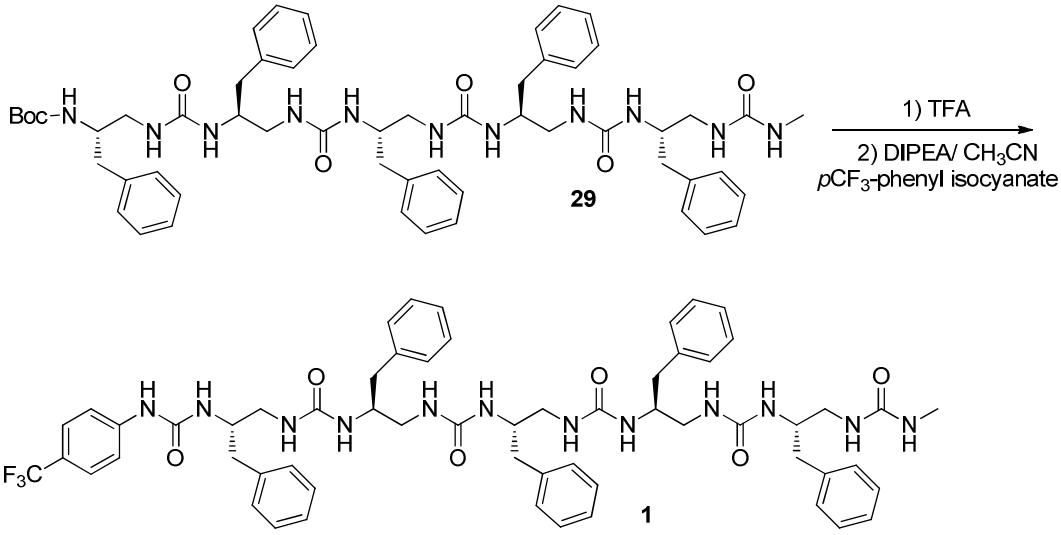


Figure S10: ^{13}C-NMR spectrum of monomer **12** recorded in $CDCl_3$ (75 MHz)

1.3 Synthesis of oligoureas 1-6

1.3.1 Parent trifluorophenyl capped pentaurea (1)



Pentamer **29**[2] (2.45 g, 2.93 mmol) was treated with TFA (20 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulting solution of TFA salt in CH_3CN (5 mL) was added DIPEA (1.49 mL, 8.79 mmol), and after 10 minutes the reaction mixture was further treated with *p*CF_3-phenylisocyanate (1.2 g, 3.07 mmol) and stirred for 2 hours. After completion of the reaction, the solvent was concentrated under reduced pressure and the crude was diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL), 1N aqueous $KHSO_4$ solution (2 × 10 mL), brine (10 mL) dried over $MgSO_4$ and the solvent was concentrated under reduced pressure. Purification by silica gel column chromatography eluting with 6.0 % MeOH in $CHCl_3$ gave **1** (2.3 g, 78 %) as white solid. HPLC t_R = 14.28 min (linear gradient, 30-100% B, 20 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.01 (s, 1NH), 7.7 (m, 1NH), 7.56 (s, 4H), 7.31−7.09 (m, 25H), 6.29 (d, J = 8.7 Hz, 1NH), 6.24−6.16 (m, 2NH), 6.15−6.1 (m, 1H), 6.09−6.02 (m, 2H), 6.01−5.99 (m, 1H), 5.98−5.92 (m, 2H), 5.91−5.86 (d, J = 8.8 Hz, 1NH), 4.16−3.71 (m, 5H), 3.43−3.24 (m, 10H), 2.95−2.53 (m, 13H); Micro TOF: *m/z* calculated for $C_{59}H_{69}F_3N_{12}O_6$: 1098.5415, found 1105.5570 $[M+Li]^+$.

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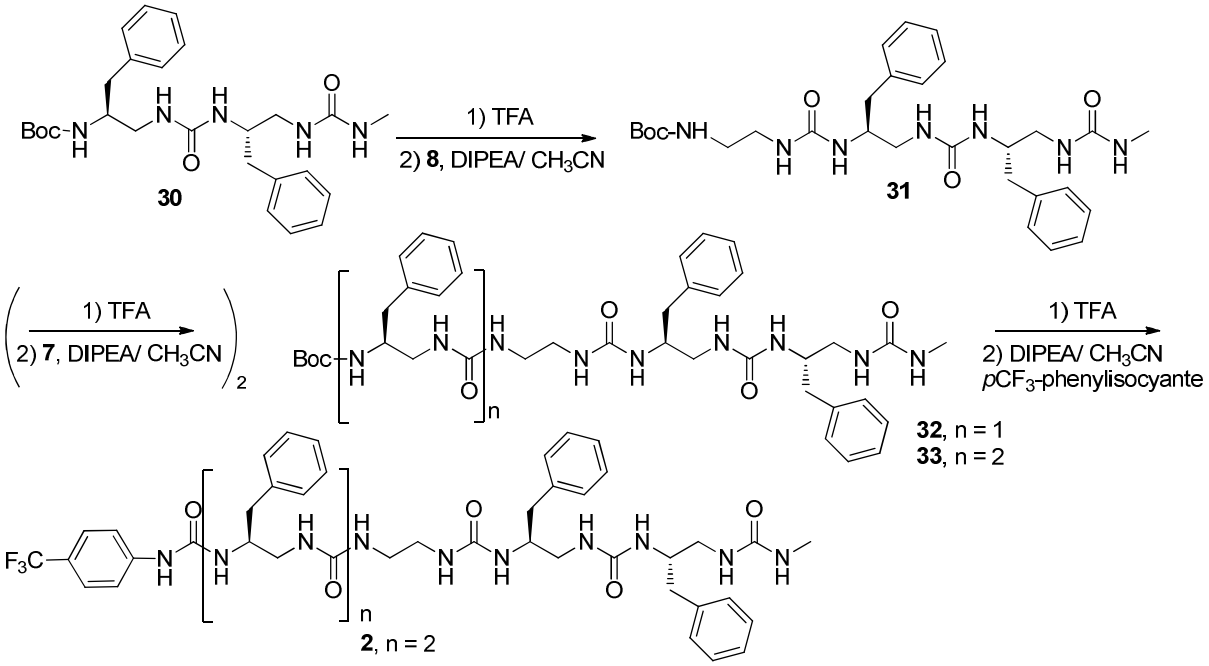
2. Fischer, L.; Claudon, P.; Pendem, N.; Miclet, E.; Didierjean, C.; Ennifar, E.; Guichard, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 1067–1070.

1.3.2 Synthesis of oligomer (2)



Triurea (31): Biurea **30** (1.22 g, 2.52 mmol) was treated with TFA (10 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. The resulting solution of TFA salt in CH_3CN (10 mL) was treated with DIPEA (1.28 mL, 7.6 mmol), and after 10 minutes **8** (0.8 g, 2.64 mmol) was added and stirring was maintained for 2 hours. Workup as described for **1** and after purification by silica gel column chromatography eluted with 3.5 % MeOH in $CHCl_3$, **29** (0.95 g, 66 %) was isolated as a white solid. HPLC t_R = 8.817 min (linear gradient, 30−100% B, 20 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.3−7.13 (m, 10H), 6.8 (t, J = 5.0 Hz, 1NH), 6.01−5.82 (m, 6NH), 3.81−3.66 (m, 2H), 3.24−3.04 (m, 2H), 3.01−2.68 (m, 6H), 2.67−2.56 (m, 4H), 2.53 (d, J = 4.5 Hz, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, DMSO−d_6) δ ppm 159.8, 158.9, 156.5, 139.8, 130.0, 128.9, 126.8, 78.4, 52.3, 44.0, 43.9, 29.0, 27.2; ESIMS: *m/z* 592.4 $[M+Na]^+$, 570.4 $[M+H]^+$, 470.4 $[M+H\text{-}Boc]^+$.

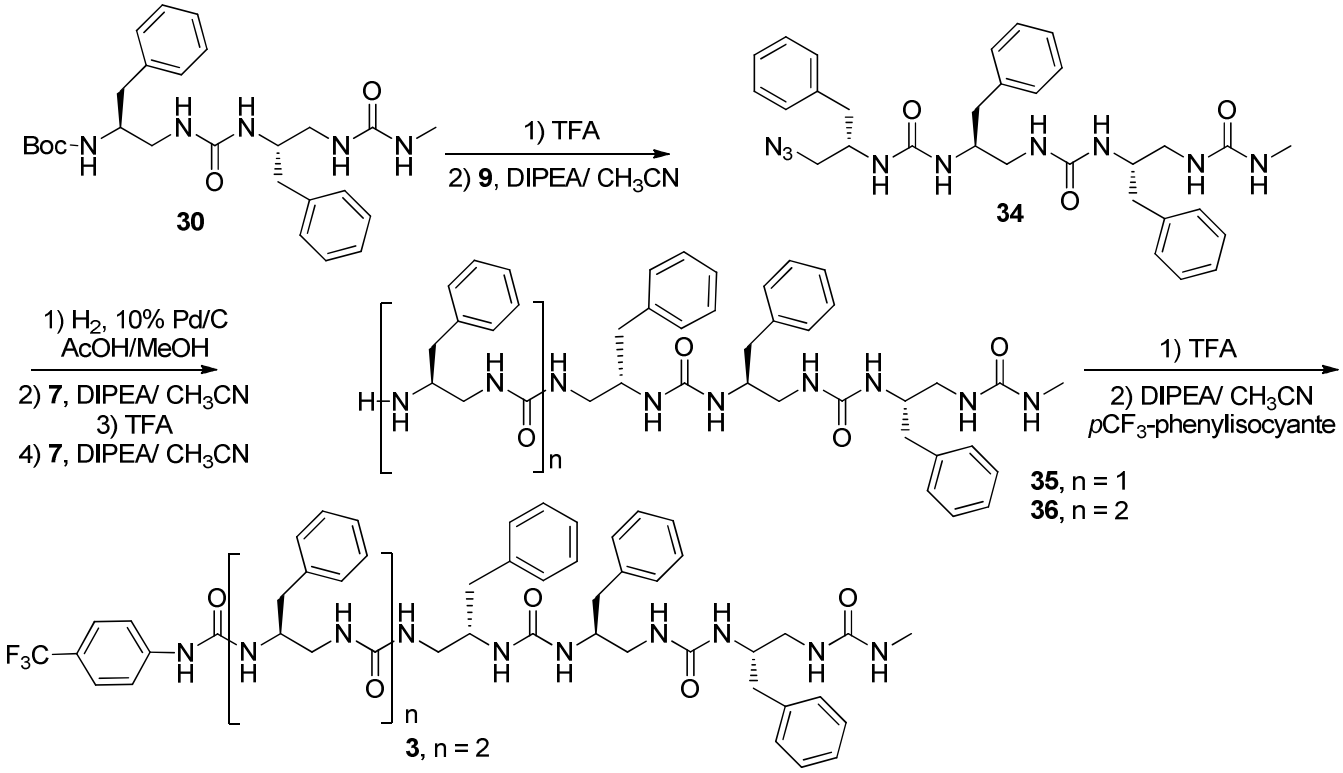
Tetraurea (32): Compound **31** (0.75 g, 1.32 mmol) was treated with TFA (8 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. The resulting solution of TFA salt in CH_3CN (8 mL) was treated with DIPEA (0.67 mL, 3.96 mmol), and after 10 minutes the reaction mixture was further treated with **7** (0.54 g, 1.38 mmol) and stirring was maintained for 2 h. Workup as described for **31** and purification by silica gel column chromatography (silica gel, 5.0 % MeOH in $CHCl_3$) furnished **32** (0.581 g, 59 %) as a white solid. HPLC t_R = 11.573 min (linear gradient, 30−100% B, 20 min); ^{1}H NMR (300 MHz, DMSO-

d$_6$) δ 7.3−7.12 (m, 15H), 6.74 (d, *J* = 8.6 Hz, 1NH), 6.08−6.0 (m, 2NH), 5.99−5.9 (m, 4NH), 5.89−5.84 (m, 2NH), 3.82−3.68 (m, 2H), 3.67−3.54 (m, 1H), 3.24−3.11 (m, 4H), 3.09−2.97 (m, 2H), 2.95−2.78 (m, 4H), 2.73−2.58 (m, 6H), 2.53 (d, *J* = 4.6 Hz, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ ppm 159.8, 158.9, 156.2, 139.8, 128.9, 126.7, 78.4, 53.3, 52.1, 51.9, 44.2, 44.1, 29.1, 27.2; ESIMS: *m/z* 768.6 $[M+Na]^+$, 746.6 $[M+H]^+$, 646.6 $[M+H\text{-}Boc]^+$.

Pentaurea (33): Compound **32** (0.4 g, 0.54 mmol) was treated with TFA (5 mL) at 0° C for 30 min. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (5 mL) was treated with DIPEA (0.28 mL, 1.62 mmol), and after 10 min the reaction mixture was further treated with **7** (0.22 g, 0.563 mmol) and stirring was maintained for 2 hours. Workup as described for **32** and purification by silica gel column chromatography (6.0 % MeOH in $CHCl_3$) gave **33** (0.280 g, 57 %) as a white solid. HPLC t_R = 14.28 min (linear gradient, 30−100% B, 20 min); ^{1}H NMR (300 MHz, DMSO d6) δ 7.29−7.14 (m, 20H), 6.74 (d, *J* = 8.2 Hz, 1NH), 6.07−5.85 (m, 10NH), 3.86−3.71 (m, 3H), 3.67−3.54 (m, 1H), 3.27−3.01 (m, 6H), 2.94−2.74 (m, 6H), 2.70−2.56 (m, 8H), 2.54 (d, *J* = 4.6 Hz, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ ppm 159.7, 158.2, 156.2, 139.7, 128.9, 78.5, 53.5, 52.3, 52.2, 44.0, 43.5, 38.7, 29.2, 27.3, 25.7, 25.0; ESIMS: *m/z* 945.9 $[M+Na]^+$, 923.8 $[M+H]^+$, 822.8 $[M+H\text{-}Boc]^+$.

Trifluorophenylpentaurea (2): Compound **33** (0.1 g, 0.108 mmol) was treated with TFA (2 mL) at 0° C for 30 min. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (2 mL) was treated with DIPEA (37 μL, 0.216 mmol), and after 10 minutes the reaction mixture was further treated with trifluorophenyl isocyanate (16 μL, 0.113 mmol) and stirring was maintained for 4 hours. Workup as described for **33** and purification by silica gel column chromatography (10 % MeOH in $CHCl_3$) gave **2** (0.08 g, 73.13 %) as a white solid. HPLC t_R = 14.657 min (linear gradient, 30−100% B, 20 min); ^{1}H NMR (300 MHz, DMSO d6) δ 9.02 (br. s, 1NH), 7.59−7.5 (m, 4H), 7.3−7.09 (m, 20H), 6.28 (d, *J* = 8.1 Hz, 1NH), 6.18−5.86 (m, 10NH), 3.95−3.7 (m, 4H), 3.26−2.7 (m, 12H), 2.73−2.53 (m, 11H); ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ ppm 159.3, 159.1, 158.7, 155.9, 139.3, 129.6, 128.5, 126.3, 78.1, 52.8, 51.6, 51.4, 44.0, 28.6, 26.8; ESIMS: *m/z* 1031.6 $[M+Na]^+$, 1009.7 $[M+H]^+$.

1.3.3 Synthesis of oligourea (3) with shifted benzyl side chain ($C_\beta \rightarrow C_\alpha$)



Triurea azide (34): Compound **30** (1.1 g, 2.27 mmol) was treated with TFA (10 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (20 mL) was added DIPEA (1.16 mL, 6.81 mmol), and after 10 minutes compound **9** (0.76 g, 2.4 mmol) was further added and stirring was maintained 2 hours. Workup as described for **31** afforded **34** (1.05 g, 79%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.28−7.14 (m, 15H), 6.13 (d, J = 7.2 Hz, 1NH), 6.01−5.82 (m, 5NH), 3.92−3.82 (m, 1H), 3.79−3.67 (m, 2H), 3.29−3.16 (m, 2H), 3.14−2.95 (m, 2H), 2.91−2.79 (m, 2H), 2.73−2.55 (m, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 159.8, 158.8, 158.0, 139.8, 139.2, 129.1, 128.9, 126.8, 54.5, 52.3, 51.6, 44.0, 39.2, 38.7, 27.2; ESIMS: *m/z* 608.1 $[M+Na]^+$, 586.1 $[M+H]^+$.

Tetraurea (35): Compound **34** (0.84g, 1.44 mmol) was dissolved in a solution of 20% AcOH in MeOH (100 mL) and hydrogenated for 2 hours in the presence of 10% Pd/C as catalyst at room temperature under the H_2 atmosphere. The catalyst was removed by filtration over celite and the filtrate was concentrated to afford corresponding free amine (0.78 g, 97%) as syrup which was used directly engaged in the

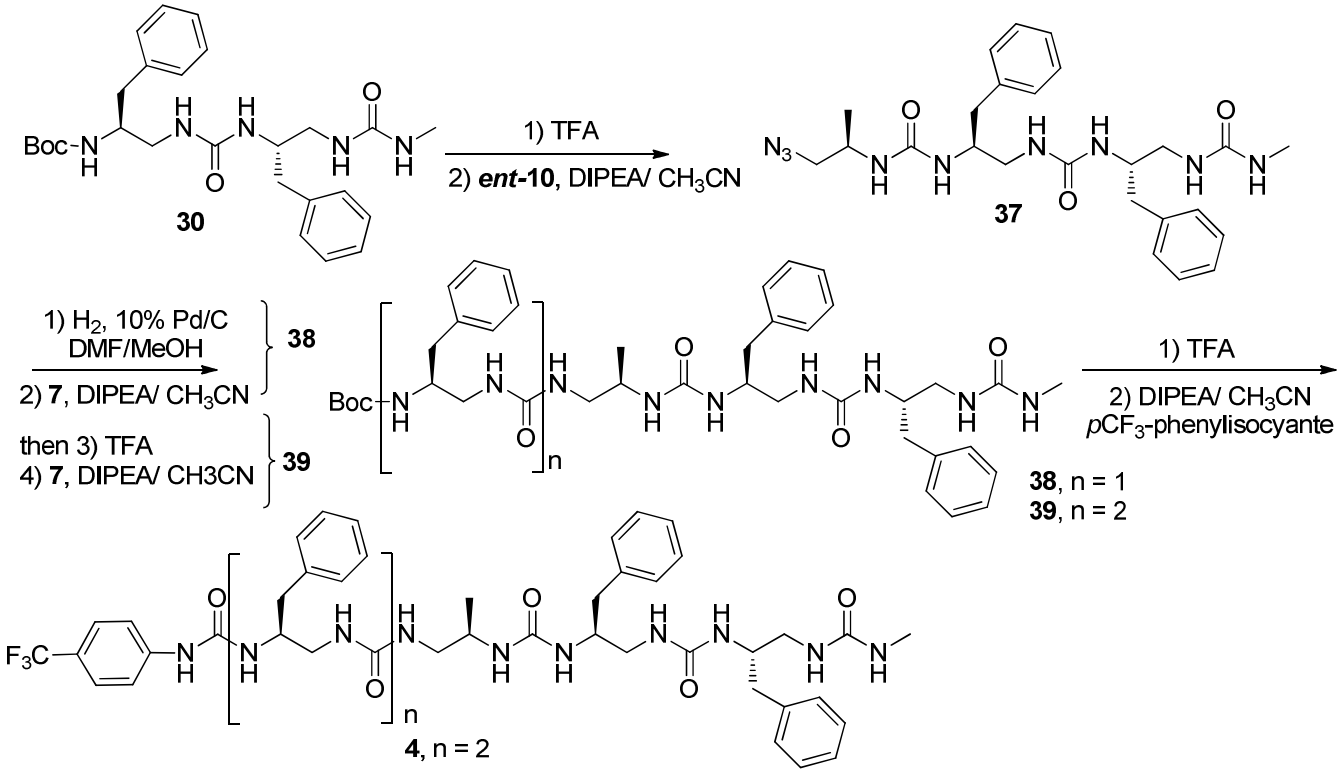
next step without purification. To a stirred solution of free amine (0.78 g, 1.39 mmol) in CH_3CN (15 mL) was added **7** (0.573 g, 1.46 mmol) and DIPEA (0.75 mL, 4.17 mmol) and stirring was maintained for 3 hours. Workup as described for **34** and purification by silica gel column chromatography eluted with $CHCl_3$/MeOH/AcOH (120:6:5, v/v/v) solution gave **35** (0.95 g, 82 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.27−7.13 (m, 20H), 6.70 (d, J = 8.2 Hz, 1NH), 6.14−6.07 (m, 2NH), 6.05−5.83 (m, 6NH), 3.80−3.54 (m, 4H), 3.19−3.08 (m, 2H), 3.06−2.97 (m, 2H), 2.95−2.9 (m, 2H), 2.89−2.79 (m, 2H), 2.72−2.53 (m, 11H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 159.8, 159.4, 158.9, 158.6, 156.0, 139.8, 130.0, 128.9, 126.7, 78.3, 53.5, 52.6, 52.3, 44.0, 38.8, 28.9, 27.2, 25.1; ESIMS: *m/z* 858.5 $[M+Na]^+$, 836.2 $[M+H]^+$, 736.4$[M+H\text{-}Boc]^+$.

Pentaurea (36): Compound **35** (0.5 g, 0.6 mmol) was treated with TFA (5 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (8 mL) was added DIPEA (0.324 mL, 1.8 mmol) and after 10 minutes **7** (0.246 g, 0.63 mmol) was added and stirring was maintained for 2 hours. Workup as described for **35** and purification by silica gel column chromatography eluted with $CHCl_3$/MeOH/AcOH (120: 6: 4, v/v/v) gave **36** (0.508 g, 84%) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.27−7.13 (m, 25H), 6.70 (d, J = 8.2 Hz, 1NH), 6.2−6.08 (m, 2NH), 6.09−5.93 (m, 7NH), 5.93−5.88 (m, 1NH), 3.79−3.53 (m, 5H), 3.18−2.79 (m, 10H), 2.74−2.53 (m, 13H), 1.3 (s, 9H); ^{13}C NMR (100 MHz, *DMSO−d6*) δ ppm 159.8, 159.4, 158.9, 158.8, 156.1, 139.9, 130.0, 128.8, 126.7, 78.3, 53.3, 52.8, 52.3, 44.0, 43.7, 38.8, 29.0, 27.2;ESIMS: *m/z* 1034.2 $[M+Na]^+$, 1012.3 $[M+H]^+$, 912.3 $[M+H\text{-}Boc]^+$.

Trifluorophenyl pentaurea (3): Compound **36** (0.13 g, 0.128 mmol) was treated with TFA (1.0 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (2 mL) was added DIPEA (44 μL, 0.257 mmol), and after 10 minutes trifluorophenylisocyanate (19 μL, 0.134 mmol) was added and stirring was maintained for 4 hours. Workup as described for **2** and purification by silica gel column chromatography eluted with $CHCl_3$/MeOH/AcOH (120:8:4, v/v/v) furnished **2** (0.135 g, 96 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.80 (s, 1NH), 7.60−7.48 (m, 4H), 7.26−7.12 (m, 25H); 6.31−6.2 (m, 2NH), 6.21−6.15 (m, 1NH); 6.13−5.98 (m, 7NH), 5.96−5.91 (m,

1NH), 3.90−3.60 (m, 5H), 3.19−3.08 (m, 4H), 3.05−2.94 (m, 4H), 2.88−2.78 (m, 2H), 2.71−2.53 (m, 13H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 159.9, 159.5, 158.9, 158.5, 155.8, 145.4, 139.9, 139.7, 130.1, 128.8, 126.7, 117.7, 53.1, 52.2, 43.8, 39.0, 27.2, 25.4; ESIMS: *m/z* 1121.4 $[M+Na]^+$, 1099.4 $[M+H]^+$, 999.3 $[M+H\text{-}Boc]^+$.

1.3.4 Synthesis of oligourea (4) with shifted methyl side chain ($C_\beta \rightarrow C_\alpha$)



Triurea azide (37): Compound **30** (1.2 g, 2.48 mmol) was treated with TFA (12 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (15 mL) was added DIPEA (1.3 mL, 7.5 mmol), and after 10 minutes reaction mixture was further treated with ***ent*-10** (0.63 g, 2.6 mmol) and stirring was maintained overnight. After completion of the reaction more than half of CH_3CN was evaporated under reduced pressure and diluted with saturated $NaHCO_3$ solution then a precipitate was formed and filtered through the cindered funnel and the residue was washed with saturated $NaHCO_3$ solution, with aqueous 1N $KHSO_4$ solution and dried over Na_2SO_4. To remove the non-polar impurities the residue was washed with *n*-pentane and Et_2O to afford **37** (1.02 g, 81%) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.30−7.16 (m, 10H), 5.99−5.59 (m, 6NH), 3.63 (m, 3H), 3.25 (bs, 2H), 3.12 (bs, 2H), 3.03−2.95 (m, 2H), 2.75 (bs, 2H), 2.42 – 2.25 (m, 7H), 0.91 (d, J = 6.7

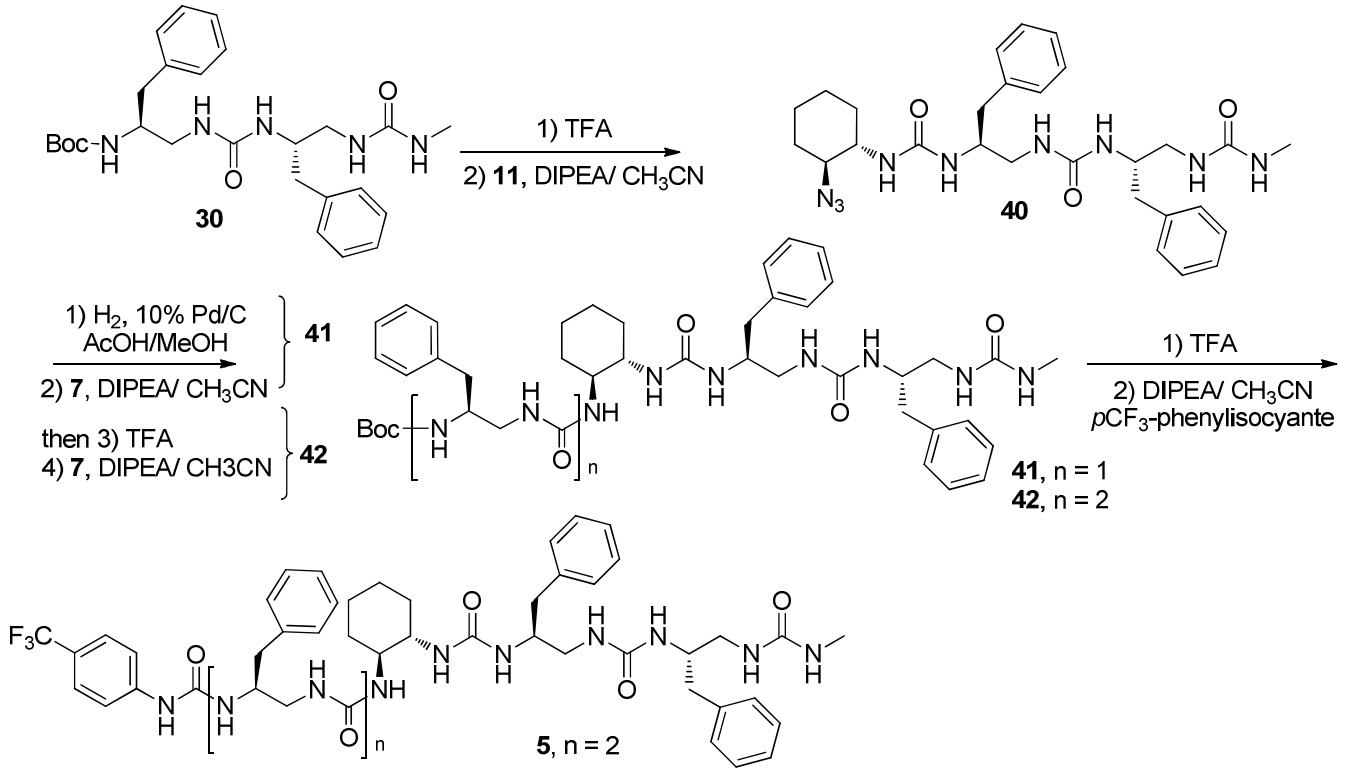
Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 159.7, 158.7, 158.1, 139.8, 139.6, 130.0, 128.9, 126.8, 56.5, 52.3, 52.0, 45.7, 44.1, 43.8, 39.3, 27.3, 19.1; ESIMS: *m/z* 532.1 $[M+Na]^+$, 510.0 $[M+H]^+$, 410.1 $[M+H\text{-Boc}]^+$.

Tetraurea (38): Compound **37** (0.89 g, 1.75 mmol) was first dissolved in 10% DMF in MeOH and hydrogenated for overnight in the presence of 10% Pd/C as a catalyst at room temperature under the H_2 atmosphere. The catalyst was removed by Millipore filtration and concentrated to give corresponding free amine (0.84 g, 99.4%) as syrup and free amine was directly used for the next step without purification. To a stirred solution of corresponding free amine (0.84 g, 1.74 mmol) in CH_3CN (10 mL) were added DIPEA (0.6 mL, 3.5 mmol) and **7** (0.715 g, 1.83 mmol) and stirring was maintained overnight. Workup as described for **35** gave **38** (0.9 g, 68 %) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.31−7.12 (m, 15H), 6.80 (d, *J* = 8.0 Hz, 1NH), 6.12 (m, 3NH), 6.03 (m, 2NH), 5.92 (d, 1NH), 5.88 (d, 1NH), 5.76 (d, 1NH), 6.64 (d, 1NH), 3.79 (m, 2H), 3.63−3.55 (m, 2H), 3.29−3.13 (m, 3H), 2.89−2.57 (m, 9H), 2.55 (d, 4H), 1.321 (s, 9H), 0.91 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 159.7, 159.3, 158.8, 158.5, 156.1, 139.8, 130.0, 128.9, 126.7, 78.3, 53.5, 52.4, 46.7, 45.9, 44.2, 44.0, 39.3, 38.8, 29.2, 27.2, 19.7; ESIMS: *m/z* 782.2 $[M+Na]^+$, 760.0 $[M+H]^+$, 660.1 $[M+H\text{-Boc}]^+$.

Pentaurea (39): Compound **38** (0.42 g, 0.55 mmol) was treated with TFA (4 mL) at 0° C for 30 min. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (6 mL) was added DIPEA (0.28 mL, 1.66 mmol), and after 10 minutes **7** (0.227 g, 0.58 mmol) was further added stirring was maintained overnight. Workup as described for **36** afforded **39** (0.43 g, 83%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.29−7.13 (m, 20H), 6.7 (d, *J* = 8.0 Hz, 1NH), 6.08−5.79 (m, 10NH), 3.79−3.67 (m, 3H), 3.63−3.46 (m, 2H), 3.18−3.01 (m, 5H), 2.97−2.81 (m, 5H), 2.72−2.54 (m, 11 H), 1.31 (s, 9H), 0.94 (d, *J* = 6.3 Hz, 3H); 13C NMR (100 MHz, DMSO−d6) δ ppm 159.9, 159.4, 158.8, 158.5, 156.2, 139.8, 130.0, 128.9, 126.8, 78.5, 53.4, 52.3, 46.7, 45.8, 44.4, 43.7, 28.9, 27.4, 19.7; ESIMS: *m/z* 958.3 $[M+Na]^+$, 936.2 $[M+H]^+$, 836.1 $[M+H\text{-Boc}]^+$.

Trifluoromethylphenylpentaurea (4): Compound **39** (0.12 g, 0.128 mmol) was treated with TFA (1.2 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (2 mL) were successively added DIPEA (0.043 mL, 0.256 mmol), and after 10 minutes 4-trifluoromethyphenylisocyanate (0.019 mL, 0.134 mmol) and stirring was maintained overnight. Workup as described for **3** furnished **4** (0.122 g, 93%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.68 (br.s, 1NH), 7.39−7.09 (m, 24H), 6.16−5.8 (m, 11NH), 3.93−3.65 (m, 5H), 3.61−3.45 (m, 2H), 3.20−3.06 (m, 4H), 3.00−2.90 (m, 4H), 2.78−2.64 (m, 13H), 0.94 (brs, 3H); 13C NMR (100 MHz, DMSO−d_6) δ ppm 159.9, 159.4, 158.8, 158.4, 155.6, 140.7, 139.8, 139.5, 132.1, 130.0, 129.0, 126.7, 120.3, 113.0, 52.3, 46.9, 45.9, 44.3, 43.9, 27.2, 19.6; ESIMS: *m/z* 1057.2 $[M+Na]^+$, 1033.0 $[M+H]^+$.

1.3.5 Synthesis of oligourea (5) with a trans-1,2-diaminocyclohexane unit



Triurea azide (40): Compound **30** (1.05 g, 2.17 mmol) was treated with TFA (10 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (10 mL) were added DIPEA (1.106 mL, 6.51 mmol), and after 10 minutes **11** (0.798 g, 2.28 mmol) and stirring was maintained for 2 hours. Workup, as described for **37,** afforded **40** (1.1 g, 92%) as a white solid.

HPLC t_R = 9.407 min (linear gradient, 30-100% B, 20 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.32−7.15 (m, 10H), 6.08 (d, J = 8.5 Hz, 1NH), 6.00−5.82 (m, 4NH), 5.76 (d, J = 8.2 Hz, 1NH), 3.81−3.67 (m, 2H), 3.25−3.13 (m, 2H), 3.12−2.98 (m, 2H), 2.91−2.79 (m, 2H), 2.7−2.56 (m, 7H), 1.97−1.69 (m, 2H), 1.64−1.53 (m, 2H), 1.29−1.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 159.4, 158.5, 157.7, 139.4, 139.2, 129.7, 128.6, 126.3, 64.3, 52.5, 51.9, 51.6, 43.8, 32.7, 30.8, 26.9, 24.3, 23.9; ESIMS: *m/z* 572.4 $[M+Na]^+$, 550.3 $[M+H]^+$.

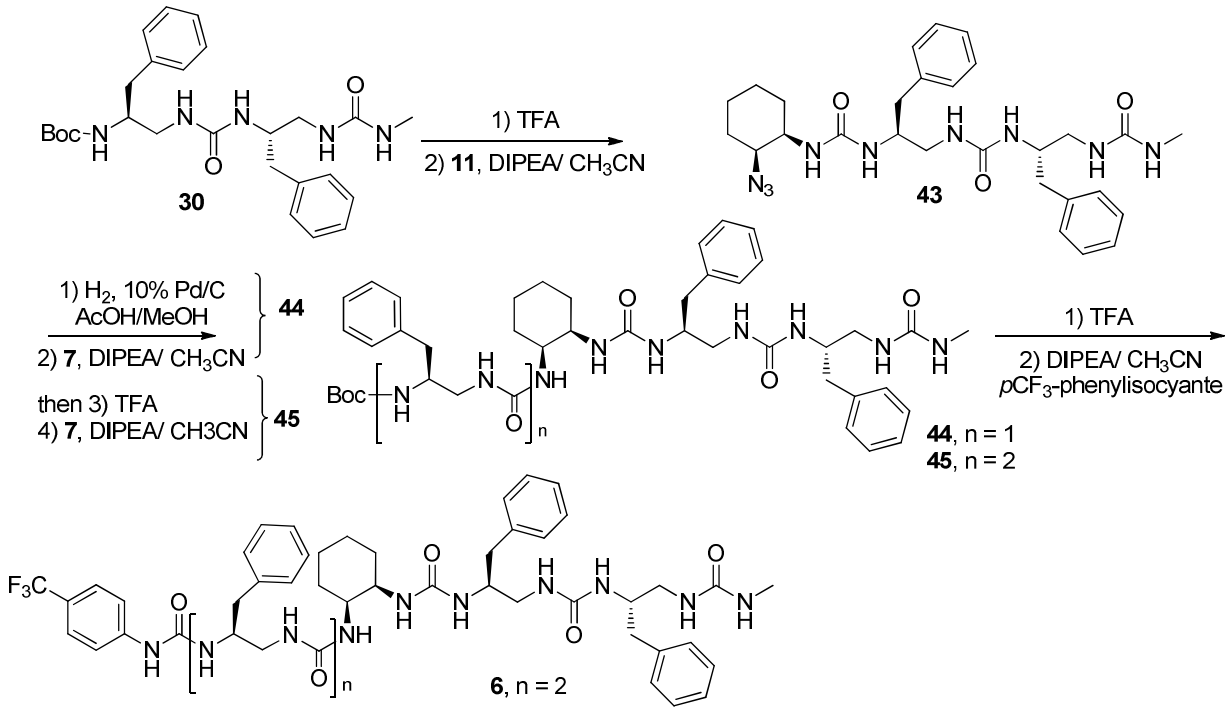
Tetraurea (41): Compound **40** (1.0 g, 1.82 mmol) was dissolved in 20% AcOH in MeOH and hydrogenated for 2 hours in the presence of 10% Pd/C as a catalyst at room temperature under the H_2 atmosphere. The catalyst was removed by filtration over celite and concentrated to afford corresponding free amine (0.9 g, 94%) as a syrup that was used as such for the next step without purification. To a stirred solution of free amine (0.9 g, 1.72 mmol) in CH_3CN (15 mL) were added **7** (0.706 g, 1.80 mmol) and DIPEA (0.58 mL, 3.44 mmol) and stirring was maintained for 3hours. Workup as described for **40** and purification by silica gel column chromatography (2.5 % MeOH in $CHCl_3$) gave **41** (0.65 g, 47 %) as a white solid. HPLC t_R = 11.876 min (linear gradient, 30−100% B, 20 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.33−7.07 (m, 15H), 6.68 (d, J = 8.4 Hz, 1NH), 6.02−5.84 (m, 8NH), 3.80−3.68 (m, 2H), 3.62−3.5 (m, 1H), 3.27−3.19 (m, 2H), 3.18−2.8 (m, 6H), 2.88−2.53 (m, 9H), 1.92−1.8 (m, 2H), 1.62−1.54 (m, 2H), 1.3 (s, 9H), 1.25−1.12 (m, 4H); ^{13}C NMR (100 MHz, DMSO−d_6) δ ppm 160.1, 158.2, 156.3, 155.1, 139.7, 130.8, 128.9, 126.7, 110.1, 78.4, 53.7, 51.8, 44.3, 43.6, 29.0, 27.2, 25.1; ESIMS: *m/z* 823.5 $[M+Na]^+$, 801.4 $[M+H]^+$, 701.5 $[M+H\text{-Boc}]^+$.

Pentaurea (42): Compound **41** (0.5 g, 0.625 mmol) was treated with TFA (5 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (10 mL) were added DIPEA (0.34 mL, 1.87 mmol), and after 10 minutes **7** (0.26 g, 0.656 mmol) and stirring was maintained for 2 hours. Workup as described for **41** and purification by silica gel column chromatography (8.0 % MeOH in $CHCl_3$) gave **42** (0.3 g, 49%) as white solid. HPLC t_R = 14.684 min (linear gradient, 30-100% B, 20 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.28−7.13 (m, 20H), 6.71 (d, J = 8.3 Hz, 1NH), 6.03−5.97 (m, 2NH), 5.96−5.84 (m, 8NH), 3.80−3.67 (m, 3H), 3.62−3.53 (m, 1H), 3.21−3.12 (m, 2H), 3.1−2.76 (m, 8H), 2.71−2.57 (m, 8H), 2.54 (brs, 3H), 1.90−1.79 (m, 2H), 1.63−1.51

(m, 2H), 1.31 (s, 9H), 1.21−1.08 (m, 4H); ESIMS: *m/z* 999.7 $[M+Na]^+$, 977.6 $[M+H]^+$, 877.7 [M+H-Boc]$^+$.

Trifluorophenyl pentaurea (5): Compound **42** (0.11 g, 0.113 mmol) was treated with TFA (1.5 mL) at 0° C for 30 minutes. Concentration under reduced pressure and co-evaporation with cyclohexane left a residue which was dried under high vacuum. To the resulted stirred solution of TFA salt in CH_3CN (2 mL) were successively added DIPEA (38 μL, 0.226 mmol), and after 10 minutes trifluorophenylisocyanate (17 μL, 0.12 mmol) and stirring was maintained for 4 hours. Workup as described for **4** and purification by silica gel column chromatography eluted with $CHCl_3$/MeOH/AcOH (120:8:5, v/v/v) gave **5** (0.086 g, 72 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.21 (br.s, 1NH), 7.63−7.48 (m, 4H), 7.28−7.10 (m, 20H), 6.31−5.89 (m, 11NH), 3.85−3.68 (m, 4H), 3.35−3.24 (m, 2H), 3.18−2.98 (m, 8H), 2.72−2.53 (m, 11H), 1.82−1.76 (m, 2H), 1.58−1.5 (m, 2H), 1.25−1.12 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 177.0, 159.8, 159.4, 158.8, 145.9, 139.8, 128.9, 126.8, 126.4, 117.7, 52.4, 51.7, 43.8, 27.1, 25.6. 25.1; ESIMS: *m/z* 1085.4 $[M+Na]^+$, 1063.2 $[M+H]^+$ 559.7.

*1.3.6 Synthesis of oligourea (**6**) with a cis-1,2-diaminocyclohexane unit*



Triurea azide (43): Same procedure to that of **40** afforded **43** (1.01 g, 89%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.34−7.13 (m, 10H), 6.03−5.81 (m, 6NH), 3.86−3.8 (m, 1H), 3.78−3.69

(m, 2H), 3.66−3.57 (m, 1H), 3.19−2.98 (m, 2H), 2.94−2.81 (m, 2H), 2.76−2.55 (m, 7H), 1.84−1.71 (m, 1H), 1.64−1.49 (m, 2H), 1.43−1.26 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 159.4, 158.5, 157.7, 139.4, 139.2, 129.7, 128.6, 126.3, 64.3, 52.5, 51.9, 51.6, 43.8, 32.7, 30.8, 26.9, 24.3, 23.9; ESIMS: *m/z* 572.4 $[M+Na]^+$, 550.3 $[M+H]^+$.

Tetraurea (44): Same procedure to that of **41** and afforded **44** (0.42 g, 79%) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.3−7.14 (m, 15H), 7.13−7.07 (m, 2NH), 7.05−6.96 (m, 1NH), 6.31−6.17 (m, 2NH), 6.14−6.07 (m, 1NH), 5.9 (d, J = 8.3 Hz, 1NH), 5.84−5.8 (m, 1NH), 5.76 (d, J = 9.4 Hz, 1NH), 3.95−3.62 (m, 5H), 3.53−3.35 (m, 6H), 2.76−2.58 (m, 6H), 2.56 (d, J = 4.2 Hz, 3H), 2.35−2.24 (m, 2H), 1.6−1.49 (m, 1H), 1.41−1.16 (m, 14H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 160.1, 158.2, 156.3, 155.1, 139.7, 130.8, 128.9, 126.7, 110.1, 78.4, 53.7, 51.8, 44.3, 43.6, 29.0, 27.2, 25.1; ESIMS: *m/z* 823.5 $[M+Na]^+$, 801.4 $[M+H]^+$, 701.5 $[M+H\text{-Boc}]^+$.

Pentaurea (45): Same procedure to that of **42** afforded **45** (0.36 g, 90%) as a white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.30−7.10 (m, 20H), 6.87 (d, J = 8.6 Hz, 1NH), 6.21−6.03 (m, 6NH), 5.99−5.81 (m, 4NH), 3.98−3.65 (m, 6H), 3.57−3.35 (m, 8H), 3.17−3.08 (m, 1H), 2.90−2.80 (m, 1H), 2.76−2.58 (m, 6H), 2.57 (d, J = 4.6 Hz, 3H), 2.31−2.10 (m, 2H), 1.44−1.28 (m, 12H), 1.27−1.23 (m, 1H), 1.21−1.12 (m, 1H); ESIMS: *m/z* 999.7 $[M+Na]^+$, 977.6 $[M+H]^+$, 877.7 $[M+H\text{-Boc}]^+$.

Trifluorophenyl pentaurea (6): Same procedure to that of **5** afforded **6** (0.16 g, 92%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.05 (brs, 1NH), 7.56 (s, 4H), 7.31-7.13 (m, 20H), 6.31 (d, J = 8.3 Hz, 1NH), 6.27-6.16 (m, 4NH), 6.15-6.1 (m, 1NH), 6.09-5.93 (m, 4NH), 5.92-5.88 (m, 1NH), 4.01-3.71 (m, 6H), 3.57-3.35 (m, 8H), 3.28-3.17 (m, 1H), 2.97-2.86 (m, 1H), 2.76-2.61 (m, 6H), 2.57 (d, J = 4.6 Hz, 3H), 2.36 (m, 1H), 1.43-1.17 (m, 7H); ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm 177.0, 159.8, 159.4, 158.8, 145.9, 139.8, 128.9, 126.8, 126.4, 117.7, 52.4, 51.7, 43.8, 27.1, 25.6. 25.1; ESIMS: *m/z* 1085.4 $[M+Na]^+$, 1063.2 $[M+H]^+$ 559.7.

1.4 ^{1}H NMR chemical shift tables of oligoureas 1-6

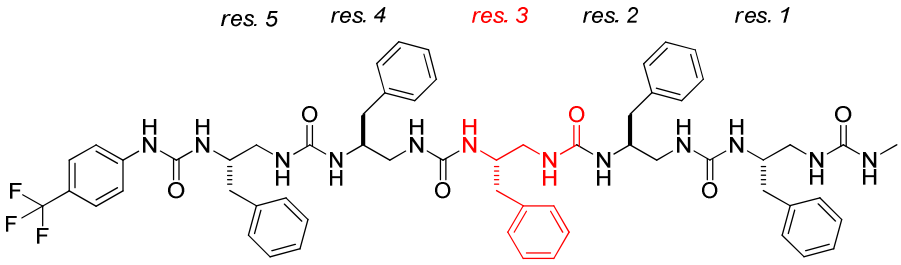


Table S1. ^{1}H-NMR Chemical Shifts (ppm) of **1** in CD_3OH at 293K

Residue	HN	N'H	$^{\alpha}CH^{1}$	$^{\alpha}CH^{2}$	$^{\beta}CH$	$^{\gamma}CH$	CH_3	$\Delta\delta$ ($^{\alpha}CH$)
NHMe	6.14						2.70	
1	6.13	6.28	3.59	2.71	3.99			0.88
2	5.95	6.29	3.52,	2.21	4.10			1.31
3	5.92	6.33	3.53	2.29	4.00			1.24
4	5.85	5.99	3.49,	2.31	3.90			1.18
5	6.18	6.16	3.54	2.66	4.13			0.88

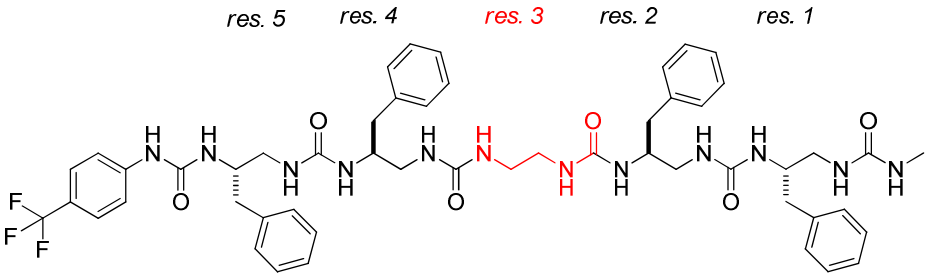


Table S2. ^{1}H-NMR Chemical Shifts (ppm) of **2** in CD_3OH at 293K

Residue	HN	N'H	$^{\alpha}CH^{1}$	$^{\alpha}CH^{2}$	$^{\beta}CH^{1}$	$^{\beta}CH^{2}$	$^{\gamma}CH$	CH_3	$\Delta\delta$ ($^{\alpha}CH$)
NHMe	6.02							2.70	
1	6.19	6.03	3.54	2.74	4.06				0.80
2	5.99	6.24	3.54	2.45	4.09		2.54		1.09
3	6.04	6.22	3.42	2.63	3.52	2.82			0.79
4	5.95	6.20	3.56	2.57	4.01				0.99
5	6.24	6.17	3.47	2.79	4.14		2.51		0.68

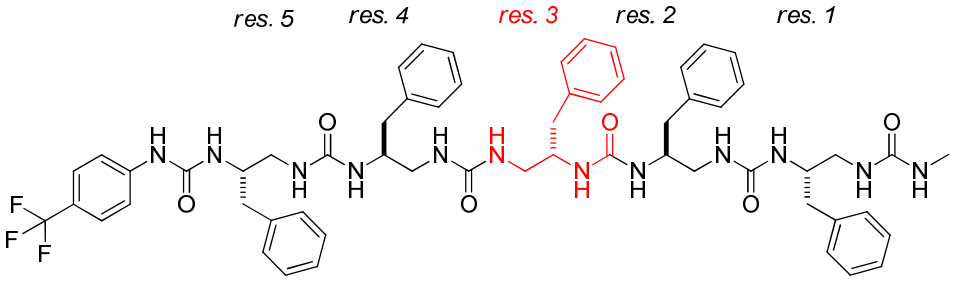


Table S3. ^{1}H-NMR Chemical Shifts (ppm) of **3** in CD_3OH at 292 K

Residue	NH	N'H	$^{\alpha}CH^{1}$	$^{\alpha}CH^{2}$	$^{\beta}CH$	$^{\gamma}CH$	CH_3	$\Delta\delta$ ($^{\alpha}CH$)
NH Term	5.99						2.61	
1	6.17	5.97	3.15	3.06	3.70	2.73, 2.67		0.09
2	6.17	5.93	3.11	2.91	3.84	2.69, 2.56		0.20
3	6.17	6.01	3.25	3.01	3.95	2.77, 2.64		0.24
4	6.26	6.01	3.29	2.96	3.98	2.74, 2.64		0.33
5	6.18	6.18	3.2	3.04	4.02	2.75, 2.66		0.16

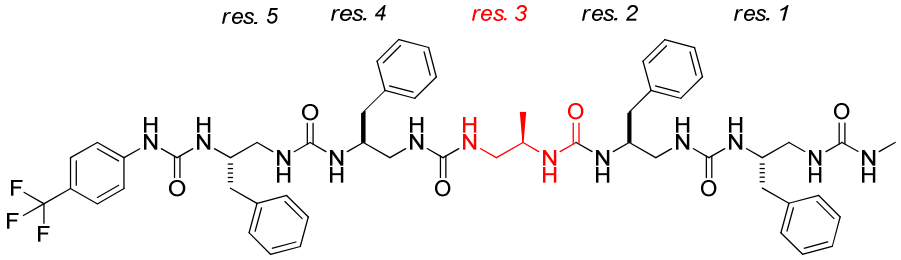


Table S4. ^{1}H-NMR Chemical Shifts (ppm) of **4** in CD_3OH at 293 K

Residue	NH	N'H	$^{\alpha}CH^{1}$	$^{\alpha}CH^{2}$	$^{\beta}CH$	$^{\gamma}CH$	CH_3	$\Delta\delta$ ($^{\alpha}CH$)
NH Term	6.05						2.69	
1	6.16	6.28	3.54	2.75	4.02	2.82, 2.76		0.79
2	5.98	6.30	3.61	2.62	4.05	2.68		0.99
3	5.88	6.28	3.67	2.56	3.81	1.10		1.11
4	6.04	6.27	3.61	2.59	3.96	2.72, 2.58		1.02
5	6.19	6.19	2.78	3.48	4.14	2.91, 2.89		0.70

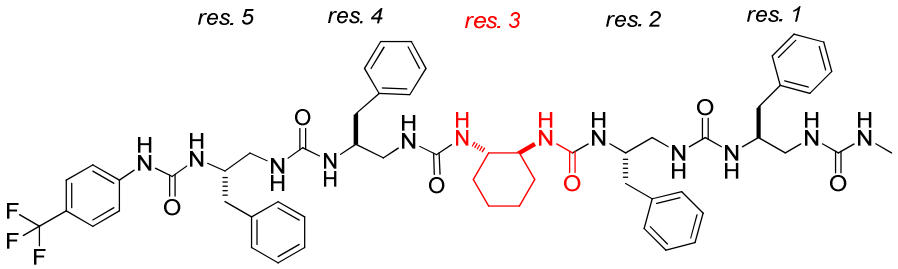


Table S5. ^{1}H-NMR Chemical Shifts (ppm) of **5** in CD_3OH at 303K (400 MHz)

Residue[a]	HN	H'N	$^{\alpha}CH^{1}$	$^{\alpha}CH^{2}$	$^{\beta}CH$	$^{\gamma}CH$	CH_3	$\Delta\delta$ ($^{\alpha}CH$)
NHMe	5.97						2.67	
-[a]	6.14	5.98	3.31	3.08	4.06	2.73		0.23
-[a]	6.03	6.15	3.32	2.99	3.95	2.69		0.33
3	5.94	5.95		3.07[b]	3.44[b]	1.84, 1.63, 1.21, 1.11		
-[a]	5.94	6.03	3.25	2.86	3.92	2.60		0.39
-[a]	6.04	6.18	3.35	2.98	3.97	2.76		0.39

[a)] Due to signal overlapping in the NH region, the total assignation of the sequence was rendered impossible. [b)]the exact assignation of these two protons was not possible..

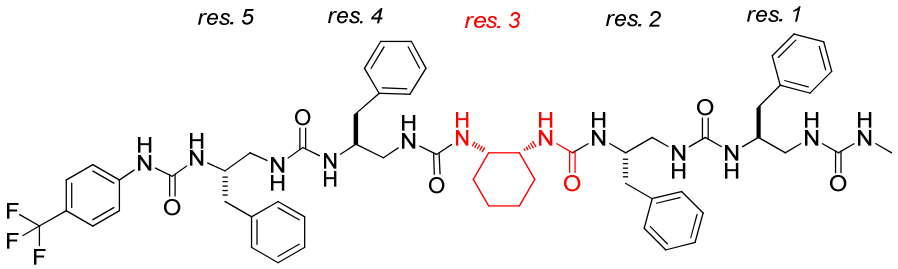


Table S6. ^{1}H-NMR Chemical Shifts (ppm) of **6** in CD_3OH at 293 K

Residue	HN	H'N	$^{\alpha}CH^{1}$	$^{\alpha}CH^{2}$	$^{\beta}CH$	$^{\gamma}CH$	CH_3	$\Delta\delta$ ($^{\alpha}CH$)
NHMe	6.07						2.70	
1	6.25	6.36	3.59	2.70	4.06	2.73		0.89
2	6.14	6.30	3.56	2.73	4.13	2.51, 2.46		0.93
3	6.25	5.94		3.60	4.03	1.46, 1.22		0.43
4	5.95	6.21	3.68	2.43	3.94	2.56, 2.44		1.25
5	6.01	6.30	3.55	2.72	4.06	2.53, 2.56		0.83

1.5 *1D* and *2D* ^{1}H-NMR spectra of oligoureas 1-6.

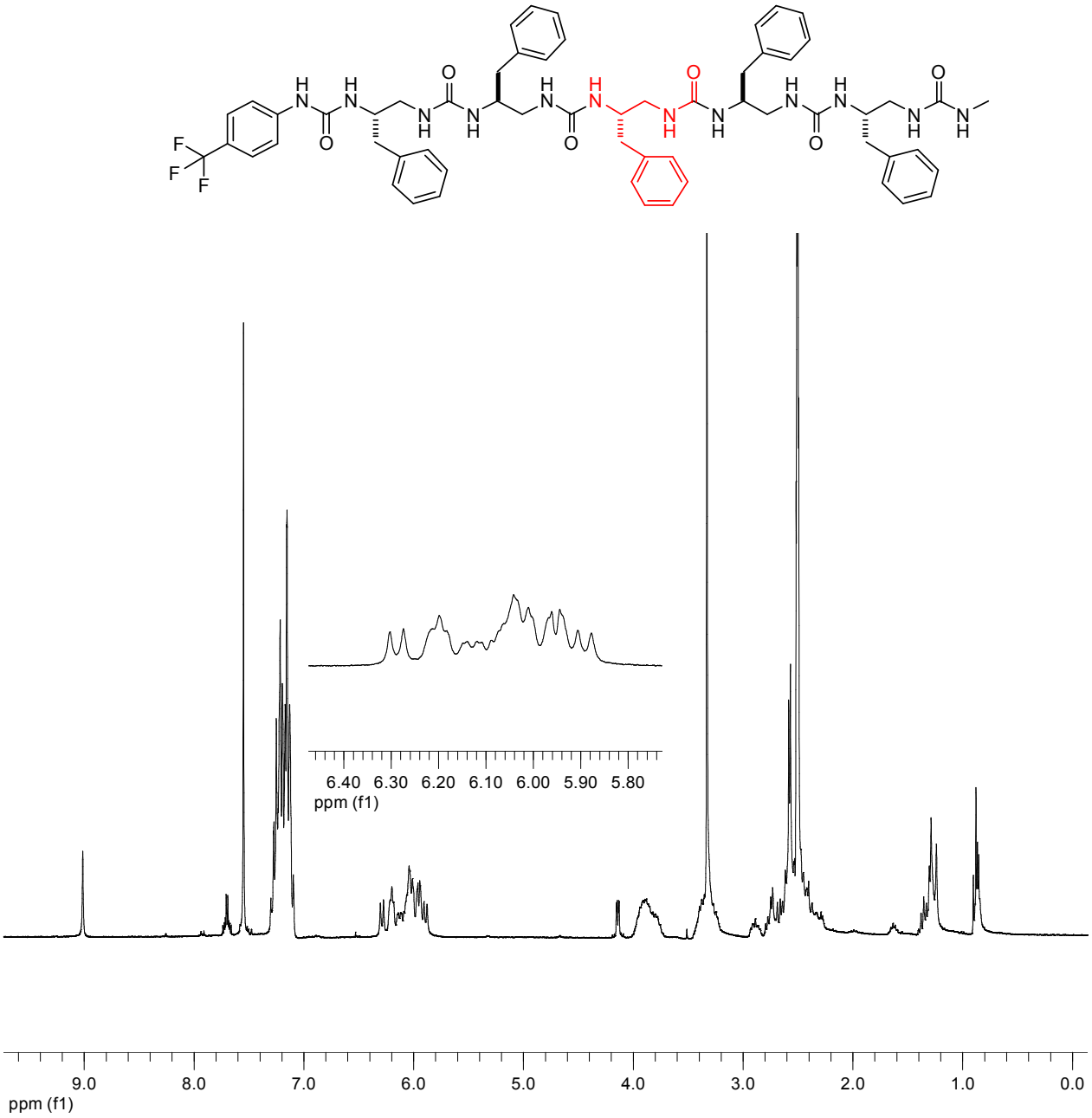


Figure S11. ^{1}H-NMR spectrum of model oligourea **1** recorded in DMSO-d_6 (300 MHz)

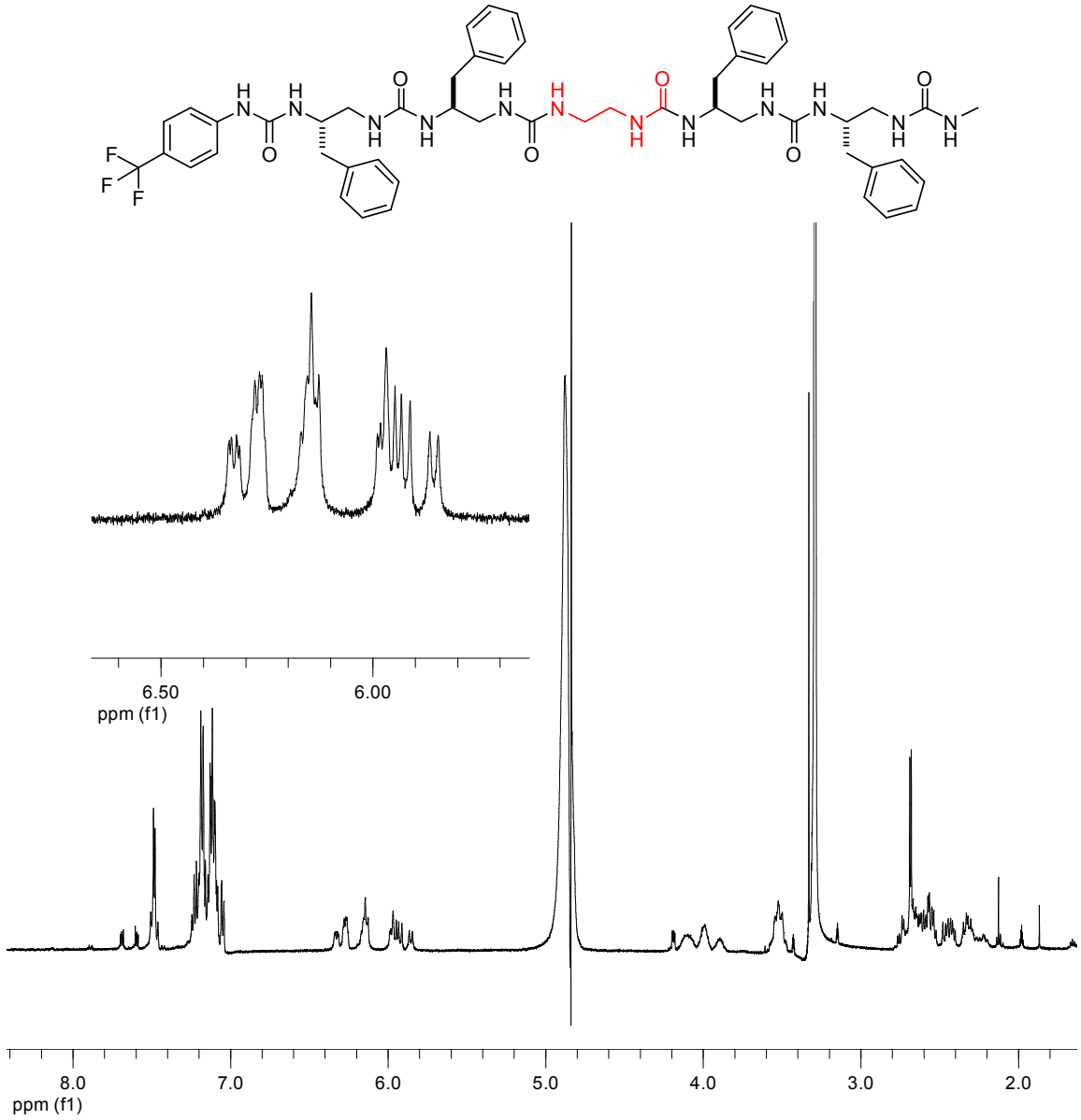


Figure S12. ^{1}H-NMR spectrum of oligourea **2** recorded in CD_3OH (500 MHz)

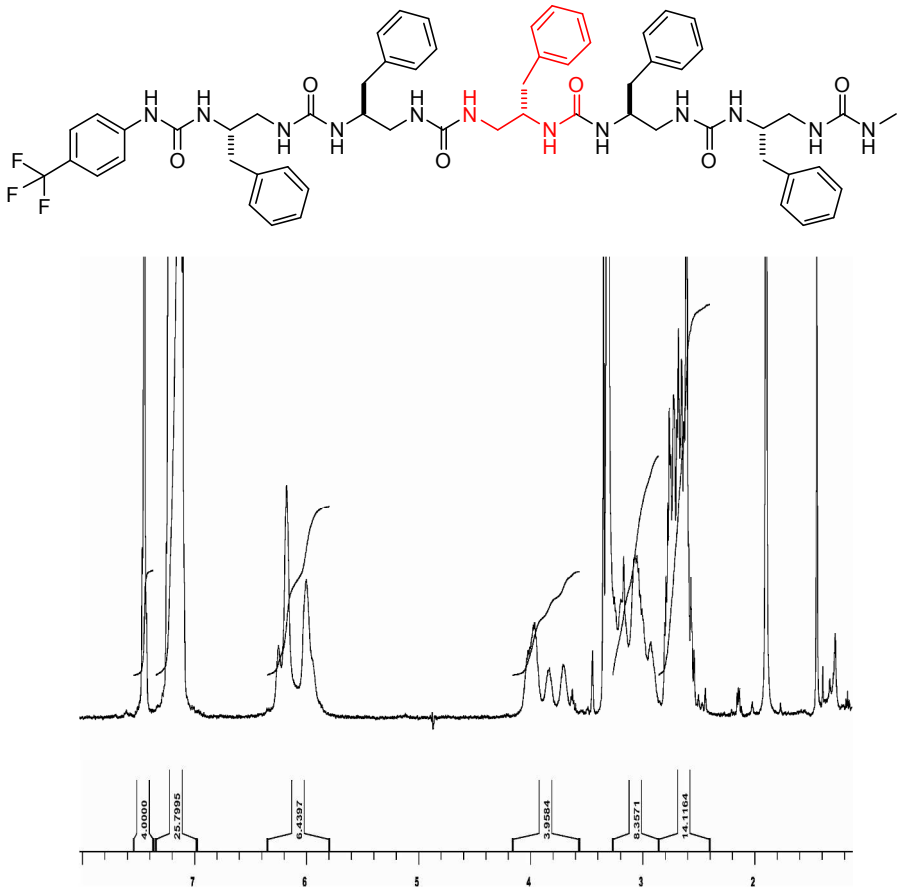


Figure S13. ^{1}H-NMR spectrum of oligourea **3** recorded in CD_3OH (500 MHz)

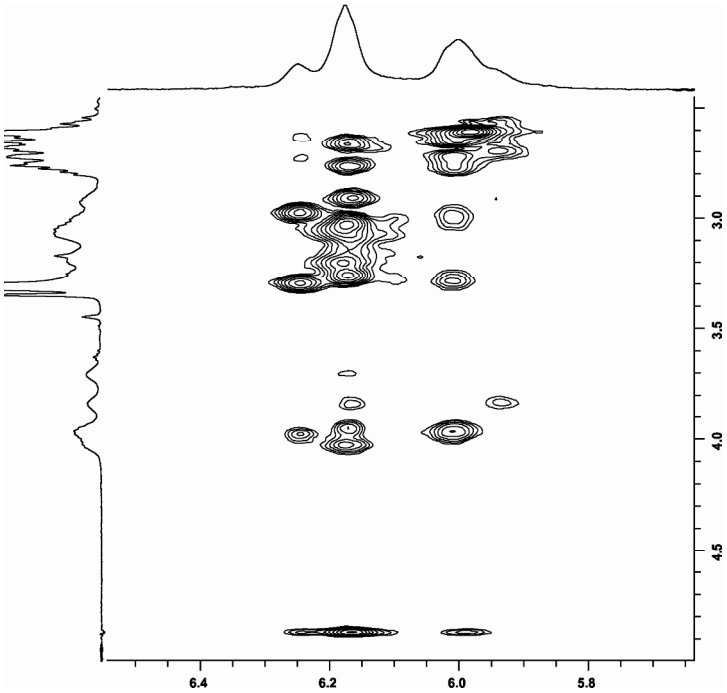


Figure S14. 2D Fingerprint NH/CH, N'H/CH of the TOCSY experiment of oligourea **3**, recorded in CD_3OH (400 MHz).

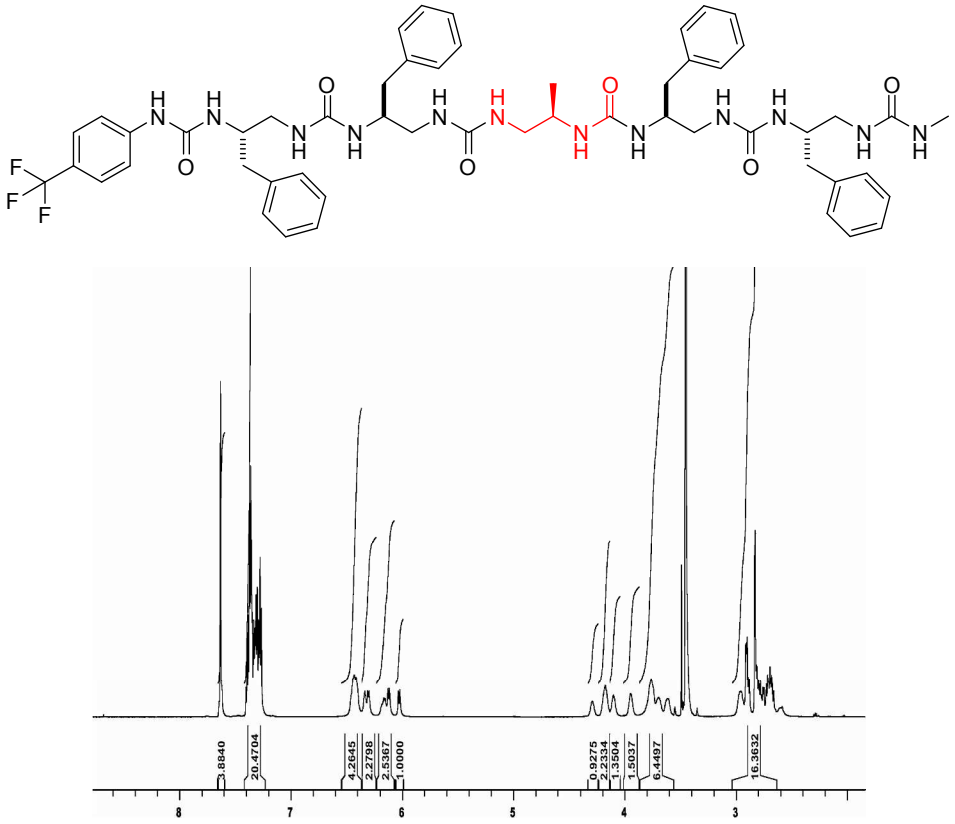


Figure S15. ^{1}H-NMR spectrum of oligourea **4** recorded in CD_3OH (500 MHz)

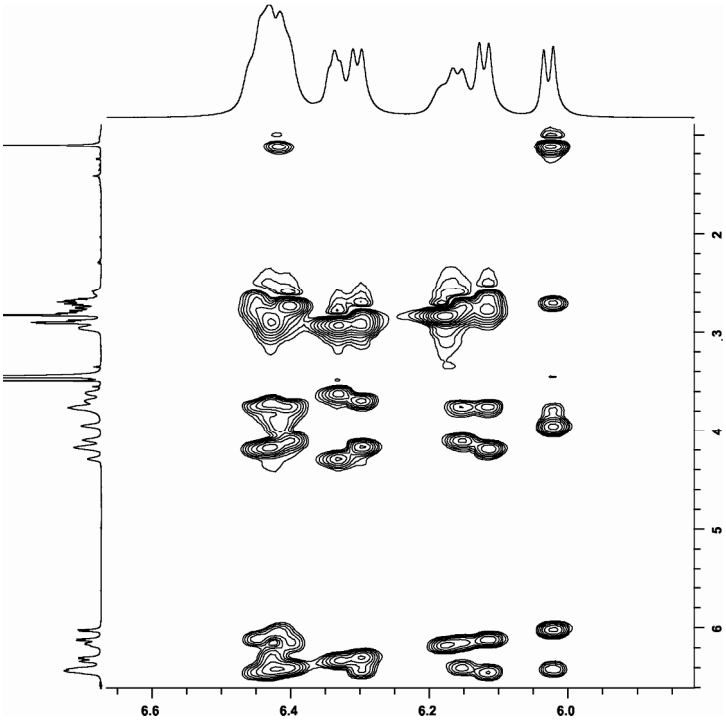


Figure S16. 2D Fingerprint NH/CH, N'H/CH of the TOCSY experiment of oligourea **4**, recorded in CD_3OH (400 MHz).

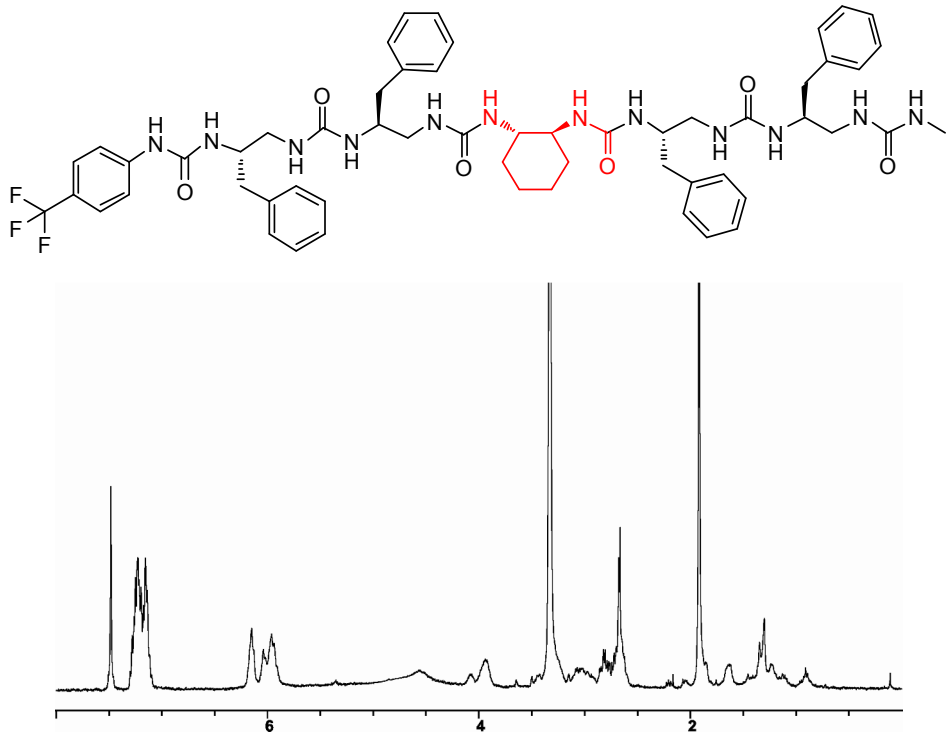


Figure S17. ^{1}H-NMR spectrum of oligoureas **5** recorded in CD_3OH (400 MHz)

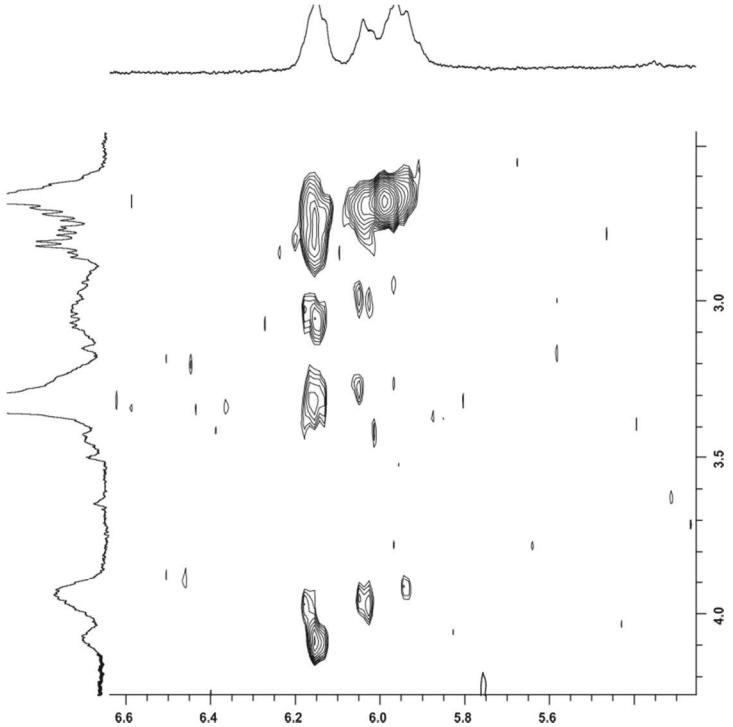


Figure S18. ^{1}H 2D Fingerprint NH/CH, N'H/CH of the TOCSY experiment of oligourea **5**, recorded in CD_3OH (400 MHz).

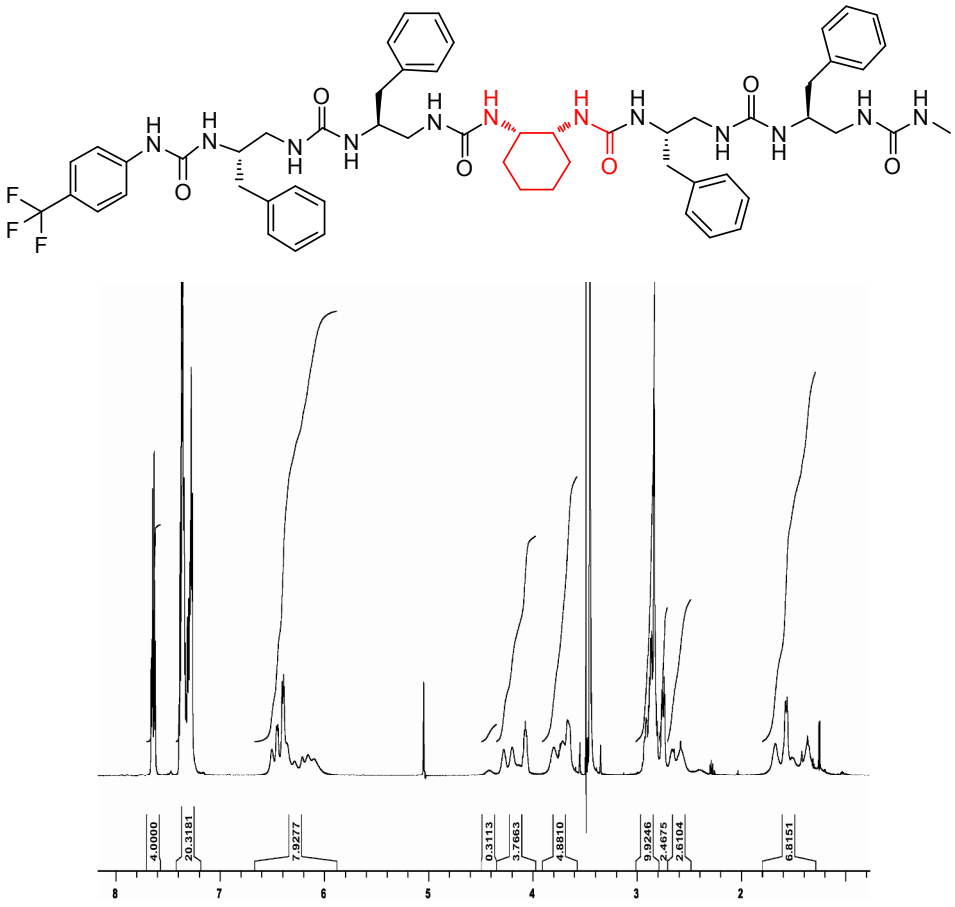


Figure S19. ^{1}H-NMR spectrum of oligoureas **6** recorded in CD_3OH (500 MHz)

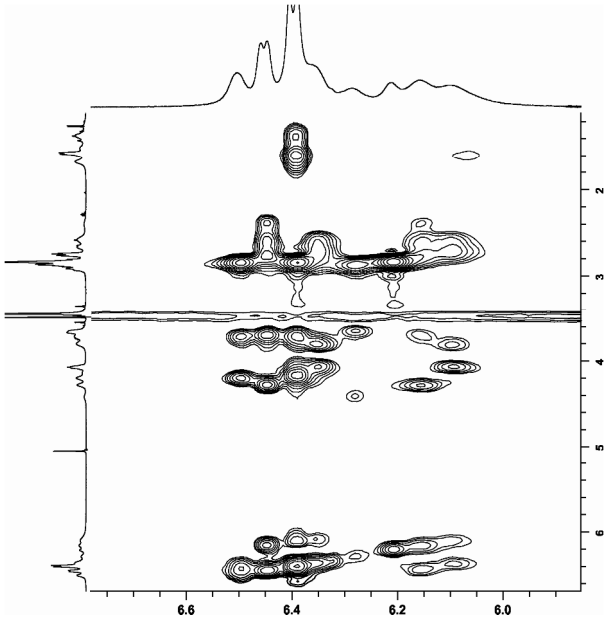


Figure S20. 2D Fingerprint NH/CH, N'H/CH of the TOCSY experiment of oligourea **6**, recorded in CD_3OH (700 MHz).

1.6 Cross-section of the TOCSY and ROESY (τm = 300 ms) spectra of oligourea 1, 2, 4 and 6.

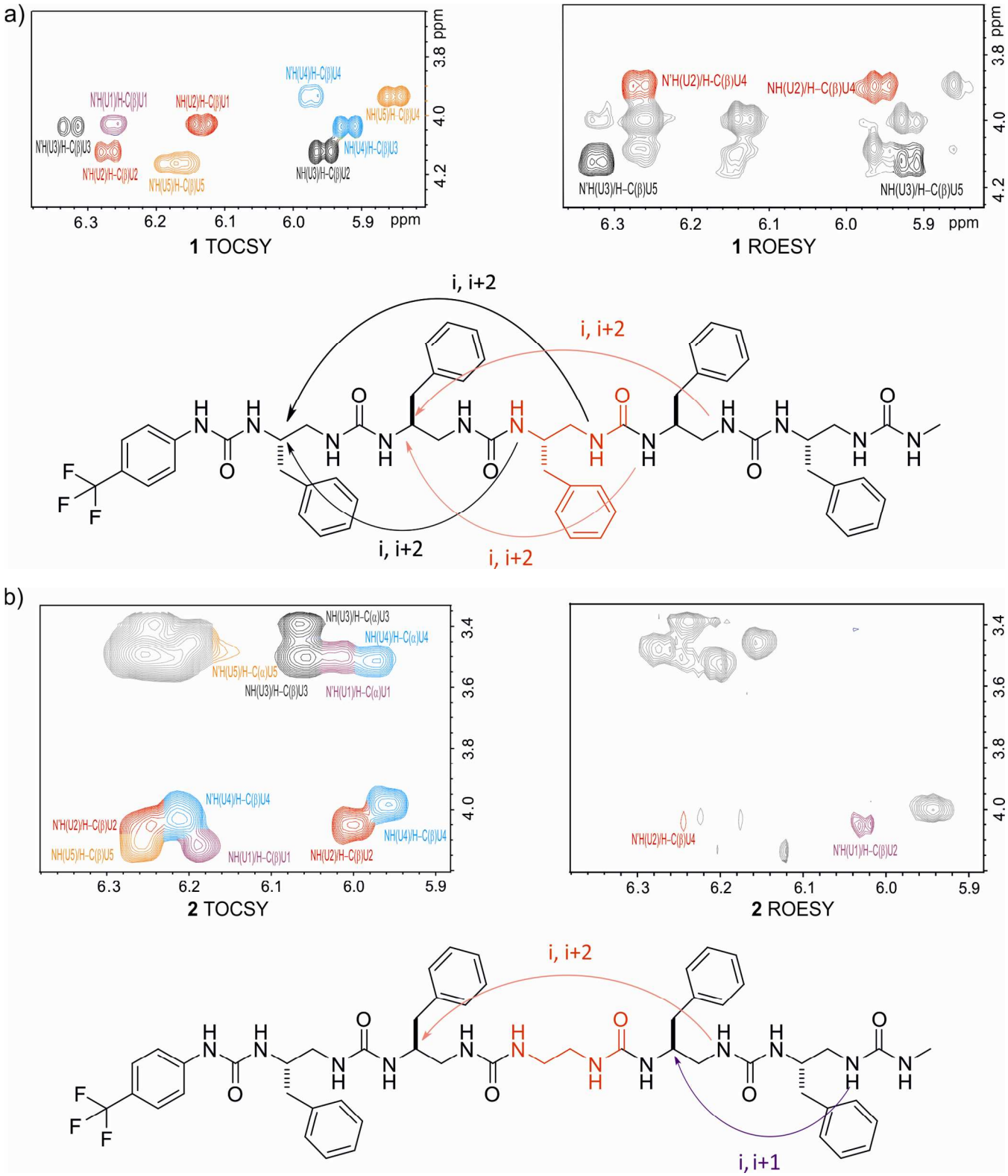
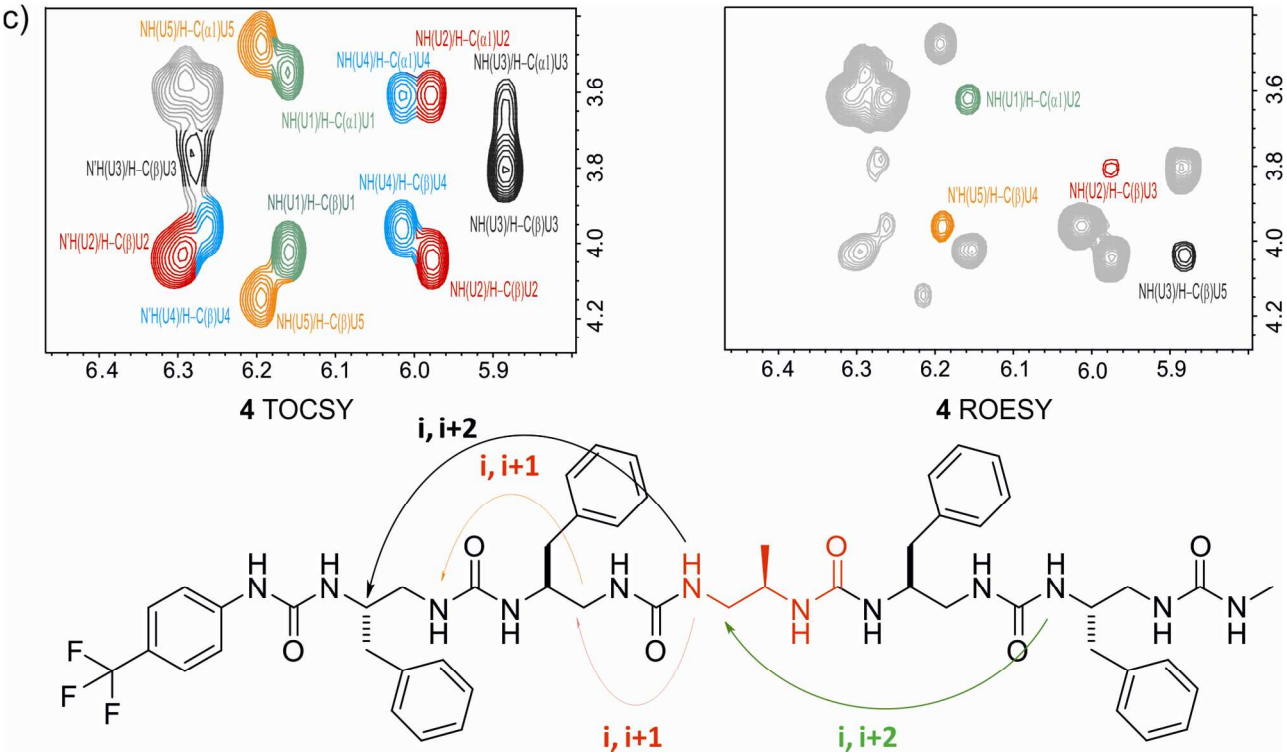


Figure S21. Selected cross-section of the TOCSY and ROESY spectra with representative interesidue nOes observed. a) oligourea **1**, b) oligourea **2**, c) oligourea **4**, and d) oligoure **6**. Spectra recorded at 298K CD_3OH at 1 mM (500 and 700 MHz) with a mixing time of 300ms for ROESY experiments.



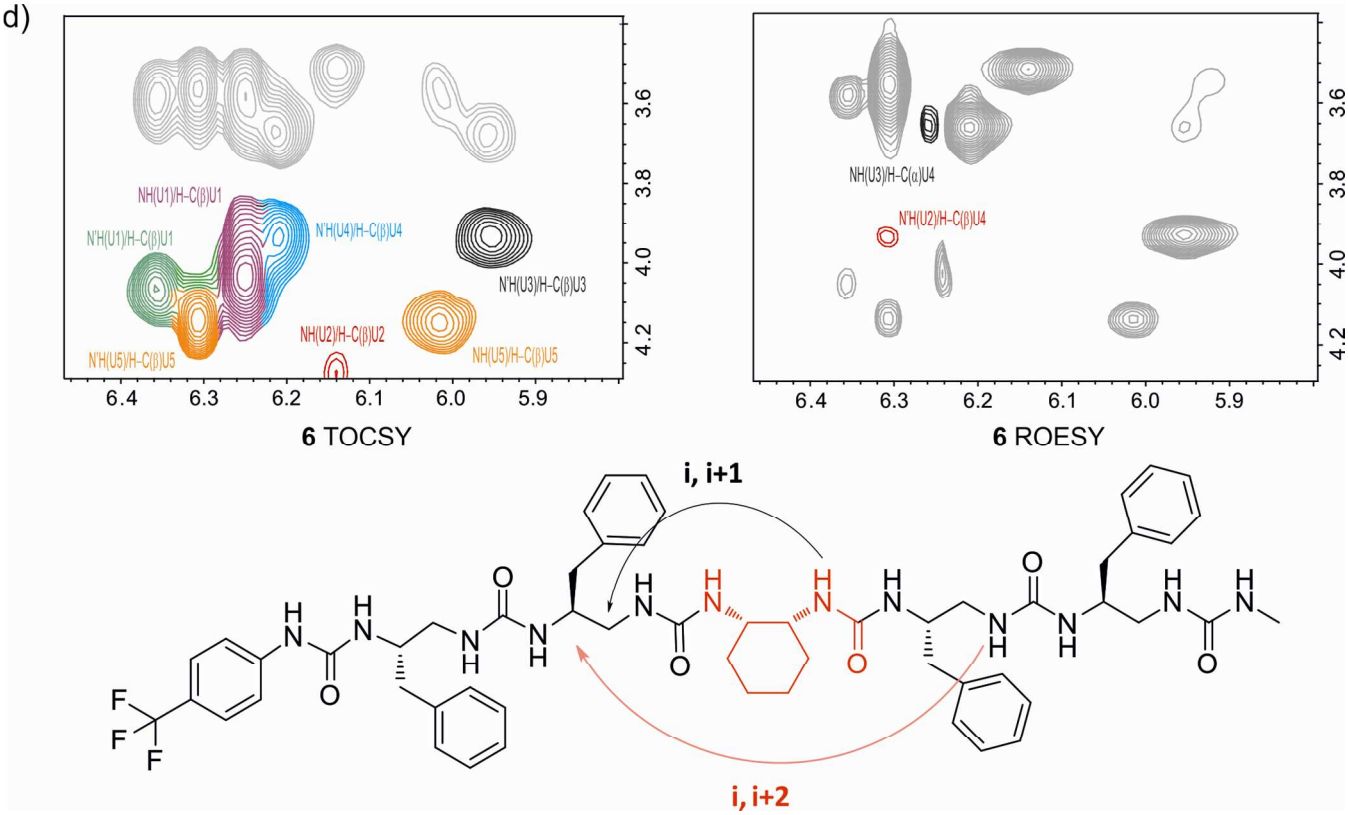


Figure S21 (continued). Selected Cross-section of the TOCSY and ROESY spectra.

1.7 Kinetic studies of urea NH H/D exchange rates.

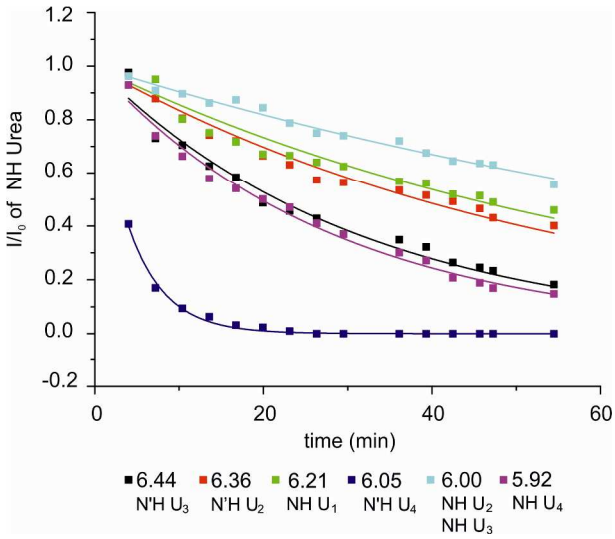


Figure S22. Exchange curves for oligourea **1** at 15°C. The NMR spectra were recorded in CD_3OD (A) 800 MHz at 1mM concentration. The intensity changes for each amide proton were determined by monitoring the HN peaks on 1D spectra.

NH	δ (ppm)	k_{ex}× 10^{-3} (min^{-1})	k_{ex} *Standard Error*
NH Me	6.16	-[a]	
N'H U_1	6.34	-[a]	
NH U_1	6.21	11.65	4.20E-04
N'H U_2	6.36	16.25	7.27E-04
NH U_2	6.00	10.04[b]	3.87E-04
N'H U_3	6.44	31.98	1.73E-03
NH U_3	6.00	10.04[b]	3.87E-04
N'H U_4	6.05	229.32	1.07E-02
NH U_4	5.92	35.27	1.40E-03
N'H U_5	6.22	-	
NH U_5	6.16	-[a]	
NH $U_{p\text{-}CF3Ph}$	8.75	-[a]	

Table S7. Individual H/D exchange rate constants (k_{ex}) for urea NHs in oligourea **1** at 15°C. [a)] H/D exchange too fast to be recorded under these conditions. [b)] The calculated H/D rate constants are the sum of two individual constants due to severe overlapping in 1D and 2D COSY spectra.

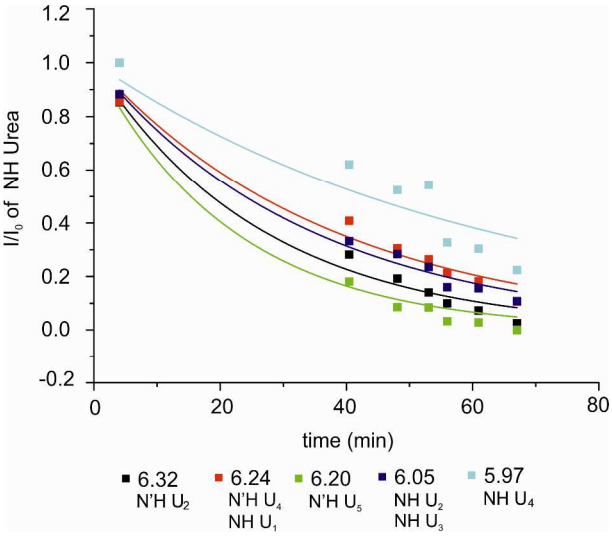


Figure S23. Exchange curves for oligourea **2** at 15°C. The NMR spectra were recorded in CD_3OD (800 MHz) at 1mM concentration. The intensity changes for each amide proton were determined by monitoring the HN peaks on 1D spectra.

NH	δ (ppm)	k_{ex}× 10^{-3} (min^{-1})	k_{ex} *Standard Error*
NHMe	6.11	-[a]	
N'H U_1	6.03	-[a]	
NH U_1	6.24	25.43[b]	0.0019
N'H U_2	6.32	37.08	0.00281
NH U_2	6.05	28.95[b]	0.00148
N'H U_3	6.28	-[a]	
NH U_3	6.05	28.95[b]	0.00148
N'H U_4	6.24	25.43[b]	0.0019
NH U_4	5.97	17.97	0.0027
N'H U_5	6.20	53.81	0.00328
NH U_5	6.18	-[a]	
NH $U_{p\text{-}CF3Ph}$	8.81	-[a]	

Table S8. Individual H/D exchange rate constants (k_{ex}) for urea NHs in oligourea **2** at 15°C. [a)] H/D exchange too fast to be recorded under these conditions. [b)] The calculated H/D rate constants are the sum of two individual constants due to severe overlapping in 1D and 2D spectra.

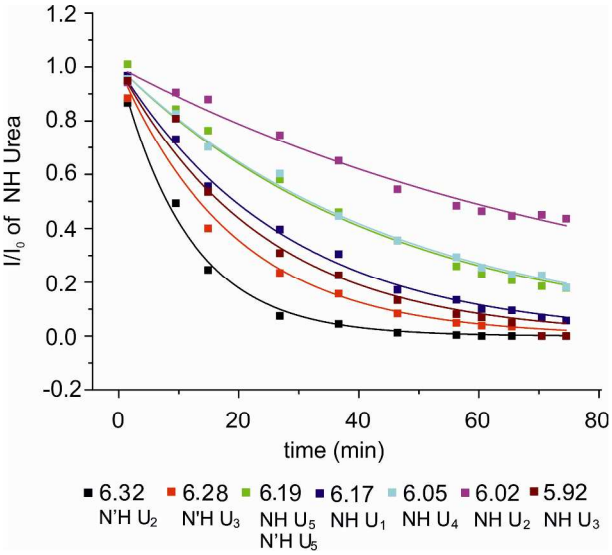


Figure S24. Exchange curves for oligourea **4** at 15°C. The NMR spectra were recorded in CD_3OD (800 MHz) at 1mM concentration. The intensity changes for each amide proton were determined by monitoring the HN peaks on 1D spectra.

NH	δ (ppm)	k_{ex}× 10^{-3} (min^{-1})	k_{ex} *Standard Error*
NHMe	6.06	-[a]	
N'H U_1	6.28	-[a]	
NH U_1	6.17	36.45	0.00108
N'H U_2	6.32	86.05	0.00421
NH U_2	6.02	11.94	5.48E-04
N'H U_3	6.28	51.69	0.00442
NH U_3	5.92	44.14	0.00307
N'H U_4	6.29	-[c]	
NH U_4	6.05	21.81	5.86E-04
N'H U_5	6.19	23.96[b]	4.96E-04
NH U_5	6.19	23.96[b]	4.96E-04
NH $U_{p\text{-}CF3Ph}$	8.81	-[a]	

Table S9. Individual H/D exchange rate constants (k_{ex}) for urea NHs in oligourea **4** at 15°C. [a)] H/D exchange too fast to be recorded under these conditions. [b)] The calculated H/D rate constants are the sum of two individual constants due to severe overlapping in 1D spectra and 2D COSY spectra. [c)] Though N'H U1 and N'H U3 exhibit the same chemical shifts, The COSY experiment recorded at t = 16 min confirmed the complete disappearance of the cross-peak between N'H U1 and αCH[1], thus allowing the attribution of the kinetic curve only to the N'H U_3 proton.

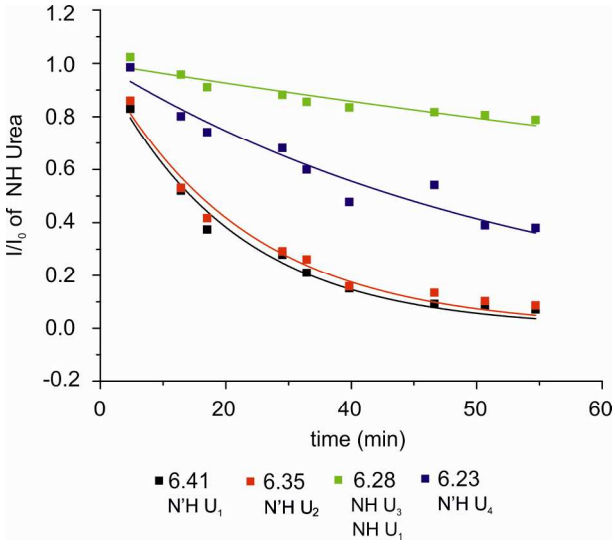


Figure S25. Exchange curves for oligourea **6** at 15°C. The NMR spectra were recorded in CD_3OD (800 MHz) at 1mM concentration. The intensity changes for each amide proton were determined by monitoring the HN peaks on 1D spectra.

NH	δ (ppm)	k_{ex}× 10^{-3} (min^{-1})	k_{ex} *Standard Error*
NH Me	6.10	-	
N'H U_1	6.41	95.9	6.99E-03
NH U_1	6.28	7.67[b]	9.44E-04
N'H U_2	6.35	87.06	6.89E-03
NH U_3	6.01	-	
N'H U_2	6.13	-[c]	
NH U_3	6.28	7.67[b]	9.44E-04
N'H U_4	6.23	29.39	3.07E-03
NH U_4	5.95	-[a]	
N'H U_5	6.35	-[a]	
NH U_5	6.28	-[a]	
NH $U_{p\text{-}CF3Ph}$	8.72	-[a]	

Table S10. Summary of individual H/D exchange rate constants (k_{ex}) for urea NHs in oligourea **6** at 15°C. [a] H/D exchange too fast to be recorded under these conditions. [b] The calculated H/D rate constants are the sum of two individual constants due to severe overlaps in 1D spectra and 2D COSY spectra. [c] An accurate measure of the integral of NH U_2 proton hampered by peak broadening in the ^1H NMR spectrum.

1.8 FT-IR data in the solid state.

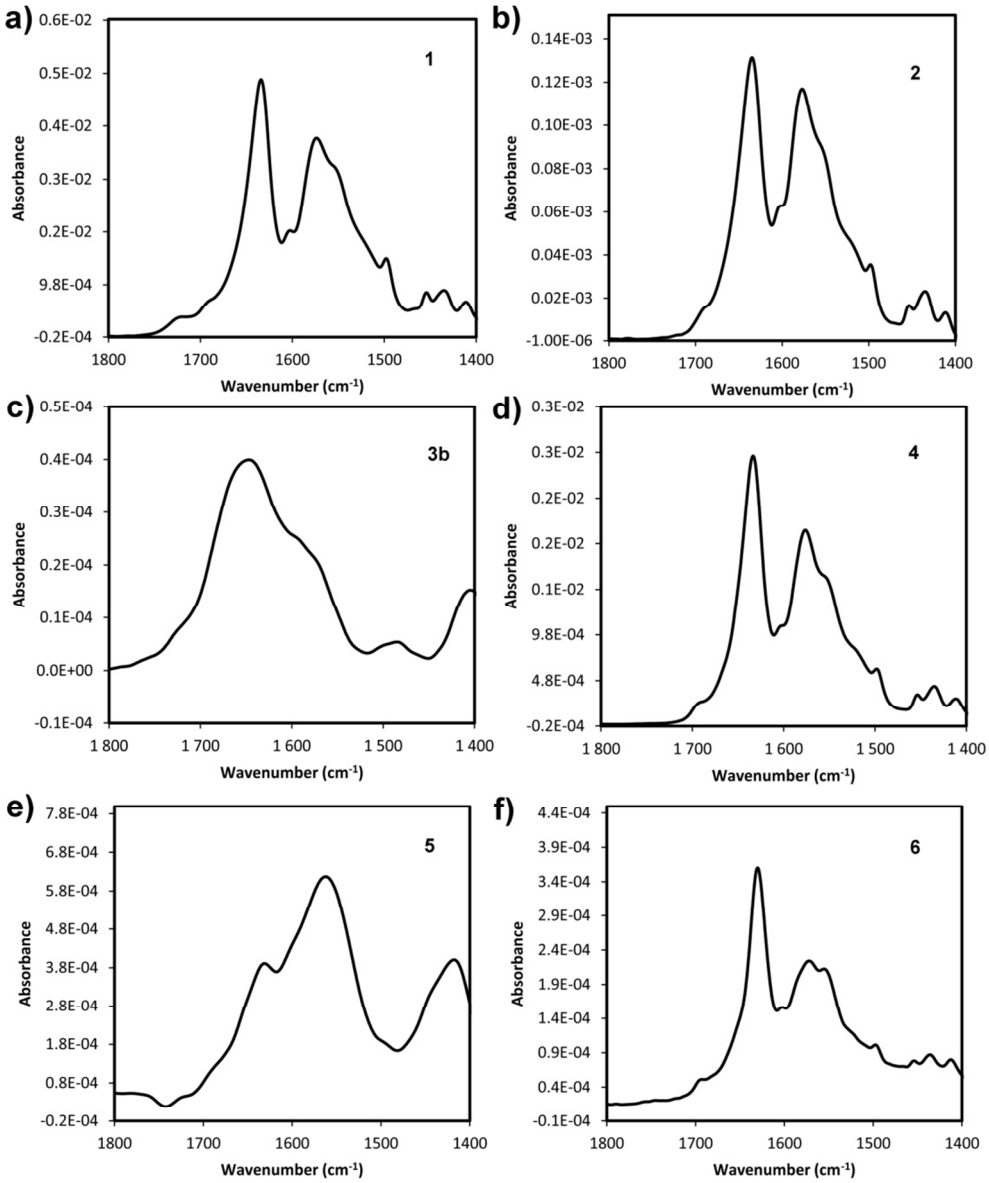


Figure S26. Part of FT-IR spectra (region 1400-1800 cm^{-1}) of oligoureas **1**-**6** in the solid state.

1.9 Monte-Carlo Conformational Analysis of oligoureas 1-6

The analysis was performed using the Monte-Carlo search as implemented in MacroModel version 8.6 via the Maestro interface version 6.5 (Schrödinger Inc.). The automatic setup was selected (with single bonds variable, chiral centers fixed and flexible ring(s) opened). In order to ensure the convergence of the search process, 10,000 steps were made per input structure by selecting an energy range of 20 $kJ \cdot mol^{-1}$ (putative conformations in solution at room temperature). Each selected conformer was fully minimized (500 cycles, TNCG method, RMS $\leq$ 0.005 $kJ \cdot Å^{-1} \cdot mol^{-1}$, AMBER* force field). The least-used structures were used as starting geometries only if their energies were within the energy window (20 $kJ \cdot mol^{-1}$ of the lowest energy structure yet found). Calculations were performed with the GB/SA continuum solvation model.[3] The solvent chosen was water. The extended cutoff option was used throughout (VdW = 8 Å, electrostatic = 20 Å and H-bond = 4 Å). Following the Monte Carlo search, a cluster analysis was performed with Xcluster 1.1,[4] using the RMS between heavy atoms as a distance criterion selection. This approach leads to a set of clusters, each of them being a family of conformers. In Xcluster, a conformer is considered to belong to a given cluster if it lies within the threshold distance from any component within this cluster and at more than this threshold distance from all components within all other clusters.

In order to choose the best force field and implicit solvent, compound **1** was tested with all available MacroModel force fields and solvents (none, water and chloroform) and the representative of the first cluster was superimposed on the X-ray structure of **1**.[5] The best results were obtained with AMBER* and water. Then all compounds were studied in these conditions (see Table S11)

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[3] Still W.C., Tempczyk A., Hawley R.C., Hendrikson T., *J. Am. Chem. Soc.*, **1990**, *112*, 6127.

[4] Shenkin P.S., McDonald D.Q.J., *J. Comput. Chem.*, **1994**, *15*, 899.

[5] Pendem, N.; Nelli, Y. R.; Fischer, L.; Douat-Casassus, C.; Ennifar, E.; Kaufmann, B.; Guichard, G. submitted.

Compound	Conformers	Clusters	Leader/members	ΔE (kJ/mole)	Helical structure (Y/N)
1	861	7	1/787	-	**Y**[a)]
			21/45	4.68	**Y**[b)]
			80/7	7.57	**Y**[b)]
			126/19	9.26	N
			449/1	15.0	N
			514/1	15.85	N
			647/1	17.28	N
2	275	6	1/225	-	N
			74/18	10.78	N
			119/11	14.19	N
			126/18	14.52	N
			189/2	16.70	**Y**
			263/1	19.34	**Y**[b)]
3a	210	3	1/145	-	N
			42/61	10.50	**Y**[b)]
			69/4	14.03	N
4	585	4	1/454	-	**Y**[b)]
			105/129	9.93	**Y**
			424/1	17.80	**Y**[b)]
			549/1	19.42	**Y**
5	966	5	1/739	-	**Y**
			7/64	4.14	N
			42/43	7.45	**Y**
			95/119	9.59	N
			940/1	19.66	N
6	539	2	1/515	-	**Y**[b)]
			34/24	10.19	**Y**[b)]

[a)]RMSD of 0.6 Å with the X-ray structure of **1**; b) partially helical

Table S11. Monte-Carlo Conformational Analysis of oligoureas **1-6**

1.10 Theoretical calculations on model trans- and *cis*-1,1'-(cyclohexane-1,2-diyl)bis(3-methylurea), CHBU

The entire conformational energy surface of *cis*- and *trans*-**CHBU** was investigated by carrying semi-empirical calculations with the simulated annealing technique implemented in the package Ampac.[6] The search of the various local minima of this surface was performed in two stages: (i) a non-local search focused on 18 dihedral angles corresponding to the torsions defining the different conformers; (ii) a local energetic relaxation of the whole degrees of freedom for each of the minima collected at each stage (i). The semi-empirical method RM1 is one of the most recently developed and performing. Twenty to fifty conformers with energies within 8 to 10 kcal/mol of the lowest energy conformer were thus determined (See Figures S27 and S28)

The geometry optimizations were calculated by Gaussian 09 program[7] at the density functional theory level using different functionals and basis sets. The checked functional are the hybrid B3PW91 functional, the CAM-B3LYP functional which is the hybrid B3LYP functional corrected by the Coulomb attenuation method in order to better taking into account the long distance forces and the recent wB97XD functional which includes an empirical dispersion and takes also into account the long distance forces. The checked basis sets are the Gaussian Pople bases 6-31G* and 6-31++G** with polarization functions (*) and/or diffuse functions (+) and cc-pVTZ a Dunning basis which includes the polarization functions by definition.

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[6] Semichem. AMPAC-8. KS : Semichem, 2004.

[7] Gaussian 09, Revision A.1 , M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

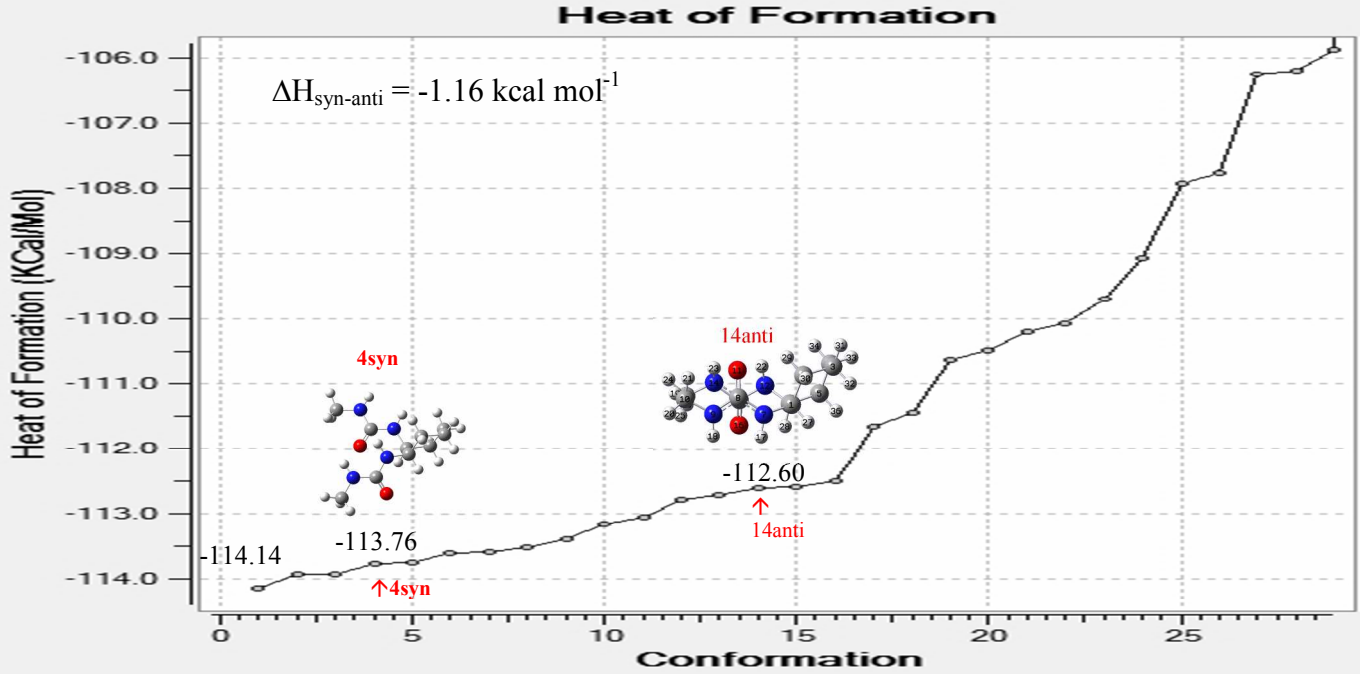

Figure S27. Low energy conformers of *cis*-**CBHU** calculated by simulated annealing using semi-empirical method RM1.

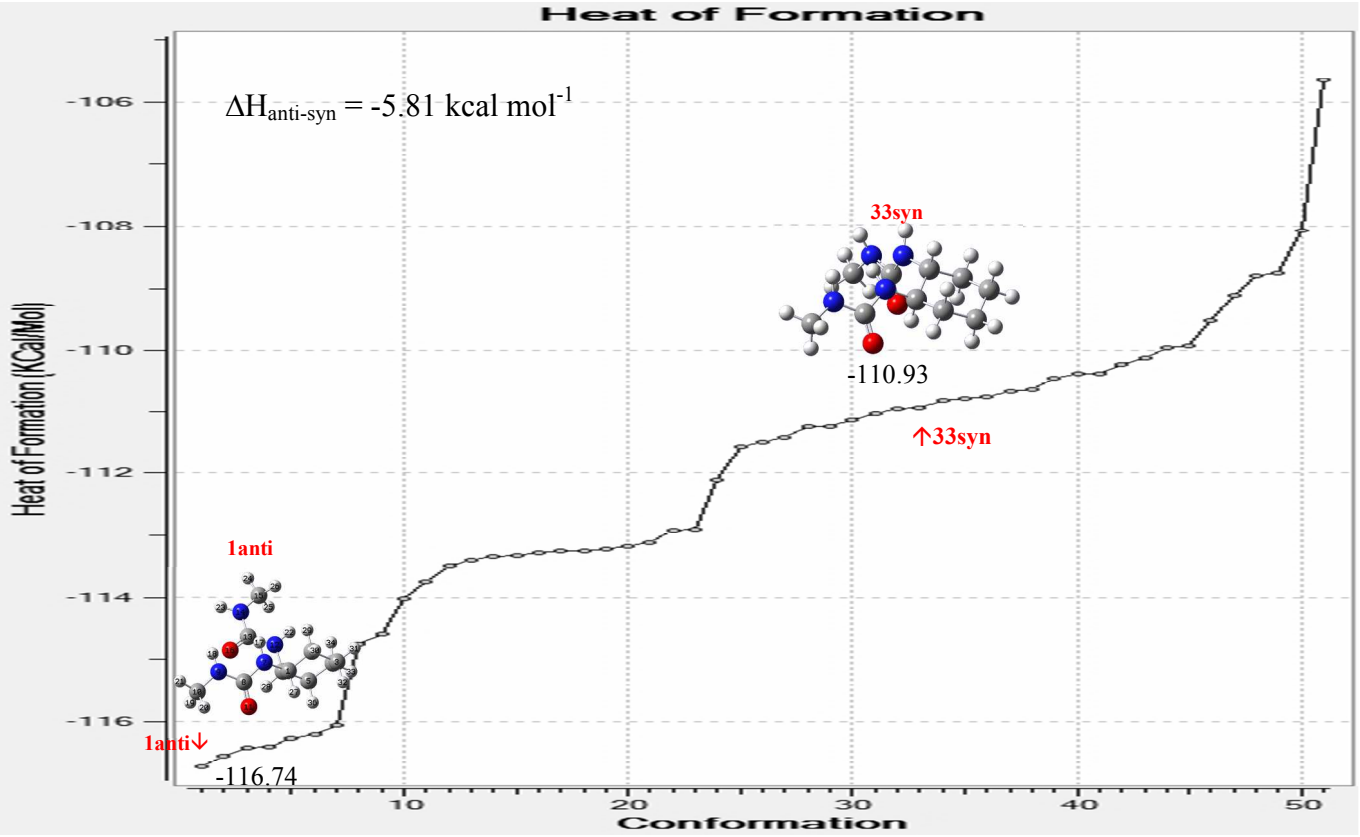

Figure S28. Low energy conformers of *trans*-**CBHU** calculated by simulated annealing using semi-empirical method RM1.

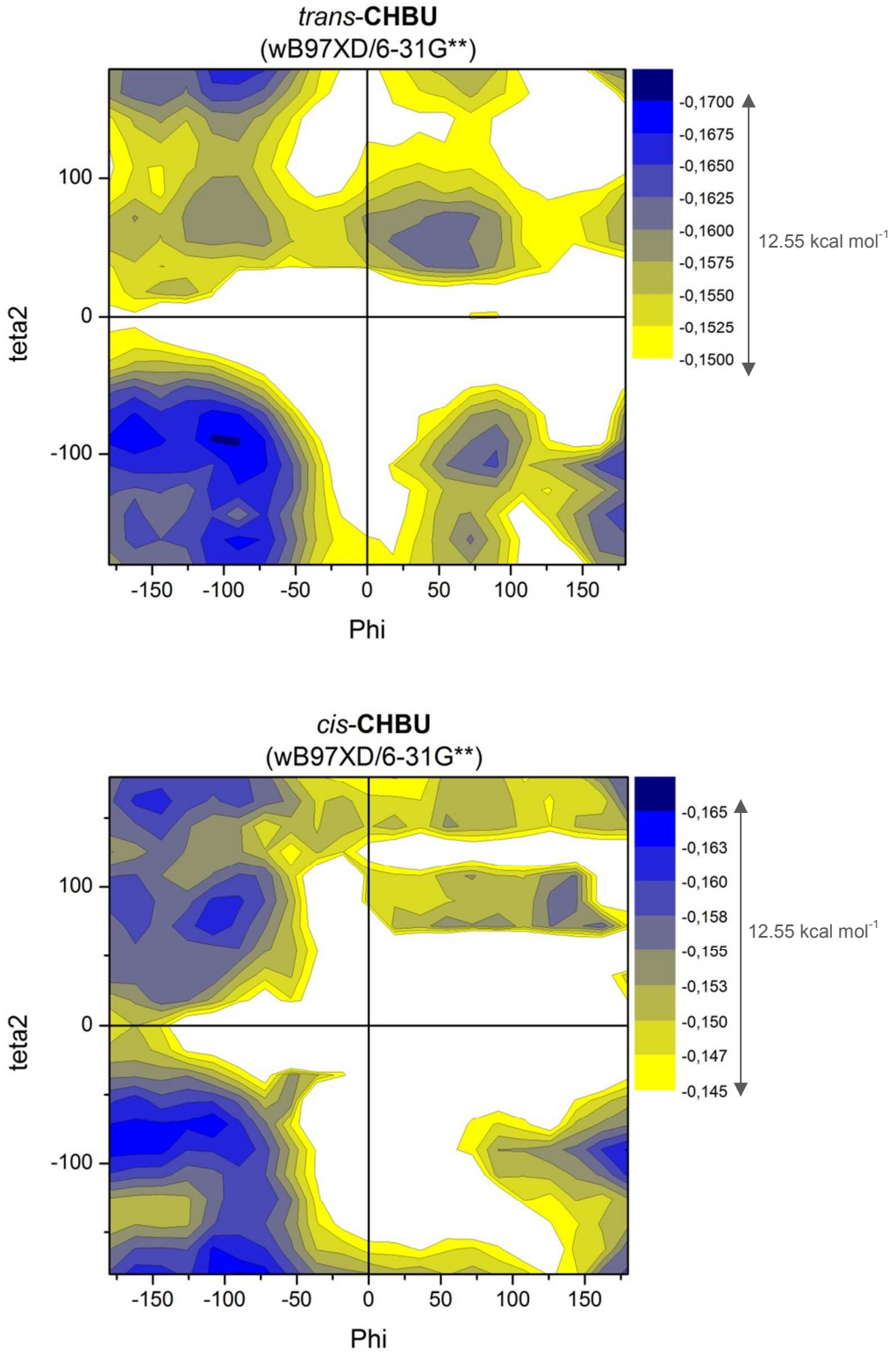

Figure S29. □ vs θ_2 energy landscapes calculated at the wB97XD/6-31G**level (in Hartree; 1Ha = 627.509469 kcal/mol) every 18° for *trans*-**CHBU** (top) and *cis*-**CHBU** (bottom).

1.11 Circular Dichroism

CD spectra of oligomers **1**, **2**, **3b**, **4**, **5** and **6** were recorded on a J-815 Jasco spectropolarimeter (Jasco France, Nantes, France). Data are expressed in terms of total molar ellipticity in $deg.cm^2.dmol^{-1}$. CD spectra of oligomers (0.1 mM) were acquired in spectrograde trifluoroethanol between 190 and 250 nm using a rectangular quartz cell with a path length of 1 mm (Hellma 110-QS 1mm, Paris, France).

1.12 X-ray diffraction studies

Crystal structures of compound **4**, **6** and **27** were collected on a RIGAKU MM07 rotating anode at the Cu Kα wavelength at IECB. The data were processed with the CrystalClear 1.36© software package including d*TREK. Crystal structures of compounds **11 and 2** had to be collected at synchrotron beam-lines (ESRF ID29 and SLS X06DA respectively). The data were integrated and scaled using the XDS package[8]. All structures were solved using the charge flipping algorithm implemented in Superflip[92] and were refined using SHELXL[103]. The positions of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. The non-H atoms were refined with anisotropic temperature parameters. H atoms were included for structure factor calculations but not refined.

8. Kabsch, W. *J. Appl. Crystallogr.* **1993**, *26*, 795–800.

9. Palatinus, L.; Chapuis, G. *Appl. Crystallogr.* **2007**, *40*, 786–790.

10. Sheldrick, G.M. *Acta Cryst.* A64, **2008**, 112-122.

Table S12. Crystal data and structure refinement for oligourea **2.**

Formula	$C_{52}H_{63}F_3N_{12}O_6$
M	1009.14
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a/Å	10.100 (2)
b/Å	19.070 (4)
c/Å	26.030 (5)
V/Å3	5013.6 (17)
T /K	100
Z	4
ρ/g cm–1	1.337
size (mm)	0.10 × 0.10 × 0.10
λ/ Å	0.75
μ/mm-1	0.10
Independent reflections	10027
measured reflections	133471
parameters/restraints	659/0
R1, wR2	0.039/ 0.100
goodness of fit	1.05
largest residuals (e $Å^{-3}$)	0.29
Flack parameter	0.0172 (5)

Table S13. Crystal data and structure refinement for oligourea **4.**

Formula	$C_{54.50}H_{63.75}F_3N_{12}O_{8.50}$
M	1079.93
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	22.104 (4)
b/Å	25.028 (5)
c/Å	23.517 (5)
β °	117.49 (3)
V/Å3	11541 (4)
T /K	213
Z	8
ρ/g cm–1	1.243
size (mm)	0.1 × 0.01 × 0.01
λ/ Å	1.54178
μ/mm-1	0.77
Independent reflections	41515
measured reflections	136732
parameters/restraints	2801/4
R1, wR2	0.101/ 0.321
goodness of fit	1.02
largest residuals (e $Å^{-3}$)	0.72
Flack parameter	0.01 (17)

Table S14. Crystal data and structure refinement for oligourea **6.**

Formula	$C_{114.88}H_{140}F_{5.60}N_{24}O_{15}$
M	2203.47
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	13.389 (2)
b/Å	25.301 (6)
c/Å	17.527 (3)
β	96.476 (15)
V/Å3	5899.5 (19)
T /K	120
Z	2
ρ/g cm–1	1.240
size (mm)	0.1 × 0.02 × 0.02
λ/ Å	1.54178
μ/mm-1	0.74
Independent reflections	21508
measured reflections	81895
parameters/restraints	2801/4
R1, wR2	0.082/ 0.210
goodness of fit	0.86
largest residuals (e $Å^{-3}$)	1.17
Flack parameter	0.01 (17)

Table S15. Crystal data and structure refinement for compound **11.**

Formula	$C_{13}H_{11}F_5N_4O_2$
M	350.26
Crystal system	Monoclinic
Space group	$P2_1$
a/Å	9.877 (2)
b/Å	25.468 (5)
c/Å	11.919 (2)
β	100.92 (3)
V/Å3	2943.9 (10)
T /K	100
Z	8
ρ/g cm–1	1.581
size (mm)	0.01 × 0.01 × 0.01
λ/ Å	0.87260
μ/mm-1	0.25
Independent reflections	31912
measured reflections	8864
parameters/restraints	788/1
R1, wR2	0.054/ 0.142
goodness of fit	1.07
largest residuals (e $Å^{-3}$)	0.54
Flack parameter	0.1 (5)

Table S16. Crystal data and structure refinement for compound **27.**

Formula	$C_{88}H_{160}N_{32}O_{16}$
M	1922.48
Crystal system	Tetragonal
Space group	$P4_12_12$
a/Å	11.949 (2)
b/Å	11.949 (2)
c/Å	18.656 (5)
V/Å3	2663.8
T /K	213
Z	8
ρ/g cm–1	1.198
size (mm)	0.1 × 0.1 × 0.1
λ/ Å	1.54178
μ/mm-1	0.69
Independent reflections	2589
measured reflections	31576
parameters/restraints	165/0
R1, wR2	0.059/ 0.170
goodness of fit	1.04
largest residuals (e $Å^{-3}$)	0.54
Flack parameter	0.3 (3)

Figure S30. Overlay of the structures of the four independent molecules of **4** (I-IV) by fitting the five pairs of β-carbons.

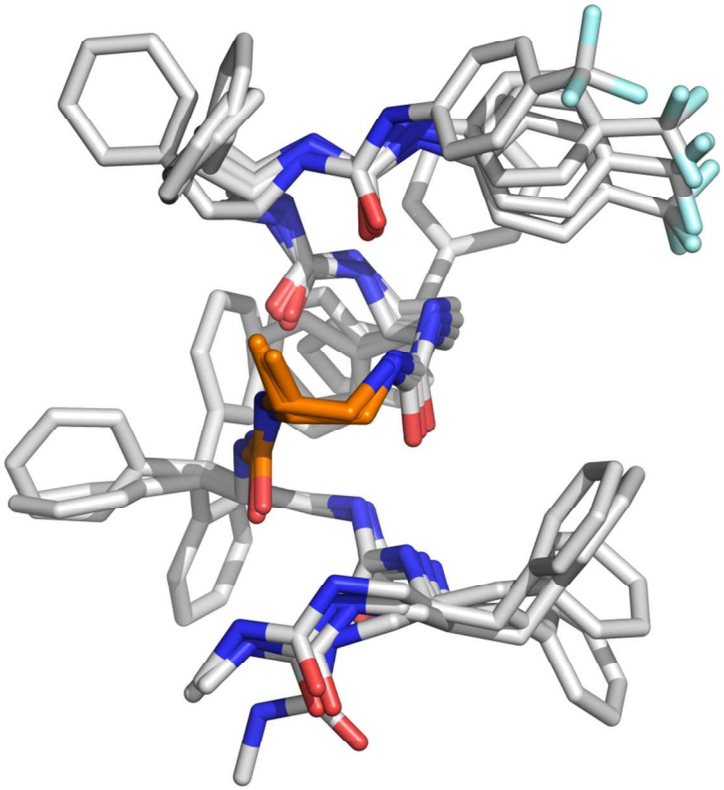

Figure S31. Overlay of the structures of the two independent molecules of **6** by fitting the five pairs of β-carbons.

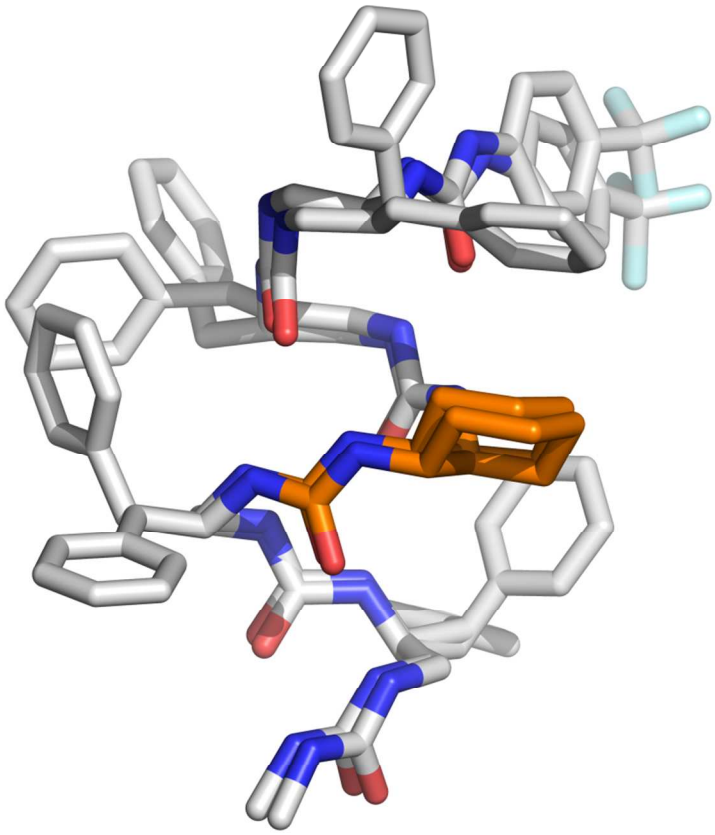

Figure S32. Distances (in Å) between side chain of residues *i*, *i*+2, and *i*+4 in the crystal structure of **1** (left) and **4** (right, molecule I).