Protein	Average MW (Da)	Monoisotopic MW (Da)	Isoelectric Point	Instability index	Aliphatic index	Grand average hydropathicity (GRAVY)	Sequence
HEWL	14313.14	14303.88	9.32	16.09	65.12	-0.472	KVFGRCELAAAMKRHGLD NYRGYSLGNWVCAAKFES NFNTQATNRNTDGSTDYGI LQINSRWWCNDGRTPGSRN LCNIPCSALLSSDITASVNCA KKIVSDGNGMNAWVAWR NRCKGTDVQAWIRGCRL
insulin	5795.65	5791.67	5.39	13.61	85.88	0.218	GIVEQCCTSICSLYQLENYC NFVNQHLCGSHLVEALYLV CGERGFFYTPKT
rIAPP	3923.43	3920.96	9.5	25.38	73.78	-0.249	KCNTATCATQRLANFLVRS SNNLGPVLPPTNVGSNTY
hIAPP	3906.32	3903.86	8.9	1.94	68.65	-0.097	KCNTATCATQRLANFLVHS SNNFGAILSSTNVGSNTY
Analogue1 (H18R S28P)	3935.4	3932.93	9.5	19.02	68.65	-0.154	KCNTATCATQRLANFLVRS SNNFGAILPSTNVGSNTY
Analogue 2 (H18R N31D)	3917.34	3914.87	8.05	11.21	68.65	-0.119	KCNTATCATQRLANFLVHS SNNFGAILPSTDVGSNTY
Analogue 3 (H18R S28P N31D)	3936.39	3933.91	8.9	23.09	68.65	-0.154	KCNTATCATQRLANFLVRS SNNFGAILPSTDVGSNTY
Pramlintide acetate	3952.43	3949.92	8.9	9.44	65.95	-0.232	KCNTATCATQRLANFLVHS SNNFGPILPPTNVGSNTY
Pramlintide recombinant	3952.43	3949.92	8.9	9.44	65.95	-0.232	KCNTATCATQRLANFLVHS SNNFGPILPPTNVGSNTY

Table S1. Using ProtParam to calculate physical and chemical parameters of proteins based on its sequence. Results show the Isoelectric point (pI), Instability index, Aliphatic index and GRAVY scores to indicate the solubility and stability of the designed analogues at physiological pH and temperature. Extinction coefficients used were 37970, 6335 and 1615 (M-1 cm-1) 280 nm in water for HEWL, Insulin and IAPP/pramlintide samples respectively.

Protein	Minimal score value	Maximal score value	Average score	Total score value
HEWL (1E8L)	-3.5618	0.1901	-1.0841	-139.8467
Insulin (2HIU)	-2.5823	2.7021	-0.2188	-11.1582
hIAPP (2L86)	-1.8579	2.9285	0.2993	11.0734
rIAPP (2KB8)	-1.7399	2.2643	-0.0094	-0.3486
Analogue 1 (H18R S28P)	-1.8579	3.0112	0.2413	8.9295
Analogue 2 (S28P N31D)	-1.836	2.8298	0.2547	9.4254
Analogue 3 (H18R S28P N31D)	-1.8593	2.9841	0.2242	8.2963
Pramlintide	-1.8579	2.9531	0.322	11.9157

Table S2: Aggrescan4D was used to calculate aggregation propensity scores for our designed analogues. For the wild-type hIAPP (PDB ID: 2L86) , rIAPP (PDB ID: 2KB8) , insulin (PDB ID: 2HIU) and HEWL (PDB ID: 1E8L) sequences, the Static Mode was used to assess aggregation based on the native structure. For the three designed hIAPP analogues and pramlintide, the Mutate Mode was employed using the 2L86 structure as a template. Single-point or multiple-point mutations corresponding to the analogue sequences were introduced through the A4D interface, enabling residue-specific aggregation predictions based on the mutated structures.

Protein	Residue 18	Residue 28	Residue 31
hIAPP (2L86)	0.0507	1.1618	-0.7928
rIAPP (2KB8)	-0.4144	0.3902	-0.2842
Analogue 1 (H18R S28P)	-0.7475	1.1984	-0.7319
Analogue 2 (S28P N31D)	0.0743	1.0002	-1.5775
Analogue 3 (H18R S28P N31D)	-0.7331	1.1607	-0.9554
Pramlintide	0.0898	1.1516	1.1762

Table S3: Calculating aggregation propensity for residues 18, 28 and 31. Residue specific scores were calculated using Aggrescan 4D for each analogue sequence to calculate how much amino acid residues 18, 28 and 31 in the sequence contributes to aggregation propensity.

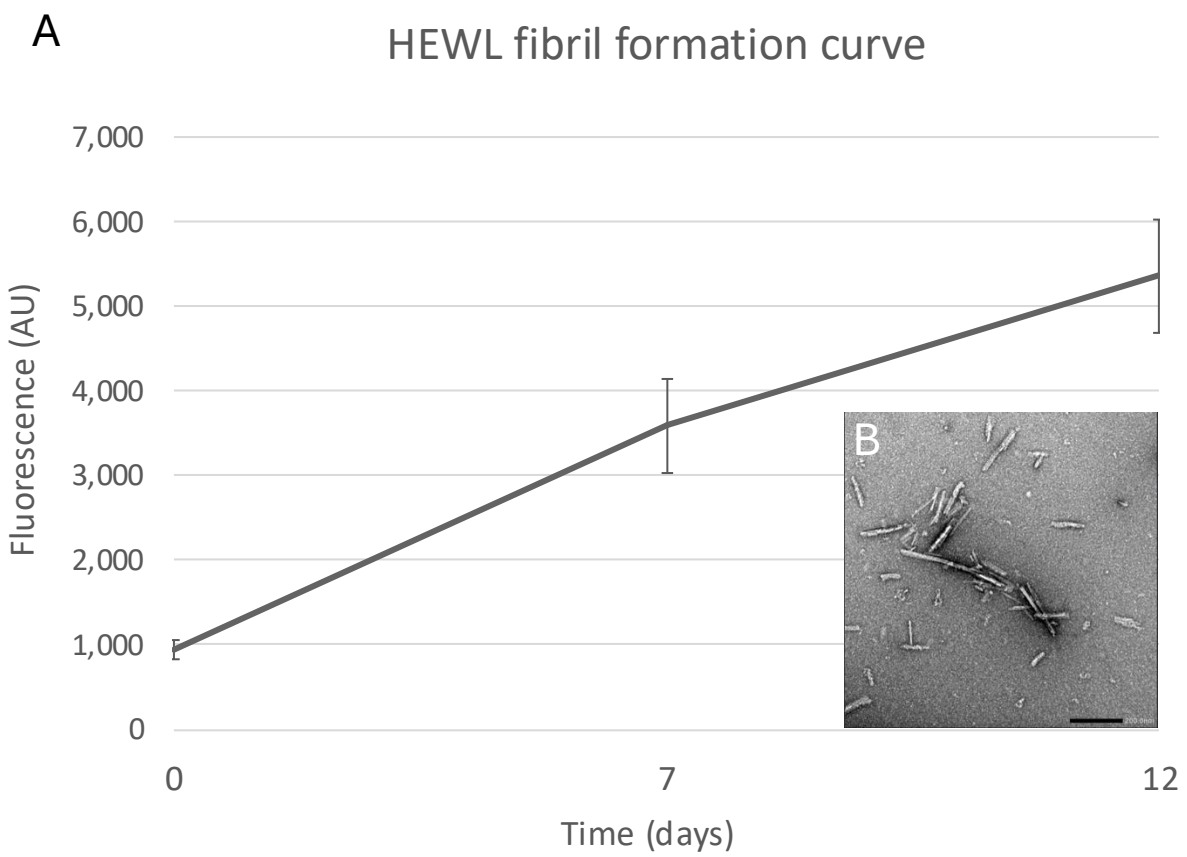
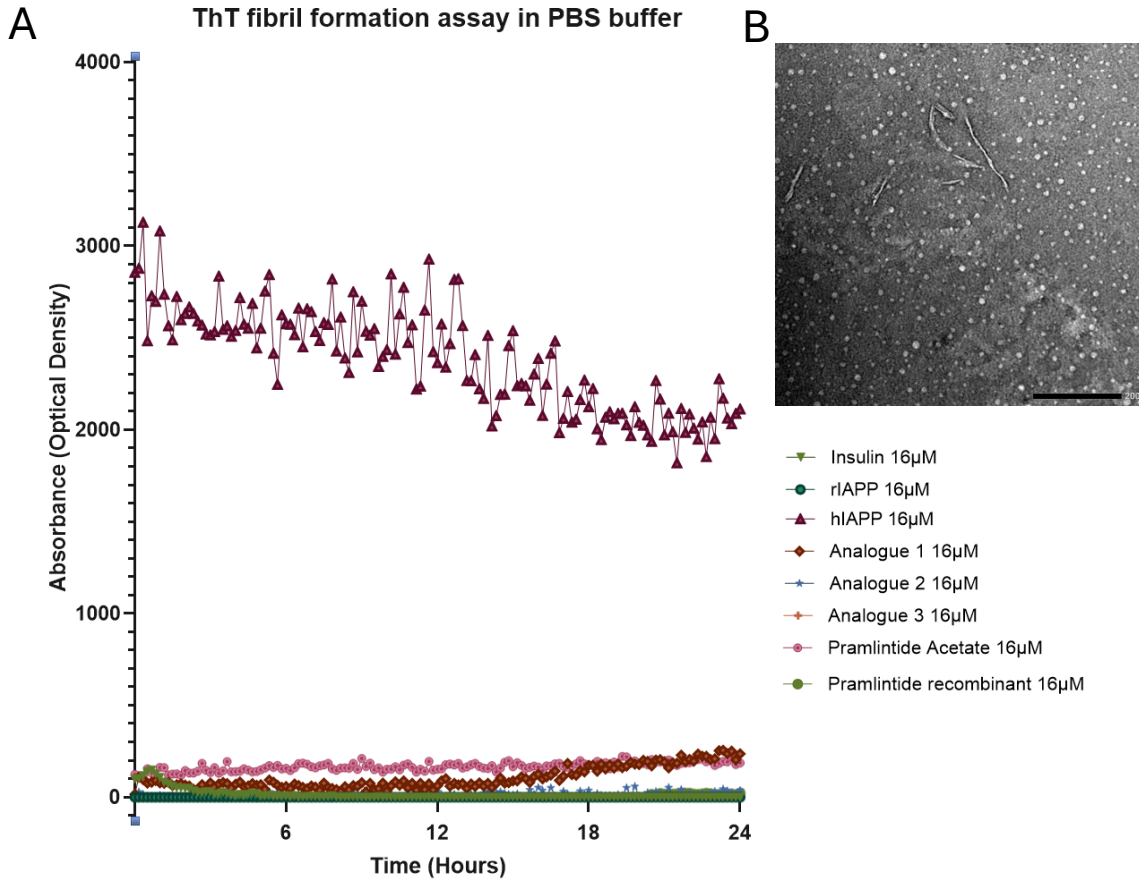


Figure S1: Thioflavin T assays and TEM analysis of HEWL. (A) Thioflavin T assays to measure fibril formation of 1mM HEWL in 0.5M glycine buffer pH 2.0, 70mM NaCl, with 50μM ThT over time. Experiments conducted at 37 °C with constant agitation 250 RPM. The error bars indicate standard deviation. Experiments were conducted in quadruplicates and readings taken using FLUOstar omega using excitation and emission of 355nm and 460nm). (B) Samples were imaged by TEM after 12 days and revealed amyloid fibrils only.



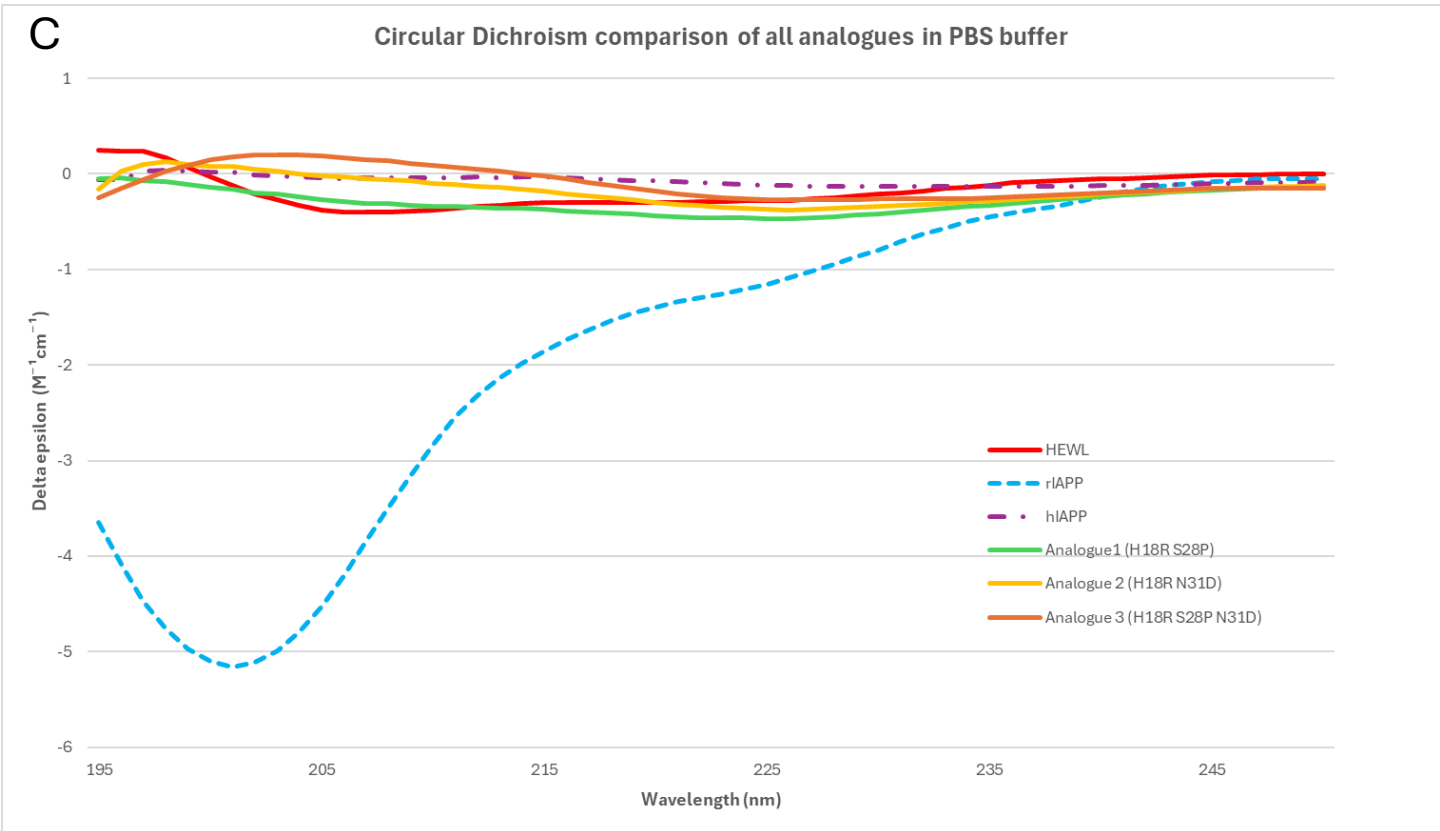


Figure S2. (A) **Analysis of fibril formation in PBS buffer using Thioflavin T assays, TEM and CD analysis**. Thioflavin T fluorescence assays were used to measure whether the analogues formed amyloid fibrils in PBS buffer (137 mM NaCl and 2.7 mM KCl,7.4) at 16 μM peptide concentration. Assays were performed in triplicate, and data presented as the mean fluorescence intensity with error bars showing standard deviations. Fluorescence readings were recorded every 10 minutes using an excitation and emission wavelength of 448 nm and 482 nm on a FLUOstar Omega plate reader. (B) Transmission Electron Microscopy (TEM) showed fibrils in hIAPP samples only. Scale bar 200 nm. (C) Circular Dichroism (CD) was used to analyse the secondary structure of samples.