Supporting Information

A Versatile Strategy for the Synthesis of Sequence-Defined Peptoids with Side-Chain and Backbone Diversity via Amino Acid Building Blocks

Shixue Wang,[ab] Yue Tao,[ac] Jianqun Wang,[ac] Youhua Tao*[ac] and Xianhong Wang[ac]

a

Key Laboratory of Polymer Ecomaterials, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Renmin Street 5625, Changchun 130022, People's Republic of China.

b

University of Science and Technology of China, Hefei 230026, People's Republic of China

***E-mail: youhua.tao@ciac.ac.cn**

Table of Contents

1. Experimental section

1.1 Materials

Amino acids, aldehydes, *tert*-butyl isocyanide, *tert*-butyl acetate, perchloric acid ($HClO_4$), benzyl carbonochloridate (CbzCl), *tert*-Butanol (^{t}BuOH), Dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine (DMAP), Pd/C, ethylformate, 2,5,8,11-tetraoxatridecan-13-ol, phthalimide, 2-(2-(2-aminoethoxy)ethoxy)ethanol, *tert*-butyl 2-bromoacetate, Potassiumtbutoxide (^{t}BuOK), triphenylphosphine (PPh_3) and 1-amino-3-chloropropane hydrochloride were purchased from Energy Chemical and used as received unless otherwise stated. Methanol (MeOH) was refluxed with magnesium and iodine for 2 h, and distilled under nitrogen atmosphere before used.

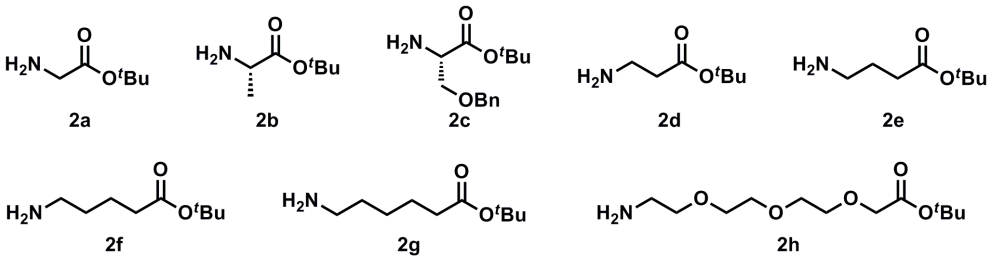
DBCO-DNA (dibenzocyclooctyne (DBCO)) was customized from Sangon Biotech (Shanghai), the sequence is 5`-DBCO-TCC ATG ACG TTC CTG ACG TTT TTT-3` (MW = 7770.0 Da).

1.2 Characterization

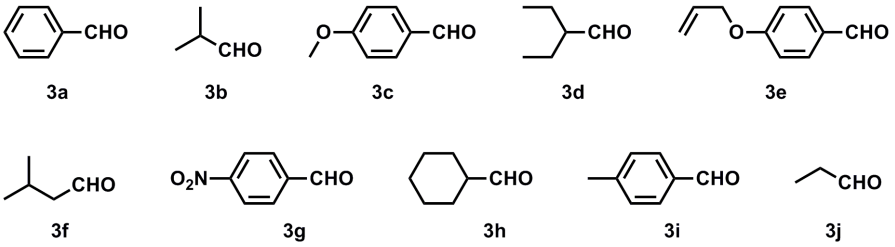
^{1}H NMR spectra and ^{13}C NMR were recorded on a Bruker AV-300 spectrometer. HRMS were measured by ESI or MALDI-TOF Mass Spectrometry. MALDI-TOF Mass was performed on a Bruker Autoflex III mass spectrometer in linear or reflectred positive ion mode. The matrix was *trans*-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB), and the solvent was $CHCl_3$. Number-average molecular weights (M_n) and polydispersity indexes (PDI) were determined by Size Exclusion Chromatography (SEC) on a Waters 1515 HPLC pump equipped with Waters 2414 Refractive index Detector (eluent: THF; flow rate: 1.0 mL/min; temperature: 35 ^{o}C; standard: polystyrene in the molecular weight range from 660 to 1.97×10^5 Da). The LCST were determined by monitoring the transmittance of a 500 nm light beam through a quartz sample cell at concentration of 2 mg/mL on a JASCO 1500 CD spectrometer. The solution was heated at rate of 1.0 ^{o}C /min from 0 to 50 ^{o}C. The cloud point temperature was determined as the temperature corresponding to that of solutions reaching 50% of the initial transmittance.

2. Monomers used in the current study

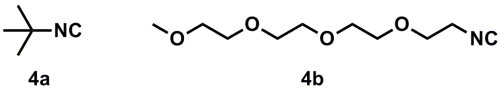
Amino acid buliding block:



Aldehyde:

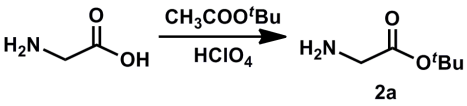


Isocyanide:



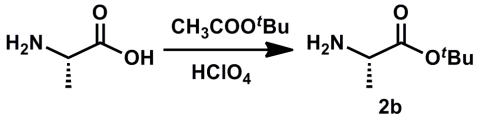
3. Monomer synthesis

3.1 Synthesis of amino acid building-block 2a



To a suspension of Glycine (11.4 g, 150 mmol) in *tert*-butyl acetate (300 mL) at 0 ^{o}C, $HClO_4$ (12.75 mL, 225 mmol) was added slowly. The reaction mixture was stirred at room temperature for 48 h then washed with water (200 mL) and 1.0 *N* HCl solution (100 mL). The resultant aqueous solution was adjusted to pH~9 by addition of 10% Na_2CO_3 solution, and then extracted with dichloromethane (3 x 100 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to give colorless oil. This was purified by flash chromatography on silica gel, using a grading of ethyl acetate/hexane ((1:5) to (2:5)), to give **2a** as a colorless oil 15.3 g, 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (s, 2H), 1.45 (s, 9H), 1.43 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.05, 80.75, 44.19, 27.82. ESI-MS of $[C_6H_{13}NO_2]^+$: calculated: 131.09, found: 131.8 $[M + H]^+$, 153.9 $[M + Na]^+$.

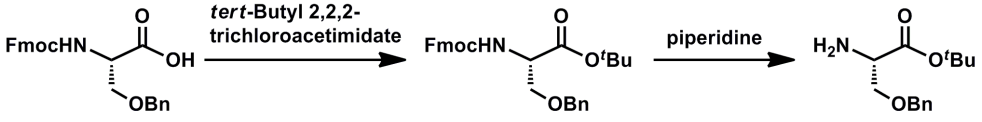
3.2 Synthesis of amino acid building-block 2b



2b

To a suspension of $_{L}$-Alanine (4.45 g, 50 mmol) in *tert*-butyl acetate (100 mL) at 0 ^{o}C, $HClO_4$ (4.25 mL, 75 mmol) was added slowly. The reaction mixture was stirred at room temperature for 48 h then washed with water (100 mL) and 1.0 *N* HCl solution (50 mL). The resultant aqueous solution was adjusted to pH~9 by addition of 10% Na_2CO_3 solution, and then extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to give colorless oil. This was purified by flash chromatography on silica gel, using ethyl acetate/hexane (1/2) as eluent, to give **2b** as a colorless oil 5.25 g, 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.39-3.32 (q, *J* = 9 Hz, 1H), 1.47 (br, 2H), 1.40 (s, 9H), 1.24 (d, *J* = 9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.41, 79.82, 50.11, 27.48, 20.31. ESI-MS of $[C_7H_{15}NO_2]^+$: calculated: 145.20, found: 145.9 $[M + H]^+$, 168.0 $[M + Na]^+$.

3.3 Synthesis of amino acid building-block 2c



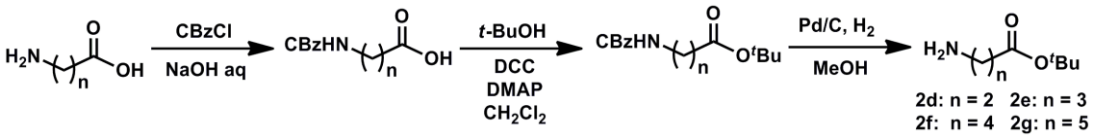
2c

To a suspension of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(benzyloxy)propanoic acid (10.44 g, 25 mmol) in dichloromethane (50 mL) at 0 ^{o}C, *tert*-Butyl 2,2,2-trichloroacetimidate (8.95 mL, 50 mmol) in diethyl ether (20 mL) was added slowly. The reaction mixture was stirred at 0 ^{o}C for 48 h then washed with saturated Na_2CO_3 solution (50 mL), water, and brine, dried with anhydrous Na_2SO_4, filtered and concentrated to give colorless oil. This was purified by flash chromatography on silica gel, using ethyl acetate/hexane (1/2) as eluent, to give (*S*)-t*ert*-butyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(benzyloxy)propanoate as a white solid 11.84 g, 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 9 Hz, 2H), 7.63 (d, *J* = 6 Hz, 2H), 7.29-7.43 (m, 9H), 5.71 (d, *J* = 9 Hz, 1H), 4.21-4.62 (m, 6H), 3.68-3.91 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.38, 156.06, 144.00, 143.87, 141.31, 137.61, 128.47, 127.88, 127.74, 127.12, 125.27, 120.01, 82.36, 73.41, 70.26, 67.18, 54.90, 47.16, 28.04.

The above intermediate (5.26 g, 11.1 mmol) was dissolved in solution of 20%

piperidine/dichloromethane, and stirred at room temperature for 3 h, then the solvent was removed in vacuum, and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate (1/1) as eluent, to give intermediate **2c** as a colorless oil 2.5 g, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.37 (m, 5H), 4.48-4.60 (q, *J* = 12 Hz, 1H), 3.64-3.73 (m, 2H), 3.50-3.53 (m, 1H), 1.69 (br, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.92, 137.93, 128.25, 127.52, 80.93, 73.12, 72.34, 55.32, 27.94. ESI-MS of $[C_{14}H_{21}NO_3]^+$: calculated: 251.32, found: 252.2 $[M + H]^+$.

3.4 Synthesis of amino acid building-block 2d-2g



To a solution of amino acid (3.51 g, 30 mmol) in NaOH aq (33 mL, 2 *N*) at 0 ^{o}C, CBzCl (4.5 mL, 33 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h then extracted with ether for two times, the resultant aqueous solution was adjusted to pH~3 by addition of 3 *N* HCl solution, and then extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to give a white solid used to the next step without further purification.

3-(((benzyloxy)carbonyl)amino) propanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.30 (m, 5H), 6.24, 5.27 (s, 1H), 5.16-5.10 (m, 2H), 3.51-3.45 (m, 2H), 2.64-2.60 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.54, 156.58, 136.31, 128.61, 128.23, 66.98, 36.38, 34.26.

4-(((benzyloxy)carbonyl) amino) butanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.31 (m, 5H), 5.77, 4.91 (s, 1H), 5.14-5.10 (m, 2H), 3.30-3.23 (m, 2H), 2.40 (t, *J* = 6 Hz, 2H), 1.89-1.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.12, 157.93, 156.74, 136.31, 135.95, 128.35, 127.93, 127.77, 67.13, 66.60, 40.54, 40.08, 31.00, 24.68.

5-(((benzyloxy)carbonyl)amino) pentanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.31 (m, 5H), 5.66, 4.81 (s, 1H), 5.15-5.09 (m, 2H), 3.25-3.19 (m, 2H), 2.38 (t, *J* = 6 Hz, 2H), 1.72-1.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.08, 156.63, 136.57, 128.60, 128.21, 67.27, 40.66, 33.60, 29.34, 21.81.

6-(((benzyloxy)carbonyl)amino) hexanoic acid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.31 (m, 5H), 5.39, 4.77 (s, 1H), 5.15-5.09 (m, 2H), 3.23-3.17 (m, 2H), 2.35 (t, *J* = 6 Hz, 2H), 1.70-1.32 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.53, 157.94, 156.58, 136.43, 136.07, 128.31, 127.88, 127.74, 66.95, 66.43, 41.05, 40.62, 33.72, 29.32, 25.94, 24.14.

The crude product of previous step was dissolved in dichloromethane, DMAP (0.1 eq) and ^{t}BuOH (3.0 eq) were added subsequently. DCC (1.2 eq) was added slowly to the solution and the reaction mixture was stirred at room temperature for 12 h. Water was added to quench the reaction, the aqueous phase extracted with dichloromethane (3 x 50 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated, then purified by flash chromatography on silica gel, using a grading of ethyl acetate/hexane to give intermediate as a white solid.

tert-butyl 3-(((benzyloxy)carbonyl)amino)propanoate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 5.28 (s, 1H), 5.09 (s, 2H), 3.46-3.40 (m, 2H), 2.45 (t, *J* = 6 Hz, 2H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.39, 156.19, 136.47, 128.29, 127.90, 127.86, 80.66, 66.35, 36.58, 35.33, 27.89. ESI-MS of $[C_{15}H_{21}NO_4]^+$: calculated: 279.15, found: 280.3 $[M + H]^+$, 302.3 $[M + Na]^+$.

tert-butyl 4-(((benzyloxy)carbonyl)amino)butanoate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 5.09 (s, 2H), 4.91 (s, 1H), 3.26-3.20 (m, 2H), 2.25 (t, *J* = 6 Hz, 2H), 1.84-1.74 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.40, 156.35, 136.51, 128.21, 127.81, 127.75, 80.06, 66.19, 40.18, 32.53, 27.81, 24.97. ESI-MS of $[C_{16}H_{23}NO_4]^+$: calculated: 293.16, found: 293.3 $[M + H]^+$, 316.3 $[M + Na]^+$.

tert-butyl 5-(((benzyloxy)carbonyl)amino)pentanoate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 5.09 (s, 2H), 4.82 (s, 1H), 3.23-3.17 (m, 2H), 2.23 (t, *J* = 6 Hz, 2H), 1.66-1.50 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.68, 156.40, 136.63, 128.27, 127.86, 127.80, 79.92, 66.21, 40.43, 34.82, 29.09, 27.91, 21.96. ESI-MS of $[C_{17}H_{25}NO_4]^+$: calculated: 307.18, found: 308.3 $[M + H]^+$, 330.3 $[M + Na]^+$.

tert-butyl 6-(((benzyloxy)carbonyl)amino)hexanoate: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 5.09 (s, 2H), 4.76 (s, 1H), 3.22-3.16 (m, 2H), 2.20 (t, *J* = 6 Hz, 2H), 1.64-1.22 (m, 6H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.82, 156.35, 136.60, 128.26, 127.84, 127.79, 79.81, 66.20, 40.64, 35.17, 29.41, 27.90, 25.96, 24.48. ESI-MS of $[C_{18}H_{27}NO_4]^+$: calculated: 321.19, found: 344.4 $[M + Na]^+$.

To a solution of the above white solid in MeOH at nitrogen atmosphere, Pd/C (10%) was added and the nitrogen atmosphere was displaced with hydrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h then Pd/C was filtered off, the solvent was evaporated in vacuum, resultant aqueous solution was adjusted to pH~3 by addition of 3 *N* HCl solution, the resulting oil was purified by flash chromatography on silica gel, using CH_2Cl_2/MeOH (10:1) as eluent, to give **2d-2g** as a colorless oil.

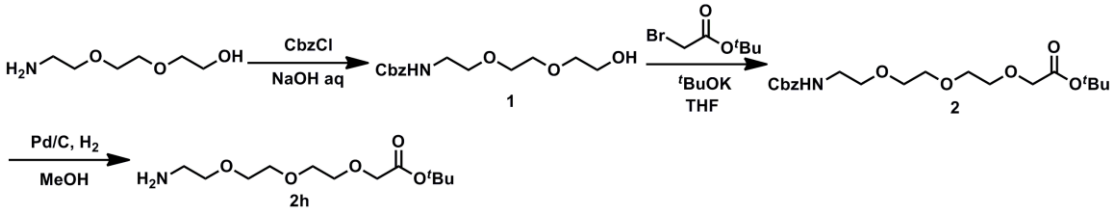
2d: 68% yield for three steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95-2.91 (t, *J* = 6 Hz, 2H), 2.39-2.35 (t, *J* = 6 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.74, 80.29, 38.48, 37.61, 27.92. ESI-MS of $[C_7H_{15}NO_2]^+$: calculated: 145.11, found: 145.9 $[M + H]^+$, 167.9 $[M + Na]^+$.

2e: 65% yield for three steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.72-2.67 (t, *J* = 6 Hz, 2H), 2.27-2.22 (t, *J* = 6 Hz, 2H), 1.76-1.66 (t, *J* = 6 Hz, 2H), 1.42 (s, 9H), 1.39 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.44, 79.63, 41.08, 32.57, 28.55, 27.70. ESI-MS of $[C_8H_{17}NO_2]^+$: calculated: 159.13, found: 159.9 $[M + H]^+$.

2f: 66% yield for three steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.73-2.68 (t, *J* = 6 Hz, 2H), 2.24-2.20 (t, *J* = 6 Hz, 2H), 1.39 (br, 2H), 1.66-1.47 (m, 4H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.59, 79.61, 41.46, 34.94, 32.75, 27.76, 22.02. ESI-MS of $[C_9H_{19}NO_2]^+$: calculated: 173.14, found: 174.0 $[M + H]^+$.

2g: 58% yield for three steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70-2.65 (t, *J* = 6 Hz, 2H), 2.23-2.18 (t, *J* = 6 Hz, 2H), 1.68-1.53 (m, 2H), 1.43 (s, 9H), 1.37-1.34 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.67, 79.52, 41.54, 35.08, 32.88, 27.73, 25.98. 24.52. ESI-MS of $[C_{10}H_{21}NO_2]^+$: calculated: 187.16, found: 188.3 $[M + H]^+$.

3.5 Synthesis of oligo-ethylene-glycol based amino acid building block 2h



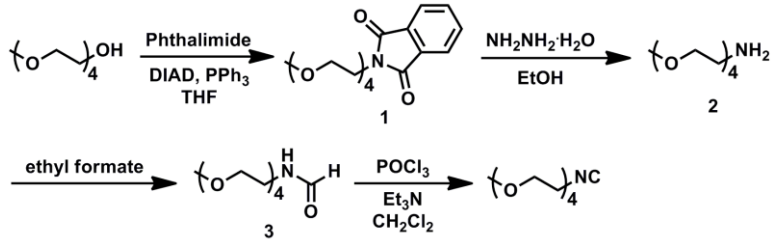
To a solution of 2-(2-(2-aminoethoxy)ethoxy)ethanol (5.0 g, 33.5 mmol) and Et_3N (4.7 mL, 33.5 mmol) in CH_2Cl_2 80 mL at 0 ^{o}C, CbzCl (4.57 mL, 33.5 mmol) was added slowly. The reaction

mixture was stirred at room temperature for 2 h, then 50 mL saturated $NaHCO_3$ solution was added, CH_2Cl_2 phase was separated and the water phase was extracted with CH_2Cl_2 for other two times. The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated then purified by flash chromatography on silica gel, using CH_2Cl_2/MeOH (10:1) as eluent, to give intermediate alcohol **1** as a colorless oil 8.83 g, 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.30 (m, 5H), 5.75, 5.47 (br, 1H), 3.71-3.55 (m, 10H), 3.42-3.37 (m, 2H), 2.55 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.62, 136.63, 128.42, 128.05, 128.00, 72.60, 70.21, 70.10, 70.01, 66.49, 61.36, 40.74.

The above intermediate alcohol (8.84 g, 31.2 mmol) was dissolved in THF (120 mL), ^{t}BuOK (3.5 g, 31.2 mmol) was added at 0 ^{o}C, the solution was stirred at this temperature for another 1 h, *tert*-butyl 2-bromoacetate was added and stirred at room temperature for 15 h, water 100 mL was added to quenched the reaction, the water phase was extracted with ethyl acetate (3 x 100 mL), the combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated, then purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate (5:1) as eluent, to give intermediate **2** as a colorless oil 6.45 g, 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.29 (m, 5H), 5.42 (br, 1H), 5.09 (s, 2H), 3.98 (s, 2H), 3.68-3.54 (m, 10H), 3.41-3.36 (M, 2H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.62, 156.50, 136.64, 128.44, 128.06, 128.00, 81.52. 70.59, 70.50, 70.45, 70.15, 69.99, 66.89, 66.51, 40.81, 28.06.

To a solution of the above intermediate **2** (6.0 g, 15.1 mmol) in MeOH at nitrogen atmosphere, Pd/C (10%) was added and the nitrogen atmosphere was displaced with hydrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h then Pd/C was filtered off, the solvent was evaporated in vacuum, the resulting oil was purified by flash chromatography on silica gel, using CH_2Cl_2/MeOH (10:1) as eluent, to give **2h** as a colorless oil 3.6 g, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01(s, 2H), 3.71-3.48 (m, 10H), 2.85 (t, J = 6 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.20, 80.90, 72.81, 70.25, 70.19, 70.14, 69.83, 68.52, 41.32, 27.70. ESI-MS of $[C_{12}H_{25}NO_5]^+$: calculated: 263.17, found: 264.3 $[M + H]^+$, 286.2 $[M + Na]^+$.

3.6 Synthesis of oligo-ethylene-glycol isocyanide ($mOEG_4NC$)

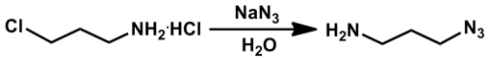


To a solution of 2, 5, 8, 11-tetraoxatridecan-13-ol (31.2 g, 150 mmol), phthalimide (27.6 g, 187.5 mmol), and PPh_3 (49.2 g, 187.5 mmol) in THF (500 mL) at nitrogen atmosphere, DIAD (37.17 mL, 187.5 mmol) was added dropwise at 0 ^oC over a period of 30 min. The resulting mixture was stirred at ambient temperature for 12 h and 250 mL ethanol was added. After evaporation of all volatiles with rotary evaporator, the residue was treated with a mixture of *n*-hexane/ethyl acetate (150 mL, 2:1) and heated to 40 ^oC for 1 h. The formed solid was filtered off and washed twice with cold *n*-hexane. All volatiles were removed with rotary evaporator, the residue was dissolved in diethyl ether (200 mL) and put it in the refrigerator (-20 ^oC) for about 24 h, the formed solid was filtered off and diethyl ether was removed in vacuum. The crude product **1** was dissolved in ethanol (400 mL) and treated with hydrazinemonohydrate (20 mL). The mixture was heated to reflux for 12 h and a white precipitate formed. After cooling to room temperature, the solid was filtered off and all volatiles were removed in vacuum. The residue was dissolved in water (100 mL) and acidized with 1 *N* HCl solution to pH~2, then the aqueous phase was extracted with dichloromethane (3 x 100 mL). The aqueous phase was basified with 1 *N* NaOH aqueous to pH~11 and extracted with dichloromethane (5 x 100 mL), the combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated, then purified by flash chromatography on silica gel, using CH_2Cl_2/MeOH (20:1) as eluent, to give intermediate amine **2** as a colorless oil 15.03 g, 49% yield for two steps. ^1H NMR (300 MHz, $CDCl_3$): δ 3.66-3.62 (m, 10H), 3.57-3.51 (m, 4H), 3.38 (s, 3H), 2.89-2.85 (t, J = 6 Hz, 2H), 1.90 (br, 2H).

The amine **2** (15.03 g, 72.5 mmol) was transferred to the corresponding formamide by refluxing with ethyl formate (250 mL) for 24 h, followed by removal of the solvent in vacuum. Then triethylamine (21 mL, 145 mmol) and 150 mL of dichloromethane was added to the crude product, the mixture was cooled in an ice bath, and phosphrous (V) oxychloride (10 mL, 108.8 mmol) was added dropwise within 3 h. The mixture was stirred for another 2 h before the K_2CO_3 (20% aqueous, w/w, 150 mL) was added to quench the reaction. The aqueous phase was extracted with

dichloromethane (3 x 100 mL), the combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated, then purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate(1:1) as eluent, to afford a pale yellow oil 14 g, 89% yield for two steps. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72-3.65 (m, 12H), 3.61-3.55 (m, 4H), 3.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.61, 71.36, 70.20, 70.06, 70.01, 69.91, 68.12, 41.38, 41.29, 41.20. ESI-MS of $[C_{10}H_{19}NO_4]^+$: calculated: 217.13, found: 218.1 $[M + H]^+$, 240.1 $[M + Na]^+$.

3.7 Synthesis of 3-azidopropan-1-amine



A solution of 1-amino-3-chloropropane hydrochloride (2.6 g, 20 mmol) and NaN_3 (5.2 g, 80 mmol) in water (30 mL) was stirred at 80 ^{o}C for 18 h. The mixture was concentrated in vacuum, the resultant aqueous solution was adjusted to pH~9 by addition of 10 % NaOH solution, and then extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to give a yellow oil. This crude product was purified by flash chromatography on silica gel, using CH_2Cl_2/MeOH (10:1) as eluent, to give 3-azidopropan-1-amineas as colorless oil 1.78 g, 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41-3.37 (t, *J* = 6 Hz, 2H), 2.84-2.80 (t, *J* = 6 Hz, 2H), 1.79-1.70 (m, 2H), 1.18 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.34, 38.48, 31.64. ESI-MS of $[C_3H_8N_4]^+$: calculated: 100.07, found: 100.8 $[M + H]^+$.

4. Typical procedure for the iterative Ugi reaction

4.1 Typical procedure for the Ugi reaction

A solution of amine (1.1 eq) and aldehyde (1.1 eq) in methanol was stirred at room temperature for 2 h, isocyanide (1.1 eq) and acid (1.0 eq, the concentration in methanol is 0.5 mol/L) were added, the mixture was stirred at room temperature for 12 h. The solvent was removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using CH_2Cl_2/MeOH (20:1) or petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid.

4.2 Typical procedure for deprotection of *tert*-butyl ester

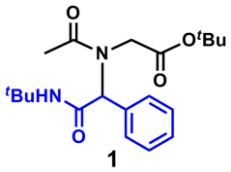
A solution of Ugi product in dichloromethane/TFA (1:1) was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water for two times and saturated NaCl aqueous for one time. The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to give a white or pale yellow solid. The crude product was used to the next Ugi reaction without further purification.

5. "Click" reaction

A solution of azide-modified Peptoid **16** (0.012 mg) and DBCO-DNA (0.082 mg) (molar ratio is 1:1) in phosphate buffer/CH_3CN (3:1) 0.1 mL was stirred at room temperature for 24 h. The mixture was concentrated in vacuum and measured by MS, and electrophoresis in agarose gels (0.5% agarose).

6. Synthesis of 10-mer Peptoid 3 using amino acid building block 2a *via* iterative Ugi reaction

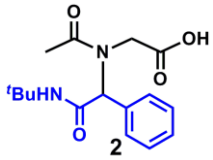
1st Ugi reaction



1

A solution of **2a** (0.55 g, 4.2 mmol) and benzaldehyde (0.43 mL, 4.2 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.48mL, 4.2 mmol) and acetic acid (0.22 mL, 3.825 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 1.26 g, 91% yield. MALDI-TOF Mass of $[C_{20}H_{30}N_2O_4]^+$: calculated: 362.46, found: 385.2 $[M + Na]^+$ and 401.2 $[M + K]^+$.

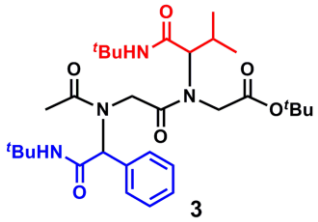
1st Deprotection



2

A solution of **1** (1.26 g, 3.48 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentratedto afford a white solid 1.06 g, quantitative yield. MALDI-TOF Mass of $[C_{16}H_{22}N_2O_4]^+$: calculated: 306.3, found: 307.2 $[M + H]^+$, 329.2 $[M + Na]^+$ and 345.1 $[M + K]^+$.

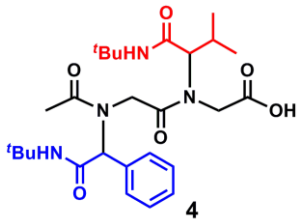
2nd Ugi reaction



3

A solution of **2a** (0.50 g, 3.83 mmol) and isobutyraldehyde (0.35 mL, 3.83 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.43 mL, 3.83 mmol) and **2** (1.06 g, 3.48 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 1.82 g, 90% yield.

2nd Deprotection

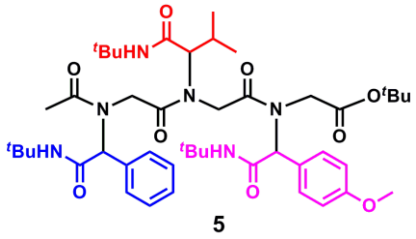


4

A solution of **3** (1.82 g, 3.17 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was

dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 1.65 g, quantitative yield.

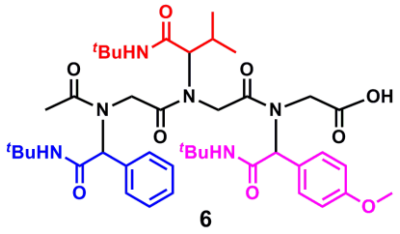
3rd Ugi reaction



5

A solution of **2a** (0.46 g, 3.5 mmol) and anisic aldehyde (0.43 mL, 3.5 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.4 mL, 3.5 mmol) and **4** (1.65 g, 3.17 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 2.43 g, 90% yield.

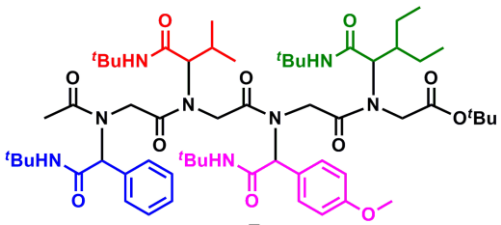
3rd Deprotection



6

A solution of **5** (2.43 g, 2.85 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 2.27 g, quantitative yield.

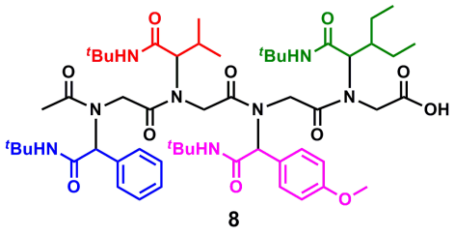
4th Ugi reaction



7

A solution of **2a** (0.42 g, 3.14 mmol) and 2-ethyl-butyraldehyde (0.385 mL, 3.14 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.35 mL, 3.14 mmol) and **6** (2.27 g, 2.85 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 2.83 g, 91% yield.

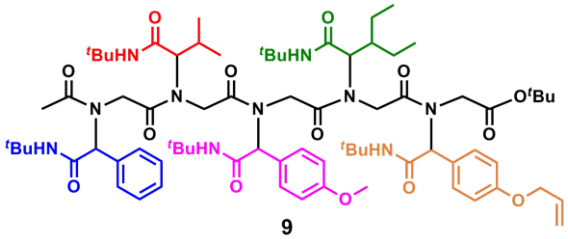
4th Deprotection



8

A solution of **7** (2.83 g, 2.6 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 2.69 g, quantitative yield.

5th Ugi reaction

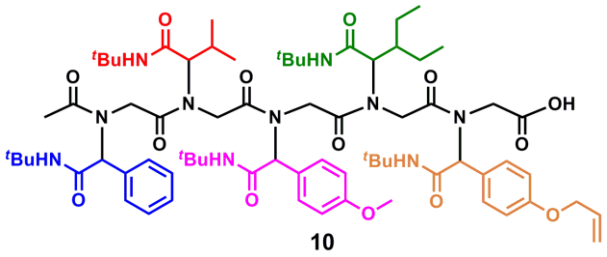


9

A solution of **2a** (0.375 g, 2.86 mmol) and 4-(allyloxy)benzaldehyde (0.47 g, 2.86 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.33 mL, 2.86 mmol) and

8 (2.69 g, 2.6 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 3.35 g, 92% yield. MALDI-TOF Mass of $[C_{76}H_{116}N_{10}O_{14}]^+$: calculated: 1393.7, found: 1415.9 $[M + Na]^+$ and 1431.8 $[M + K]^+$.

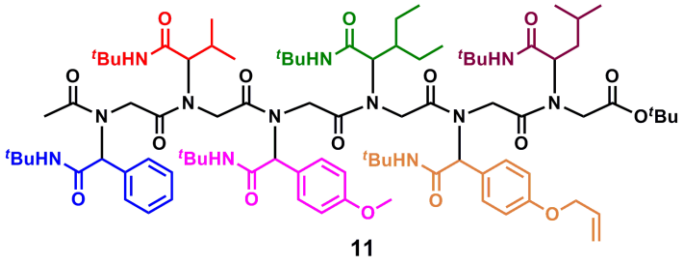
5th Deprotection



10

A solution of **9** (3.35 g, 2.4 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 3.21 g, quantitative yield.

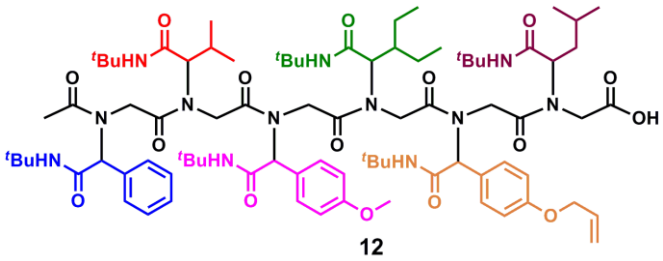
6th Ugi reaction



11

A solution of **2a** (0.35 g, 2.64 mmol) and isovaleraldehyde (0.29 mL, 2.64 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.3 mL, 2.64 mmol) and **10** (3.2 g, 2.4 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 3.5 g, 90% yield.

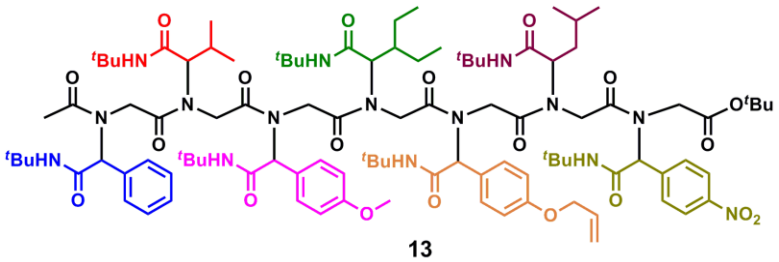
6th Deprotection



12

A solution of **11** (3.5 g, 2.16 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 3.38 g, 99% yield.

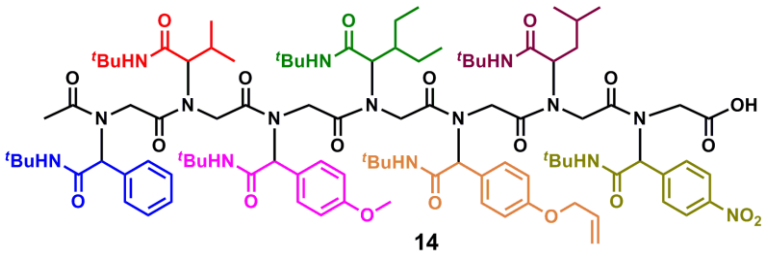
7th Ugi reaction



13

A solution of **2a** (0.32 g, 2.38 mmol) and 4-nitrobenzaldehyde (0.36 g, 2.38 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.27 mL, 2.38 mmol) and **12** (3.38 g, 2.14 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 3.8 g, 92% yield. MALDI-TOF Mass of $[C_{102}H_{155}N_{15}O_{20}]^+$: calculated: 1911.4, found: 1933.1 $[M + Na]^+$.

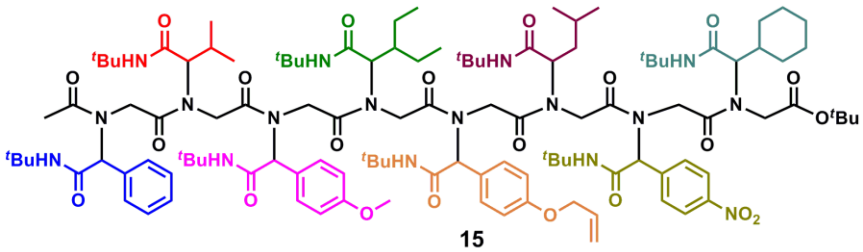
7th Deprotection



14

A solution of **13** (3.8 g, 1.99 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 3.65 g, 99% yield.

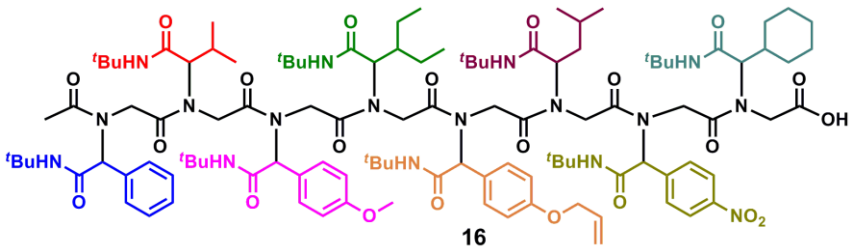
8th Ugi reaction



15

A solution of **2a** (0.28 g, 2.19 mmol) and cyclohexanecarbaldehyde (0.26 mL, 2.19 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.25 mL, 2.19 mmol) and **14** (3.65 g, 1.97 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 3.96 g, 93% yield.

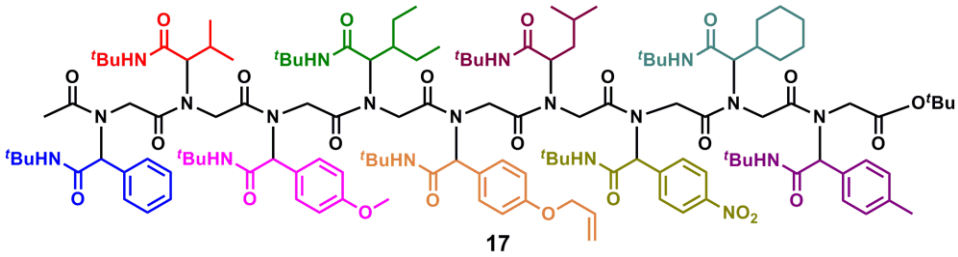
8th Deprotection



16

A solution of **15** (3.96 g, 1.83 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 3.86 g, quantitative yield.

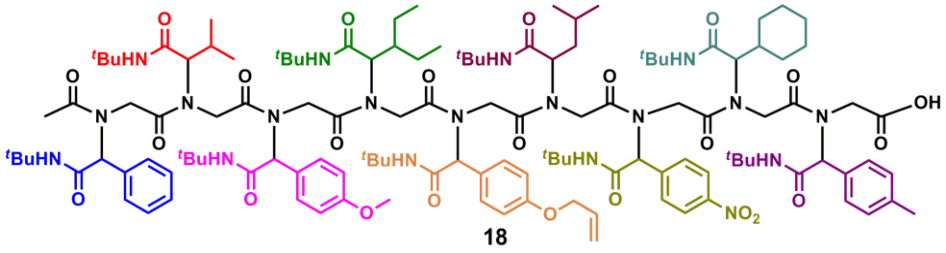
9thUgi reaction



17

A solution of **2a** (0.26 g, 2.01 mmol) and 4-methylbenzaldehyde (0.24 g, 2.01 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.23 mL, 2.01 mmol) and **16** (3.86 g, 1.83 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 4.17 g, 94% yield.

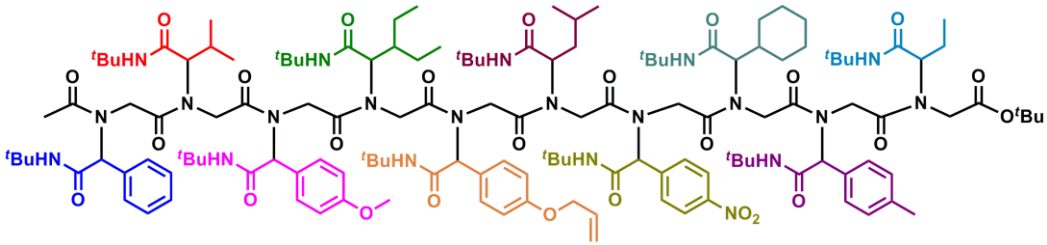
9thDeprotection



18

A solution of **17** (4.17 g, 1.72 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 4.07 g, quantitative yield.

10thUgi reaction

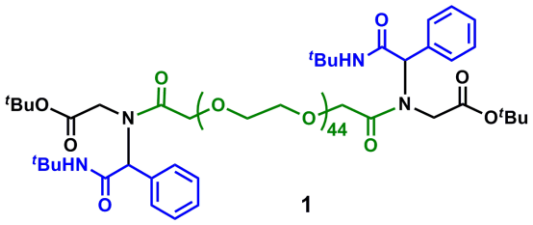


Peptoid 3

A solution of **2a** (0.25 g, 1.89 mmol) andpropionaldehyde (0.14 mL, 1.89 mmol) in methanol was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.22 mL, 1.89 mmol) and **18** (4.07 g, 1.72 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 4.01 g 10-mer Peptoid **3**, 89% yield. MALDI-TOF Mass of $[C_{141}H_{217}N_{21}O_{26}]^+$: calculated: 2622.3, found: 2645.3 $[M + Na]^+$.

7. Synthesis of Peptoid 4 using amino acid building block 2a and bis-COOH-functionalized PEG (M_n = 2000 Da) as the starting materials *via* iterative Ugi reaction

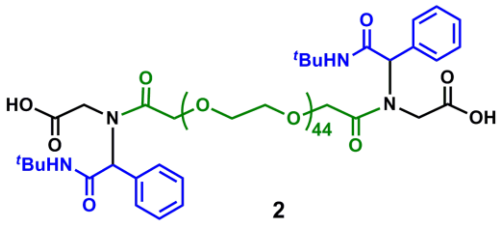
1stUgi reaction



1

A solution of **2a** (0.2 g, 1.5 mmol) and benzaldehyde (0.16 mL, 1.5 mmol) in methanol 2 mL was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.17 mL, 1.5 mmol) and bis-COOH-functionalized PEG (M_n = 2000 Da) (1.0 g, 0.5 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in diethyl ether 20 mL. Centrifugal to afford a white solid 1.25 g, 95% yield.

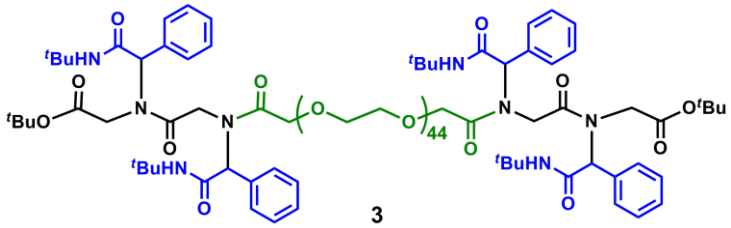
1st Deprotection



2

A solution of **1** (1.25 g, 0.47 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in diethyl ether 20 mL. Centrifugal to afford a white solid 1.20 g, 96% yield.

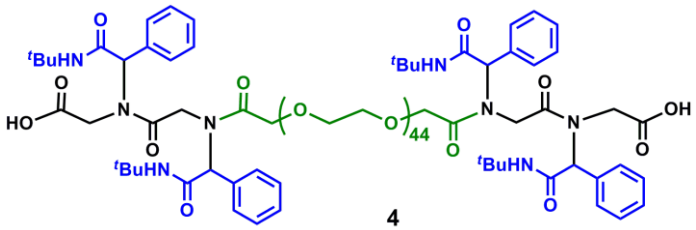
2nd Ugi reaction



3

A solution of **2a** (0.18 g, 1.35 mmol) and benzaldehyde (0.14 mL, 1.35 mmol) in methanol 2 mL was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.16 mL, 1.35 mmol) and **2** (1.2 g, 0.45 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in diethyl ether 20 mL. Centrifugal to afford a white solid 1.32 g, 94% yield.

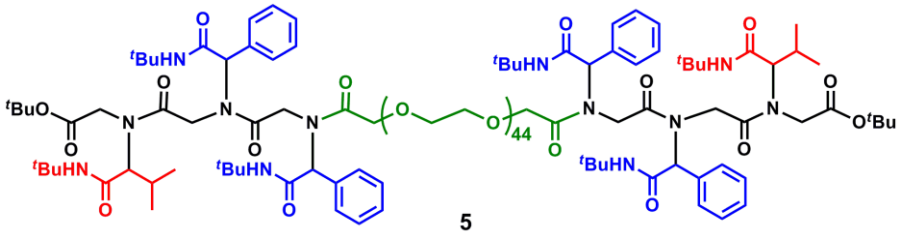
2nd Deprotection



4

A solution of **3** (1.32 g, 0.42 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in diethyl ether 20 mL. Centrifugal to afford a white solid 1.18 g, 93% yield.

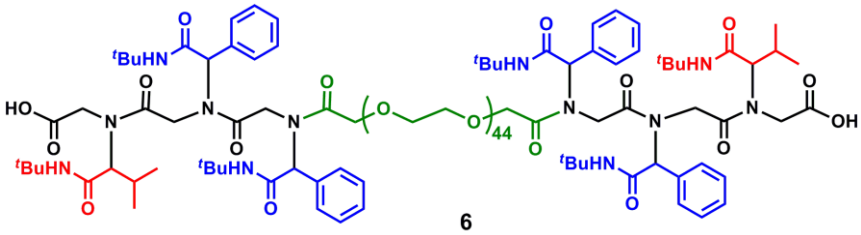
3rd Ugi reaction



5

A solution of **2a** (0.16 g, 1.17 mmol) and isobutyraldehyde (0.11 mL, 1.17 mmol) in methanol 1.5 mL was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.14 mL, 1.17 mmol) and **4** (1.18 g, 0.39 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in diethyl ether 20 mL. Centrifugal to afford a white solid 1.27 g, 92% yield.

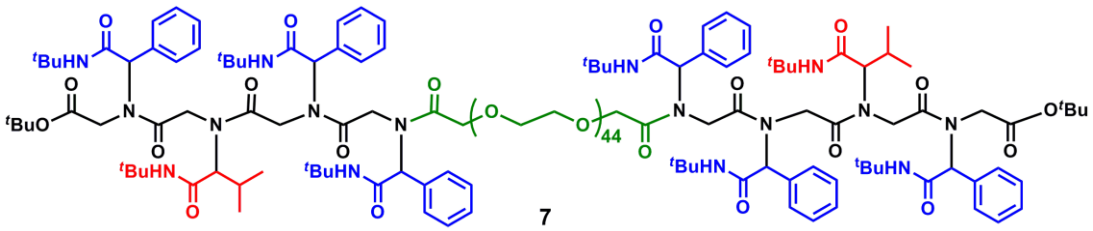
3rd Deprotection



6

A solution of **5** (1.27 g, 0.36 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in diethyl ether 20 mL. Centrifugal to afford a white solid 1.20 g, 97% yield.

4th Ugi reaction

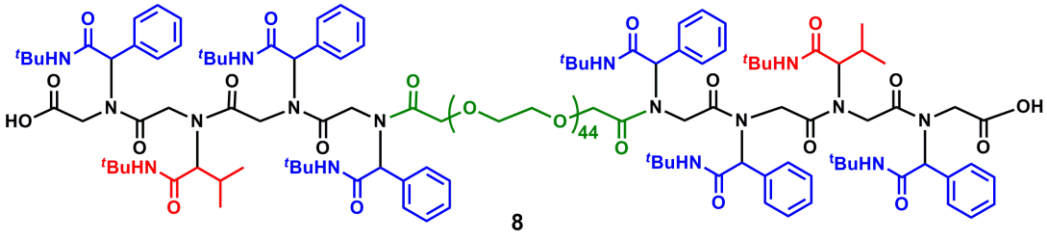


7

A solution of **2a** (0.14 g, 1.05 mmol) and benzaldehyde (0.11 mL, 1.05 mmol) in methanol 1.5 mL was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.12 mL, 1.05 mmol) and **6** (1.2 g, 0.35 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in

diethyl ether 20 mL. Centrifugal to afford a white solid 1.3 g, 92% yield.

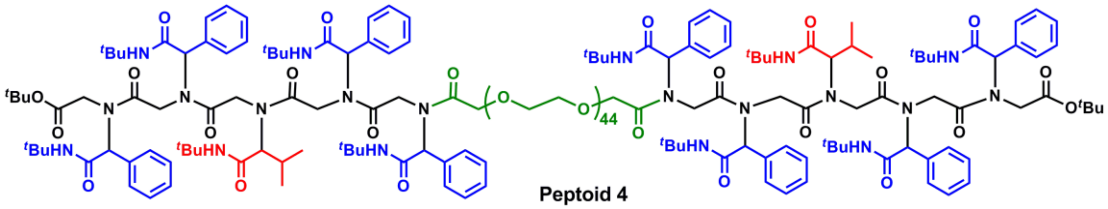
4thDeprotection



8

A solution of **7** (1.3 g, 0.32 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in diethyl ether 20 mL. Centrifugal to afford a white solid 1.18 g, 94% yield.

5thUgi reaction

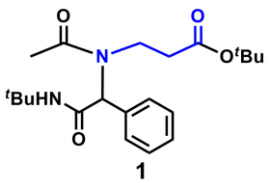


Peptoid 4

A solution of **2a** (0.12 g, 0.9 mmol) and benzaldehyde (0.1 mL, 0.9 mmol) in methanol 1.2 mL was stirred at room temperature for 12 h, *tert*-butyl isocyanide (0.1 mL, 0.9 mmol) and **8** (1.0 g, 0.3 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue was dissolved in dichloromethane 2 mL and precipitated in diethyl ether 20 mL. Centrifugal to afford a white solid 1.29 g, 95% yield.

8. Synthesis of 10-mer *β*-Peptoid 7 using amino acid building block 2d *via* Ugi reaction

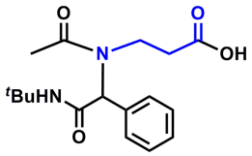
1stUgi reaction



1

A solution of **2d** (0.58 g, 4.0 mmol) and benzaldehyde (0.41 mL, 4.0 mmol) in methanol 8 mL was stirred at room temperature for 2 h, *tert*-butyl isocyanide (0.45 mL, 4.0 mmol) and acetic acid (0.21 mL, 3.64 mmol) were added, the mixture was stirred at room temperature for 12 h. All volatiles were removed in vacuum, the residue dissolved in dichloromethane and purified by flash chromatography on silica gel, using petroleum ether/ethyl acetate/CH_2Cl_2 (1:1:1) as eluent, to give a white solid 1.18 g, 86% yield.

1stDeprotection

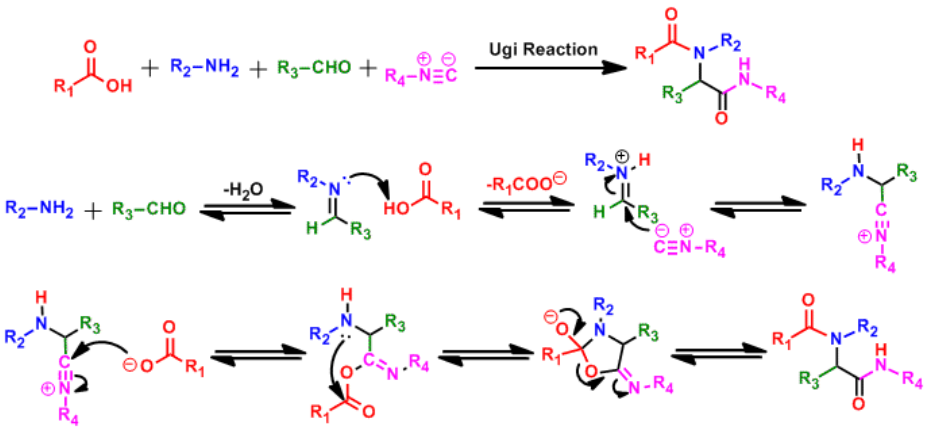


2

A solution of **1** (1.18 g, 3.13 mmol) in dichloromethane/TFA (1:1) 20 mL was stirred at room temperature for 5 h. The dichloromethane and TFA were evaporated in vacuum, the residue was dissolved in dichloromethane and washed with water (2 x 20 mL) and saturated NaCl aqueous (1 x 20 mL). The organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to afford a white solid 1.0 g, 99% yield.

The **10-mer *β*-Peptoid 7** was then synthesized by repeating the above two successive steps for nine times, finally, 1.98 g pale yellow solid was obtained, the total yield of 19 steps is 20%. MALDI-TOF Mass of $[C_{156}H_{212}N_{20}O_{22}]^+$: calculated: 2719.4, found: 2742.4 $[M + Na]^+$.

9. Supplementary Scheme and Figures



Scheme S1. Reaction mechanism of Ugi reaction.

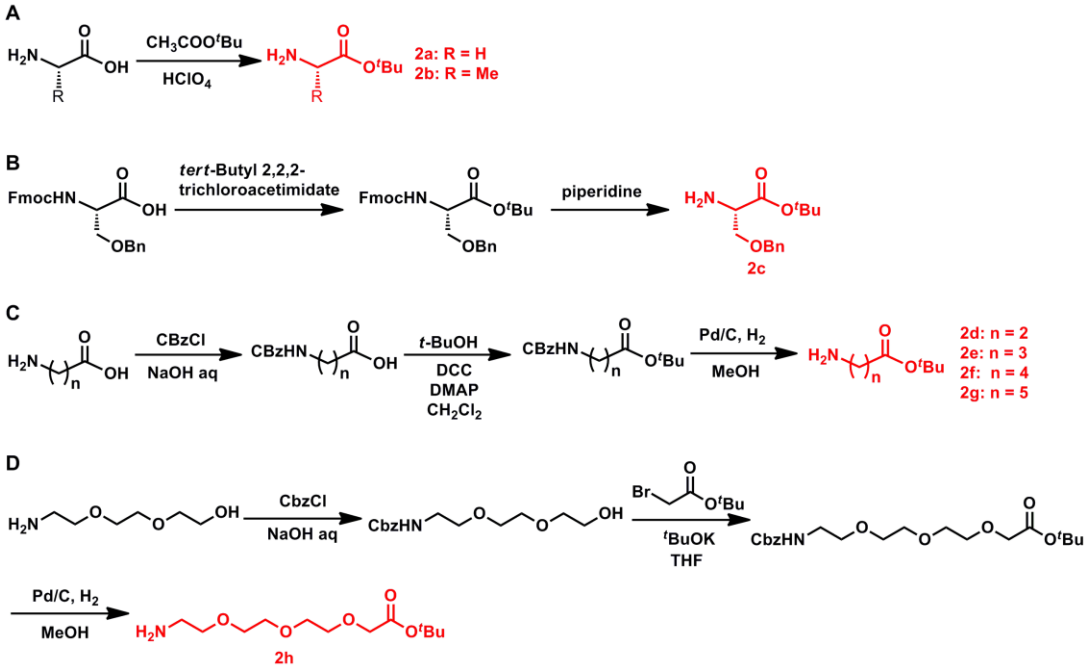


Figure S1. Synthesis of amino acid building-blocks **2a** and **2b** (A), **2c** (B), **2d-2g** (**C**), and **2h** (D).

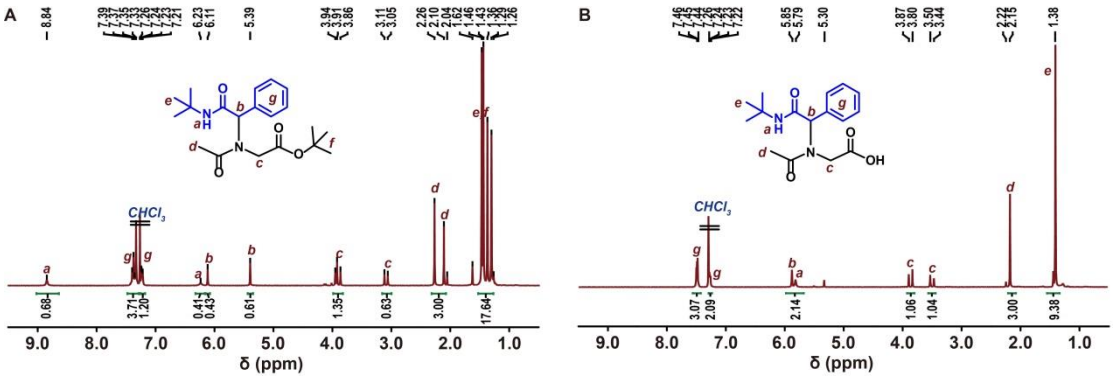


Figure S2. ^{1}H NMR spectra of 1-mer peptoid terminated with -O^{t}Bu from the model reaction (A) and ^{1}H NMR spectra of 1-mer peptoid terminated with –OH from the model reaction (B) (in $CDCl_3$ at 25 ℃).

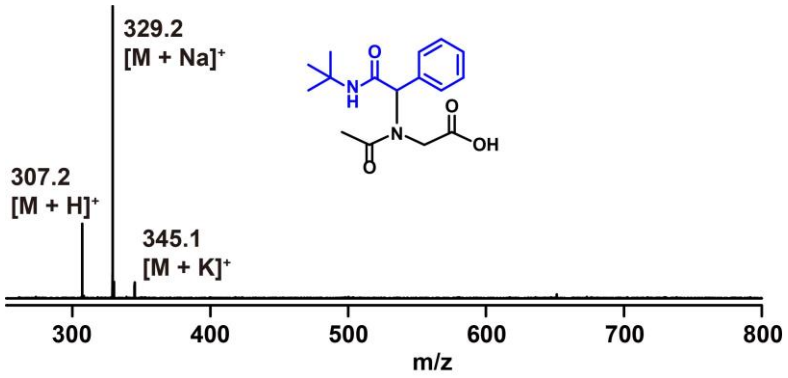


Figure S3. MALDI-TOF-MS spectra of 1-mer peptoid terminated with –OH.

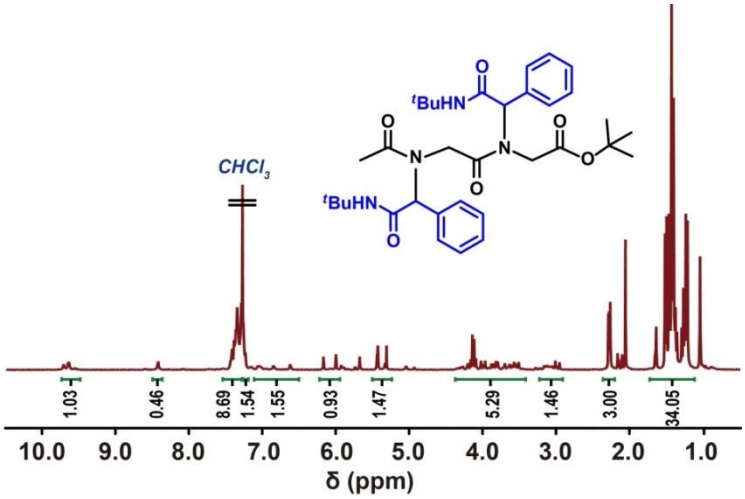


Figure S4. ^{1}H NMR spectra of 2-mer peptoid terminated with -O^{t}Bu from the model reaction (in $CDCl_3$ at 25 ℃).

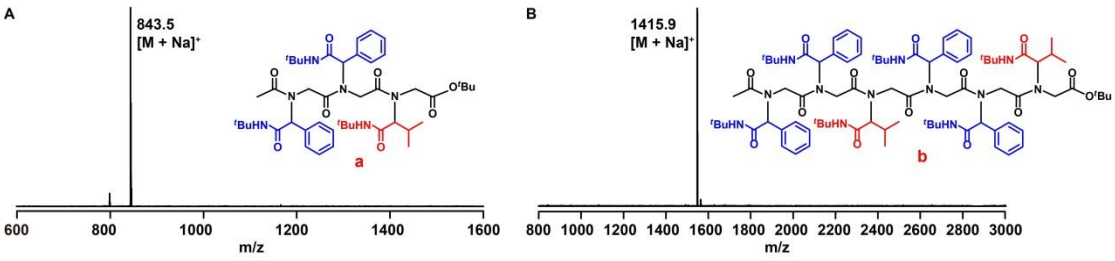


Figure S5. MALDI-TOF-MS spectra of **a** and **b** from the intermediate steps of 9-mer Peptoid **1**.

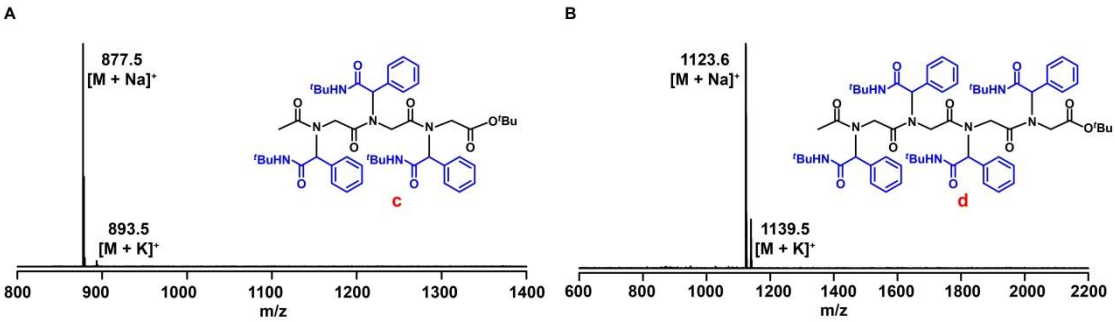


Figure S6. MALDI-TOF-MS spectra of **c** and **d** from the intermediate steps of 10-mer Peptoid **2**.

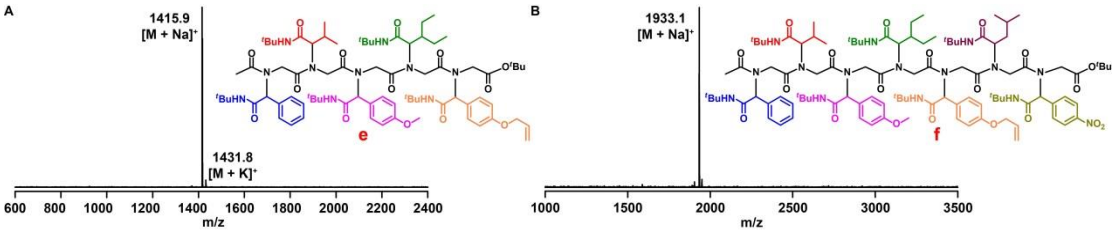


Figure S7. MALDI-TOF-MS spectra of **e** and **f** from the intermediate steps of 10-mer Peptoid **3**.

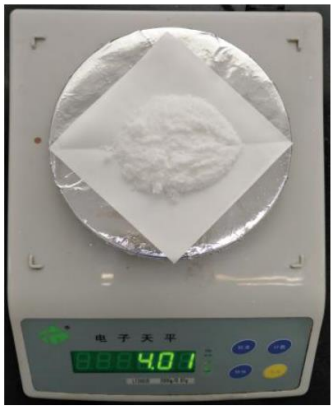


Figure S8. The image shows the total amount of 10-mer Peptoid **3** obtained from the iterative Ugi reaction.

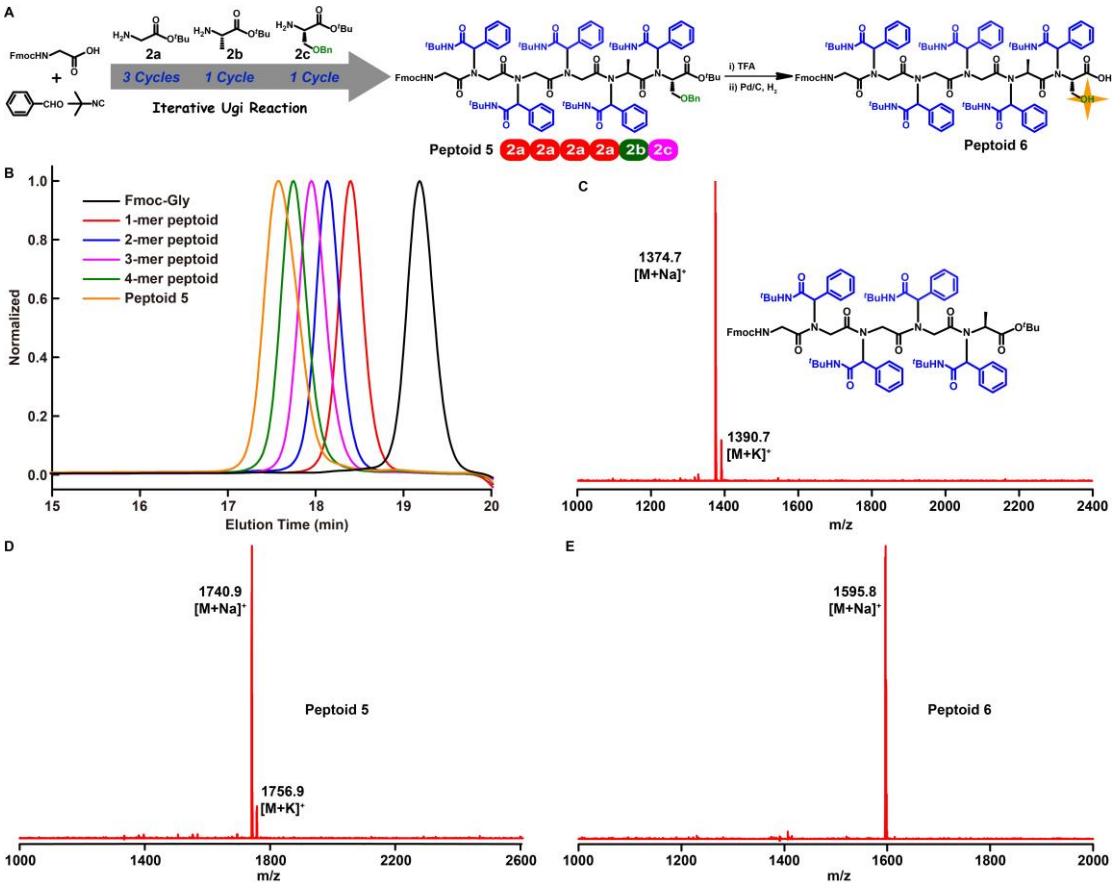


Figure S9. (A) Illustration of peptoid **5** and peptoid **6** synthesizd by iterative Ugi reaction. (B) SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **5** (in THF, 35 ℃, polystyrene as standard). (C) MALDI-TOF-MS spectrum of 4-mer peptoid after Ugi reaction with L-alanine *tert*-butyl ester **2b** as building block. (D) MALDI-TOF-MS spectrum of peptoid **5**. (E) MALDI-TOF-MS spectra of Peptoid **6**.

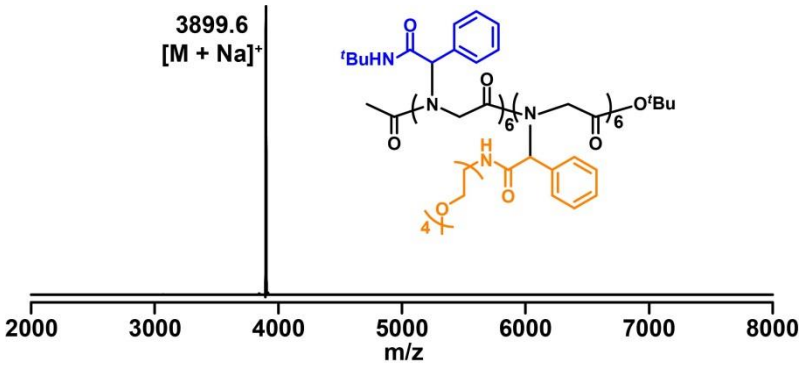


Figure S10. MALDI-TOF-MS spectrum of 12-mer Peptoid **9**.

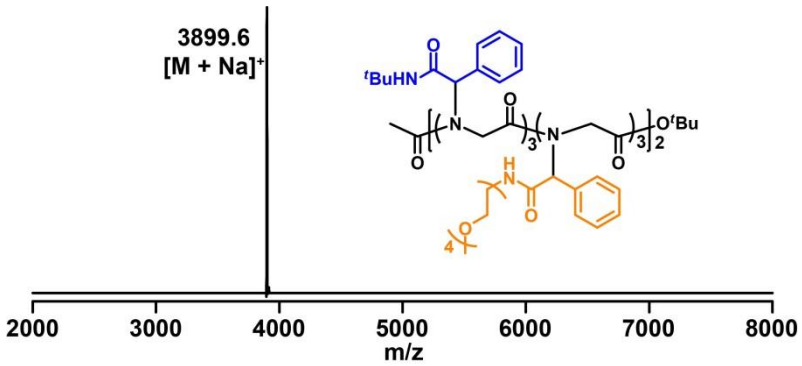


Figure S11. MALDI-TOF-MS spectrum of 12-mer Peptoid **10**.

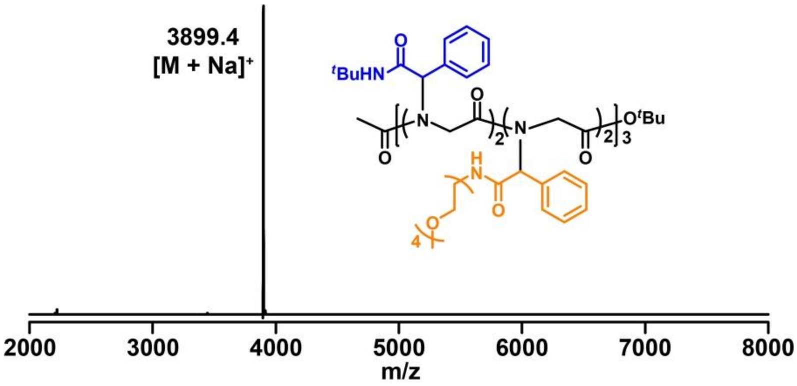


Figure S12. MALDI-TOF-MS spectrum of 12-mer Peptoid **11**.

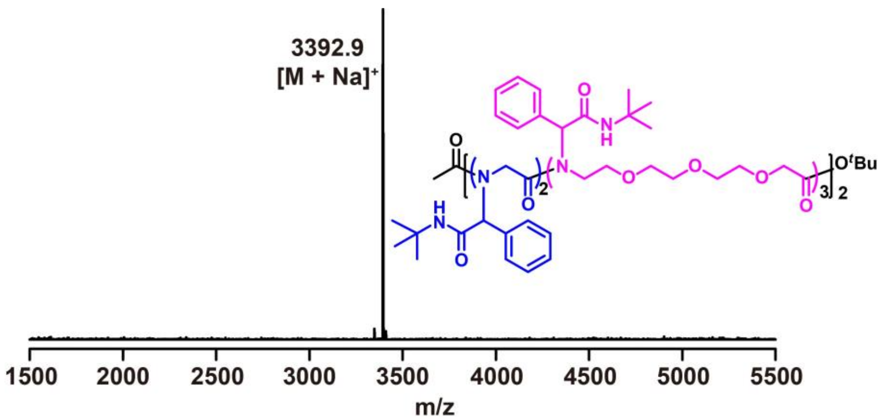


Figure S13. MALDI-TOF-MS spectrum of 12-mer Peptoid **14**.

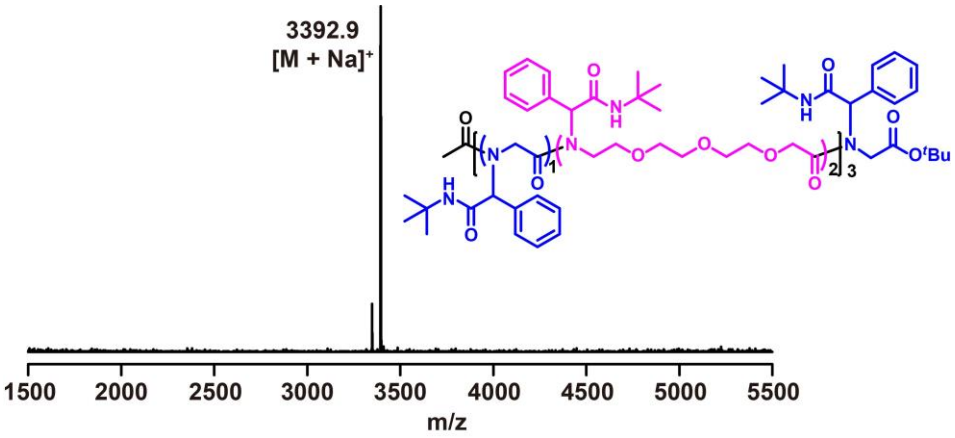


Figure S14. MALDI-TOF-MS spectrum of 12-mer Peptoid **15**.

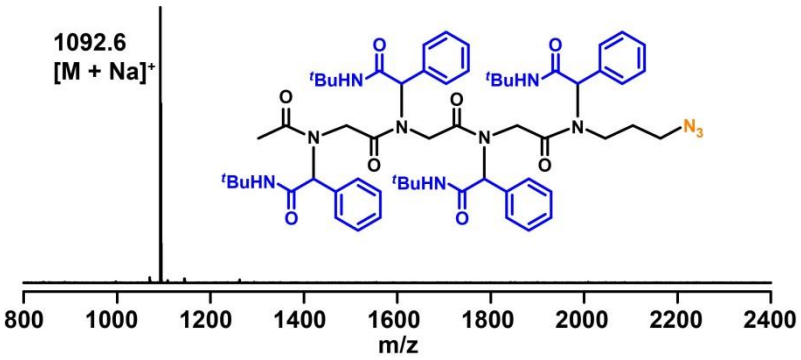


Figure S15. MALDI-TOF-MS spectrum of 4-mer Peptoid **16**.

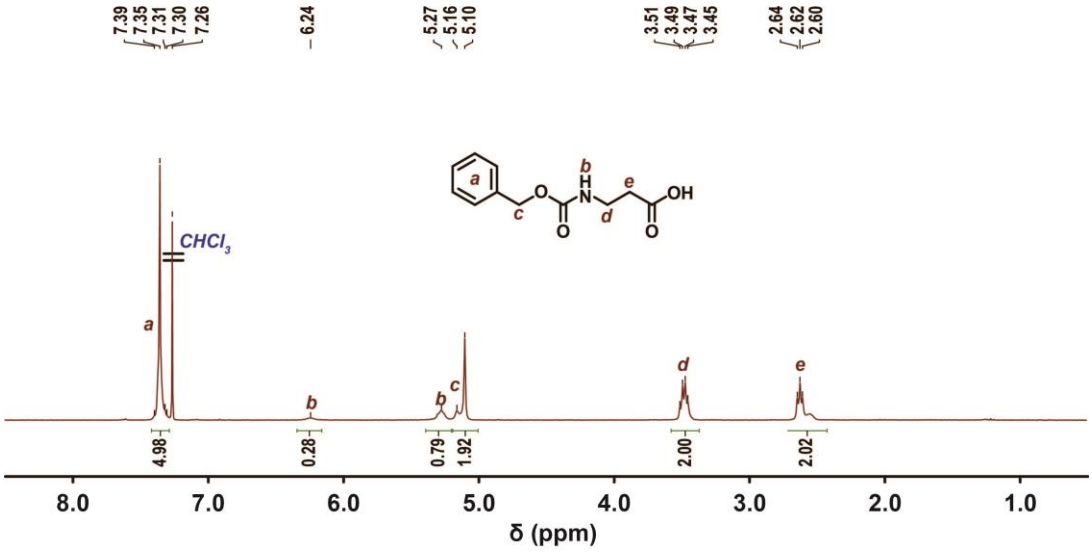


Figure S16. ^{1}H NMR spectra of 3-(((benzyloxy)carbonyl)amino) propanoic acid (in $CDCl_3$ at 25 ℃).

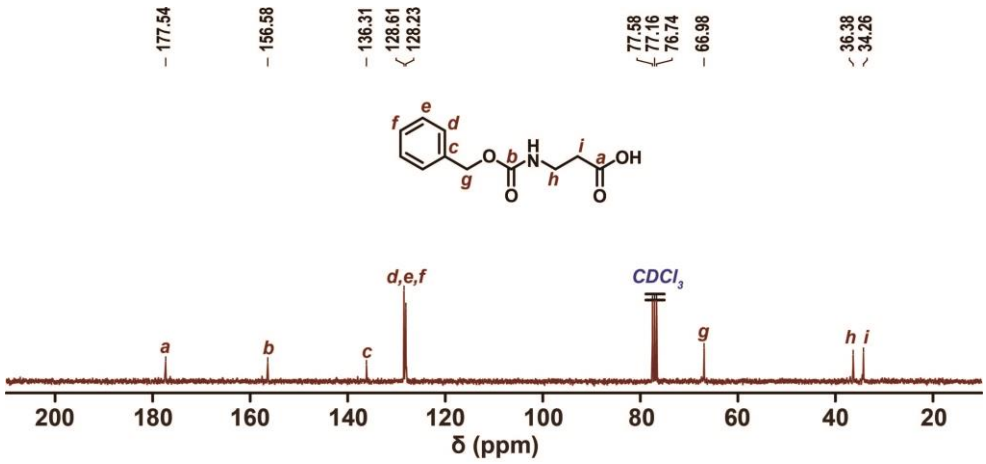


Figure S17. ^{13}C NMR spectra of 3-(((benzyloxy)carbonyl) amino) propanoic acid (in $CDCl_3$ at 25 ℃).

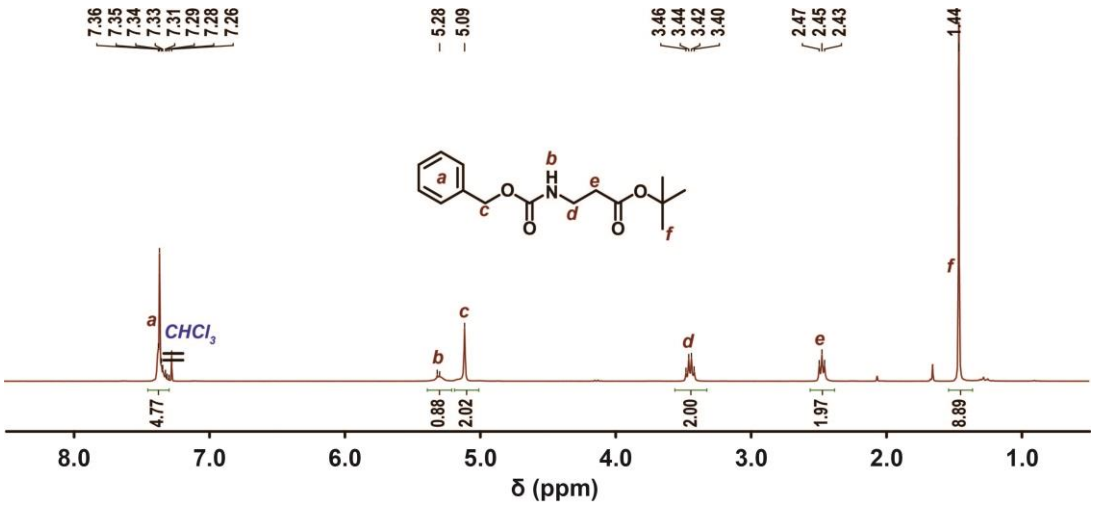


Figure S18. ^{1}H NMR spectra of *tert*-butyl 3-(((benzyloxy) carbonyl) amino) propanoate (in $CDCl_3$ at 25 ℃).

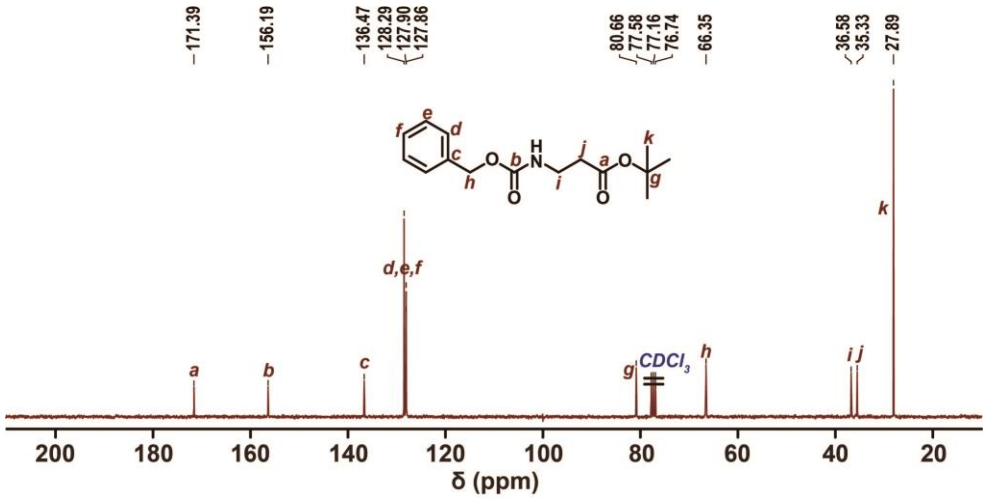


Figure S19. ^{13}C NMR spectra of *tert*-butyl 3-(((benzyloxy)carbonyl) amino) propanoate (in $CDCl_3$ at 25 ℃).

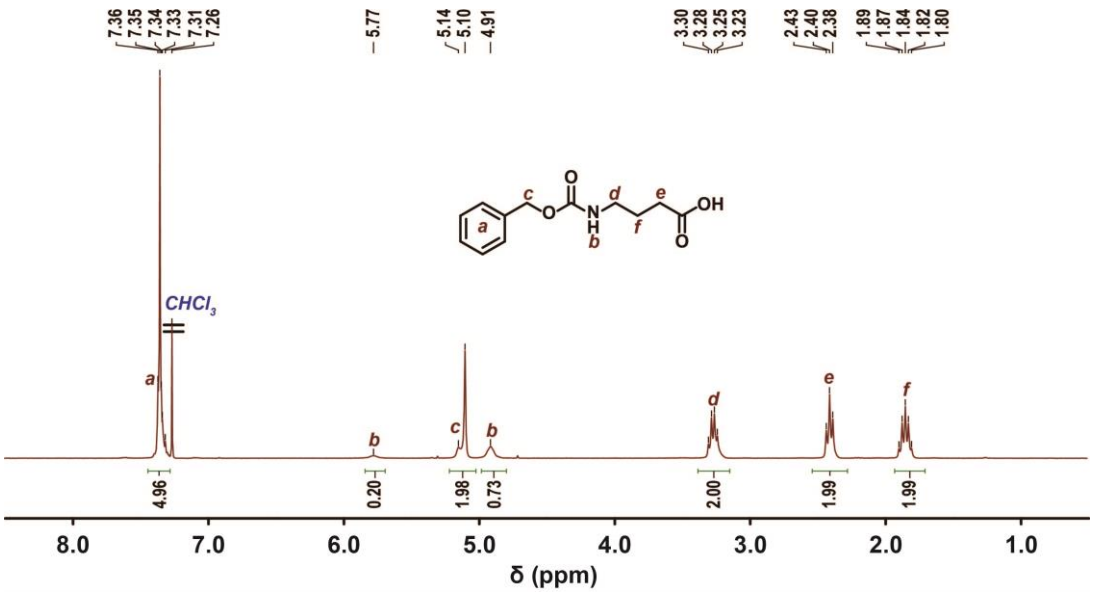


Figure S20. ^{1}H NMR spectra of 4-(((benzyloxy)carbonyl) amino) butanoic acid (in $CDCl_3$ at 25 ℃).

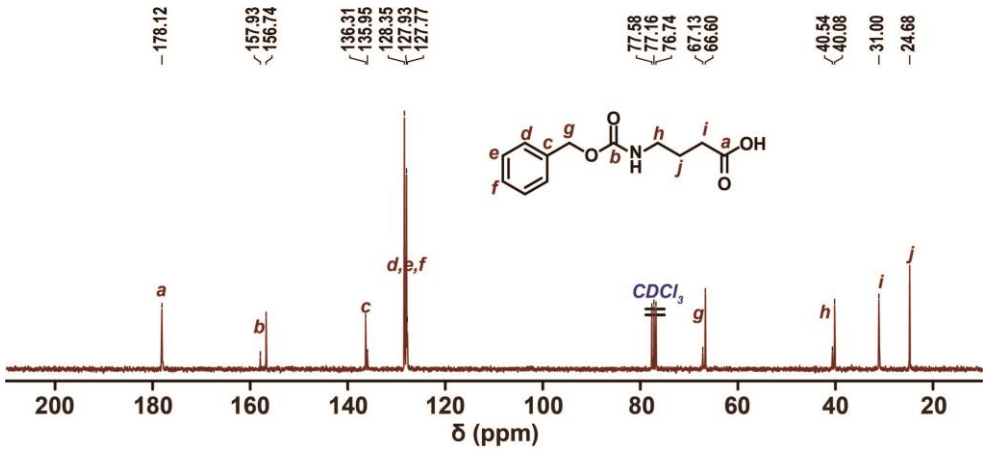


Figure S21. ^{13}C NMR spectra of 4-(((benzyloxy)carbonyl) amino) butanoic acid (in $CDCl_3$ at 25 ℃).

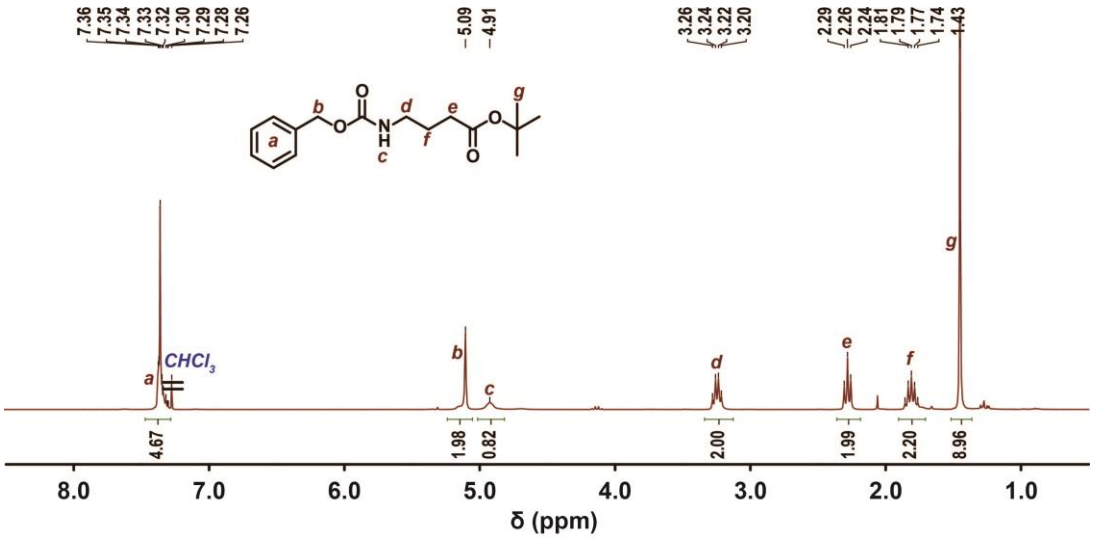


Figure S22. ^{1}H NMR spectra of *tert*-butyl 4-(((benzyloxy)carbonyl) amino) butanoate (in $CDCl_3$ at 25 ℃).

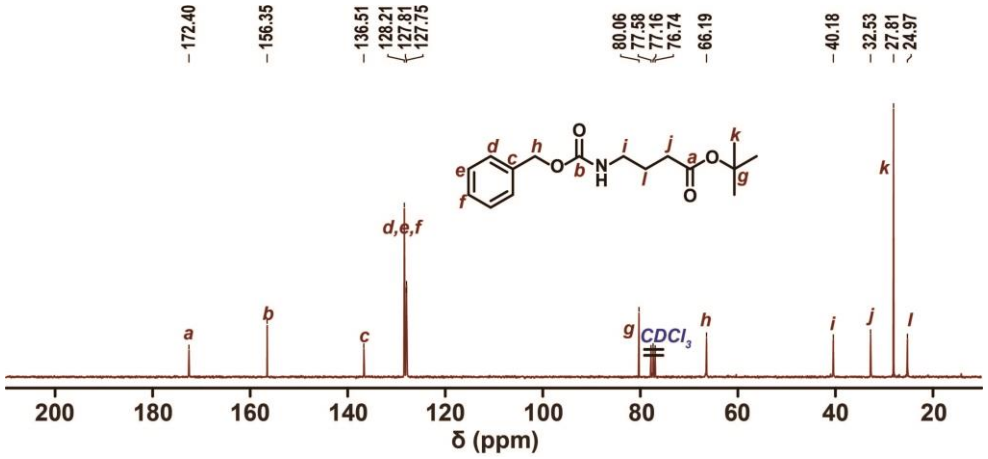


Figure S23. ^{13}C NMR spectra of *tert*-butyl 4-(((benzyloxy)carbonyl) amino) butanoate (in $CDCl_3$ at 25 ℃).

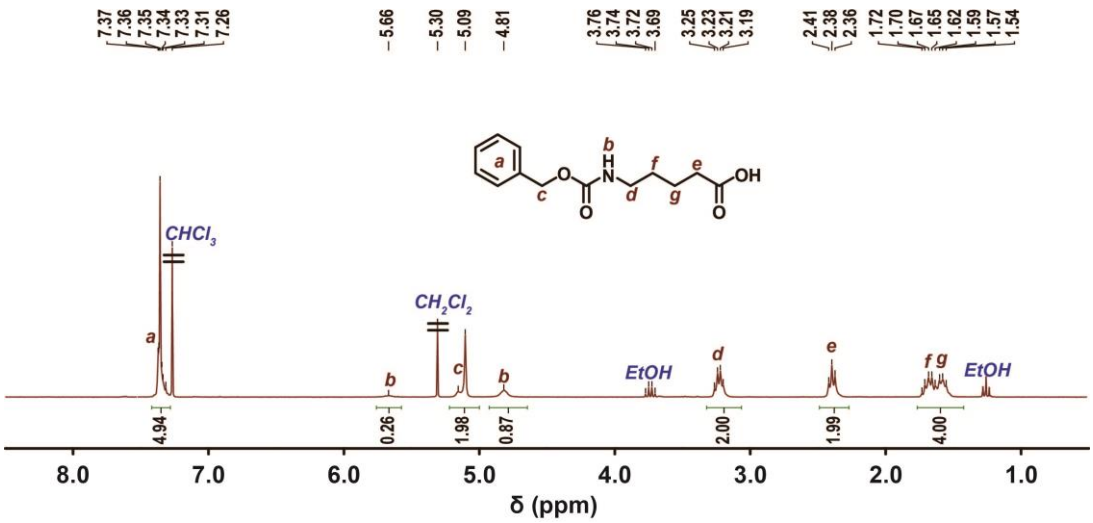


Figure S24. ^{1}H NMR spectra of 5-(((benzyloxy)carbonyl) amino) pentanoic acid (in $CDCl_3$ at 25 ℃).

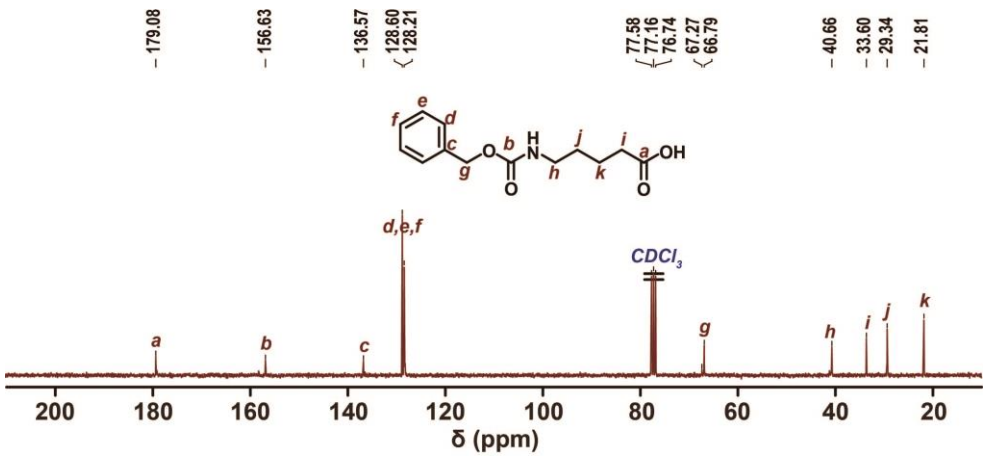


Figure S25. ^{13}C NMR spectra of 5-(((benzyloxy) carbonyl) amino) pentanoic acid (in $CDCl_3$ at 25 ℃).

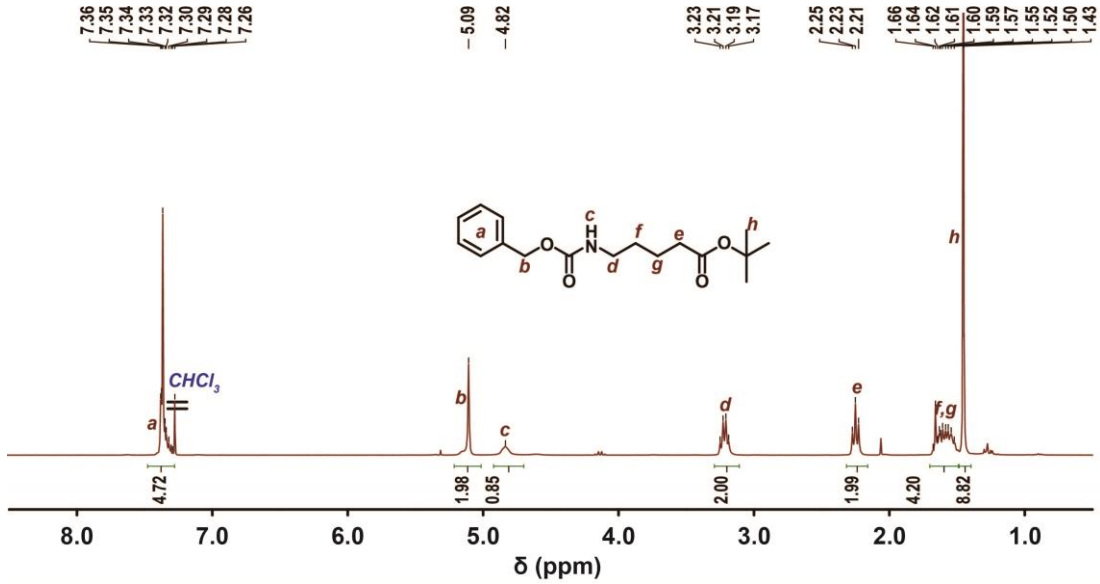


Figure S26. ^{1}H NMR spectra of *tert*-butyl 5-(((benzyloxy) carbonyl) amino) pentanoate (in $CDCl_3$ at 25 ℃).

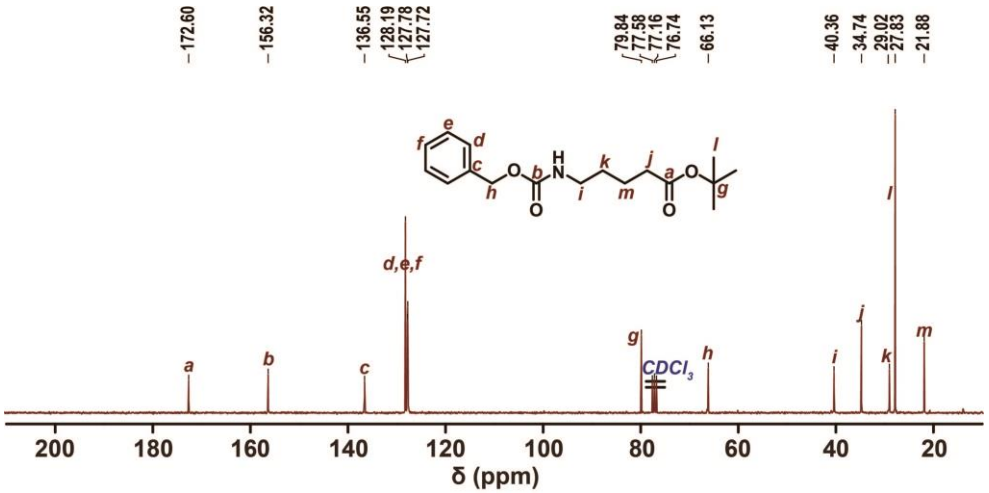


Figure S27. ^{13}C NMR spectra of *tert*-butyl 5-(((benzyloxy) carbonyl) amino) pentanoate (in $CDCl_3$ at 25 ℃).

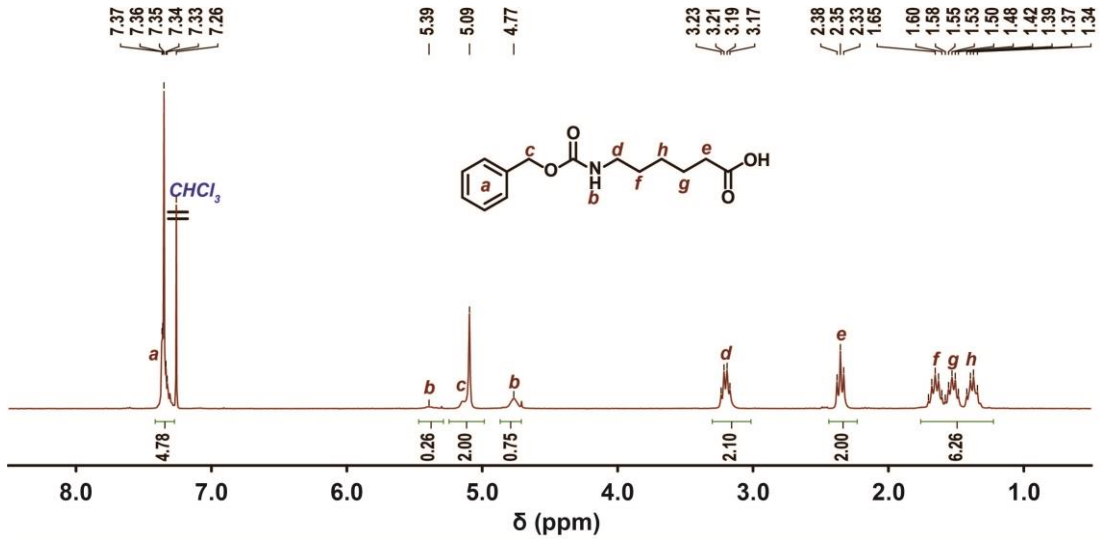


Figure S28. ^{1}H NMR spectra of 6-(((benzyloxy) carbonyl) amino) hexanoic acid (in $CDCl_3$ at 25 ℃).

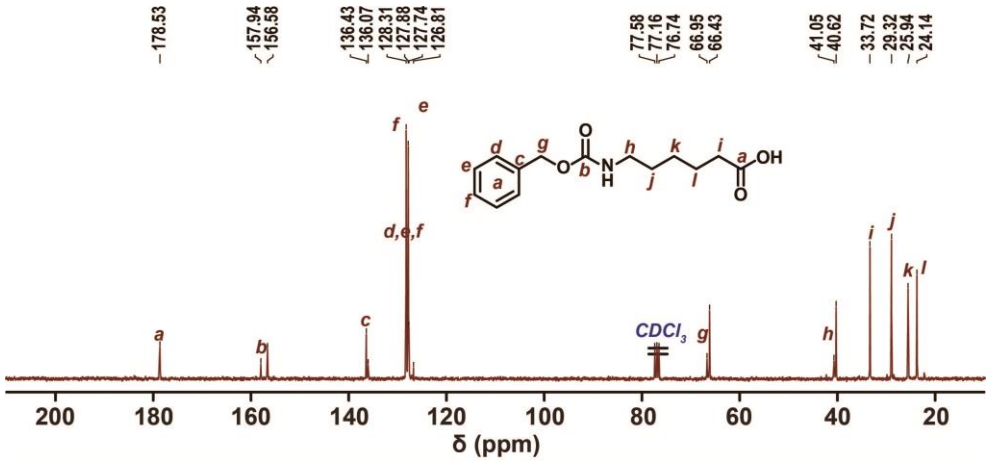


Figure S29. ^{13}C NMR spectra of 6-(((benzyloxy) carbonyl) amino) hexanoic acid (in $CDCl_3$ at 25 ℃).

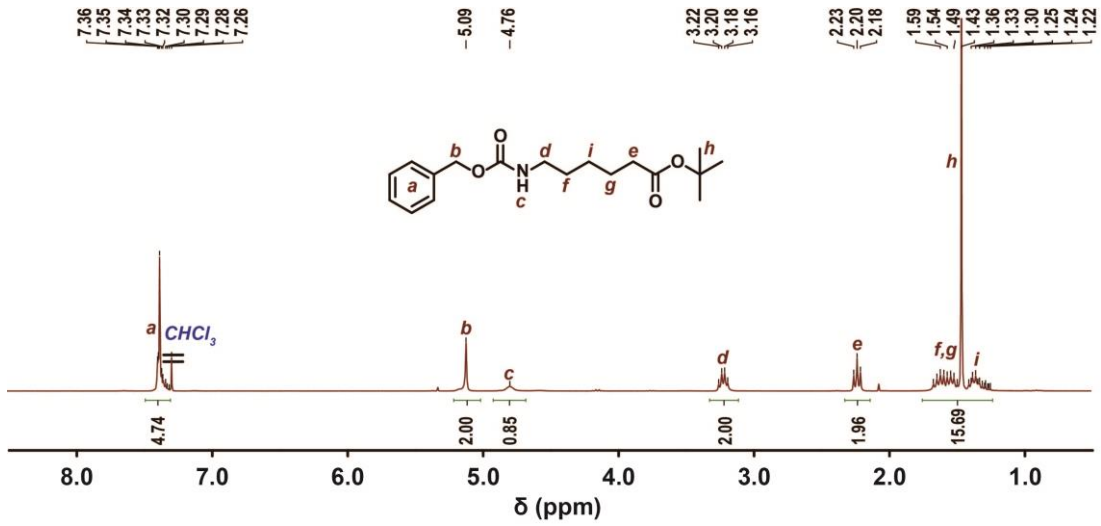


Figure S30. ^{1}H NMR spectra of *tert*-butyl 6-(((benzyloxy) carbonyl) amino) hexanoate (in $CDCl_3$ at 25 ℃).

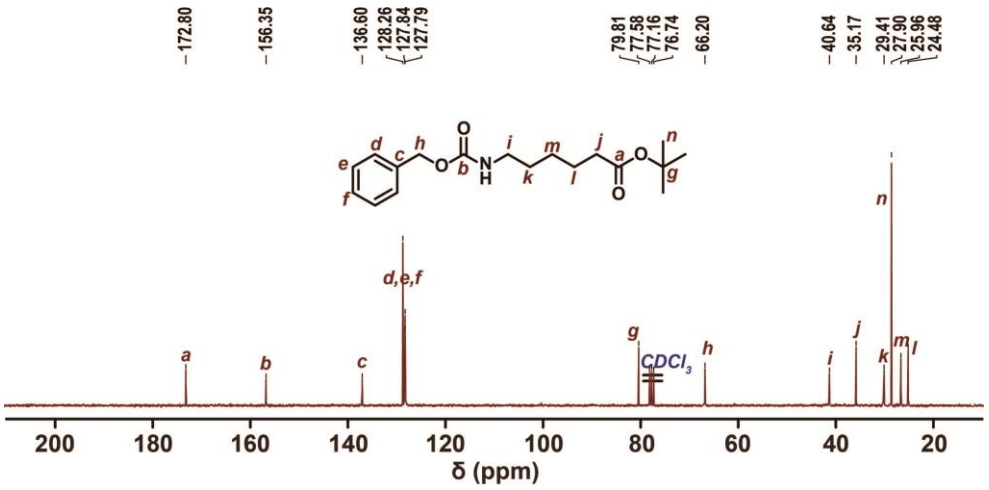


Figure S31. ^{13}C NMR spectra of *tert*-butyl 6-(((benzyloxy) carbonyl) amino) hexanoate (in $CDCl_3$ at 25 ℃).

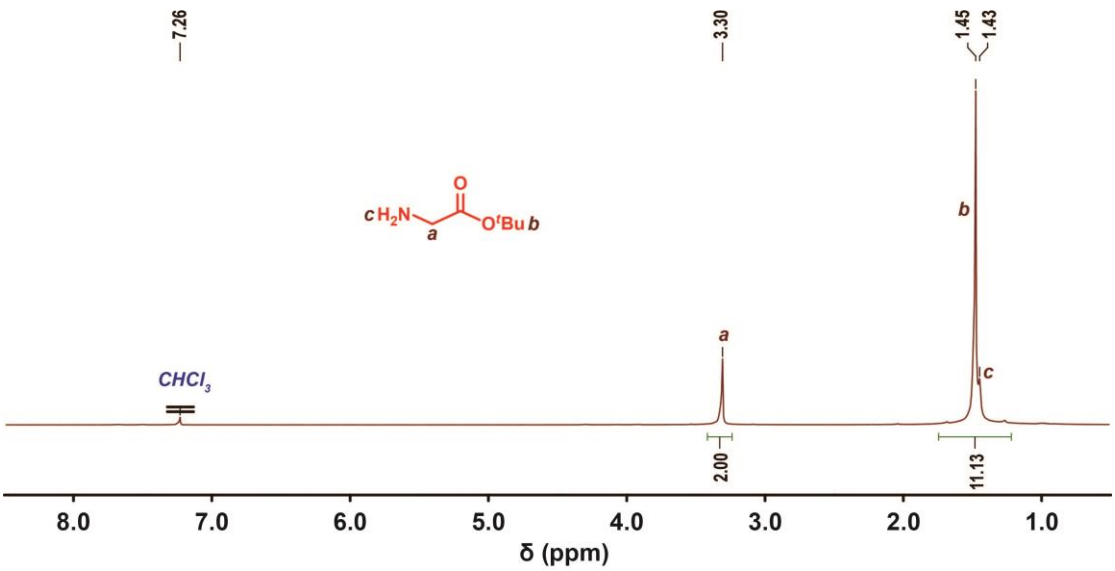


Figure S32. ^{1}H NMR spectra of amino acid building block **2a** (in $CDCl_3$ at 25 ℃).

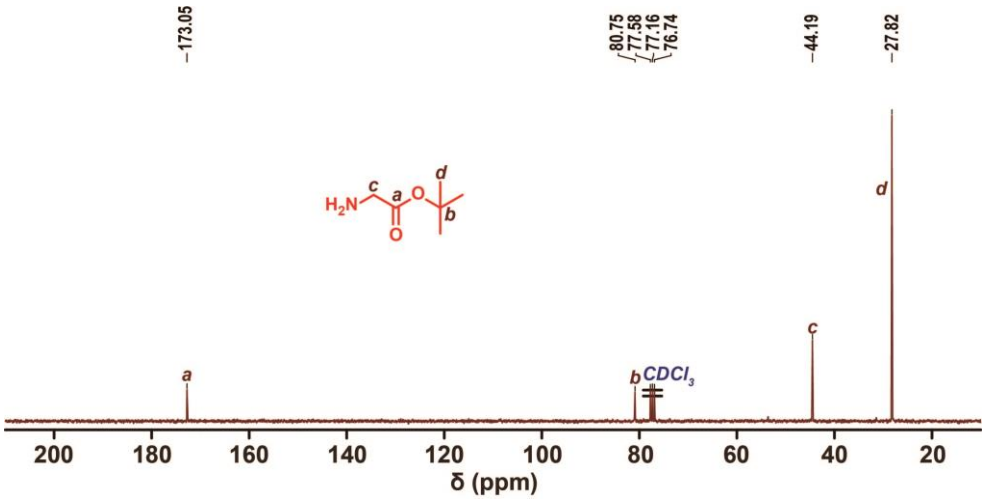


Figure S33. ^{13}C NMR spectra of amino acid building block **2a** (in $CDCl_3$ at 25 ℃).

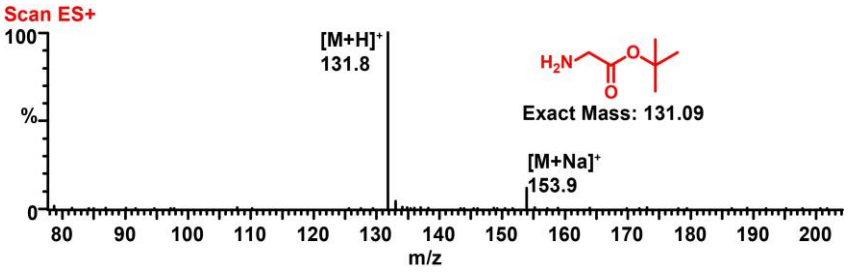


Figure S34. ESI-MS spectra of amino acid building block **2a**.

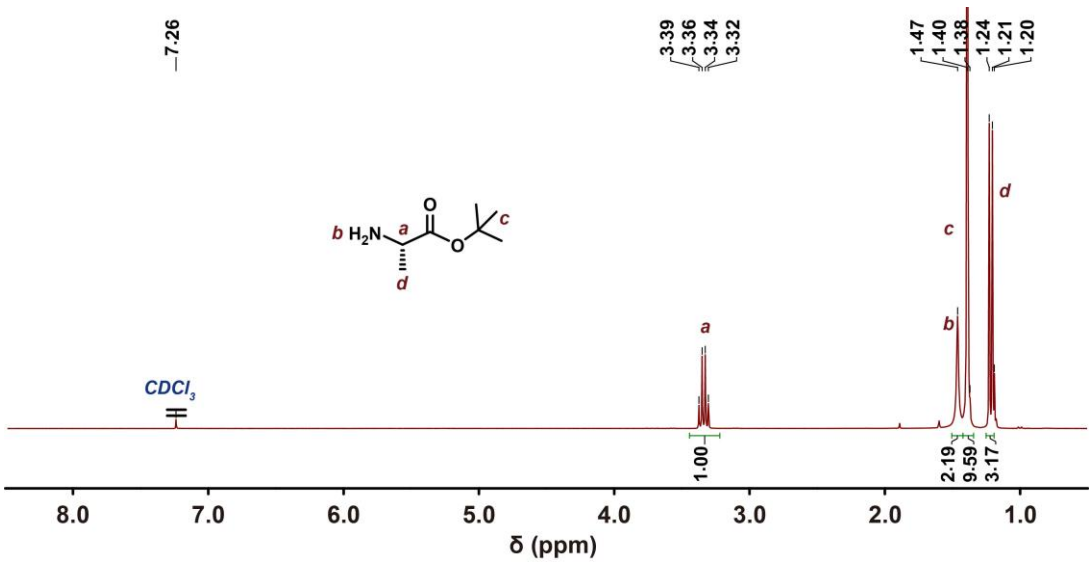


Figure S35. ^{1}**H** NMR spectra of amino acid building block **2b** (in $CDCl_3$ at 25 ℃).

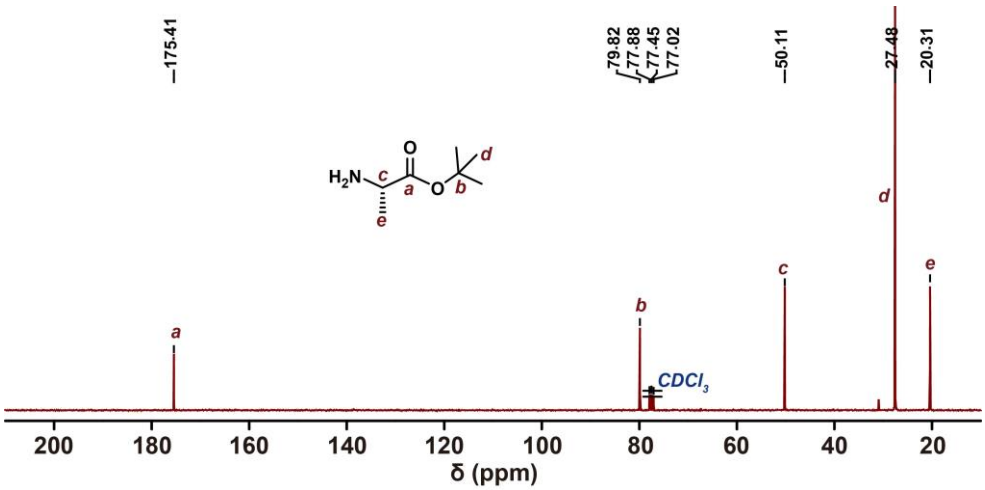


Figure S36. ^{13}C NMR spectra of amino acid building block **2b** (in $CDCl_3$ at 25 ℃).

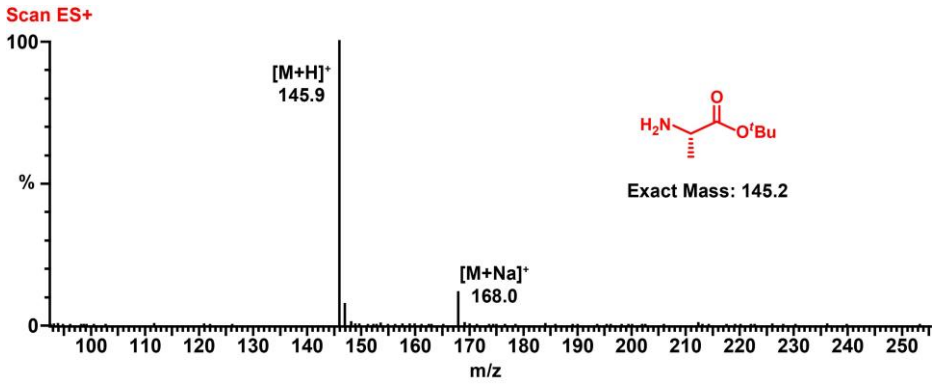


Figure S37. ESI-MS spectrum of amino acid building block **2b**.

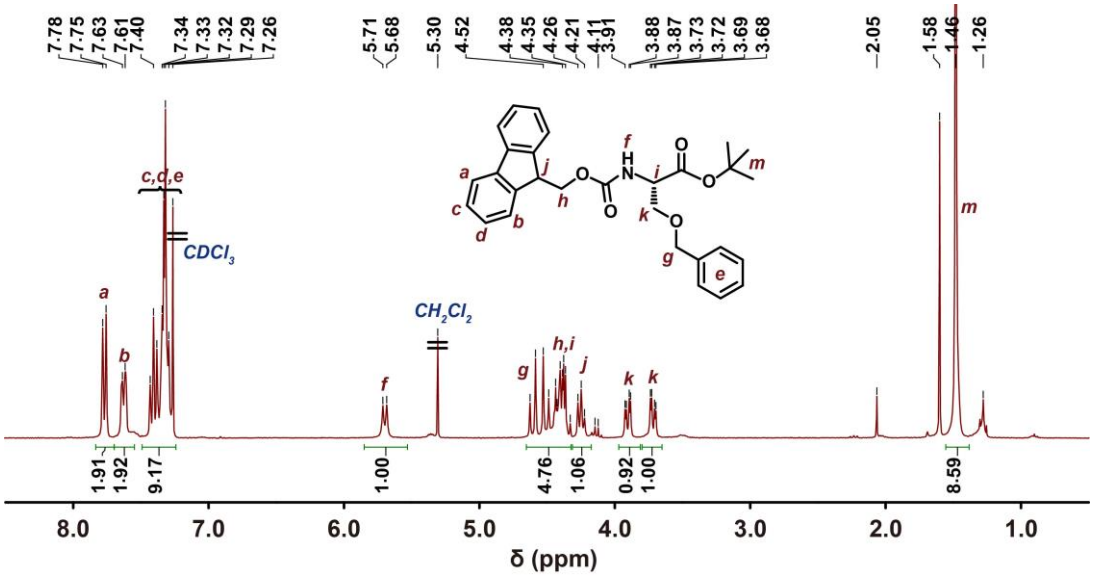


Figure 38. [1]H NMR spectra of (S)-tert-butyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(benzyloxy)propanoate (in $CDCl_3$ at 25 ℃).

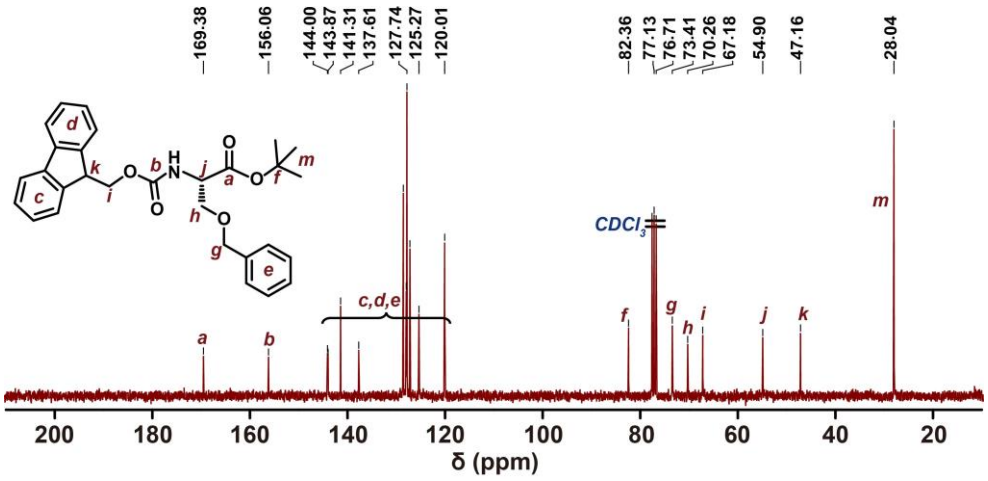


Figure S39. [13]C NMR spectra of (S)-tert-butyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(benzyloxy)propanoate (in $CDCl_3$ at 25 ℃).

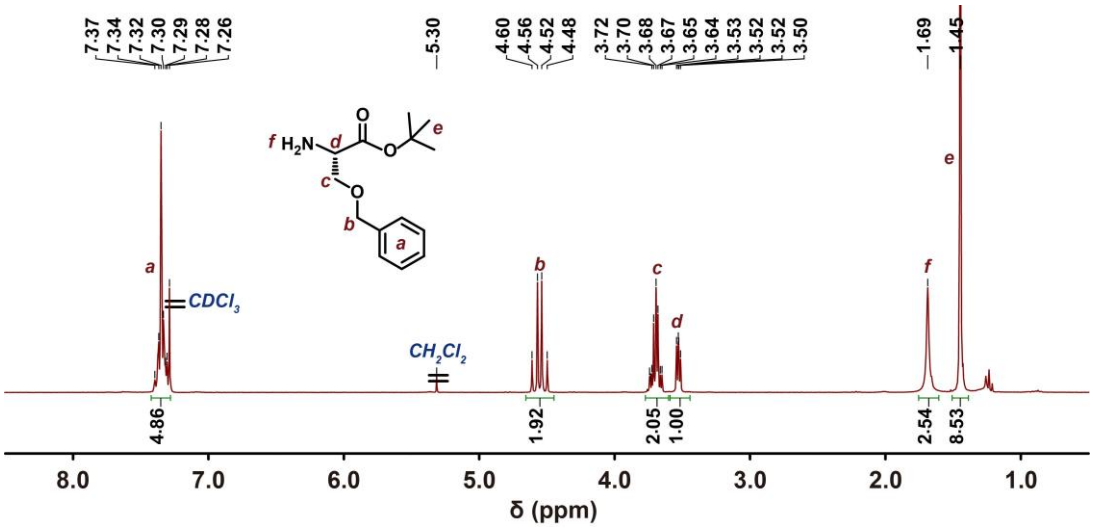


Figure S40. ^{1}H NMR spectra of amino acid building block **2c** (in $CDCl_3$ at 25 ℃).

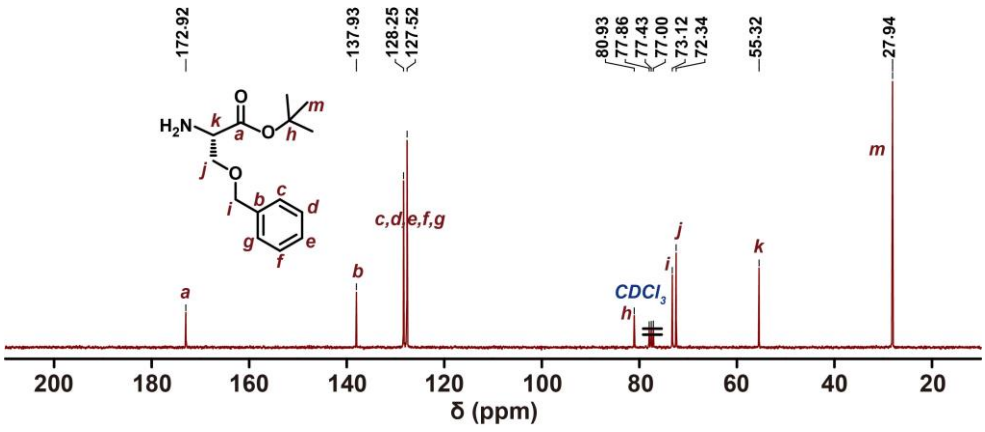


Figure S41. ^{13}C NMR spectra of amino acid building block **2c** (in $CDCl_3$ at 25 ℃).

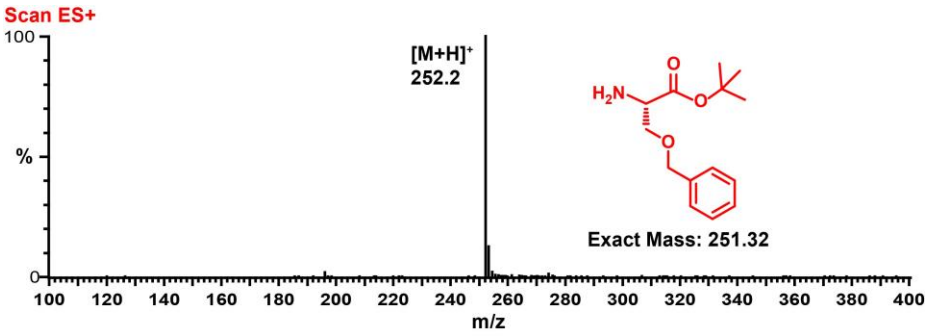


Figure S42. ESI-MS spectrum of amino acid building block **2c**.

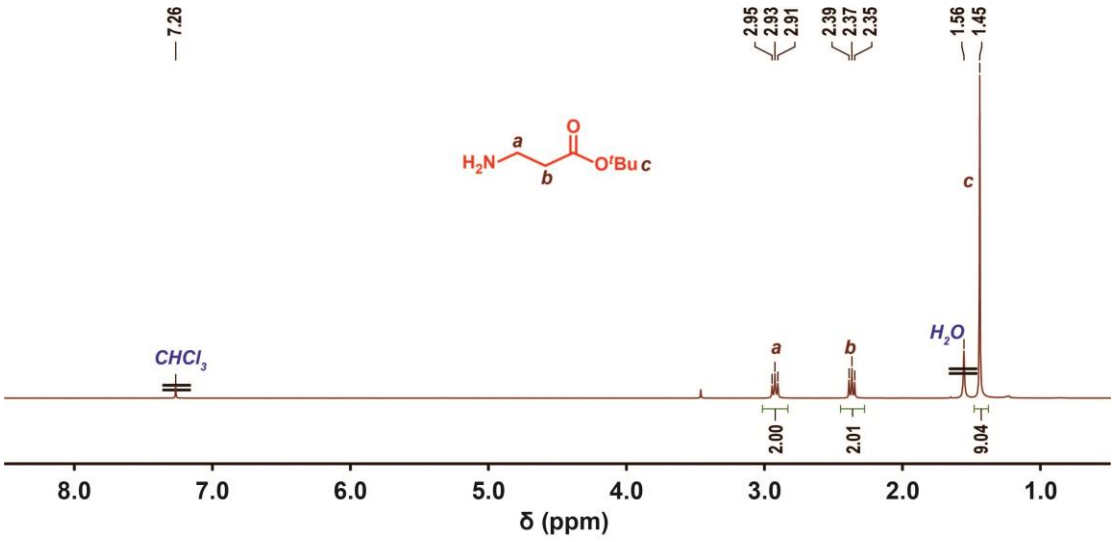


Figure S43. ^{1}H NMR spectra of amino acid building block **2d** (in $CDCl_3$ at 25 ℃).

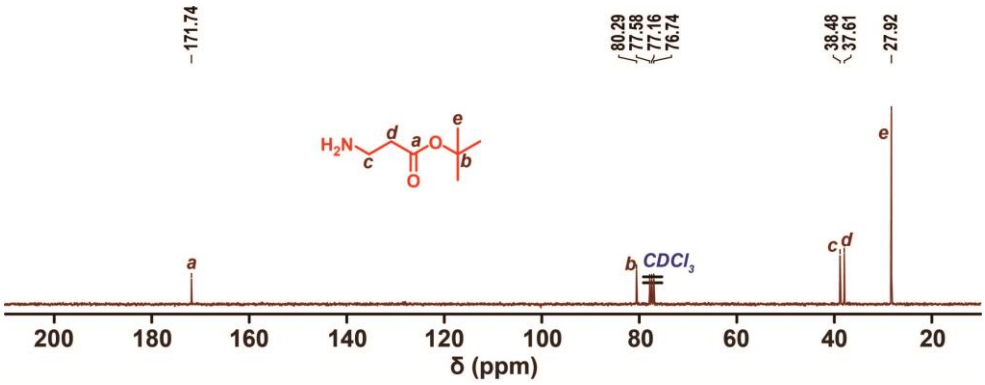


Figure S44. ^{13}C NMR spectra of amino acid building block **2d** (in $CDCl_3$ at 25 ℃).

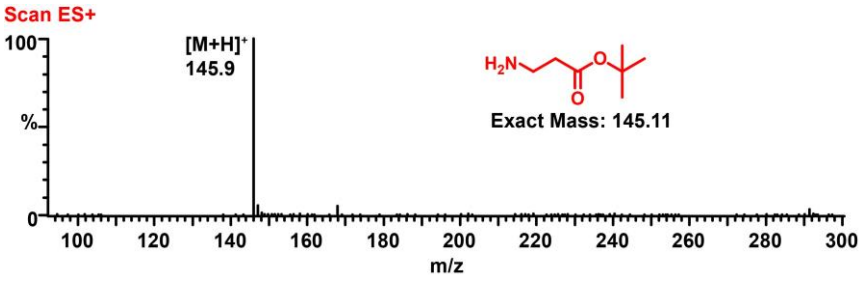


Figure S45. ESI-MS spectra of amino acid building block **2d**.

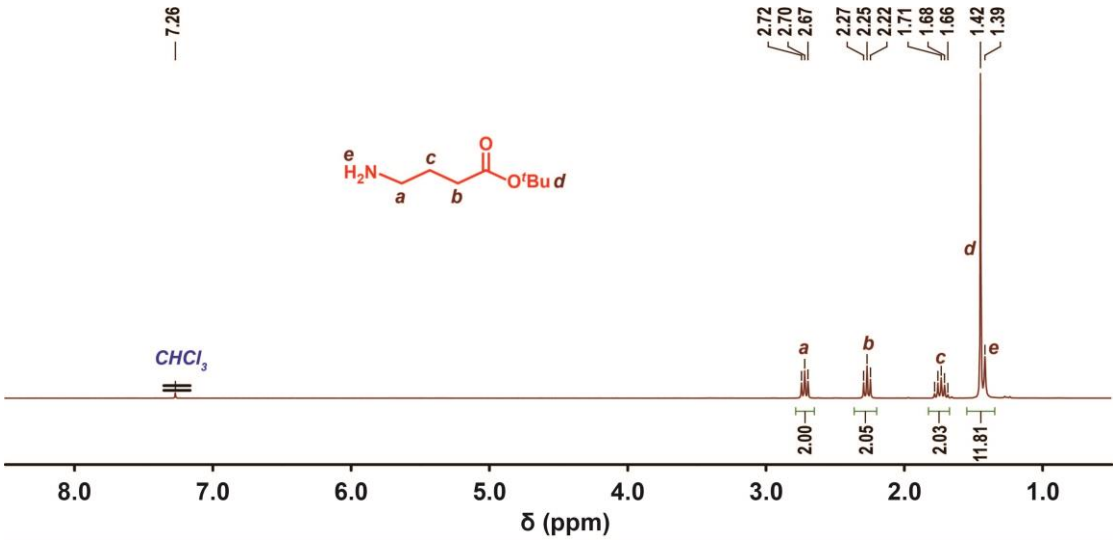


Figure S46. ^{1}H NMR spectra of amino acid building block **2e** (in $CDCl_3$ at 25 ℃).

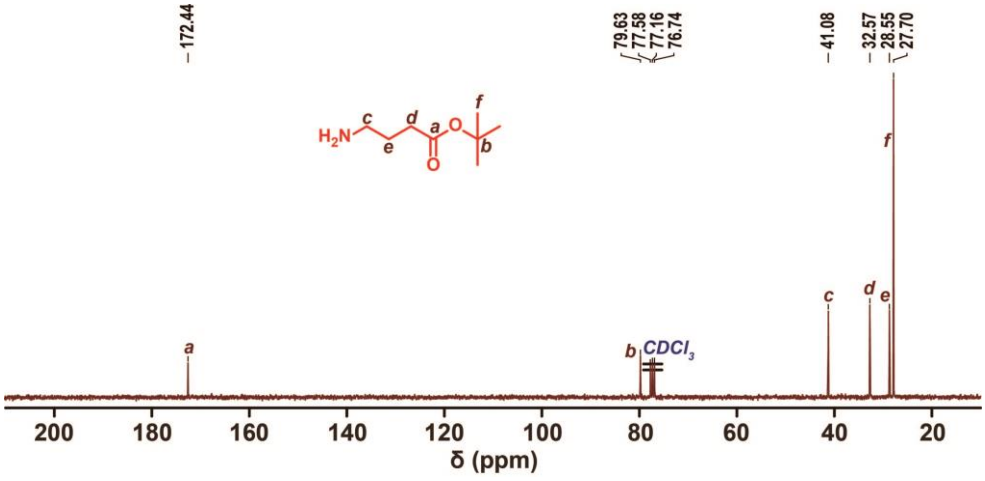


Figure S47. ^{13}C spectra of amino acid building block **2e** (in $CDCl_3$ at 25 ℃).

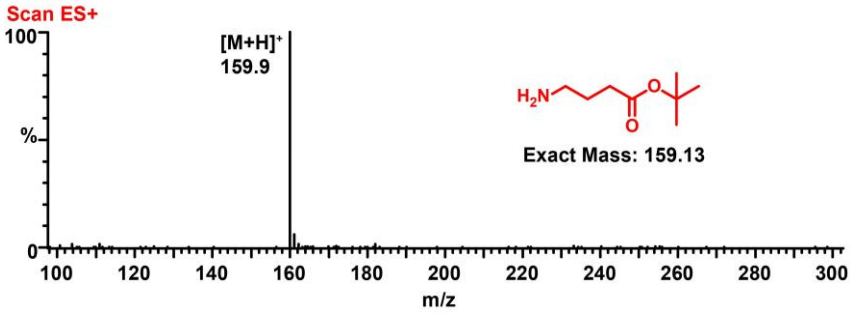


Figure S48. ESI-MS spectra of amino acid building block **2e.**

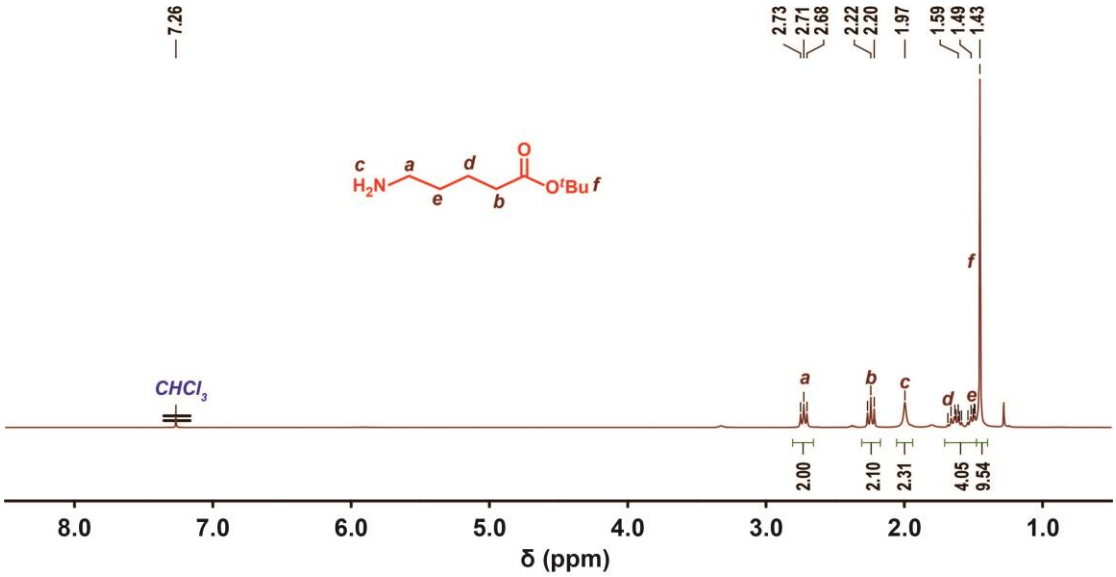


Figure S49. ^{1}H NMR spectra of amino acid building block **2f** (in $CDCl_3$ at 25 ℃).

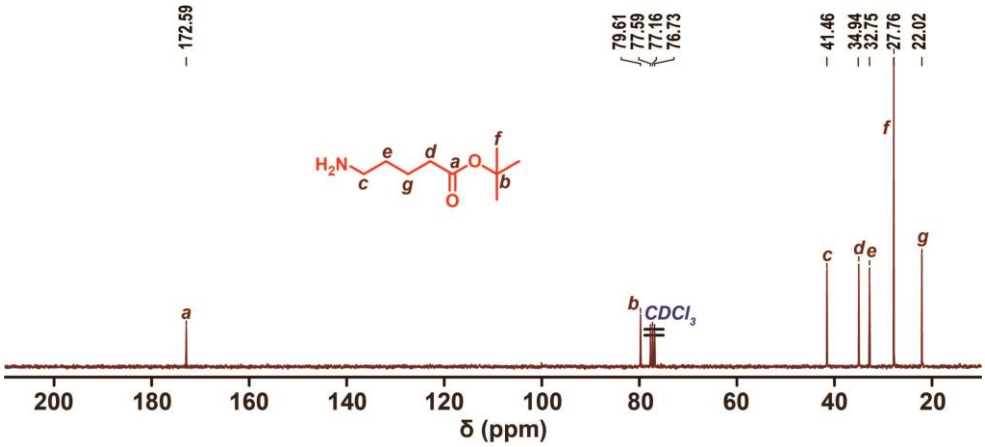


Figure S50. ^{13}C NMR spectra of amino acid building block **2f** (in $CDCl_3$ at 25 ℃).

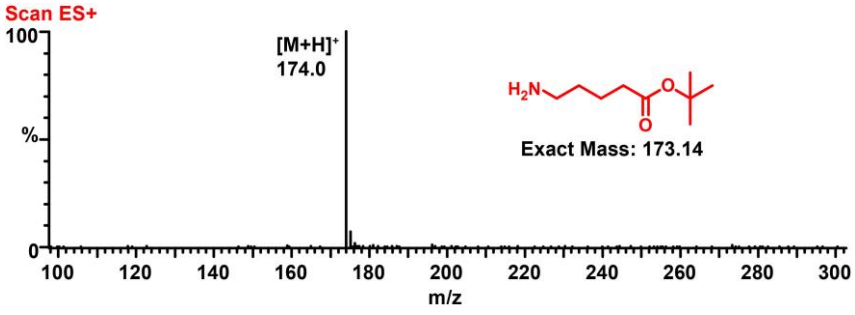


Figure S51. ESI-MS spectrum of amino acid building block **2f**.

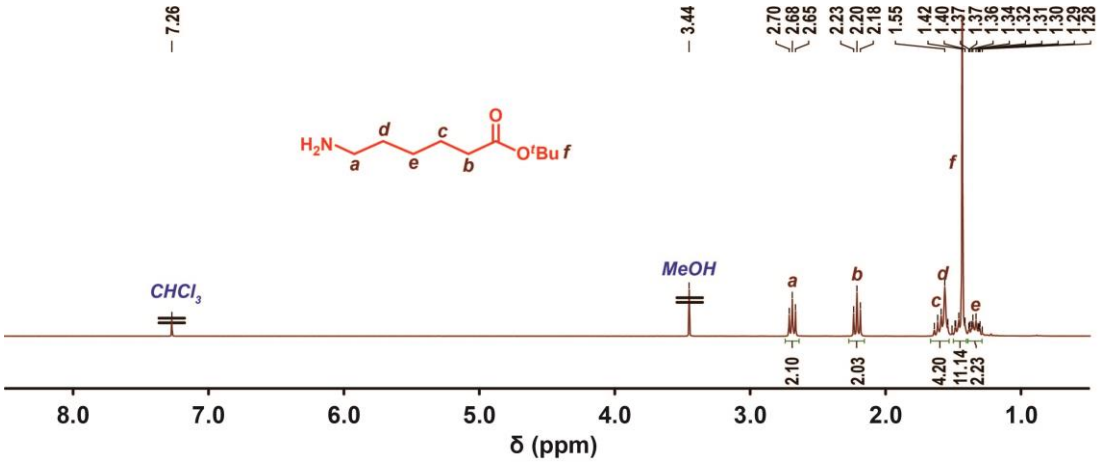


Figure S52. [1]H NMR spectra of amino acid building block **2g** (in $CDCl_3$ at 25 ℃).

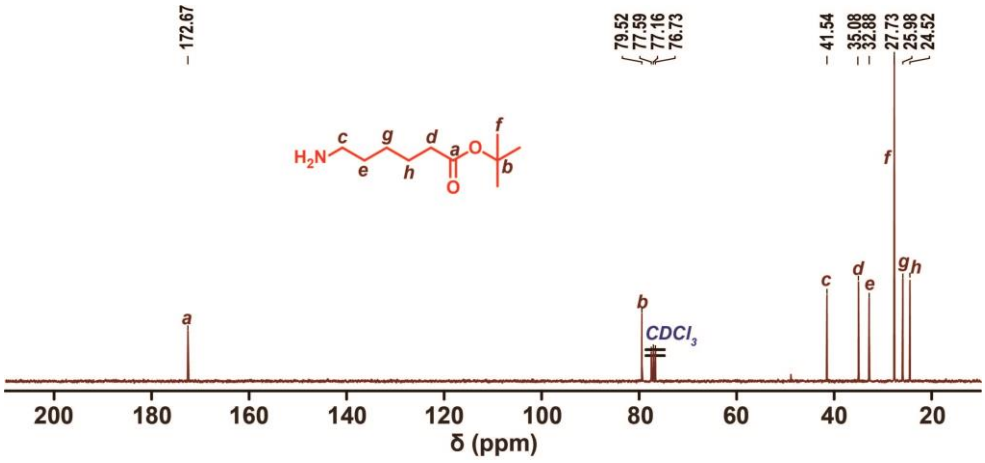


Figure S53. [13]C NMR spectra of amino acid building block **2g** (in $CDCl_3$ at 25 ℃).

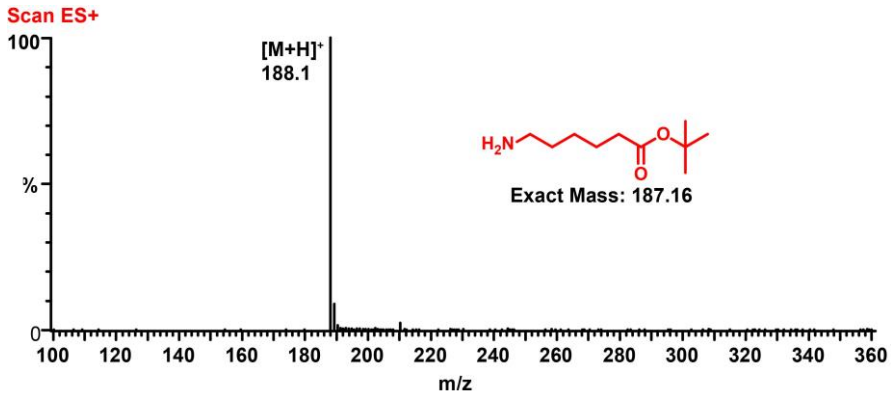


Figure S54. ESI-MS spectrum of amino acid building block **2g**.

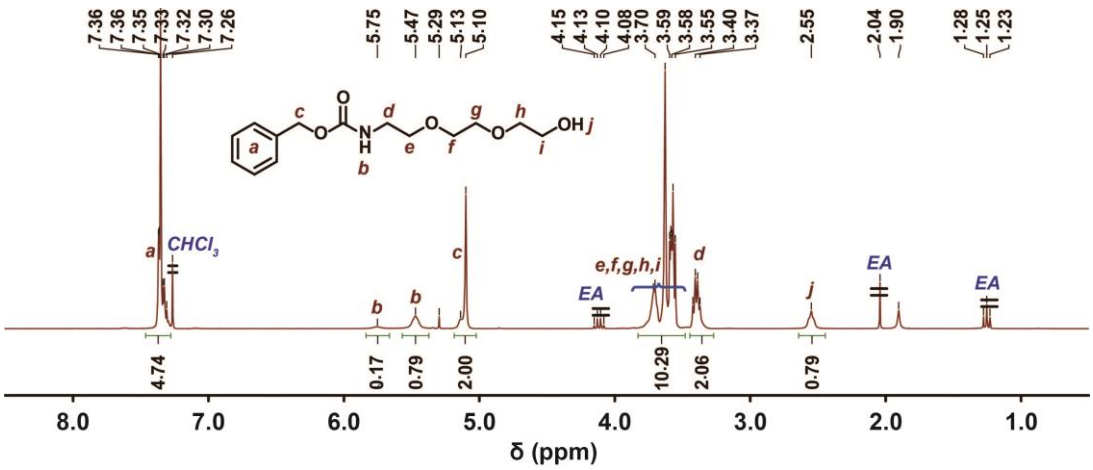


Figure S55. ^{1}H NMR spectra of benzyl (2-(2-(2-hydroxyethoxy) ethoxy) ethyl) carbamate (in $CDCl_3$ at 25 ℃).

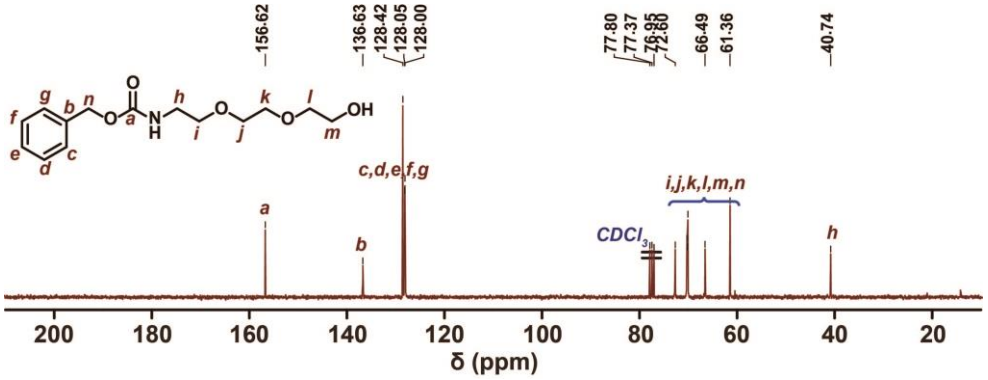


Figure S56. ^{13}C NMR spectra of benzyl (2-(2-(2-hydroxyethoxy) ethoxy) ethyl) carbamate (in $CDCl_3$ at 25 ℃).

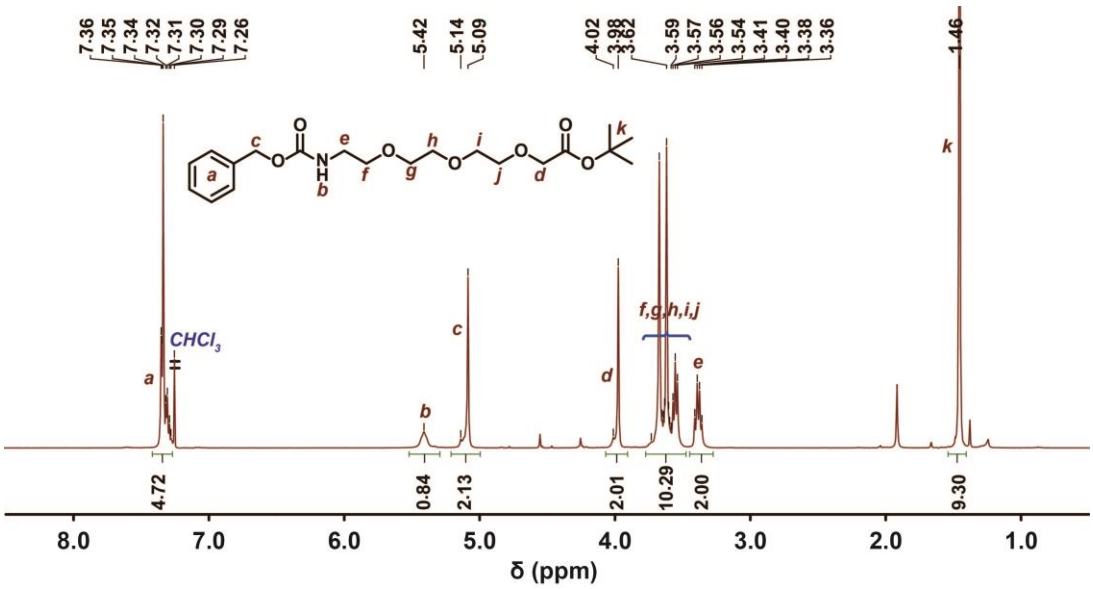


Figure S57. ^{1}H NMR spectra of *tert*-butyl 3-oxo-1-phenyl-2,7,10,13-tetraoxa-4-azapentadecan-15-oate (in $CDCl_3$ at 25 ℃).

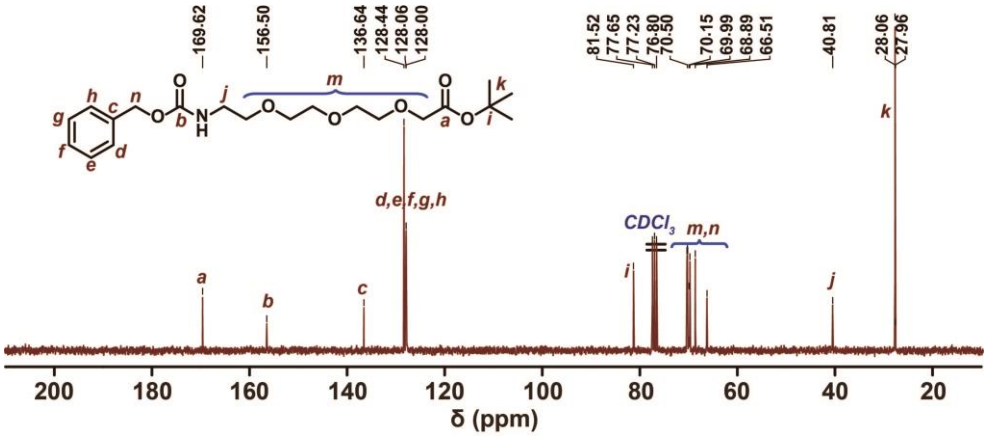


Figure S58. ^{13}C NMR spectra of *tert*-butyl 3-oxo-1-phenyl-2,7,10,13-tetraoxa-4-azapentadecan-15-oate (in $CDCl_3$ at 25 ℃).

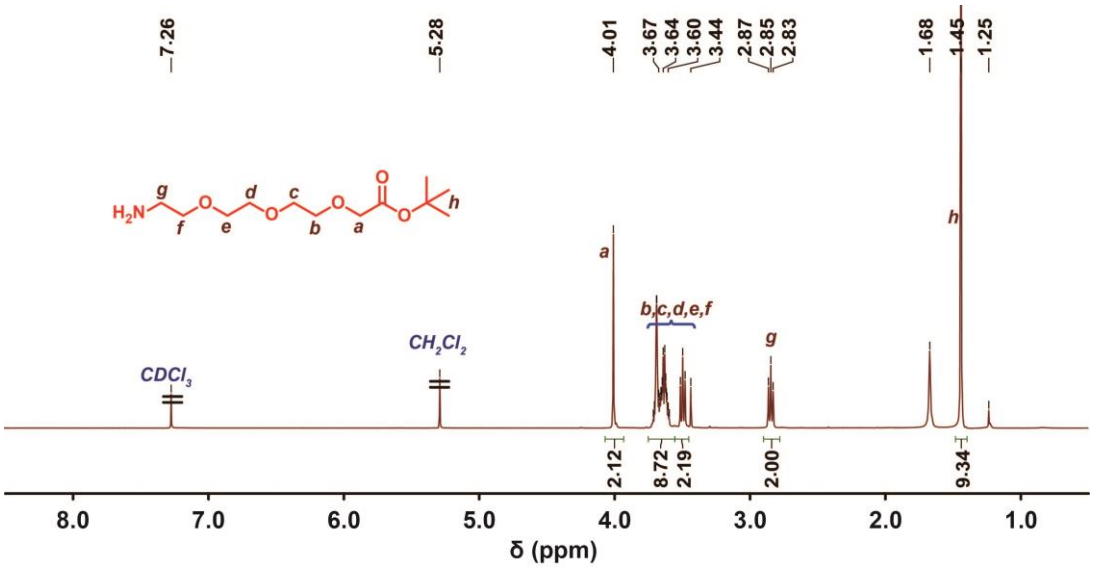


Figure S59. ^{1}H NMR spectra of amino acid building block **2h** (in $CDCl_3$ at 25 ℃).

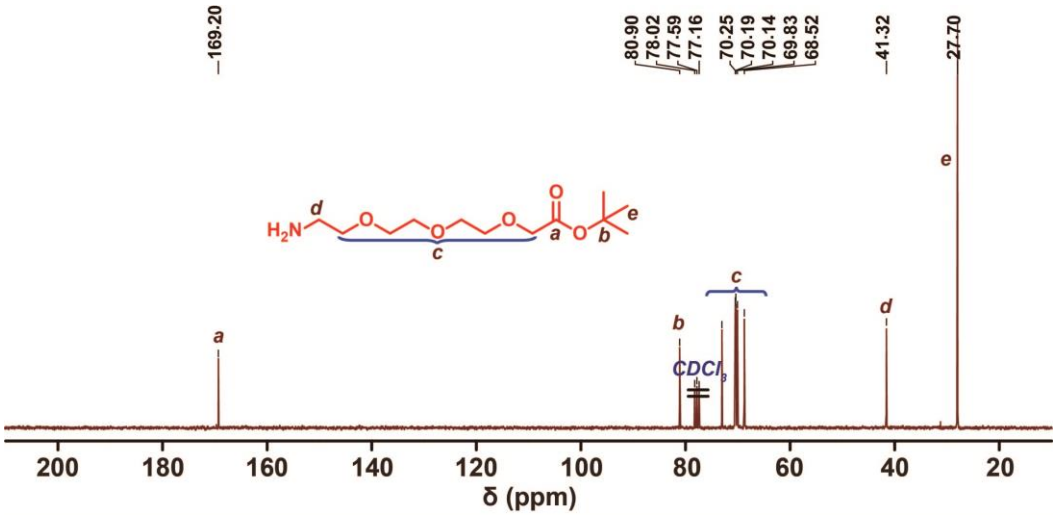


Figure S60. ^{13}C NMR spectra of amino acid building block **2h** (in $CDCl_3$ at 25 ℃).

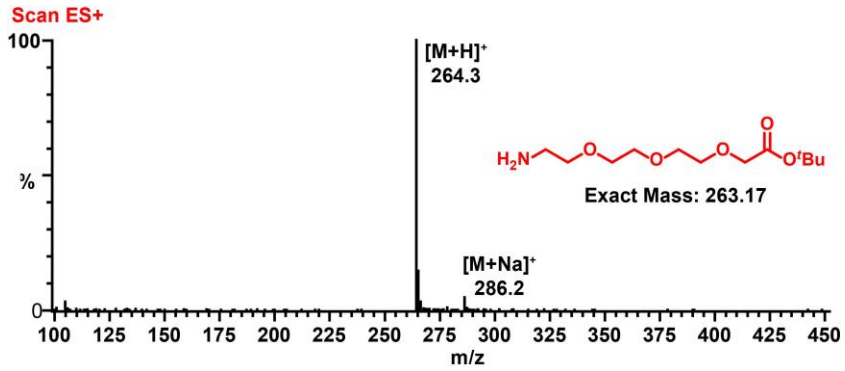


Figure S61. ESI-MS spectrum of amino acid building block **2h**.

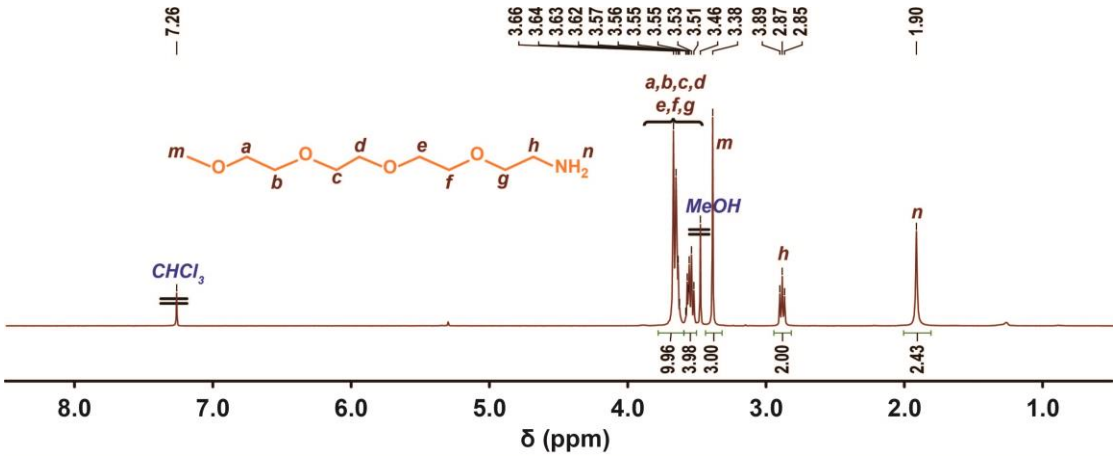


Figure S62. ^{1}H NMR spectra of 2,5,8,11-tetraoxatridecan-13-amine (in $CDCl_3$ at 25 ℃).

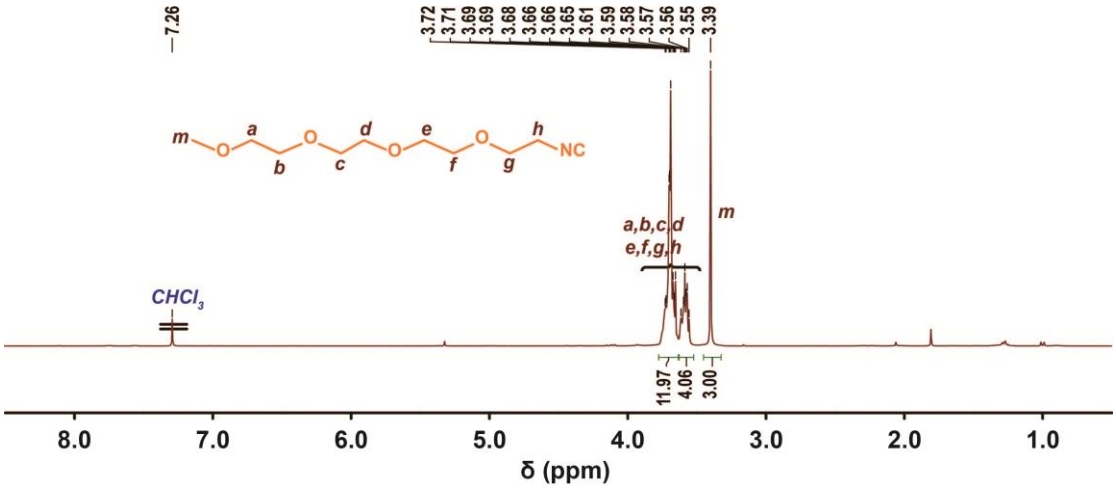


Figure S63. ^{1}H NMR spectra of 13-isocyano-2,5,8,11-tetraoxatridecane **($mOEG_4$-NC)** (in $CDCl_3$ at 25 ℃).

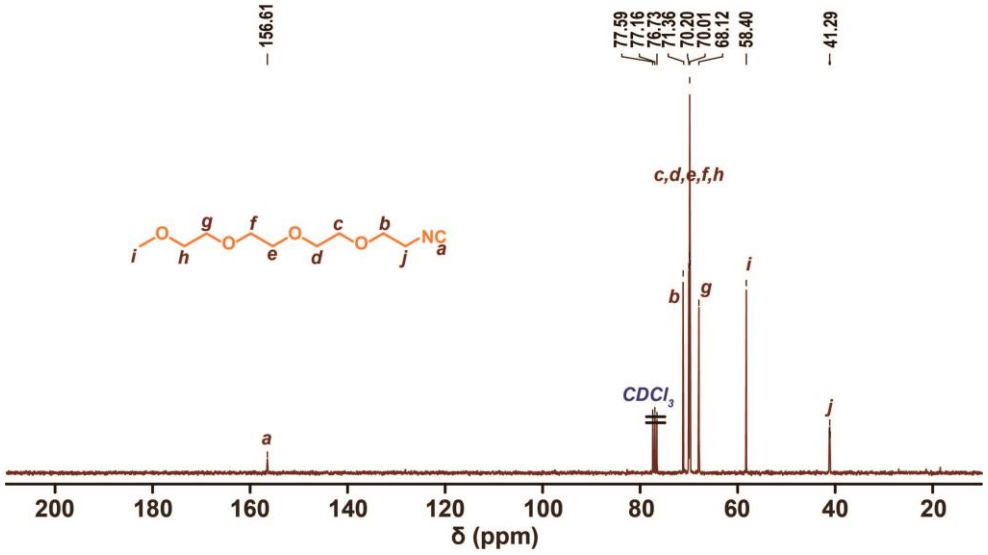


Figure S64. ^{13}C spectra of 13-isocyano-2,5,8,11-tetraoxatridecane **($mOEG_4$-NC)** (in $CDCl_3$ at 25 ℃).

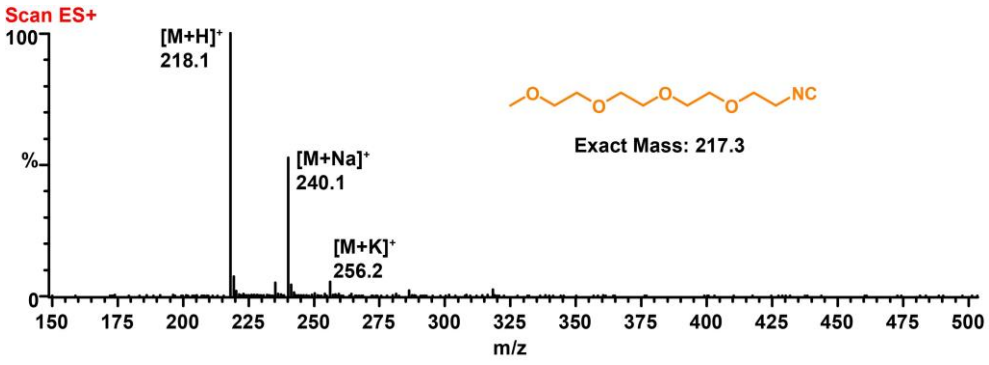


Figure S65. ESI-MS spectrum of 13-isocyano-2,5,8,11-tetraoxatridecane **($mOEG_4$-NC).**

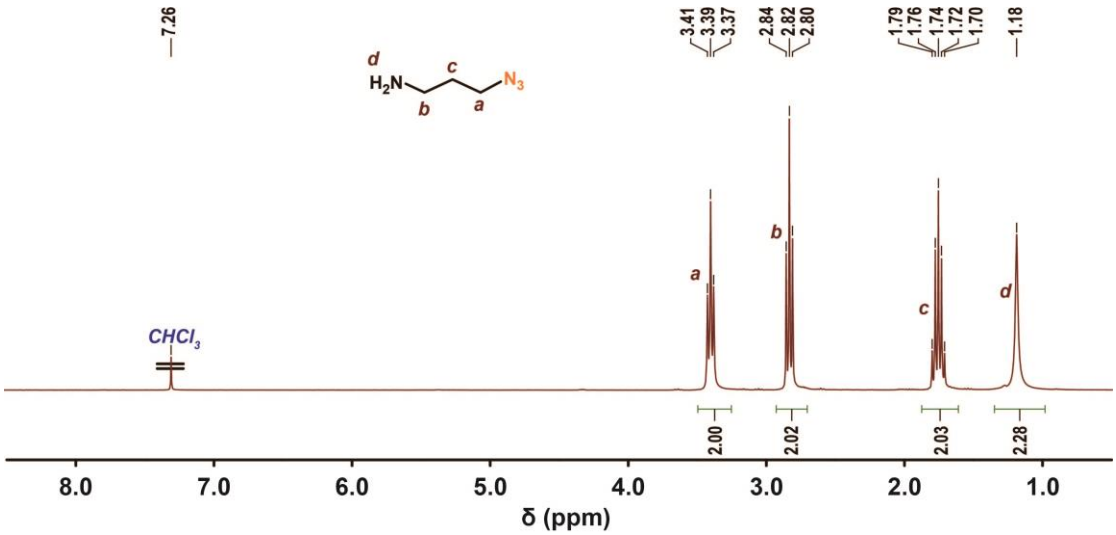


Figure S66. ^{1}H NMR spectra of 3-azidopropan-1-amine (in $CDCl_3$ at 25 ℃).

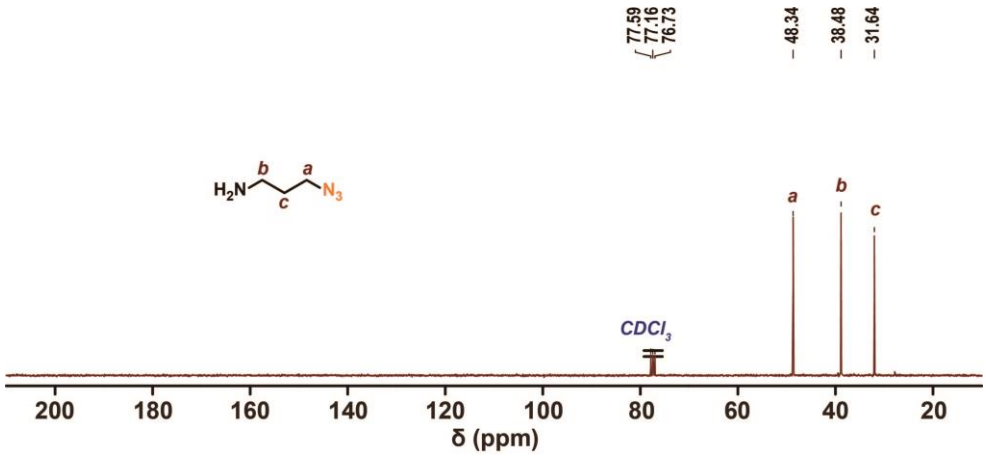


Figure S67. ^{13}C NMR spectra of 3-azidopropan-1-amine (in $CDCl_3$ at 25 ℃).

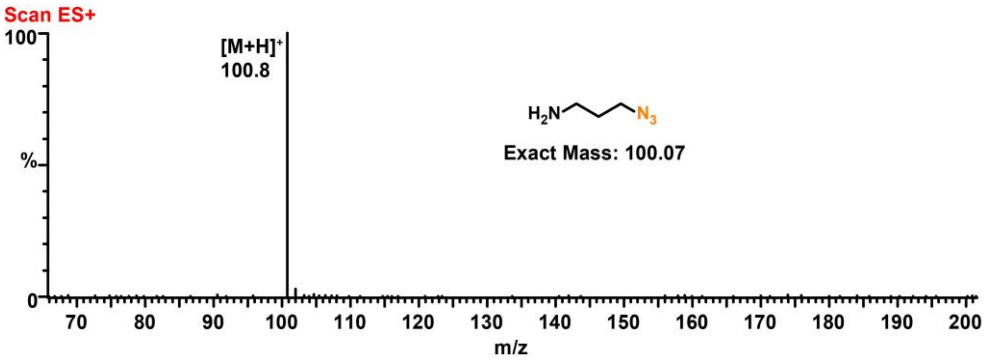


Figure S68. ESI-MS spectrum of 3-azidopropan-1-amine.

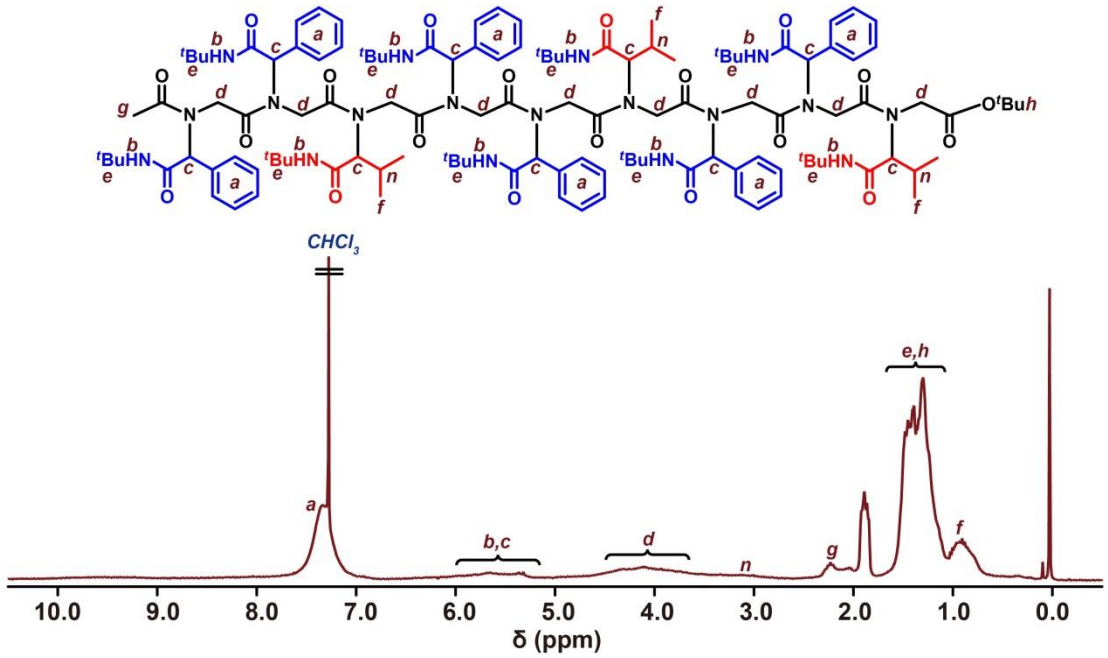


Figure S69. ^{1}H NMR spectra of 9-mer Peptoid **1** (in $CDCl_3$ at 25 ℃).

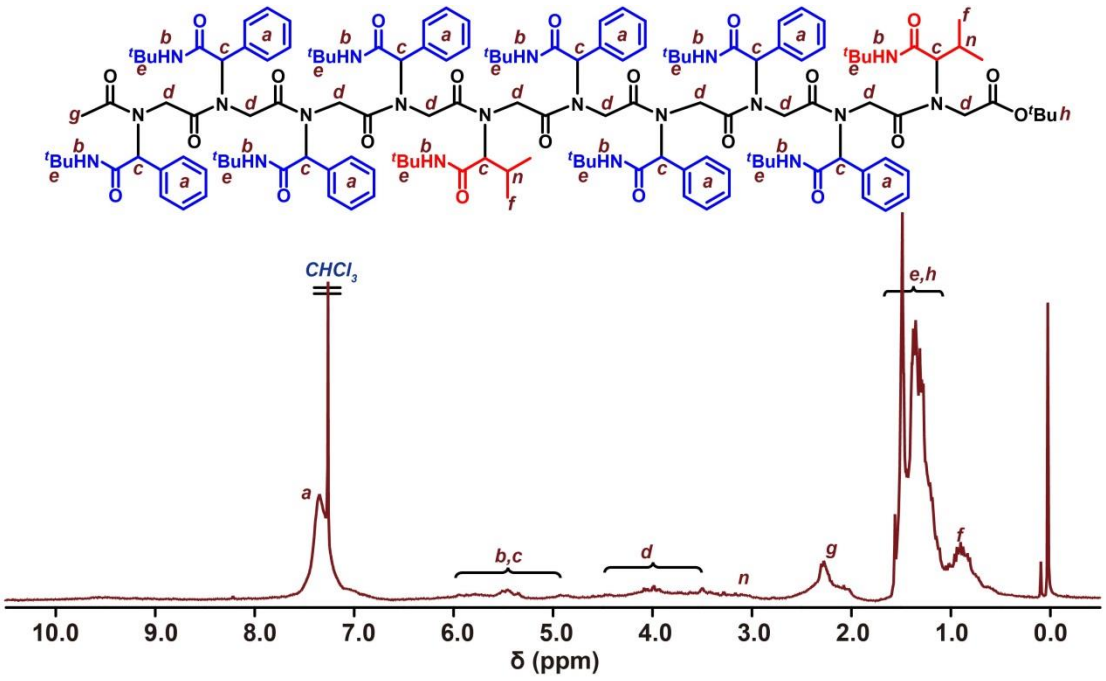


Figure S70. ^{1}H NMR spectra of 10-mer Peptoid **2** (in $CDCl_3$ at 25 ℃).

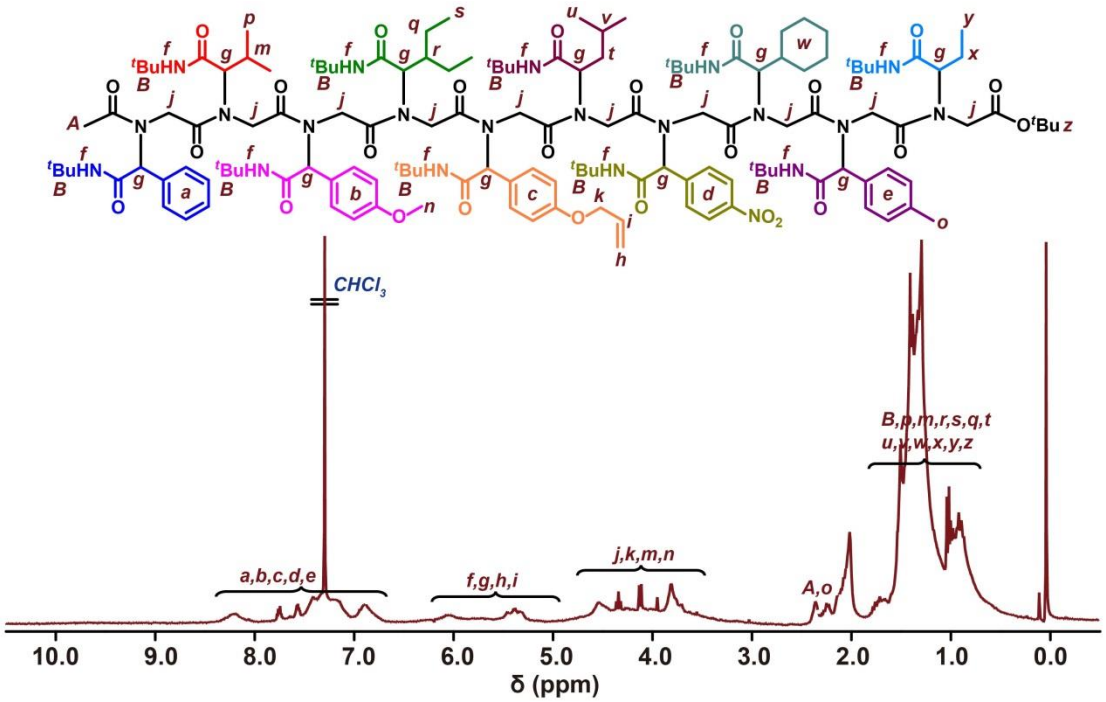


Figure S71. ^{1}H NMR spectra of 10-mer Peptoid **3** (in $CDCl_3$ at 25 ℃).

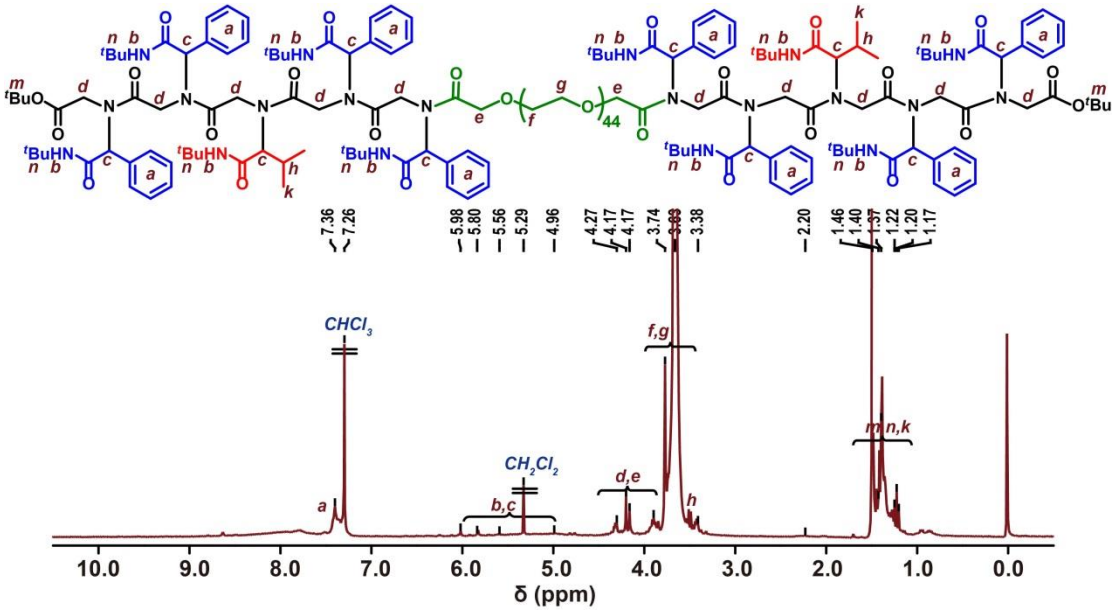


Figure S72. ^{1}H NMR spectra of Peptoid **4** (in $CDCl_3$ at 25 ℃).

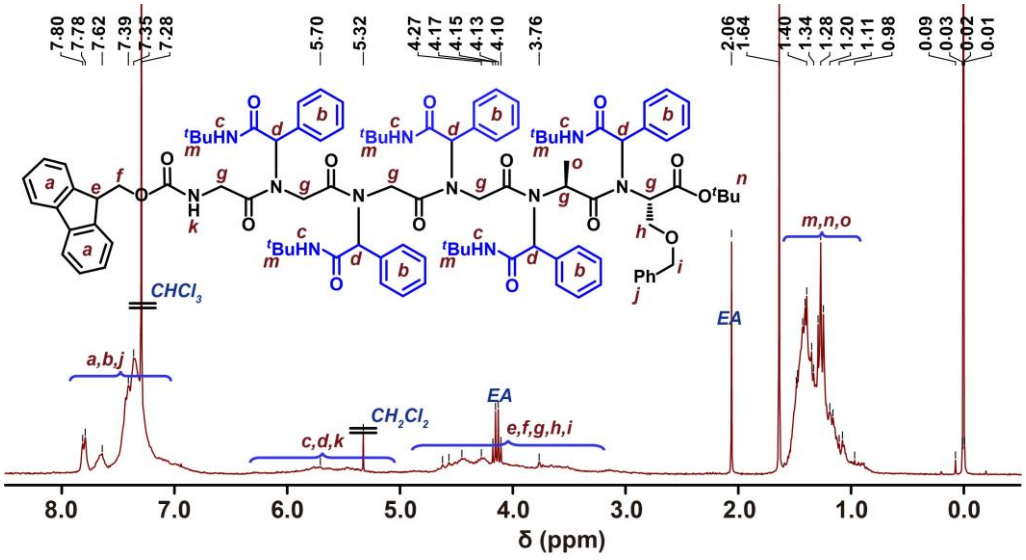


Figure S73. ^{1}H NMR spectra of 5-mer Peptoid **5** (in $CDCl_3$ at 25 ℃).

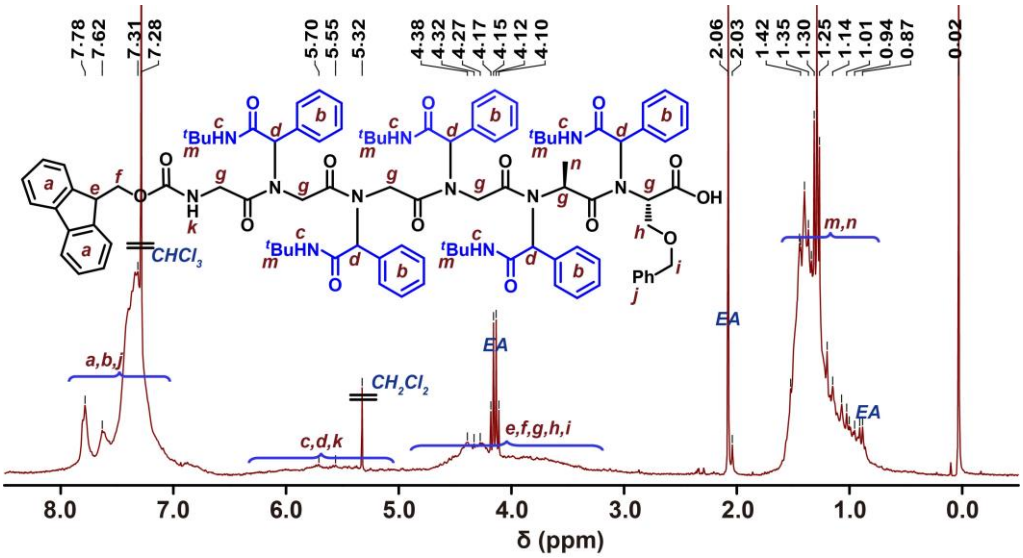


Figure S74. ^{1}H NMR spectra of 5-mer Peptoid **5-OH** (in $CDCl_3$ at 25 ℃).

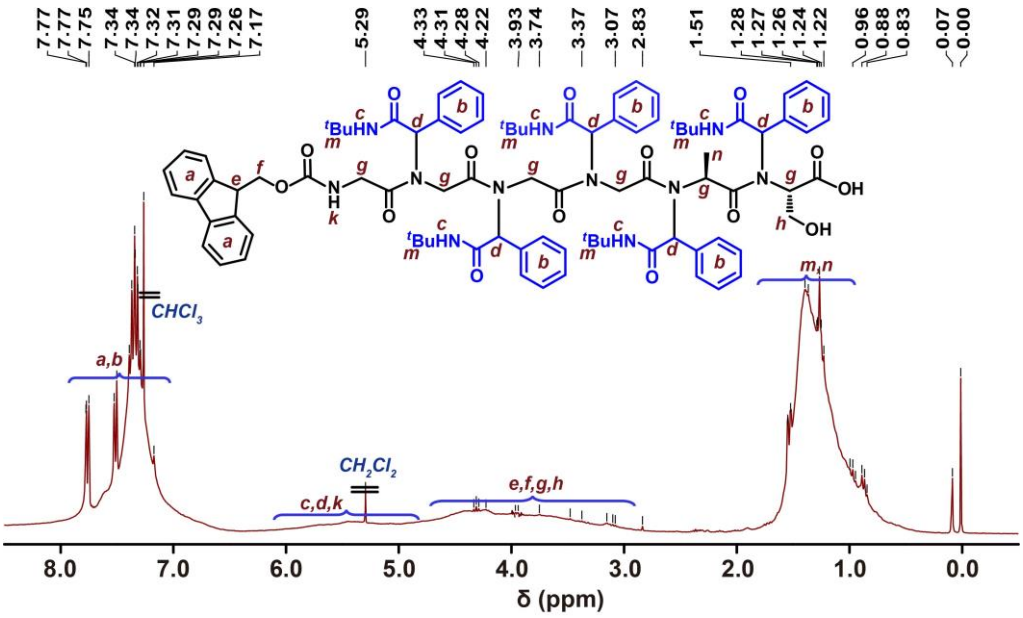


Figure S75. ^{1}H NMR spectra of 5-mer Peptoid **6** (in $CDCl_3$ at 25 ℃).

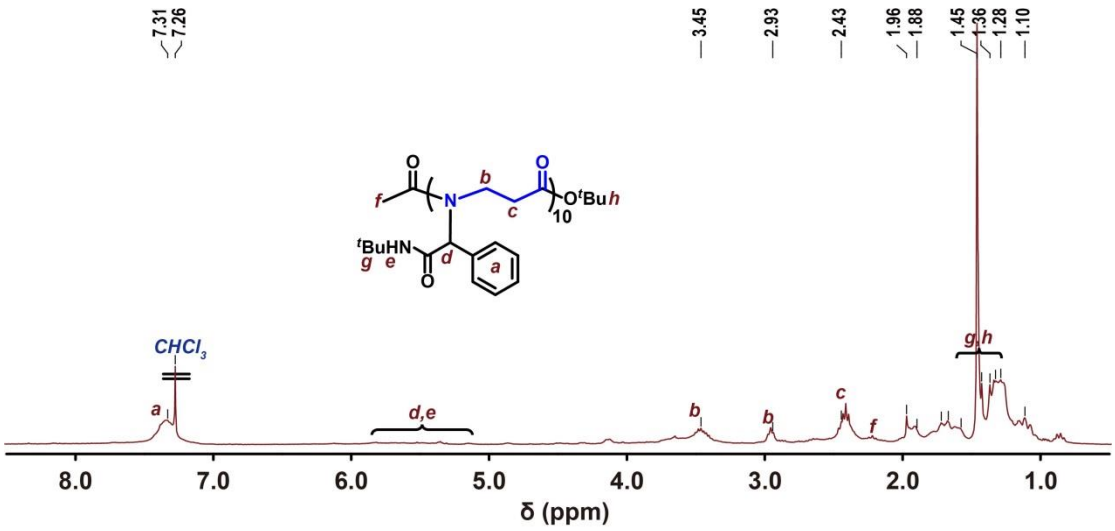


Figure S76. ^{1}H NMR spectra of 10-mer *β*-Peptoid **7** (in $CDCl_3$ at 25 ℃).

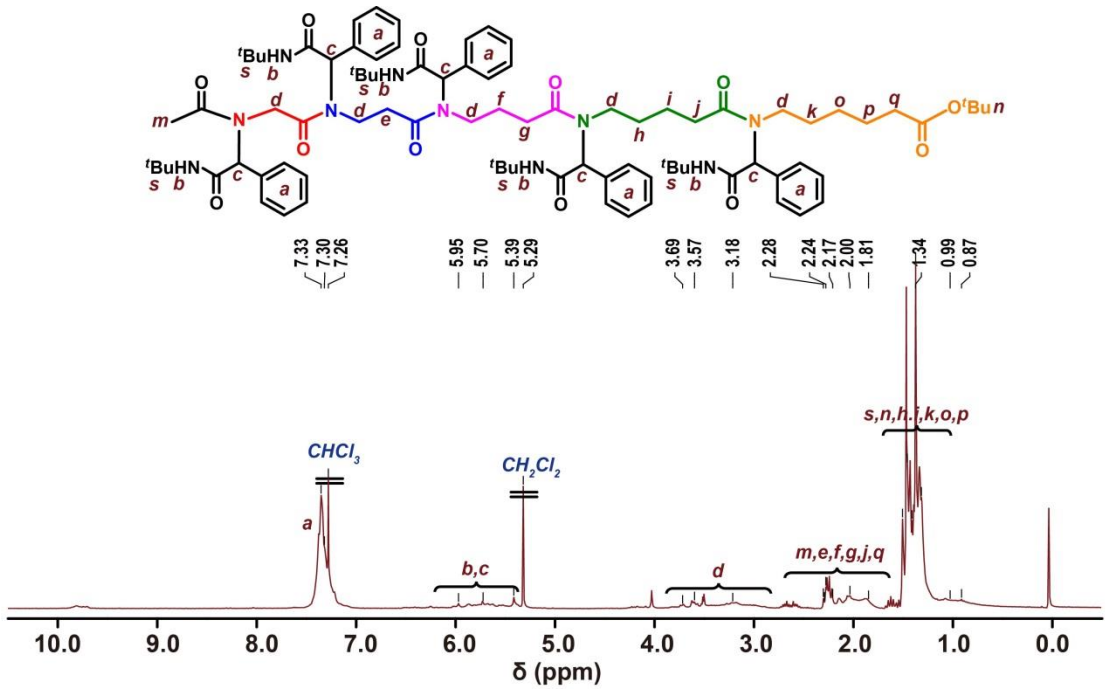


Figure S77. ^{1}H NMR spectra of 5-mer Peptoid **8** (in $CDCl_3$ at 25 ℃).

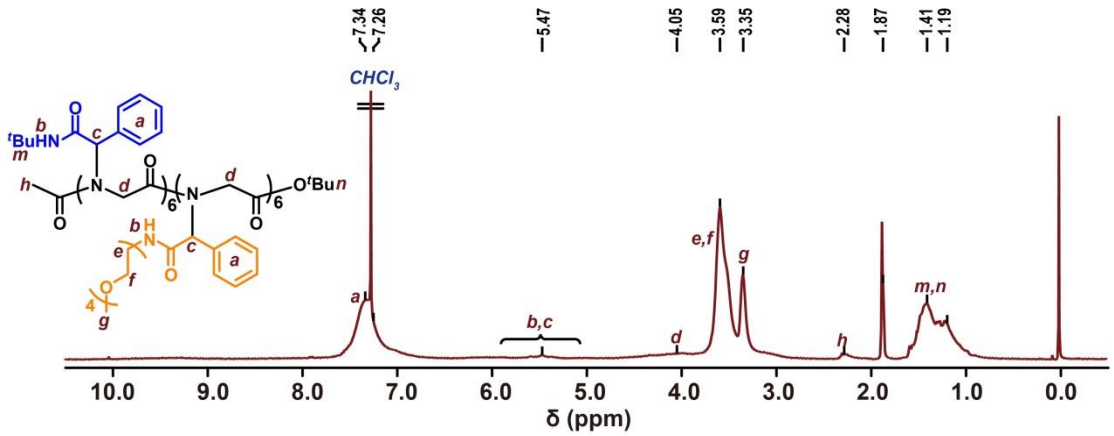


Figure S78. ^{1}H NMR spectra of 12-mer Peptoid **9** (in $CDCl_3$ at 25 ℃).

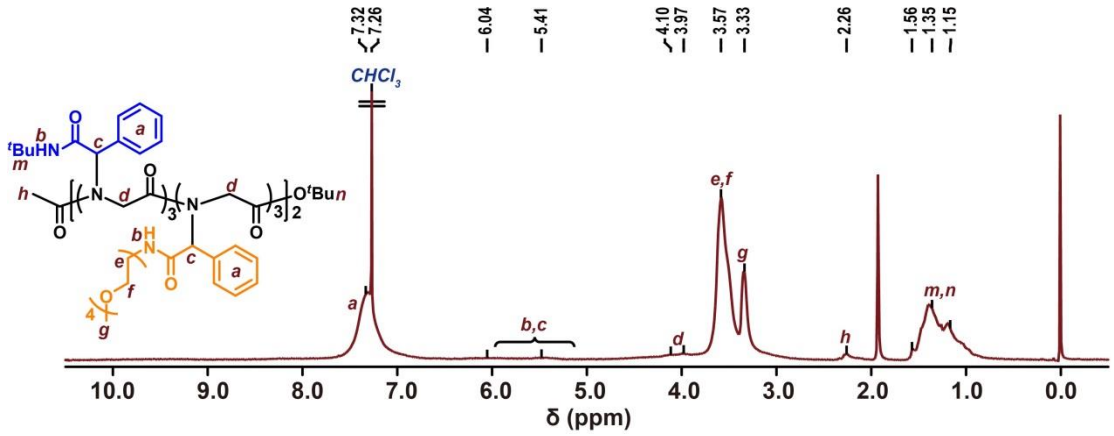


Figure S79. ^{1}H NMR spectra of 12-mer Peptoid **10** (in $CDCl_3$ at 25 ℃).

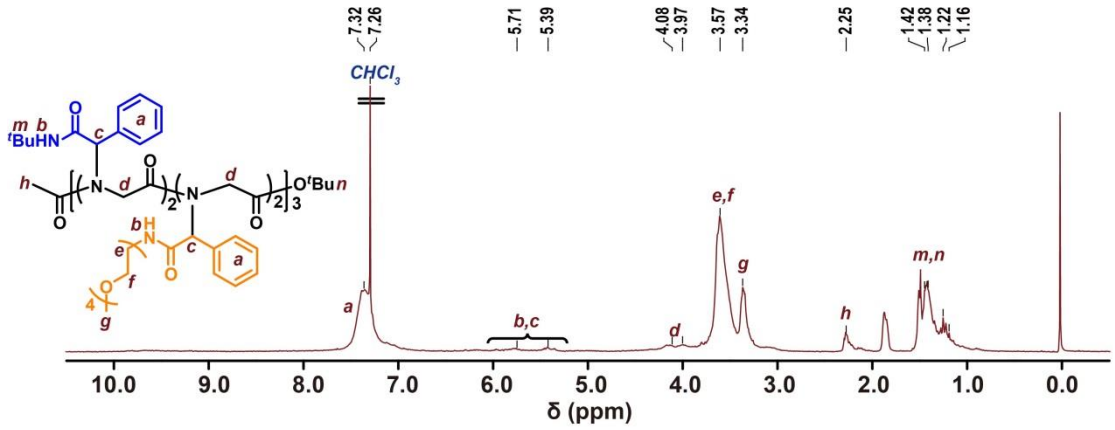


Figure S80. ^{1}H NMR spectra of 12-mer Peptoid **11** (in $CDCl_3$ at 25 ℃).

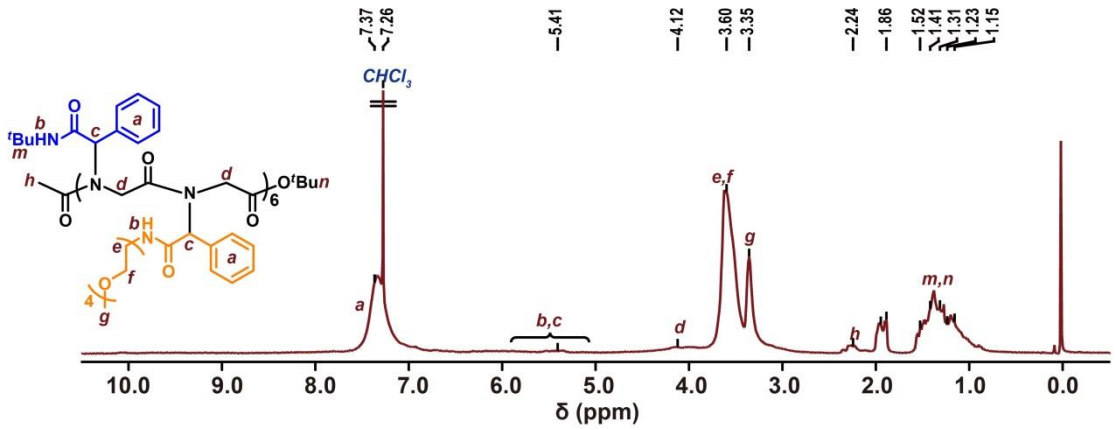


Figure S81. ^{1}H NMR spectra of 12-mer Peptoid **12** (in $CDCl_3$ at 25 ℃).

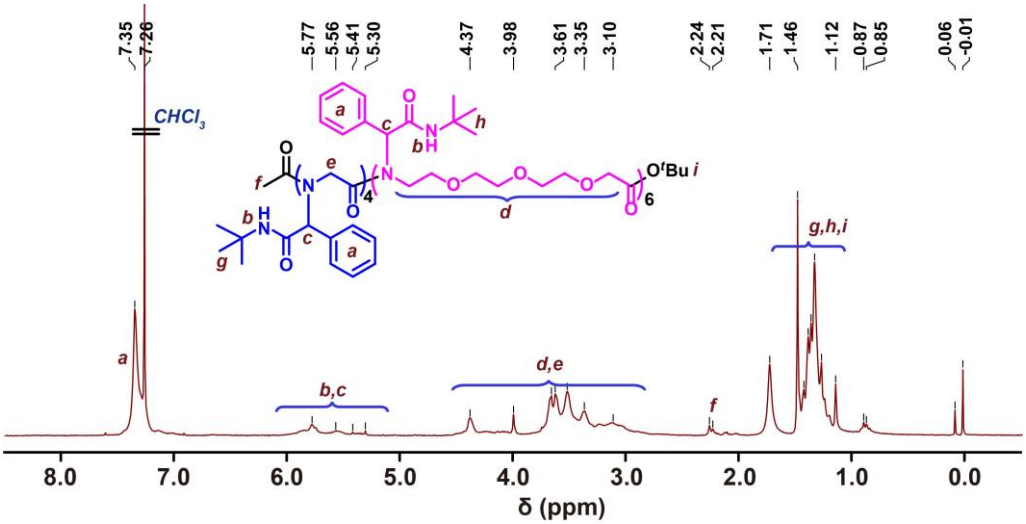


Figure S82. ^{1}H NMR spectra of 10-mer Peptoid **13** (in $CDCl_3$ at 25 ℃).

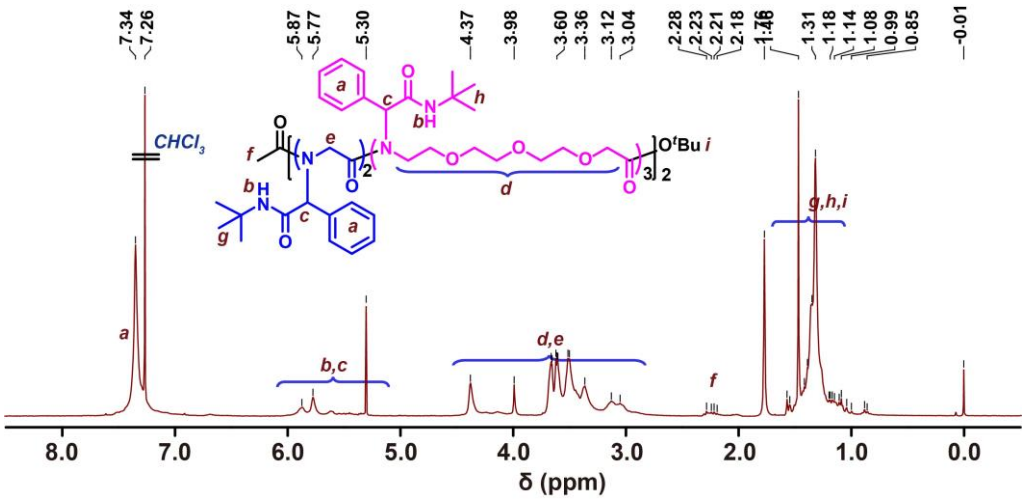


Figure S83. ^{1}H NMR spectra of 10-mer Peptoid **14** (in $CDCl_3$ at 25 ℃).

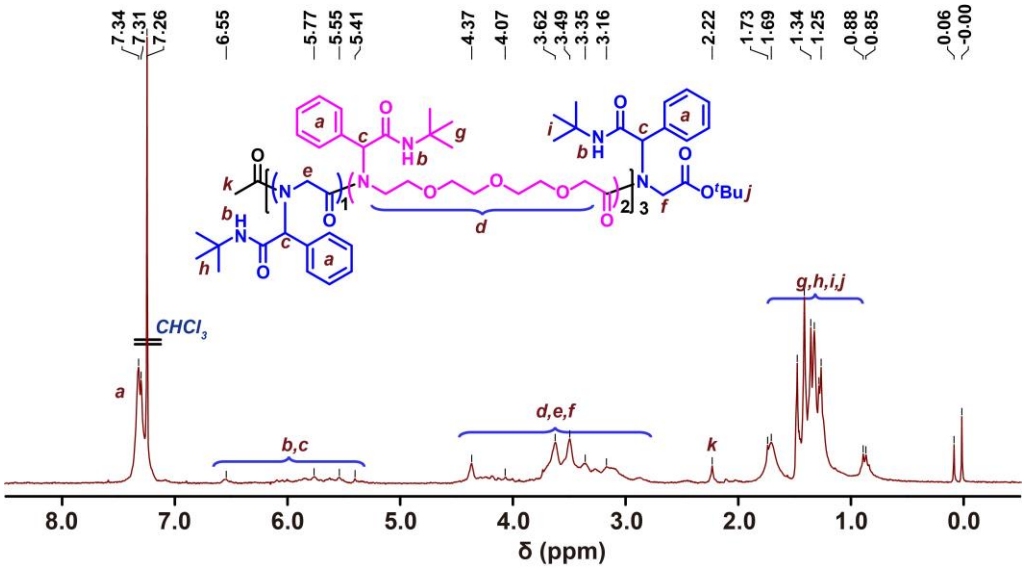


Figure S84. ^{1}H NMR spectra of 10-mer Peptoid **15** (in $CDCl_3$ at 25 ℃).

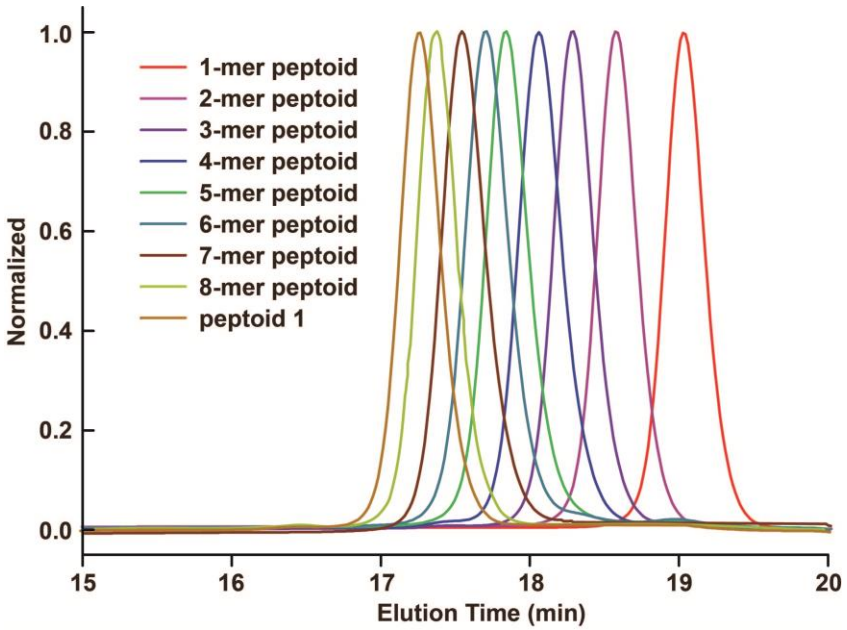


Figure S85. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **1** (in THF, 35 ℃, polystyrene as standard).

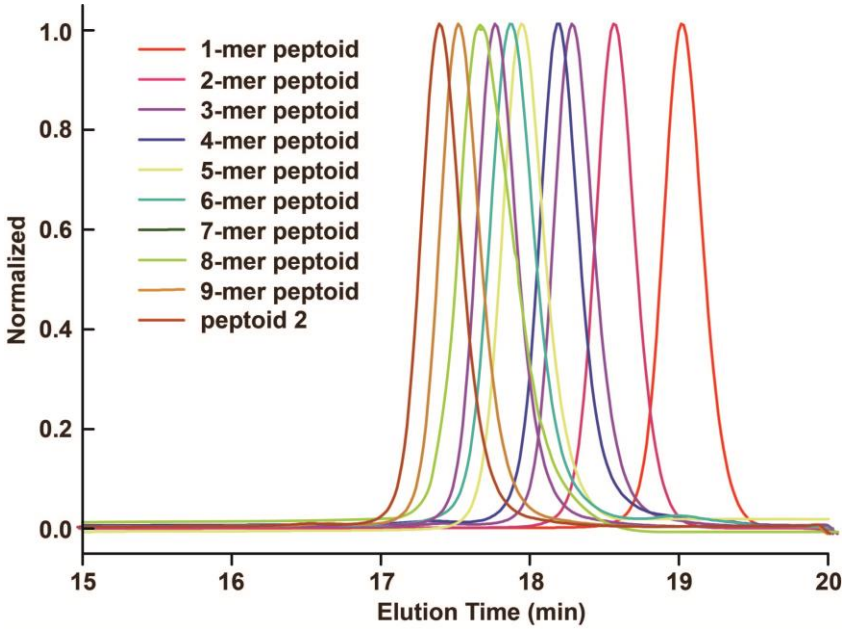


Figure S86. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **2** (in THF, 35 ℃, polystyrene as standard).

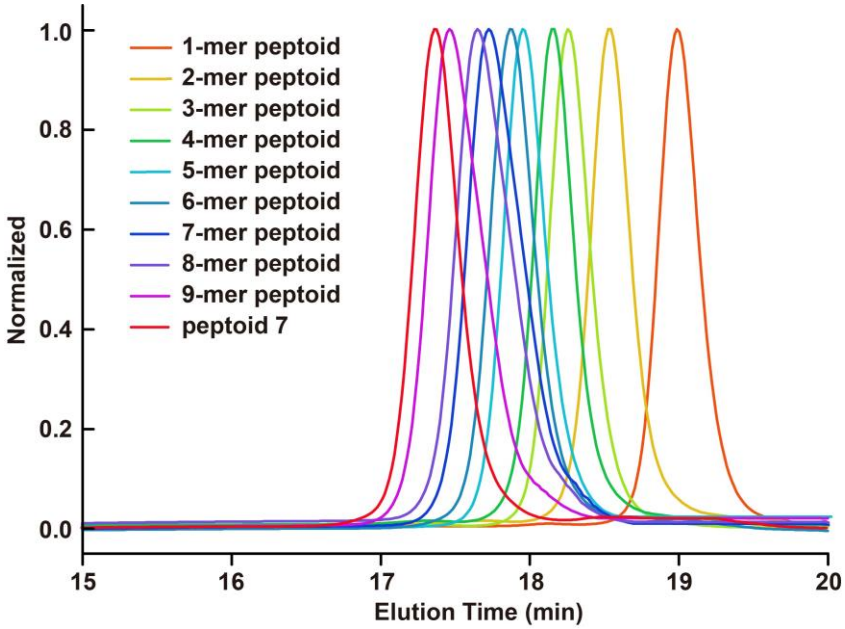


Figure S87. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **7** (in THF, 35 ℃, polystyrene as standard).

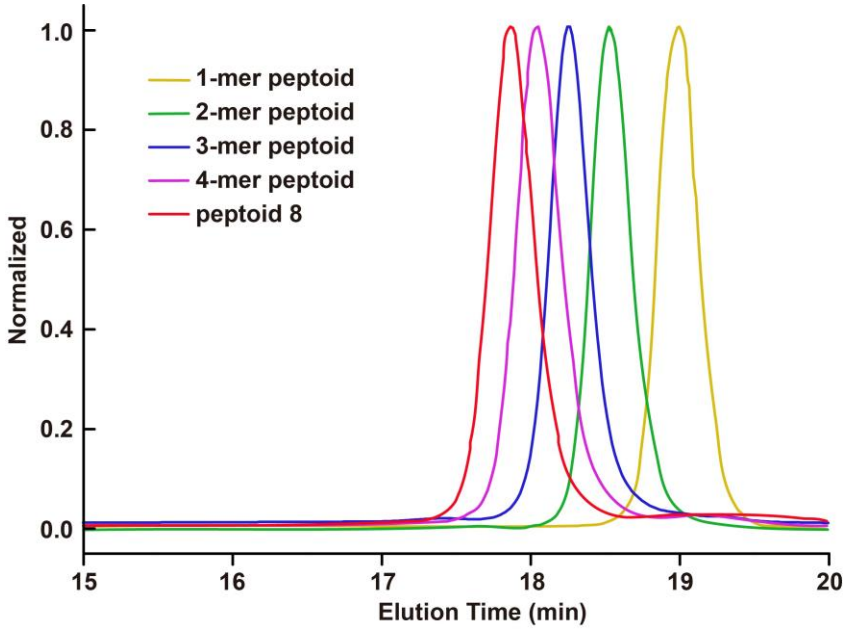


Figure S88. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **8** (in THF, 35 ℃, polystyrene as standard).

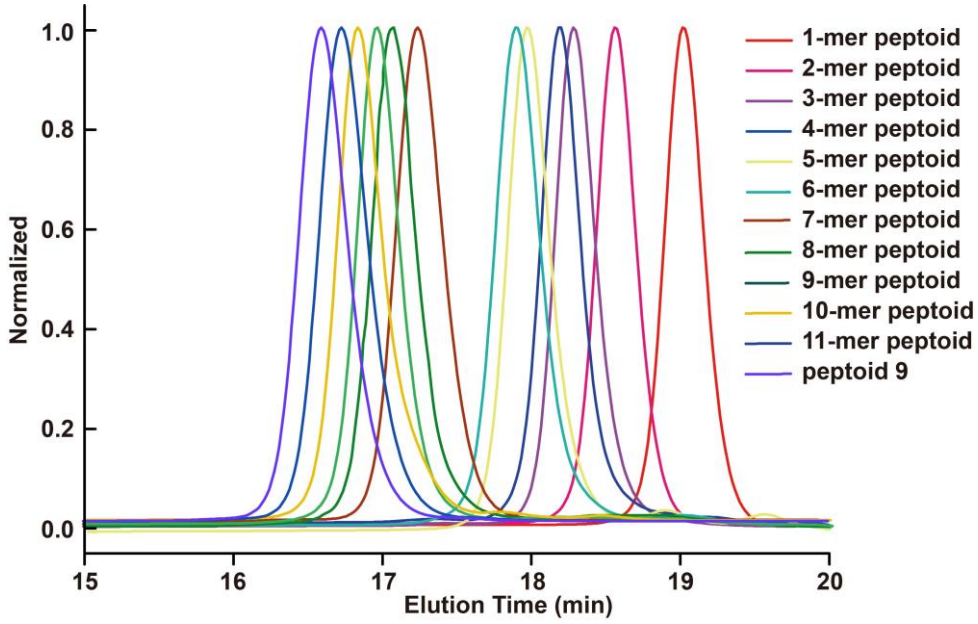


Figure S89. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **9** (in THF, 35 ℃, polystyrene as standard).

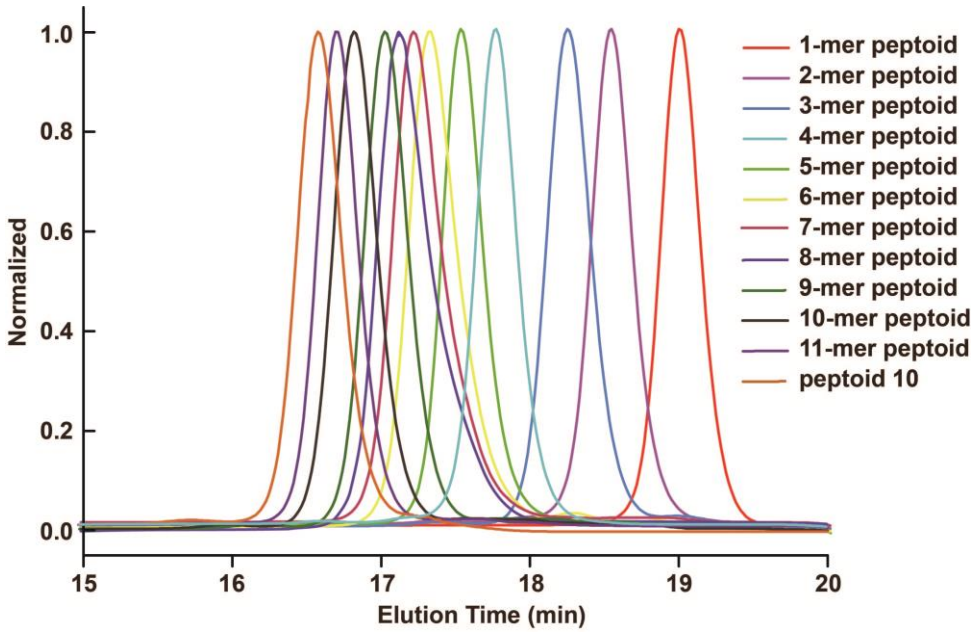


Figure S90. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **10** (in THF, 35 ℃, polystyrene as standard).

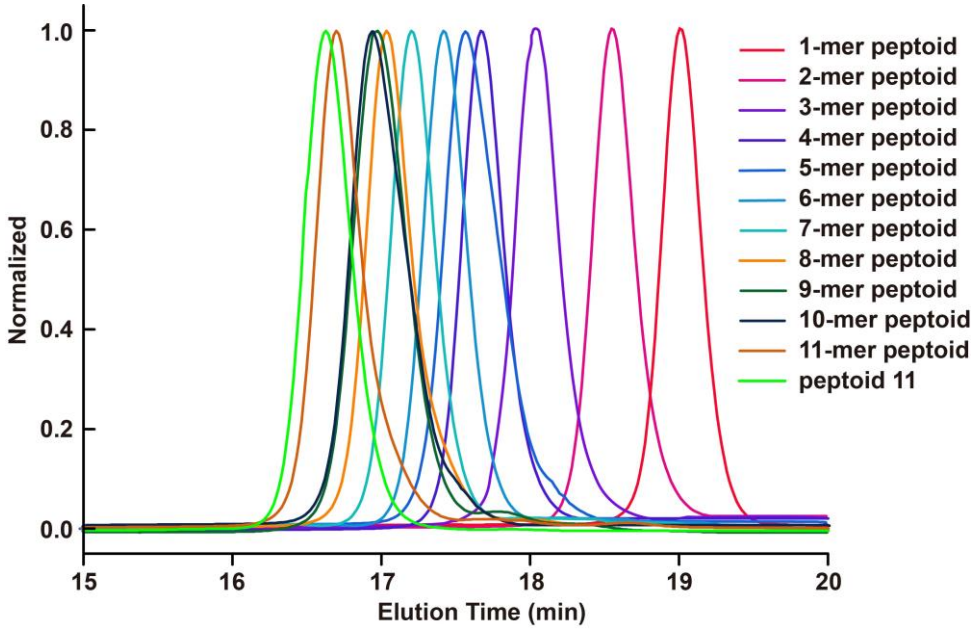


Figure S91. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **11** (in THF, 35 ℃, polystyrene as standard).

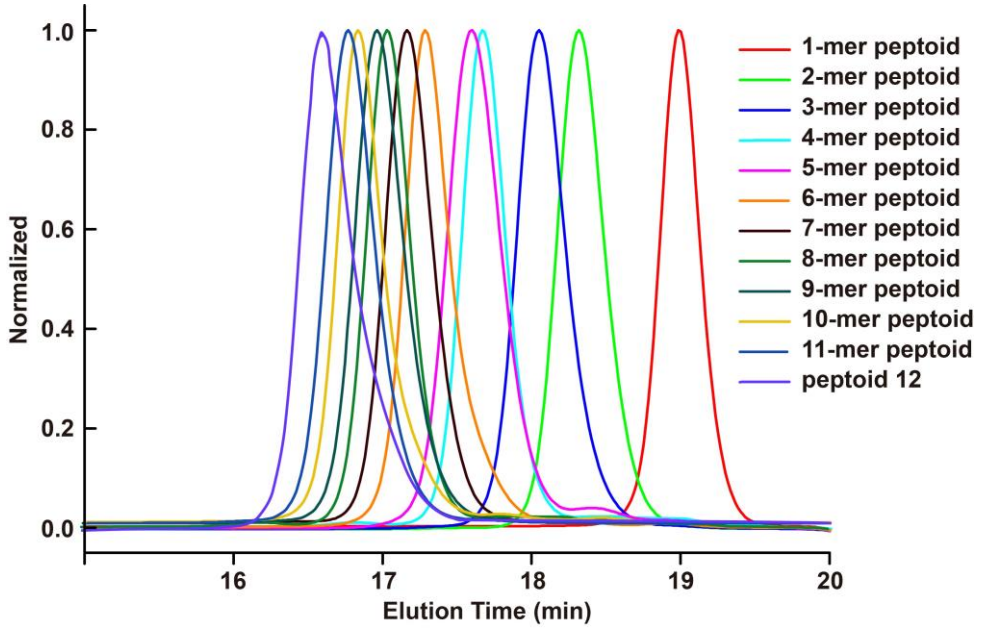


Figure S92. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **12** (in THF, 35 ℃, polystyrene as standard).

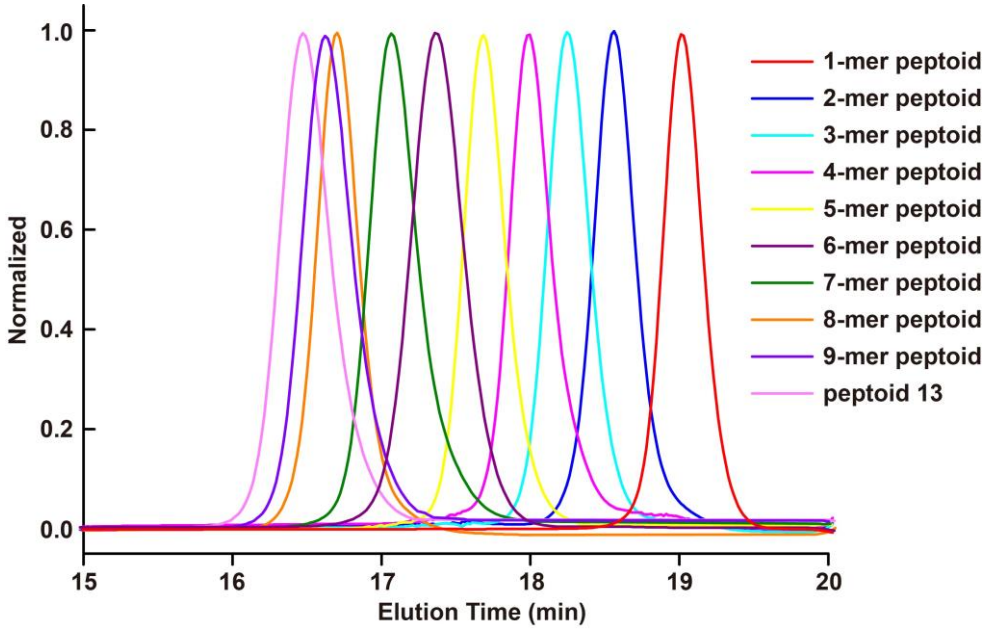


Figure S93. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **13** (in THF, 35 ℃, polystyrene as standard).

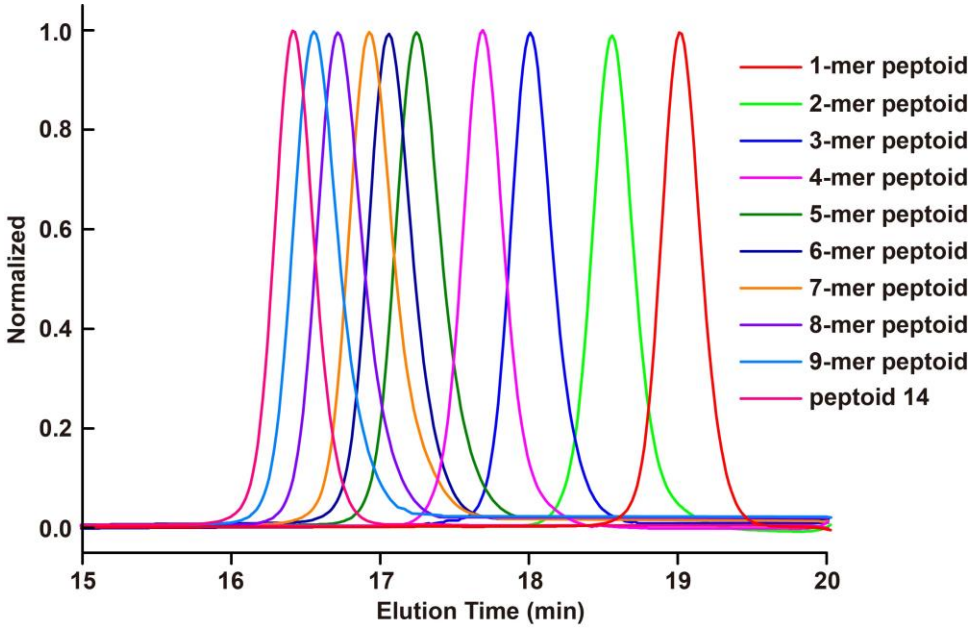


Figure S94. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **14** (in THF, 35 ℃, polystyrene as standard).

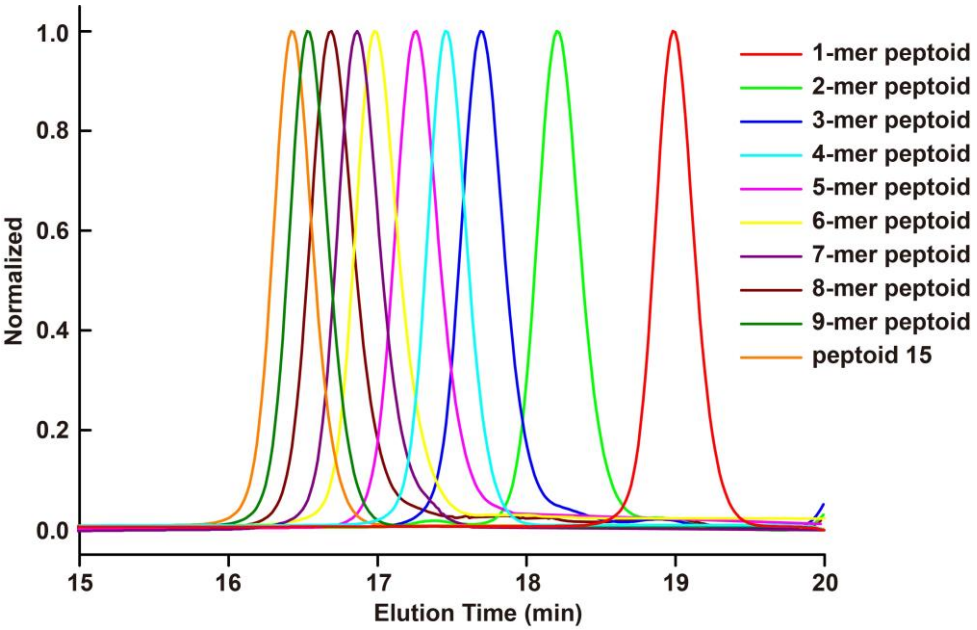


Figure S95. SEC traces obtained after Ugi reactions in the synthesis of the sequence-defined peptoid **15** (in THF, 35 ℃, polystyrene as standard).