Supporting Information

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SI Materials and Methods

Materials and General Methods. Aβ_{1-40} and Aβ_{1-42} were purchased from Bachem and stored at −70 °C until use. Aβ_{12-28} (VHHQKLVFFAEDVGSNK), Aβ_{13-23} (HHQKLVFFAED) with 4 alanine residues added at both the N terminus and C terminus (hereafter referred to as Aβ_{13-23A}), and a scrambled variant of Aβ_{13-23} (DHQFAVHLEFK) with 4 alanine residues added at both the N terminus and C terminus (hereafter referred to as scrambled Aβ_{13-23A}) were purchased from Thermo Electron. All Aβ fragments were acetylated at the N terminus and amidated at the C terminus and stored at −20 °C until use. All protected amino acids were purchased from Bachem or IRIS Biotech. All other reagents were of commercial grade, and all solvents were of analytic grade and were purchased from Fluka, Merck, or Aldrich Chemical. All reactions were monitored by TLC using silica-coated plates with fluorescence indicator (SiO_2-60, F-254) and visualizing under UV light and by spraying with molybdate reagent [21 g $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, 1 g $Ce(SO_4)_2$, 31 mL H_2SO_4, and 470 mL H_2O] followed by heating. Silica gel 60 (particle size 0.040–0.063 mm; Merck) was used for flash column chromatography, and Silica gel 60 (particle size 0.015–0.040 mm; Merck) was used for column vacuum chromatography. After column chromatography, fractions containing product were pooled, evaporated to dryness under reduced pressure, and dried for 12 h under vacuum to give the product unless otherwise specified. For building of the initial molecular models of Aβ_{13-26}, standard α-helical parameters as implemented in the InsightII software package from Accelrys were used. The brief molecular dynamics runs were carried out for 20 ps at 310 K with the Discover module from the same software package and use of the amber force field as implemented there. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100.61 MHz on a Bruker 400 GSX instrument. Chemical shifts are reported in ppm relative to either tetramethylsilane or the deuterated solvent as internal standard for ^{1}H NMR and ^{13}C NMR spectroscopy. Coupling constants (*J* values) are given in hertz. Assignments of NMR spectra, when given, are based on 2D spectra. All compounds were characterized by electrospray ionization time-of-flight (ESI-TOF) MS on a Micromass LCT instrument.

To ensure a monomeric starting solution Aβ_{1-40} was dissolved, sonicated, and vortexed at 1 mg/mL (231 μM) in DMSO (Merck) and diluted in 10 mM sodium phosphate buffer (pH 7) to the working concentration immediately before use. For the CD measurements DMSO could not be used because of its high absorbance, and for those experiments the peptides were instead dissolved in trifluoroethanol (TFE; Sigma) but otherwise treated as above. The different variants of Aβ_{13-23} were dissolved in TFE and briefly sonicated before being diluted to the working concentrations in 10 mM sodium phosphate buffer (pH 7) with a final TFE concentration of 25% (vol/vol) to promote a helical structure. Aβ_{1-42} used in the cell culture experiments was prepared in 2 different manners. First, for treatment of PC12 cells for 4 h, Aβ_{1-42} was dissolved in hexafluoroisopropanol at 1 mg/mL, dried with speed vacuum centrifugation, and thereafter dissolved in DMSO at 100 μM, briefly sonicated in water bath, and subsequently diluted in 2× PBS (pH 7.4) to 20 μM. Second, for treatment of PC12 cells with Aβ_{1-42} for 18 h, the peptide was dissolved in 10 mM NaOH at 100 μM, briefly sonicated in water bath, and thereafter diluted in 2× PBS (pH 7.4) to 50 μM. For both Aβ_{1-42} dissolving protocols the 2× PBS was diluted to 1× PBS before addition to cells.

Thioflavin T Binding. All experiments were carried out with an Aβ concentration of 25 μM in 10 mM sodium phosphate buffer (pH 7) containing 10% (vol/vol) DMSO. Aβ_{1-40} was incubated in the presence of different concentrations of ligand (0, 25, 125, and 250 μM) at 37 °C under agitation. At various time points, 10-μL aliquots were removed and diluted to 100 μL with 10 μM thioflavin T (Aldrich) in 10 mM sodium phosphate buffer with 150 mM NaCl (pH 6). The samples were incubated for 5 min in the dark before fluorescence was measured in a FarCyte fluorescence plate reader (GE Healthcare). The wavelengths for excitation and emission were 440 nm and 480 nm, respectively. Each sample was measured in duplicate.

Aβ_{1-42} Transgenic Flies Climbing Assay. To monitor mobility, 9 to 10 flies were placed in a 10-cm glass vial with fresh food, and the tubes were filmed as the Aβ_{1-42} transgenic flies were allowed to climb for 0.5 min. Movie S1 shows climbing behavior of Dec-DETA–treated and nontreated 16-day-old flies kept at 28 °C.

Histologic Examination. At different time points flies were decapitated and the heads fixed in 4% (wt/vol) paraformaldehyde in PBS (pH 7.4) for 48 h. After fixation the heads were imbedded in paraffin wax. Immunostaining was performed on 5-μm sections with the 4G8 anti-Aβ monoclonal antibody (Signet Laboratories) diluted 1:2,500, 1:400, or 1:40 in 0.05 M Tris-buffered saline (TBS; pH 7.4), a biotinylated antimouse secondary antibody (DAKO) diluted 1:200 in TBS (pH 7.4), and streptavidin–HRP (DAKO) diluted 1:500 in TBS (pH 7.4) with 3,3′-diaminobenzidine tetrahydrochloride (DAB) for developing. In our hands, no detectable specific staining of amyloid or Aβ was seen in the immunohistochemistry experiments using any of the titers, probably owing to low levels of Aβ present or difficulties in antigen retrieval.

Effects of Pep1b in *Drosophila* Huntington's Disease Model. The constitutive expression of mutant huntingtin in the *Drosophila* eye represents a powerful model of Huntington's disease in the fly. Progressive neurotoxicity of the transgenic polypeptide can be quantified by counting the number of surviving photoreceptor cells (rhabdomeres) within each facet of the fly's compound eye (1). In a wild-type fly the maximum number of rhabdomeres visible is 7, and this number declines with time in flies expressing huntingtin exon 1 with a 120 glutamine expansion (*gmr-httQ120*) (1). Previous work has shown that this experimental paradigm is sensitive to rescue by several proposed therapeutic compounds, such as lithium and rapamycin (2).

Rearing flies in medium containing Peb1b did not affect rhabdomere number in 4-day-old male *gmr-httQ120* flies, whether the drug was dosed at 2 μM (2.8 ± 0.1; $P = 0.7$) or 200 μM (3.0 ± 0.4; $P = 0.2$), as compared with control flies treated with water alone (2.9 ± 0.3). Moreover, treatment with Peb1b did not change the frequency distribution of rhabdomere counts as compared with control (significance vs. controls, $P = 0.5$ for 2 μM Peb1b, $P = 0.4$ for 200 μM Peb1b; Mann-Whitney test; Fig. S5). Likewise in females there was no beneficial effect on rhabdomere number of treatment with 2 μM Peb1b (1.9 ± 0.3; $P = 0.4$) or 200 μM (1.7 ± 0.1; $P = 0.03$) as compared with control untreated flies (2.2 ± 0.1). Rhabdomere numbers are expressed as mean ± SEM of 3 independent experiments and compared using paired *t* tests. The criterion for significance was adjusted using the Bonferroni correction for multiple testing to $P < 0.0125$.

Taken together these data show that Peb1b treatment is not beneficial in *gmr-httQ120* flies.

Alcohol Dehydrogenase Inhibition Assay. Liver alcohol dehydrogenase (ADH; Sigma) was dissolved in 10 mM potassium phosphate buffer (pH 7.5) at a concentration of 10 mg/mL. The enzyme reactions were performed at room temperature and contained 0.05 M ethanol, 3 mM NAD^+, and 2 μM ADH in 50 mM sodium pyrophosphate buffer (pH 8.8). Ligands, 25 or 250 μM end concentration, were incubated together with the enzyme for 3 min before the reaction was initiated by the addition of ethanol and NAD^+. The increase in NADH concentration was monitored at 340 nm on a Hitachi U-2000 spectrophotometer. See Table S1.

Synthesis of Decanoyl-DETA. Diethylentriamine (10.80 mL, 100 mmol) and TFA (15.41 mL, 200 mmol) were dissolved in methanol (300 mL) and kept at 0 °C. Dekanoic acid (1.81 g, 10.5 mmol) was activated at 0 °C with isobutyl chloroformate (1.31 mL, 10.0 mmol) and triethylamine (2.77 mL, 20.0 mmol) in dichloromethane (DCM) (60 mL). The activated fatty acid solution was then added dropwise during 30 min to the methanolic solution with diethylenetriamine. After 1 h the ice bath was removed, and stirring was continued for 19 h at room temperature. The solvents were then evaporated under reduced pressure, and the residue was partitioned between DCM (300 mL) and NaOH (*aq*, 1 M, 100 mL). The organic layer was collected and washed with NaOH (1 M, 2 × 100 mL), dried with Na_2SO_4, and evaporated under reduced pressure, yielding 2.01 g of crude product in the amine form. The residue was dissolved in ethyl acetate, TFA was added, and the compound was crystalized as the di-TFA salt: 2.94 g (61%). ^{1}H-NMR (D_3COD + 1% TFA): δ 3.50 (2H t J = 5.67 Hz *CH2*), 3.39 (2H t J = 6.55 Hz CH2); 3.37–3.27 (2H m CH2); 3.22 (2H t J = 5.67 Hz CH2); 2.24 (2H t J = 7.70 Hz decanoyl-α-CH2); 1.61 (2H m 7.1 Hz decanoyl-β-CH2); 1.38–1.20 (12H m 6 X CH2); 0.90 (3H t J = 6.76 Hz CH3); MS (ESI-TOF) *m/z* calculated: 258,2545; found: 258,2538.

Synthesis of Peptoids Pep1a and -b. Both peptoids were synthesized by solution synthesis using activated pentafluorophenyl esters and appropriate protected and/or activated D-diaminobutanoic acid (D-Dab), D-Trp, L-Arg, and D-Glu or glutarate derivatives. The synthesis of Pep1a is outlined in Scheme S1, and the synthesis of Pep1b is outlined in Scheme S2.

Synthesis of Pep1a. ***Intermediate S1.*** Z-Dab-OH [2.52 g (10.00 mmol)] of was dissolved in 50 mL of 50 mM $Na_2B_4O_7$ (pH 8.5). Fmoc-*D*-Trp-OPfp [5.93 g (10.00 mmol)] was dissolved in 50 mL of cold dimethylformamide (DMF) (0 °C) and added slowly to the solution of Z-Dab-OH. The mixture was stirred at 0 °C for 1 h and then 10 h at room temperature. The reaction was monitored by TLC. After completion of reaction the solvent (H_2O/DMF) was evaporated under reduced pressure. The oily product S1 was crystallized from ethyl acetate, collected, and dried under reduced pressure. Yield: 5.94 g (90%).
Intermediate S2. S1 was treated with a solution of 20% piperidine in DMF (0.5 h). The reaction mixture was concentrated, and the oily product was crystalized from ether. The product was filtered off, washed with ether, and dried under reduced pressure. Yield: 98%.
Intermediate S3. S2 [0.93 g (2.18 mmol)] was dissolved in 30 mL of DMF, and 1.5 g of Boc-Arg (Pbf)-OPfp (2.2 mmol) dissolved in cold DMF was added slowly. The reaction mixture was stirred for 6 h at room temperature. The reaction mixture was concentrated, and the oily material was washed by cold ether. Precipitation occurred, and the mixture was kept in the freezer for 1 h. The precipitate was filtered off, washed with ether, and dried under reduced pressure. Yield: 0.70 g.
Intermediate S4. The Z-group was removed from S3 by catalytic hydrogenation using H_2 and Pd/C in DMF, containing AcOH. The Pd/C catalyst was filtered off, and the solution was evaporated under reduced pressure. The resulting oily product was worked up by addition of ether. Precipitation occurred, and the mixture was kept in the freezer, filtered off, washed with ether, and dried under reduced pressure. The product [0.46 g (0.53 mmol)] was dissolved in a mixture of EtOAc/DMF, and 53 μL (0.53 mmol) N-methylmorpholine was added. The reaction was stirred for 1 h, the liquid evaporated, and the peptide with free amino group precipitated with ether.
Intermediate S5. S4 [0.46 g (0.53 mmol)] was dissolved in DMF. Fmoc-*D*-Glu(OtBu)-OPfp [344.5 mg (0.58 mmol)] was dissolved in cold DMF and was added slowly at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then 8 h at room temperature. The solvent was evaporated and the product worked up with ether.
Intermediate S6. The Fmoc group was removed from 0.57 g of S5 by treatment with a solution of 20% piperidine in DMF (0.5 h). The peptide was then acetylated in pyridine containing 20% acetic anhydride (15 min). The reaction mixture was concentrated and worked up with ether. Yield: 0.40 g.
Pep1a. S6 was treated with a cleavage mixture containing 10 mL TFA, 1 mL H_2O, 0.75 g phenol, and 0.5 mL thioanisole. The reaction was stirred for 1 h at room temperature. Deprotection was monitored by TLC. After completion the reaction mixture was concentrated, and ether was added. The mixture was kept in the freezer, whereupon the formed solid was filtered off, washed with ether, and dried under reduced pressure. Yield: 0.35 g crude peptide. Purification of the crude peptide was done by reverse-phase HPLC on a Vydac semipreparative column using a gradient of acetonitrile/water, containing 0.1% TFA (0–80% acetonitrile over 2 h at a flow rate of 3.5 mL/min). The purity and molecular weight of the final peptide was determined by analytical HPLC and ESI-MS analysis (Micromass LCT); MS (ESI, M + 1): *m/z* found: 632.64; calculated: 632.31.

Synthesis of Pep1b. ***Intermediate S7.*** Boc-Dab-OH (1.00 g, 4.58 mmol) was dissolved in 50 mM $Na_2B_4O_7$ (22 mL, pH 8.5). Fmoc-D-Trp-OPfp (2.7 g, 4.58 mmol) was dissolved in cold DMF (30 mL) and added slowly to a cold solution of Boc-Dab-OH. The reaction mixture was stirred at 0 °C for 1 h and then overnight at room temperature. The solvent was evaporated to dryness under reduced pressure. The residue obtained was purified by column chromatography (20% MeOH/$CHCl_3$) to afford 2.59 g (90%) of S7 as a white solid. R_f 0.51 (methanol/chloroform 20:80, vol/vol); ES-TOF: *m/z* calculated for $C_{35}H_{38}N_4O_7$ $[M+Na]^+$: 649.26; found: 649.07.
Intermediate S8. Dry DMSO (20 mL) was added to a flask containing S7 (2.59 g, 4.13 mmol), $KHCO_3$ (0.620 g, 6.19 mmol), and tetrabutyl ammonium iodide (0.153 g, 0.414 mmol) (4). The resulting solution was stirred at room temperature for 15 min. Benzyl bromide (1.5 mL, 12.40 mmol) was added slowly to the above reaction mixture and stirred at room temperature overnight. The reaction was quenched by addition of water, and the DMSO–H_2O layer was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), saturated aqueous $Na_2S_2O_3$ (2 × 50 mL), and brine (2 × 50 mL). The separated organic phase was dried (Na_2SO_4), filtered, and concentrated to dryness under reduced pressure. The crude product was purified by column chromatography (6% MeOH/CH_2Cl_2) to give 2.56 g (86%) of S8 as a white solid. R_f 0.44 (methanol/dichloromethane 6:94, vol/vol); ES-TOF: *m/z* calculated for $C_{42}H_{44}N_4O_7$ $[M+H]^+$: 717.32; found: 717.13.
Intermediate S9. S8 (2.56 g, 3.57 mmol) was treated with 20% piperidine in DMF (15 mL). The reaction mixture was stirred for 1 h at room temperature and was evaporated to dryness under reduced pressure. The oil obtained was purified by flash column

chromatography (7% $MeOH/CH_2Cl_2$) to give S9 (1.69 g, 96%) as a white solid. R_f 0.39 (methanol/dichloromethane 7:93, vol/vol); ES-TOF: m/z calculated for $C_{27}H_{34}N_4O_5$ [M+H]$^+$: 495.26; found: 495.14.

Intermediate S10. Fmoc-Arg(Pbf)-OPfp (2.47 g, 3.03 mmol) was dissolved in cold DCM (30 mL) and added slowly to S9 (1.00 g, 2.02 mmol) dissolved in DMF (30 mL) containing triethyl amine (0.56 mL). The reaction mixture was stirred overnight at room temperature. The solvent was concentrated under reduced pressure, and the residue was purified by column chromatography (5% $MeOH/CH_2Cl_2$) to afford 2.05 g (90%) of S10 as a white solid. R_f 0.31(methanol/dichloromethane 5:95, vol/vol); ES-TOF: m/z calculated for $C_{61}H_{72}N_8O_{11}S$ [M+H]$^+$: 1,125.51; found: 1,125.35.

Intermediate S11. A solution of S10 (1.00 g, 0.89 mmol) in acetonitrile–H_2O (4.1 mL:85 μL) was treated with $BiCl_3$ (0.280 g, 0.89 mmol) and stirred at 55 °C for 1 h (5). After 1 h, an additional $BiCl_3$ (0.280 g, 0.89 mmol) was added and stirred for 1 h more; after that an additional aliquot of $BiCl_3$ (0.280 g, 0.89 mmol) was added and the reaction mixture was allowed to continue at 55 °C for 1 h. After the completion of the reaction, solid $NaHCO_3$ was added and the reaction mixture filtered through Celite. The solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography (7% $MeOH/CH_2Cl_2$) to give S11 0.504 g (55.32%) as a light-yellow solid. R_f 0.37(methanol/dichloromethane 7:93, vol/vol); ES-TOF: m/z calculated for $C_{56}H_{64}N_8O_9S$ [M+H]$^+$: 1,025.45; found: 1,025.24.

Intermediate S12. A suspension of amine (0.400 g, 0.390 mmol) and glutaric anhydride (0.54 g, mmol) in dry DMF (40 mL) and pyridine (10 mL) was stirred for 2 h at room temperature. The solvent was concentrated to dryness under reduced pressure and dissolved in ether. The white solid precipitated out, which was purified by column chromatography (7% $MeOH/CH_2Cl_2$) to give S12 as a white solid 0.345 g (77.61%). R_f0.25 (methanol/dichloromethane 7:93, vol/vol); ES-TOF: m/z calculated for $C_{61}H_{70}N_8O_{12}S$ [M+H]$^+$: 1,139.49; found: 1,139.16.

Pep 1b. Pd-C catalyst (0.150 g) was added to a solution of S12 (0.300 g, 0.26 mmol) in THF/MeOH (1:1) and stirred while H_2 was bubbled through the reaction mixture at a moderate rate. After 1 h, TLC examination showed clean conversion of starting material to product. The H_2 flow was then replaced by Ar for another 10 min, and the reaction mixture was filtered and washed (THF) through a pad of reverse-phase silica gel and Celite. The solvent was evaporated under reduced pressure, and the obtained sticky foam was coevaported with $CHCl_3$ (5 mL $\times$ 3) to afford light-yellow solid material (0.346 g). The solid obtained was treated with ether, and the obtained solid was used as such without any further purification (ES-TOF: m/z calculated for $C_{54}H_{64}N_8O_{12}S$ [M+H]$^+$: 1,049.44; found: 1,048.14). The Fmoc group was removed by treatment with a solution of 20% piperidine (8 mL) in DMF for 0.5 h. The solvent was concentrated to dryness under reduced pressure and dissolved in ether. The obtained solid (0.162 g) was used in the next step without any purification (ES-TOF: m/z calculated for $C_{39}H_{54}N_8O_{10}S$ [M+H]$^+$: 827.37; found: 827.19). The Pbf group was removed by treatment with a mixture of triisopropysilane/phenol/H_2O/TFA (2:5:5:88) (6) (8 mL) for 1 h at room temperature. After completion the reaction mixture was concentrated under reduced pressure and treated with ether. The formed solid was filtered off, washed with ether, and the obtained solid dissolved in water and lyophilized. The crude peptide was purified by reverse-phase HPLC on a Vydac semipreparative column using a gradient of acetonitrile/water, containing 0.1% TFA to give Pep1b as a white solid (0.062 g, 43%); ^{1}H NMR (D_2O): δ 0.75–0.76 (2H, m, CH_2), 1.35–1.38 (2H, m, CH_2), 1.52–1.58 (1H, m, CH_2 1a), 1.67–1.92 (3H, m, $CH_2$1b, CH_2), 2.15–2.21 (2H, t, CH_2), 2.24–2.25 (2H, t, CH_2), 2.50–2.66 (2H, m, CH_2), 2.95 (1H, dd, J = 14.5 and 14.5 Hz, CH_2-2a), 3.01–3.14 (2H, m, CH_2), 3.18 (1H, dd, J = 14.6 and 11.2 Hz, CH_2 –2b), 3.76–3.89 (1H, t, CH), 4.00 (1H, dd, J = 9.6 and 9.7 Hz, CH), 4.61 (1H, dd, J = 10.1 and 10.1 Hz, CH), 6.96–7.00 (1H, t, CH), 7.03–7.07 (1H, t, CH), 7.09 (1H, brs, CH), 7.29 (1H, d, J = 8.0 Hz, CH), 7.50 (1H, d, J = 7.8 Hz).; ^{13}C NMR (D_2O): δ 22.4 (CH_2), 23.3 (CH_2), 27.5 (CH_2), 27.9 (CH_2), 29.8 (CH_2), 32.8 (CH_2), 34.4 (CH_2), 35.8 (CH_2) and 40.2 (CH_2), 51.2 (CH), 52.9 (CH) and 54.7 (CH), 108.9 (Cq), 112.0 (CH), 117.8 (CH), 119.2 (CH), 121.9 (CH) and 124.4 (CH, aromatic) 126.5 (Cq), 136.1 (Cq), 156.4 (C = NH), 169.2, 172.9, 175.8, 176.1 and 177.9 (C = O); ES-TOF: m/z calculated for $C_{26}H_{38}N_8O_7$ [M+H]$^+$: 575.2942; found: 575.2936.

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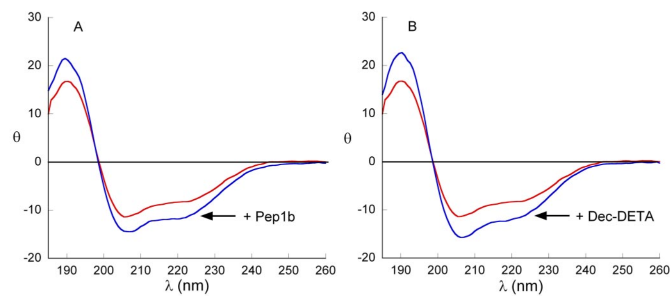

Fig. S1. CD spectra of A$\beta_{13\text{–}23A}$ alone (red lines) or with (blue lines) ligands Pep1b (*A*) and Dec-DETA (*B*) present in a 1:1 molar ratio. Spectra were recorded in 10 mM phosphate buffer (pH 7) containing 25% TFE. The mean molar residual ellipticity is expressed as kdeg $\times$ cm^2/dmol. Using the residual molar ellipticities at 208 and 222 for estimation of helical contents (3), the ligands at 1:1 molar ratio to A$\beta_{13\text{–}23A}$ gave an approximately 35% increase in helical content.

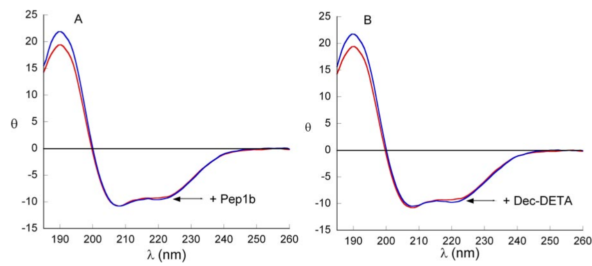

Fig. S2. CD spectra of scrambled Aβ_{13-23A} alone (red lines) or with (blue lines) ligands Pep1b (*A*) and Dec-DETA (*B*) present in a 1:1 molar ratio. Spectra were recorded in 10 mM phosphate buffer (pH 7) containing 25% TFE. The mean molar residual ellipticity is expressed as kdeg $\times$ cm^2/dmol.

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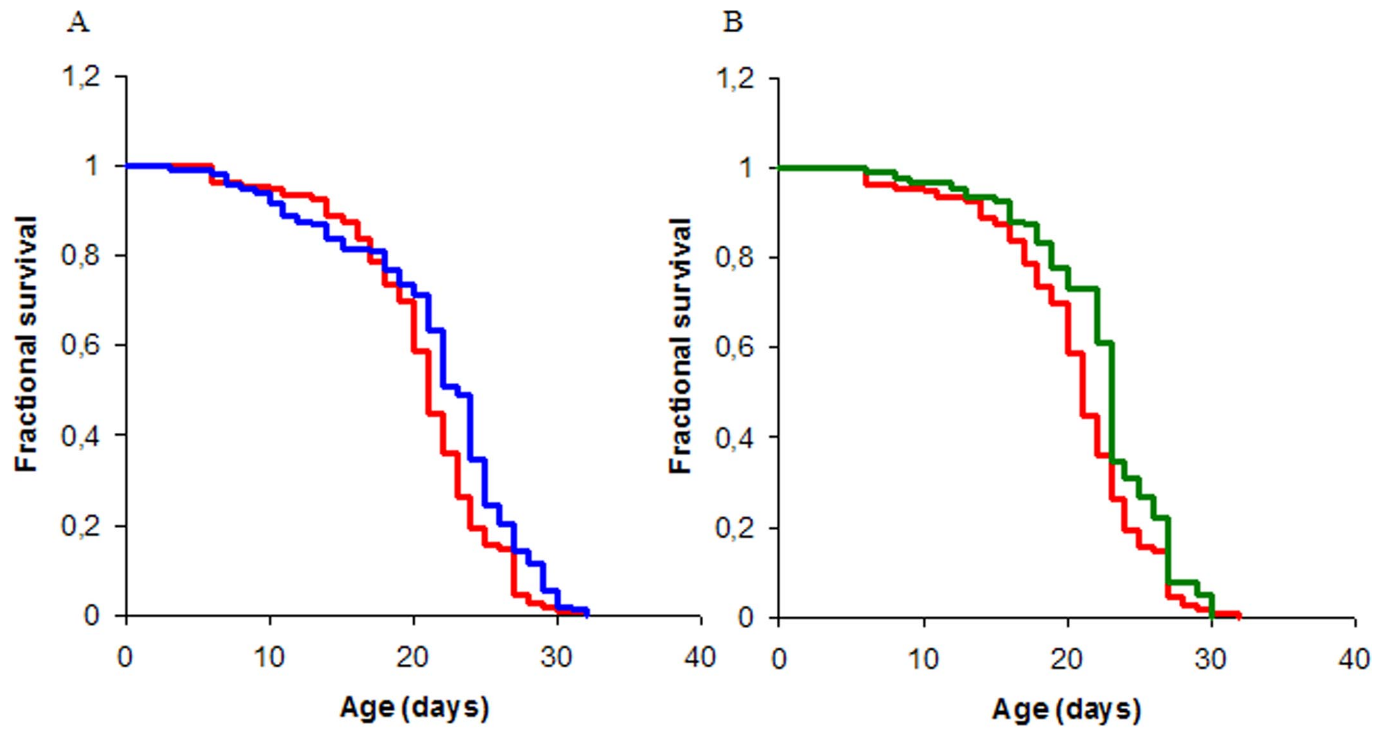
Fig. S3. Ligands affect fibril formation of Aβ_{1-40}. Thioflavin T fluorescence after different times of incubation of 25 μM Aβ_{1-40} alone in 10 mM sodium phosphate buffer (pH 7) with 10% DMSO (vol/vol) (red line) or in the presence of 25 (black line), 125 (dark-blue line), or 250 (light-blue line) μM of ligands (*A*) Pep1a, (*B*) Pep1b, and (*C*) Dec-DETA, as well as 125 μM of each ligand alone (green line). The samples were measured in duplicate and showed a variability of between 2% and 15%. Transmission electron micrographs show fibrils formed from (*D*) 25 μM Aβ_{1-40} incubated alone in 10 mM sodium phosphate buffer (pH 7) with 10% DMSO (vol/vol) or with addition of 125 μM of (*E*) Dec-DETA, (*F*) Pep1a, or (*G*) Pep1b. Arrow in *E* identifies a thicker-than-normal fibril. All incubations were performed at 37 °C with agitation. (Scale bars, 100 nm.)



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Treatment	Median survival	p-value
Dec-DETA 4.9 mM	23 days	<0.0123
Pep1a 0.65 mM	23 days	<0.0045
No ligand	21 days	

Fig. S4. Longevity analysis of *Drosophila melanogaster* at 28 °C. Kaplan-Maier survival plots of nontreated Aβ_{1-42} flies (red lines; n = 109) and Aβ_{1-42} flies treated with (*A*) 4.9 mM Dec-DETA (blue line; n = 98) and (*B*) 0.65 mM Pep1a (green line; n = 119). (*C*) List of median survival and *P* values for Kaplan-Maier curves presented in *A* and *B*.

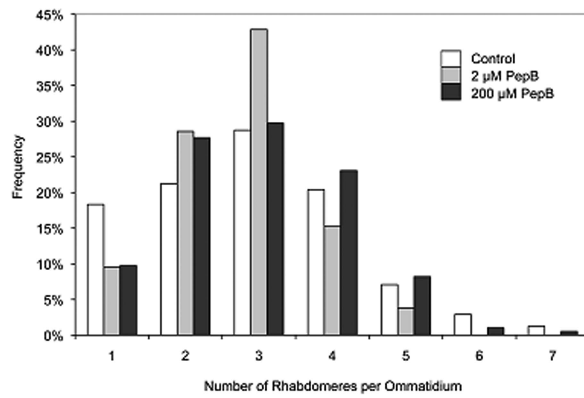
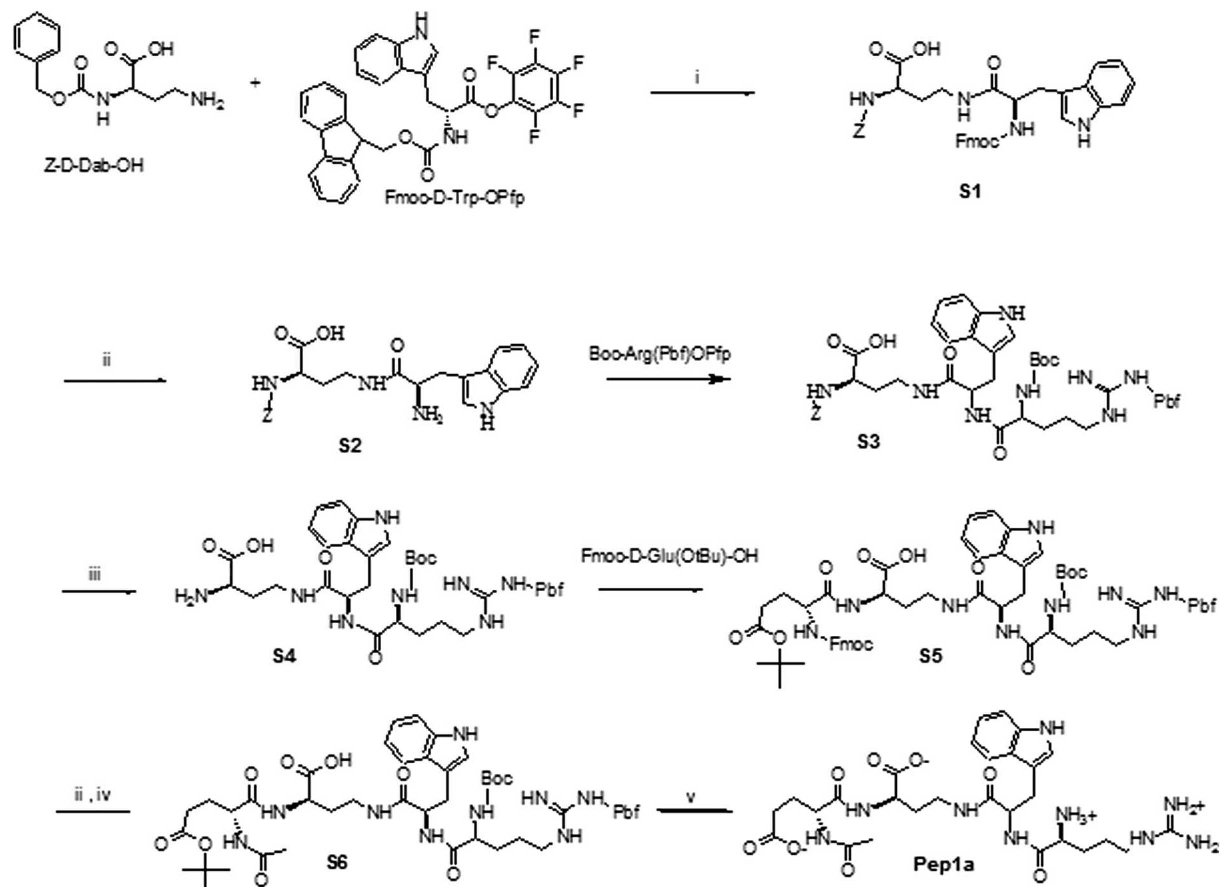
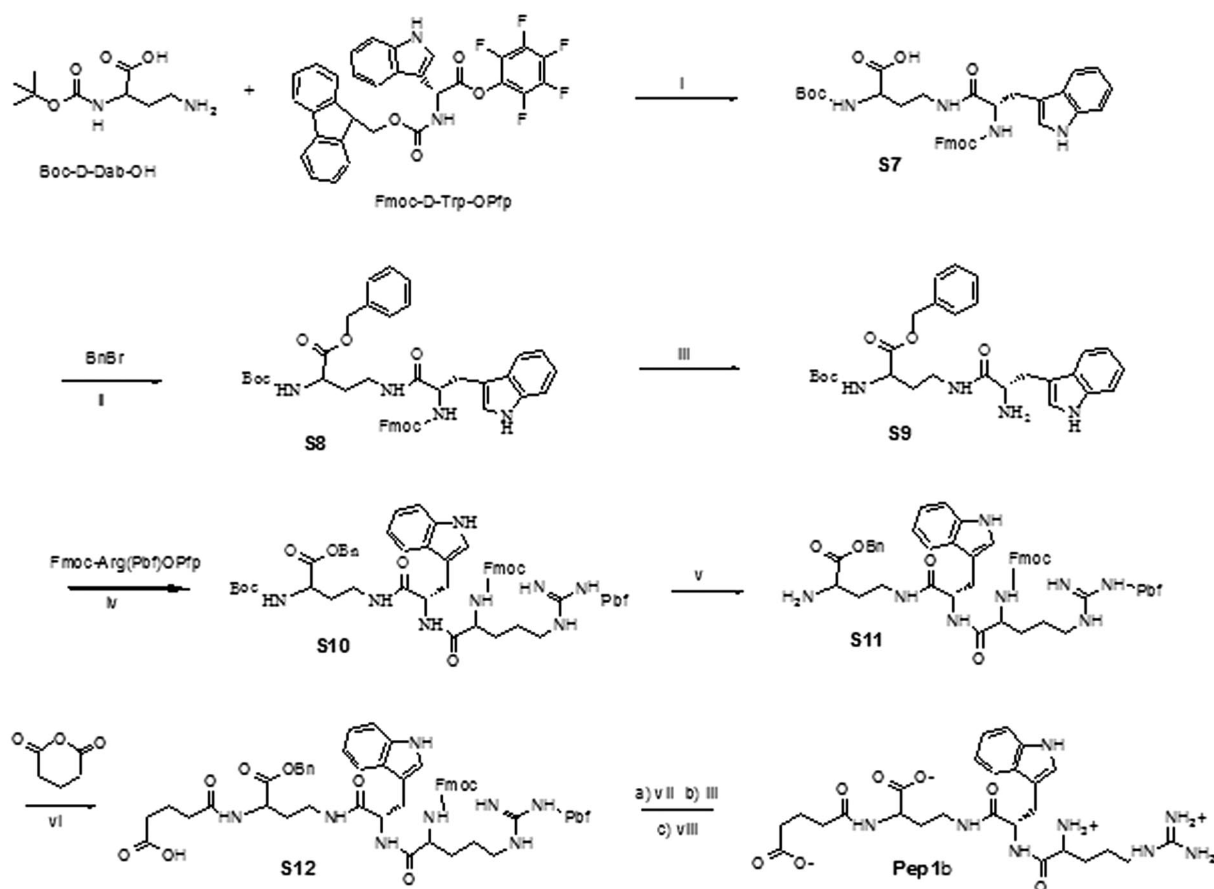


Fig. S5. Effect of Pep1b treatment on *gmr-httQ120* flies. Treatment of 4-day-old *gmr-httQ120* male flies with 2 μM (gray; $n = 194$ ommatidia) and 200 μM PepB (black; $n = 104$ ommatidia) did not change the frequency distribution of rhabdomere numbers per ommatidium as compared with flies treated with vehicle alone (white; $n = 239$ ommatidia).



Scheme S1. Reagents and conditions: (*i*) $Na_2B_4O_7$ (pH = 8.5), DMF, 0 °C to room temperature, 10 h; (*ii*) 20% piperidine in DMF, room temperature, 0.5 h; (*iii*) (*a*) Pd/C, DMF, acetic acid, room temperature, (*b*) N-methylmorpholine; (*iv*) 20% acetic anhydride in pyridine, room temperature, 15 min; (*v*) TFA-H_2O-phenol-thioanisole, room temperature, 1 h.



Scheme S2. Reagents and conditions: (*i*) $Na_2B_4O_7$ (pH 8.5), DMF, 0 °C to room temperature; (*ii*) $KHCO_3$, $Bu_4N^+I^-$, DMSO, room temperature; (*iii*) 20% piperidine in DMF, room temperature, 1 h; (*iv*) DCM, DMF, triethylamine, room temperature; (*v*) acetonitrile, H_2O, $BiCl_3$, 55 °C, 3 h; (*vi*) DMF and pyridine, room temperature, 2 h; (*vii*) Pd/C, THF, MeOH, room temperature, 1 h; (*viii*) triisopropylsilane-phenol-H_2O-TFA, room temperature, 1 h.

Movie S1. Climbing assay performed on 16-day-old transgenic *Drosophila* expressing the human Aβ_{1-42} gene in the neurones of the central nervous system, kept at 28 °C. The tube on the left contains flies fed Dec-DETA, whereas the tube on the right contains nontreated control flies.

Movie S1 (AVI)

Table S1. Alcohol dehydrogenase (ADH) activity in the presence of Dec-DETA and Pep1b

Compound (concentration)	% of ADH activity
Dec-DETA (25 μM)	100
Dec-DETA (250 μM)	111
Pep1b (25 μM)	100
Pep1b (250 μM)	126

Values are means of duplicates and expressed as the activity relative to the enzyme without compounds present.

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