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Soluble polymer-supported convergent parallel library synthesis

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Experimental Section

Synthesis of MeO-PEG-OH ester of 4-carboxyphenylboronic acid (5b). In a 200 mL round-bottomed flask, were added MeO-PEG$_{5000}$-OH (5.000 g, 1 mmol), 4-carboxyphenylboronic acid (0.830 g, 5 mmol), diisopropylcarbodiimide (0.8 mL, 5 mmol), and freshly distilled DCM (50 mL). The resulted suspension was stirred at room temperature under an argon atmosphere for 30 min before *N*,*N*-dimethylaminopyridine (0.610 g, 5 mmol) was added in one portion. The reaction mixture was stirred at room temperature under an argon atmosphere for 24 h, and filtered through Celite. The solution was concentrated under reduced pressure and slowly added to cold, vigorously stirred isopropanol (500 mL). The resulting white precipitate was filtered, washed with cold isopropanol (300 mL) and diethyl ether (300 mL), and dried under reduced pressure (4.921g, 96%): ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 8.3

Hz, 2H), 6.36 (bs, 2H), 4.47 (t, J = 4.6 Hz, 2H, PEG-α-methylene), 3.83-3.50 (m, PEG-methylenes), 3.36 (s, 3H, PEG-methoxy).

Suzuki cross-coupling reaction of the MeO-PEG bound 4-iodobenzoic acid and 4-carboxyphenylboronic acid; Synthesis of 6. Into a 10 mL-pressure tube, were added the iodide (**5a**, 0.262 g, 0.05 mmol, 10 mM), the boronic acid (**5b**, 0.260 g, 0.05 mmol, 10 mM), $PdCl_2$(dppf) (4 mg, 10 mol%), K_2CO_3 (21 mg, 3 equiv.), and degassed DMF (5 mL). The reaction mixture was stirred at 100 ^oC under argon atmosphere for 24 h, and cooled to room temperature. The reaction mixture was added to cold, vigorously stirred diethyl ether (300 mL), and the resulting prepicitate was filtered, washed with cold isopropanol (150 mL) and diethyl ether (150 mL), and dried under reduced pressure (0.503 g, 99%): ^1H-NMR (600 MHz, $CDCl_3$) δ 8.13 (d, J = 8.2 Hz, 4H), 7.68 (d, J = 8.3 Hz, 4H), 4.49 (t, J = 4.6 Hz, 4H, PEG-α-methylene), 3.85-3.50 (m, PEG-methylenes), 3.36 (s, 6H, PEG-methoxy).

Transesterification of 7. Into a 25 mL round-bottomed flask, were added the biphenyl dicarboxylate (**6**, 990 mg, 0.1 mmol), KCN (104 mg, 8 equiv.), and freshly distilled MeOH (10 mL). The reaction mixture was stirred at room temperature under argon atmosphere for 24 h. The solution was added to cold, vigorously stirred diethyl ether (150 mL), and the precipitate was removed by filtration. The diethyl ether solution was concentrated and purified by silica gel chromatography (25% EtOAc/hexane, 23 mg, 85%): ^1H-NMR (600 MHz, $CDCl_3$) δ 8.13 (d, J = 8.8 Hz, 4H), 7.69 (d, J = 8.8 Hz, 4H), 3.95 (s, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 166.80, 144.33, 130.19, 129.66, 127.23, 52.22; ESI-MS calcd for $[M + H]^+$ 271.1, found 271.3.

Synthesis of MeO-PEG ester of Boc-Gly. Into a 250 mL-round bottomed flask, were added MeO-PEG$_{5000}$-OH (5.000 g, 1 mmol), Boc-Gly (0.876 g, 5 mmol), and freshly distilled DCM (50 mL), and the solution was chilled to 0 ^{o}C. To this solution, 1,3-diisopropylcarbodiimide (0.8 mL, 5 mmol) was added, and the mixture was stirred at 0 ^{o}C for 1 h. Then, *N,N*-dimethylaminopyridine (0.610 g, 5 mmol) was added to the mixture in one portion, and the reaction mixture was stirred at room temperature under an argon atmosphere overnight. The reaction mixture was filtered through celite, and concentrated under reduced pressure to a volume of *ca*. 50 mL. This concentrated solution was slowly added to cold, vigorously stirred isopropanol (600 mL), and the precipitate was filtered, washed with cold isopropanol (300 mL) and diethyl ether (300 mL), and dried under reduced pressure (4.834 g, 94%): ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.09 (bs, 1H), 4.29 (t, J = 4.6 Hz, 2H, PEG-α-methylene), 3.92 (d, J = 5.7 Hz, 2H), 3.74-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.44 (s, 9H).

General procedure for the synthesis of MeO-PEG esters of tripeptide aryiodides (L1 a-i) and arylboronic acids (L2, a-i). MeO-PEG$_{5000}$ ester of Boc-Gly (0.500 g, 0.1 mmol) was placed in a 50 mL-polystyrene tube and treated with 4 mL of 50% TFA/DCM for 1 h. The reaction mixture was added to cold diethyl ether (35 mL), and the precipitate was separated by centrifugation. The precipitate was washed with cold diethyl ether (2 x 35 mL) and dried under reduced pressure. For the coupling of each Boc-amino acid; Boc-amino acid (0.3 mmol), HBTU (0.3 mmol), and HOBt (0.3 mmol) in DMF (4 mL) were stirred at room temperature for 1 h. The preactivated amino acid solution and DIEA (0.16 mL, 0.6 mmol) in DMF (2 mL) were then added to the dried, deprotected PEG ester. The reaction mixture was stirred at room temperature for 3 h, and added to cold isopropanol (35 mL). The resulting precipitate was separated by centrifugation, washed with cold isopropanol (2 x 35 mL) and diethyl ether (2 x 35 mL), and dried under reduced pressure. These deprotection and coupling procedures were repeated to construct N^{α}-Boc protected MeO-PEG ester of tripeptide. Then, the *N*-terminal Boc group was deprotected with 50% TFA/DCM as described above and either 4-iodobenzoic acid or 4-carboxyphenylboronic acid was coupled to the tripeptide in the same manner as described above.

I-Ph-CO-Ala-Ala-Gly-OPEG$_{5000}$-OMe (L1, a). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.12 (bd, 1H), 7.01 (bs, 1H), 6.92 (bd, 1H), 4.60 (t, *J* = 6.8 Hz, 1H), 4.54 (t, *J* = 7.2 Hz, 1H), 4.26-4.16 (m, 2H, PEG-α-methylene), 4.15-3.97 (m, 2H), 3.75-3.49 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.50 (d, *J* = 7.0 Hz, 3H), 1.40 (d, *J* = 7.0 Hz, 3H).

I-Ph-CO-Phe-Ala-Gly-OPEG$_{5000}$-OMe (L1, b). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.30-7.23 (m, 5H), 6.86 (bs, 1H), 6.61 (bs, 1H), 6.56 (bs, 1H), 4.80 (q, *J* = 6.8 Hz, 1H), 4.46 (quintet, *J* = 7.0 Hz, 1H), 4.29-4.27 (m, 2H, PEG-α-methylene), 4.08-3.93 (m, 2H), 3.75-3.50 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.19 (m, 2H), 1.34 (d, *J* = 7.0 Hz, 3H).

I-Ph-CO-Leu-Ala-Gly-OPEG$_{5000}$-OMe (L1, c). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 6.90 (bs, 1H), 6.80 (bs, 1H), 6.77 (bs, 1H), 4.63 (bs, 1H), 4.51 (m, 1H), 4.28-4.20 (m, 2H, PEG-α-methylene), 4.10-4.00 (m, 2H), 3.75-3.49 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.77-1.65 (m, 3H), 1.40 (d, *J* = 7.0 Hz, 3H), 0.97-0.96 (m, 6H).

I-Ph-CO-Ala-Phe-Gly-OPEG$_{5000}$-OMe (L1, d). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.19-7.12 (m, 5H), 6.87 (bs, 1H), 6.81 (bs, 2H), 4.72 (q, *J* = 6.6 Hz, 1H), 4.53 (quintet, *J* = 6.5 Hz, 1H), 4.28-4.19 (m, 2H, PEG-α-methylene), 4.13-3.93 (m, 2H), 3.75-3.49 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.23-3.03 (m, 2H), 1.41 (d, *J* = 7.0 Hz, 3H).

I-Ph-CO-Phe-Phe-Gly-OPEG$_{5000}$-OMe (L1, e). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.31-7.08 (m, 10H), 6.65 (bs, 1H), 6.43 (bs, 2H), 4.71 (q, *J* = 7.0 Hz, 1H), 4.63 (q, *J* = 7.0 Hz, 1H), 4.27 (m, 2H, PEG-α-methylene), 4.06-3.88 (m, 2H), 3.75-3.49 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.16-2.99 (m, 4H).

I-Ph-CO-Leu-Phe-Gly-OPEG$_{5000}$-OMe (L1, f). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.16-7.11 (m, 5H), 6.78 (bs, 1H), 6.71 (bs, 1H), 6.57 (bs, 1H), 4.70 (q, *J* = 7.4 Hz, 1H), 4.54 (q, *J* = 6.1 Hz, 1H), 4.26-4.23 (m, 2H, PEG-α-methylene), 4.09-3.93 (m, 2H), 3.75-3.49 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.19-3.01 (m, 2H), 1.69-1.55 (m, 3H), 0.93-0.90 (m, 6H).

I-Ph-CO-Ala-Leu-Gly-OPEG$_{5000}$-OMe (L1, g). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.05 (bd, 1H), 6.92 (bs, 1H), 6.72 (bd, 1H), 4.60 (quintet, *J* = 6.8 Hz, 1H), 4.50 (m, 1H), 4.29-4.18 (m, 2H, PEG-α-methylene), 4.14-3.97 (m, 2H), 3.75-3.49 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.75 (m, 1H), 1.61 (m, 1H), 1.56 (m, 1H), 1.50 (d, *J* = 7.0 Hz, 3H), 0.91-0.89 (m, 6H).

I-Ph-CO-Phe-Leu-Gly-OPEG$_{5000}$-OMe (L1, h). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.31-7.23 (m, 5H), 6.82 (bs, 1H), 6.58 (bs, 1H), 6.35 (bs, 1H), 4.79 (q, J = 7.0 Hz, 1H), 4.43 (m, 1H), 4.28 (m, 2H, PEG-α-methylene), 4.07-3.94 (m, 2H), 3.75-3.49 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.19 (m, 2H), 1.67 (m, 1H), 1.54 (m, 1H), 1.46 (m, 1H), 0.88-0.85 (m, 6H).

I-Ph-CO-Leu-Leu-Gly-OPEG$_{5000}$-OMe (L1, i). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 6.83 (bs, 1H), 6.73 (bd, 1H), 6.64 (bd, 1H), 4.61 (q, J = 5.9 Hz, 1H), 4.48 (m, 1H), 4.28-4.21 (m, 2H, PEG-α-methylene), 4.09-4.00 (m, 2H), 3.75-3.49 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.72-1.53 (m, 6H), 0.96-0.86 (m, 12H).

(OH)$_2$B-Ph-CO-Ala-Ala-Gly-OPEG$_{5000}$-OMe (L2, a). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 7.9 Hz, 2H), 7.26 (bs, 1H), 7.22 (bs, 1H), 7.06 (bd, 1H), 4.61-4.56 (m, 2H), 4.26-4.16 (m, 2H, PEG-α-methylene), 4.14-3.92 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.52 (d, J = 7.0 Hz, 3H), 1.39 (d, J = 7.0 Hz, 3H).

(OH)$_2$B-Ph-CO-Phe-Ala-Gly-OPEG$_{5000}$-OMe (L2, b). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 6.97 (bd, 1H), 6.84 (bt, 1H), 6.76 (bd, 1H), 4.81 (q, J = 7.0, 2H), 4.51 (quintet, J = 7.4 Hz, 1H), 4.26-4.19 (m, 2H, PEG-α-methylene), 4.09-3.88 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.22 (d, J = 7.0 Hz, 2H), 1.34 (d, J = 7.0 Hz, 3H).

(OH)$_2$B-Ph-CO-Leu-Ala-Gly-OPEG$_{5000}$-OMe (L2, c). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 7.7 Hz, 2H), 7.79 (d, J = 7.9 Hz, 2H), 7.13 (bs, 1H), 6.98 (bd, 2H), 4.63 (bs, 1H), 4.54 (m, 1H), 4.27-4.14 (m, 2H, PEG-α-methylene), 4.10-3.95 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.80-1.68 (m, 3H), 1.39 (d, J = 7.0 Hz, 3H), 0.98-0.96 (m, 6H).

$(OH)_2$B-Ph-CO-Ala-Phe-Gly-OPEG$_{5000}$-OMe (L2, d). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.16-7.14 (m, 5H), 7.11 (bs, 1H), 7.05 (bs, 1H), 6.95 (d, J = 8.1 Hz, 1H), 4.76 (q, J = 5.9 Hz, 1H), 4.50 (quintet, J = 6.8 Hz, 1H), 4.25-4.16 (m, 2H, PEG-α-methylene), 4.12-3.91 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.29-3.02 (m, 2H), 1.40 (d, J = 7.2 Hz, 3H).

$(OH)_2$B-Ph-CO-Phe-Phe-Gly-OPEG$_{5000}$-OMe (L2, e). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.79 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.26-7.07 (m, 10H), 6.76 (bs, 2H), 6.64 (bs, 1H), 4.71 (m, 2H), 4.26-4.19 (m, 2H, PEG-α-methylene), 4.09-3.86 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.16-2.99 (m, 4H).

$(OH)_2$B-Ph-CO-Leu-Phe-Gly-OPEG$_{5000}$-OMe (L2, f). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.16-7.10 (m, 5H), 7.04 (bs, 1H), 6.88 (bd, 1H), 6.75 (bd, 1H), 4.75 (q, J = 5.9, 1H), 4.49 (m, 1H), 4.22-4.16 (m, 2H, PEG-α-methylene), 4.13-3.90 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.27-3.01 (m, 2H), 1.64 (m, 2H), 1.56 (m, 1H), 0.93-0.89 (m, 6H).

$(OH)_2$B-Ph-CO-Ala-Leu-Gly-OPEG$_{5000}$-OMe (L2, g). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.92 (d, J = 7.9 Hz, 2H), 7.83 (d, J = 7.9 Hz, 2H), 7.21 (bs, 1H), 6.89 (d, J = 8.1 Hz, 1H), 4.58 (m, 1H), 4.54 (m, 1H), 4.25-4.16 (m, 2H, PEG-α-methylene), 4.13-3.92 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.80 (m, 2H), 1.62 (m, 1H), 1.53 (d, J = 7.0 Hz, 3H), 0.90-0.88 (m, 6H).

$(OH)_2B$-Ph-CO-Phe-Leu-Gly-OPEG$_{5000}$-OMe (L2, h). ^1H-NMR (600 MHz, $CDCl_3$) δ 7.89 (d, J = 7.7 Hz, 2H), 7.67 (d, J = 7.6 Hz, 2H), 7.29-7.23 (m, 5H), 6.97 (bd, 1H), 6.88 (bs, 1H), 6.59 (bd, 1H), 4.81 (q, J = 6.8 Hz, 1H), 4.47 (m, 1H), 4.28-4.19 (m, 2H, PEG-α-methylene), 4.09-3.89 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 3.23 (d, J = 6.9 Hz, 2H), 1.72 (m, 1H), 1.54 (m, 1H), 1.48 (m, 1H), 0.88-0.85 (m, 6H).

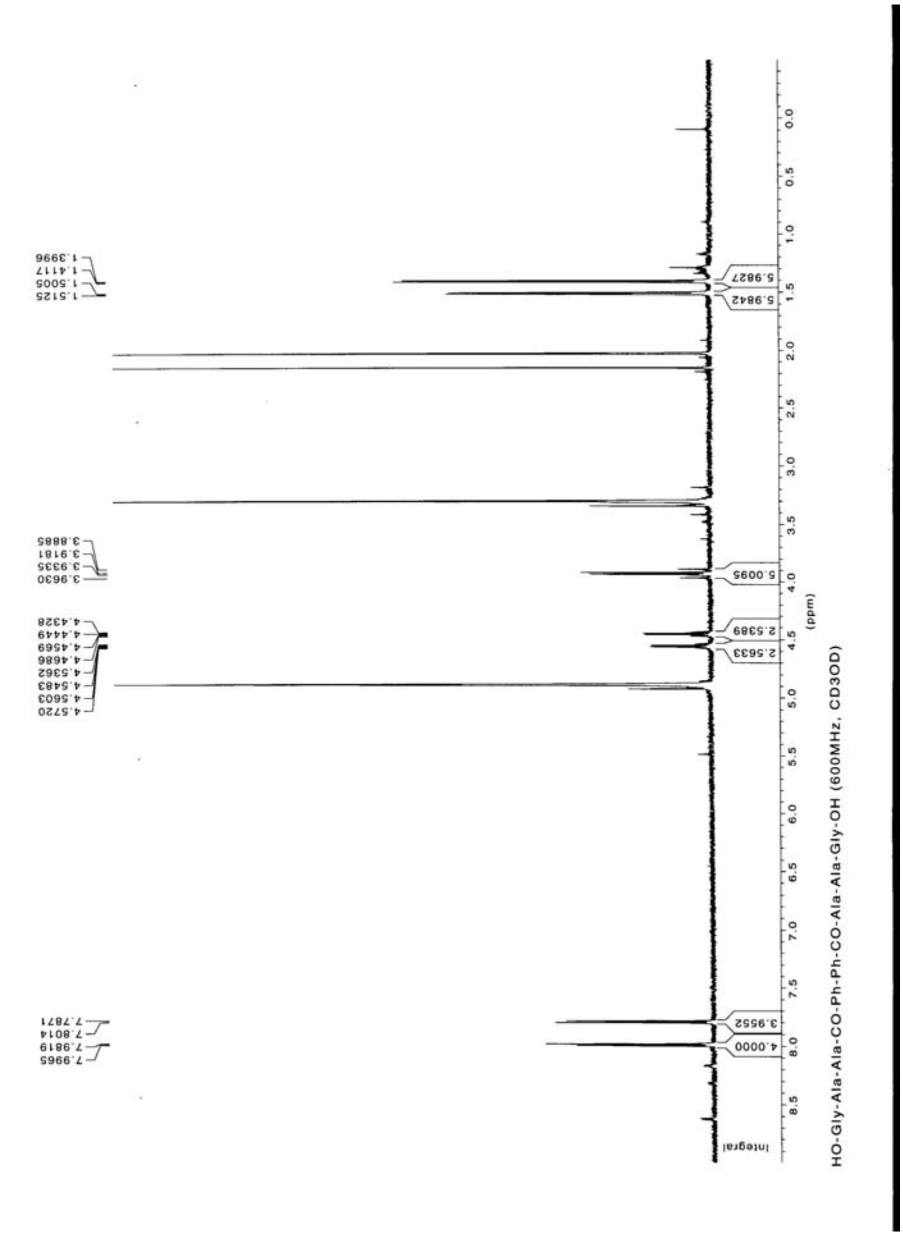
$(OH)_2B$-Ph-CO-Leu-Leu-Gly-OPEG$_{5000}$-OMe (L2, i). ^1H-NMR (600 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 7.11 (bs, 1H), 6.95 (bd, 1H), 6.85 (bd, 1H), 4.60 (m, 1H), 4.50 (m, 1H), 4.25-4.15 (m, 2H, PEG-α-methylene), 4.10-3.95 (m, 2H), 3.75-3.51 (m, PEG-methylenes), 3.37 (s, 3H, PEG-methoxy), 1.70-1.69 (m, 4H), 1.61 (m, 1H), 1.55 (m, 1H), 0.98-0.85 (m, 12H).

Synthesis of biaryl-linked hexapeptide library, L3. MeO-PEG$_{5000}$-supported tripeptide iodide library **L1a-i** (20 mg, 4 μmol; 10 mM), MeO-PEG$_{5000}$-supported tripeptide boronic acid library **L2a-i** (20 mg, 4 μmol; 10 mM), K_2CO_3 (1.6 mg, 12 □mol), $PdCl_2$(dppf) (0.33 mg, 10 mol%) and degassed DMF (0.4 mL) were added to thick-walled glass vials. The vials were sealed under Ar and the reaction mixture was stirred at 100 °C for 24 h. The reaction mixture was then cooled to room temperature and added into cold diethyl ether (10 mL). The precipitated PEG-bound hexapeptides **L3** were separated by centrifugation, washed with cold diethyl ether (10 mL) and dried under reduced pressure.

Hydrolysis of MeO-PEG esters of hexapeptide library. The PEG ester of hexapeptide (4 μmol) was treated with LiOH/water (3.6 mg/1 mL) at room temperature for 24 h. Then, the reaction mixture was acidified with 10% aq. citric acid (1 mL), and lyophilized.

Removal of MeO-PEG-OH from the crude hexapeptides (L4). Weakly basic anion-exchange resin (IRA-67), that was treated with saturated aq. sodium bicarbonate solution previously, was washed with deionized water (30 mL). The lyophilized hexapeptide (**L4**) was dissolved in MeOH (or DMF)/water (3:1), added to the resin, and shaken for 3 h. Then, the solution was drained and the resin was washed with water (30 mL) to remove MeO-PEG-OH. The hexapeptide was extracted from the resin by the treatment of CH_3CN/1M HCl (aq.) (1:1, 4 mL, 3 hr), and the combined solution was lyophilized. The obtained crude peptide was examined by LC/MS for its purity, purified by HPLC, and analyzed by ^{1}H-NMR spectroscopy. Characterization of the selected members from the biphenyl-linked hexapeptide library by LC/MS and HR-MALDI-MS is summarized in Table 1.

HO-Gly-Ala-Ala-CO-Ph-Ph-CO-Ala-Ala-Gly-OH. (85 %); ^{1}H-NMR (600 MHz, CD_3OD) δ 7.99 (d, J = 8.8 Hz, 4H), 7.80 (d, J = 8.6 Hz, 4H), 4.56 (q, J = 7.3 Hz, 2H), 4.45 (q, J = 7.0 Hz, 2H), 3.93 (dd, J = 17.7 and 27.0 Hz, 4H), 1.51 (d, J = 7.2 Hz, 6H), 1.41 (d, J = 7.3 Hz, 6H) (see supp. Figure 1); HR-MALDI-MS calcd for $[M + Na]^+$ 663.2385, found 663.2377.



Supp. Figure 1 ^{1}H NMR (600 MHz) of HO-Gly-Ala-Ala-CO-Ph-Ph-CO-Ala-Ala-Gly-OH.

HO-Gly-Ala-Ala-CO-Ph-Ph-CO-Ala-Phe-Gly-OH. ^{1}H-NMR (600 MHz, CD_3OD) δ 8.00 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 7.24-7.12 (m, 5H), 4.69 (dd, J = 5.5 and 9.7 Hz, 1H), 4.56 (q, J = 7.4 Hz, 1H), 4.50-4.45 (m, 2H), 3.93 (dd, J = 18.0 and 29.2 Hz, 4H), 2.96 (dd, J = 9.2 and 14.0 Hz, 2H), 1.51 (d, J = 7.0 Hz, 3H), 1.41 (d, J = 7.2 Hz, 3H), 1.36 (d, J = 7.2 Hz, 3H); HR-MALDI-MS calcd for $[M + Na]^+$ 739.2698, found 739.2704.

HO-Gly-Ala-Ala-CO-Ph-Ph-CO-Ala-Leu-Gly-OH. ^{1}H-NMR (600 MHz, CD_3OD) δ 7.99 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.3 Hz, 4H), 4.59-4.54 (m, 2H), 4.50-4.45 (m, 2H), 3.95-3.87 (m, 4H), 1.74 (m, 1H), 1.67 (m, 2H), 1.51 (d, J = 7.3 Hz, 3H), 1.50 (d, J = 7.0 Hz, 3H), 1.41 (d, J = 7.3 Hz, 3H), 0.96-0.92 (m, 6H); HR-MALDI-MS calcd for $[M + Na]^+$ 705.2854, found 705.2846.

HO-Gly-Ala-Phe-CO-Ph-Ph-CO-Leu-Ala-Gly-OH. ^{1}H-NMR (600 MHz, CD_3OD) δ 7.96 (d, J = 8.6 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.33-7.19 (m, 5H), 4.65 (dd, J = 4.4 and 9.8 Hz, 1H), 4.45 (q, J = 6.6 Hz, 2H), 3.97-3.86 (m, 4H), 3.08 (dd, J = 9.2 and 13.8 Hz, 2H), 1.79 (m, 2H), 1.72 (m, 1H), 1.40 (d, J = 7.3 Hz, 3H), 1.39 (d, J = 7.0 Hz, 3H), 1.01-0.98 (m, 6H); HR-MALDI-MS calcd for $[M + Na]^+$ 781.3167, found 781.3154.

HO-Gly-Ala-Phe-CO-Ph-Ph-CO-Phe-Phe-Gly-OH. ^{1}H-NMR (600 MHz, CD_3OD) δ 7.84-7.73 (m, 8H), 7.34-7.09 (m, 15H), 4.80 (m, 1H), 4.68 (m, 1H), 4.45 (m, 1H), 3.89 (m, 4H), 3.10 (dd, J = 10.1 and 23.9 Hz, 2H), 2.99 (dd, J = 9.8 and 14.5 Hz, 2H), 2.92 (dd, J = 8.8 and 13.6 Hz, 2H), 1.39 (m, 3H); HR-MALDI-MS calcd for $[M + Na]^+$ 891.3324, found 891.3314.

HO-Gly-Ala-Phe-CO-Ph-Ph-CO-Leu-Leu-Gly-OH. ^{1}H-NMR (600 MHz, CD_3OD) δ 7.95 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.75-7.19 (m, 5H), 4.65 (m, 1H), 4.48 (m, 1H), 4.45 (m, 1H), 3.98-3.85 (m, 4H), 3.08 (dd, J = 9.7 and 14.0 Hz, 2H), 1.80-1.69 (m, 4H), 1.65 (m, 2H), 1.39 (m, 3H), 1.02-0.91 (m, 12H); HR-MALDI-MS calcd for $[M + Na]^+$ 823.3637, found 823.3618.

HO-Gly-Ala-Leu-CO-Ph-Ph-CO-Phe-Phe-Gly-OH. ^{1}H-NMR (600 MHz, CD_3OD) δ 7.97 (d, J = 8.5 Hz, 2H), 7.80-7.75 (m, 6H), 7.25-7.08 (m, 10H), 4.69 (m, 1H), 4.64 (m, 1H), 4.45 (m, 1H), 3.97-3.87 (m, 4H), 2.99 (dd, J = 10.1 and 13.6 Hz, 2H), 2.92 (dd, J = 9.4 and 13.8 Hz, 2H), 1.79 (m, 2H), 1.72 (m, 1H), 1.40 (d, J = 7.2 Hz, 3H), 1.02-0.99 (m, 6H); HR-MALDI-MS calcd for $[M + Na]^+$ 857.3480, found 857.3479.

HO-Gly-Ala-Leu-CO-Ph-Ph-CO-Leu-Leu-Gly-OH. ^{1}H-NMR (600 MHz, CD_3OD) δ 7.97 (d, J = 8.5 Hz, 2H), 7.96 (d, J = 8.3 Hz, 2H), 7.80 (d, J = 8.1 Hz, 4H), 4.65 (m, 2H), 4.47 (m, 1H), 4.45 (m, 1H), 3.97-3.86 (m, 4H), 1.81 (m, 6H), 1.64 (m, 3H), 1.40 (d, J = 7.3 Hz, 3H), 1.02-0.91 (m, 18H); HR-MALDI-MS calcd for $[M + Na]^+$ 789.3793, found 789.3792.

HO-Gly-Phe-Ala-CO-Ph-Ph-CO-Ala-Phe-Gly-OH. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.56 (d, J = 7.7 Hz, 2H), 8.33 (t, J = 6.1 Hz, 2H), 7.99 (d, J = 8.3 Hz, 4H), 7.96 (d, J = 8.6 Hz, 2H), 7.87 (d, J = 8.6 Hz, 4H), 7.23-7.12 (m, 10H), 4.55 (m, 2H), 4.46 (m, 2H), 3.81-3.73 (m, 4H), 3.05 (dd, J = 4.1 and 14.0 Hz, 2H), 2.83 (dd, J = 9.4 and 14.0 Hz, 2H), 1.26 (m, 6H); HR-MALDI-MS calcd for $[M + Na]^+$ 815.3011, found 815.3008.

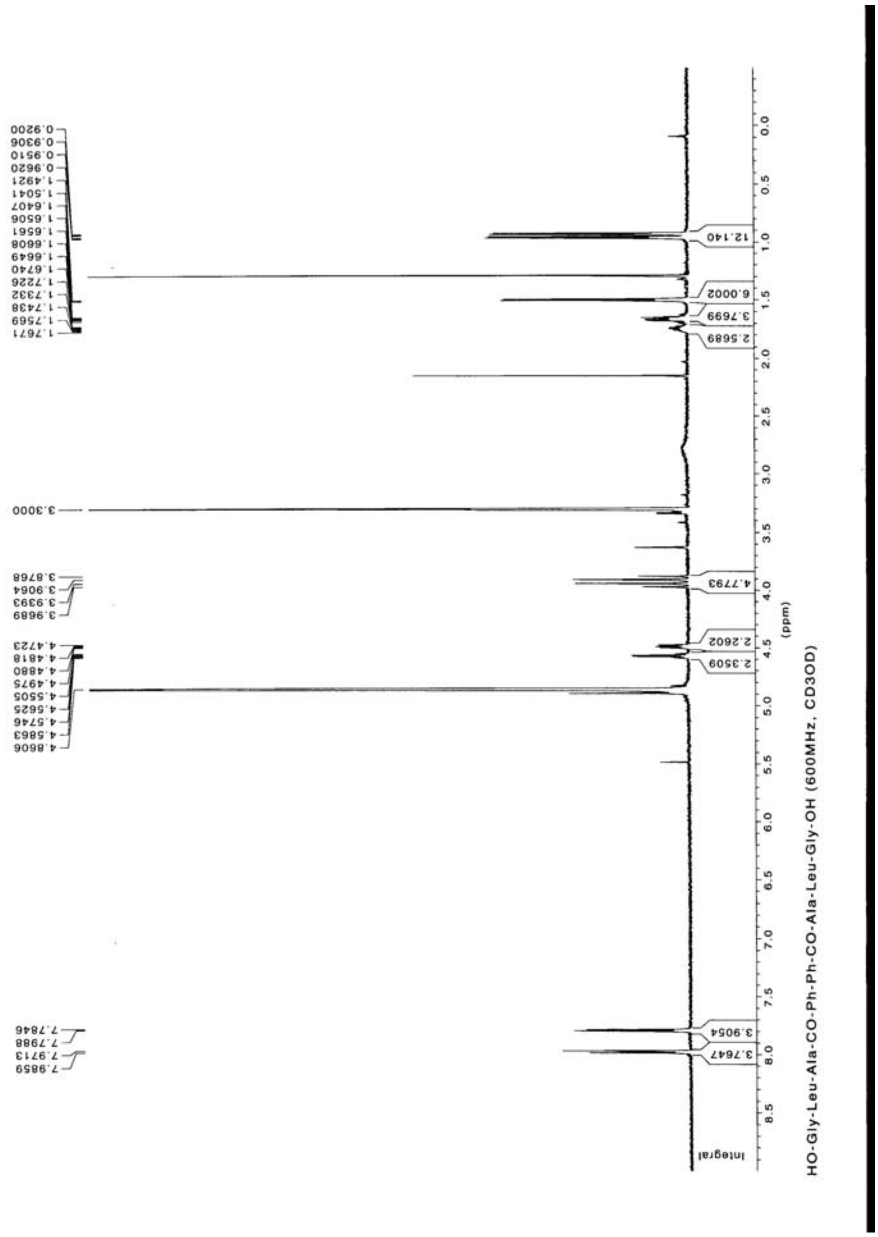
HO-Gly-Phe-Phe-CO-Ph-Ph-CO-Phe-Phe-Gly-OH. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.61 (d, J = 8.2 Hz, 2H), 8.38 (t, J = 6.1 Hz, 2H), 8.16 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.5 Hz, 4H), 7.82 (d, J = 8.3 Hz, 4H), 7.30-7.13 (m, 20H), 4.71 (m, 2H), 4.60 (m, 2H), 3.79 (m, 4H), 3.07 (d, J = 13.6 Hz, 4H), 2.94 (dd, J = 10.7 and 13.9 Hz, 2H), 2.85 (dd, J = 8.5 and 13.8 Hz, 2H); HR-MALDI-MS calcd for $[M + Na]^+$ 967.3637, found 967.3635.

HO-Gly-Phe-Leu-CO-Ph-Ph-CO-Leu-Phe-Gly-OH. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.51 (d, *J* = 7.6 Hz, 2H), 8.35 (t, *J* = 5.7 Hz, 2H), 8.00 (d, *J* = 8.6 Hz, 4H), 7.94 (d, *J* = 8.8 Hz, 2H), 8.87 (d, *J* = 8.6 Hz, 4H), 7.24-7.14 (m, 10H), 4.58 (m, 2H), 4.49 (m, 2H), 3.82-3.74 (m, 4H), 3.05 (dd, *J* = 4.1 and 14.0 Hz, 2H), 2.83 (dd, *J* = 9.4 and 13.8 Hz, 2H), 1.59 (m, 4H), 1.45 (m, 2H), 0.89-0.83 (m, 12H); HR-MALDI-MS calcd for $[M + Na]^+$ 899.3950, found 899.3936.

HO-Gly-Leu-Phe-CO-Ph-Ph-CO-Phe-Phe-Gly-OH. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.65 (d, *J* = 8.3 Hz, 1H), 8.60 (d, *J* = 9.0 Hz, 1H), 8.37 (t, *J* = 6.2 Hz, 1H), 8.21 (t, *J* = 5.9 Hz, 1H), 8.16 (m, 2H), 7.89-7.81 (m, 8H), 7.38-7.13 (m, 15H), 4.74 (m, 2H), 4.61 (m, 1H), 4.39 (m, 1H), 3.80-3.73 (m, 4H), 3.01 (m, 2H), 2.95 (m, 2H), 2.84 (m, 2H), 0.90-0.85 (m, 6H); HR-MALDI-MS calcd for $[M + Na]^+$ 933.3793, found 933.3807.

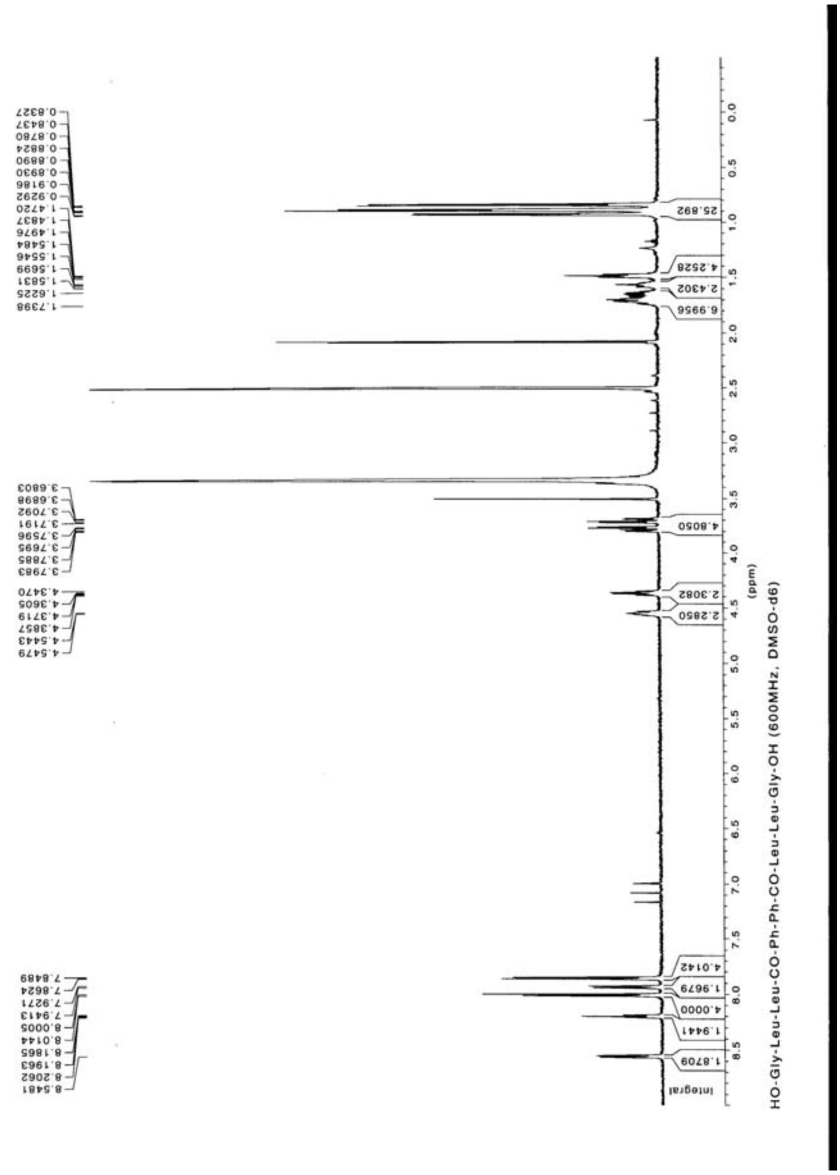
HO-Gly-Leu-Leu-CO-Ph-Ph-CO-Leu-Phe-Gly-OH. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.56 (d, *J* = 8.3 Hz, 1H), 8.51 (d, *J* = 8.1 Hz, 1H), 8.35 (t, *J* = 5.5 Hz, 1H), 8.20 (t, *J* = 5.7 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.94 (m, 2H), 7.86 (d, *J* = 6.8 Hz, 4H), 7.24-7.13 (m, 5H), 4.56 (m, 2H), 4.48 (m, 1H), 4.37 (dd, *J* = 7.9 and 14.2 Hz, 1H), 3.82-3.68 (m, 4H), 2.83 (dd, *J* = 9.7 and 14.0 Hz, 2H), 1.75-1.56 (m, 6H), 1.50-1.43 (m, 3H), 0.93-0.83 (m, 18H); HR-MALDI-MS calcd for $[M + Na]^+$ 865.4106, found 865.4106.

HO-Gly-Leu-Ala-CO-Ph-Ph-CO-Ala-Leu-Gly-OH. ^{1}H-NMR (600 MHz, CD_3OD) δ 7.98 (d, *J* = 8.8 Hz, 4H), 7.79 (d, *J* = 8.5 Hz, 4H), 4.58 (q, *J* = 7.0 Hz, 2H), 4.48 (dd, *J* = 5.7 and 9.4 Hz, 2H), 3.92 (q, *J* = 19.7 Hz, 4H), 1.75 (m, 2H), 1.65 (m, 4H), 1.50 (d, *J* = 7.2 Hz, 6H) (see supp. Figure 2); HR-MALDI-MS calcd for $[M + Na]^+$ 747.3324, found 747.3331.



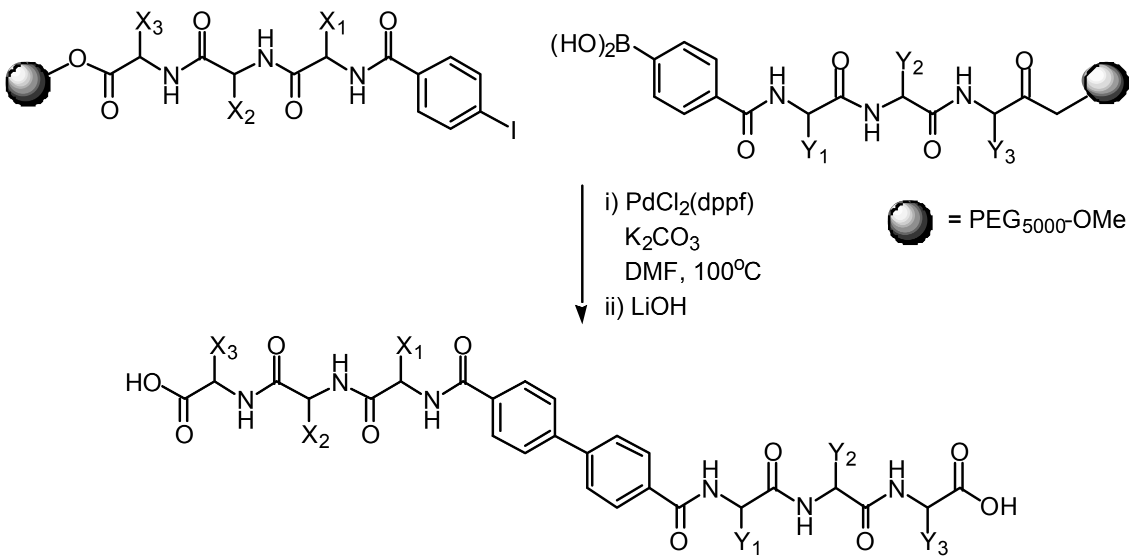
Supp. Figure 2 ^{1}H NMR (600 MHz) of HO-Gly-Leu-Ala-CO-Ph-Ph-CO-Ala-Leu-Gly-OH.

HO-Gly-Leu-Leu-CO-Ph-Ph-CO-Leu-Leu-Gly-OH. ^{1}H-NMR (600 MHz, DMSO-d_6) δ 8.56 (d, *J* = 8.3 Hz, 2H), 8.20 (t, *J* = 5.9 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 4H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 4H), 4.54 (m, 2H), 4.37 (dd, *J* = 8.3 and 15.1 Hz, 2H), 3.80-3.68 (m, 4H), 1.77-1.63 (m, 6H), 1.62 (m, 2H), 1.48 (m, 4H), 0.93-0.83 (m, 24H) (see Supp. Figure 3); HR-MALDI-MS calcd for $[M + Na]^+$ 831.4263, found 831.4283.



Supp. Figure 3 ^{1}H NMR (600 MHz) of HO-Gly-Leu-Leu-CO-Ph-Ph-CO-Leu-Leu-Gly-OH.

Table 1. Characterization of the selected members of the hexapeptide library synthesized by polymer-supported Suzuki cross-coupling reaction.



Sequence		Purity (%)	Molecular Weight $[M + Na]^+$	
$X_1X_2X_3$	$Y_1Y_2Y_3$	Desired Product (Homodimeric Byproduct)	Observed	Expected
GAA	AAG	83	663.2377	663.2385
GAA	AFG	52 (24)	739.2704	739.2698
GAA	ALG	67 (13)	705.2846	705.2854
GAF	LAG	52 (8)	781.3154	781.3167
GAF	FFG	61 (21)	891.3314	891.3324
GAF	LLG	73 (12)	823.3618	823.3637
GAL	FFG	70 (8)	857.3479	857.3480
GAL	LLG	76 (9)	789.3792	789.3793

Table 1. Continued.

Sequence		Purity (%)	Molecular Weight $[M+Na]^+$	
$X_1X_2X_3$	$Y_1Y_2Y_3$	Desired Product (Homodimeric Byproduct)	Observed	Expected
GFA	AFG	72	815.3008	815.3011
GFF	FFG	92	967.3635	967.3637
GFF	LLG	56 (10)	899.3960	899.3950
GFL	LFG	74	899.3936	899.3950
GLA	AFG	61 (7)	781.3186	781.3167
GLA	ALG	80	747.3331	747.3324
GLF	FFG	69 (13)	933.3807	933.3793
GLL	LFG	71 (11)	865.4106	865.4106
GLL	LLG	95	831.4283	831.4263