Electronic Supplementary Material (ESI) for Chemical Communications.

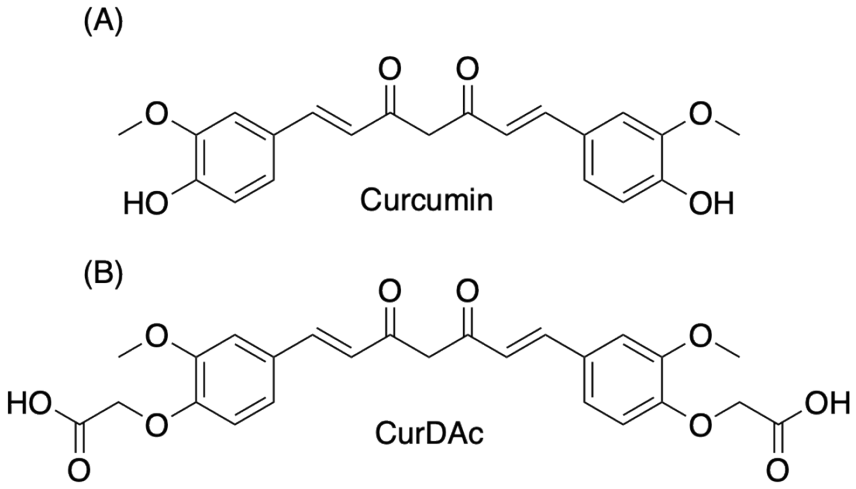


Figure S1. Chemical structures of curcumin (A) and its water-soluble derivative, CurDAc (B).

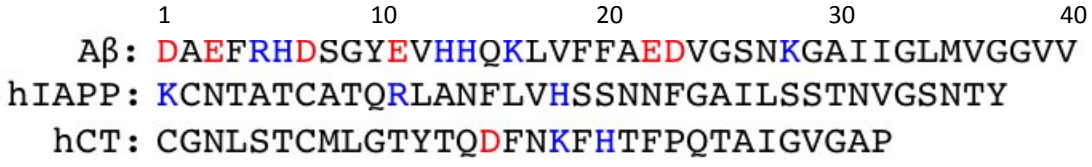


Figure S2. Amino acid sequences of the three different amyloid peptides (amyloid-beta, human-IAPP and human-calcitonin) investigated in this study. Color indicates the charge of the residue at pH 7.4: red is acidic, blue is basic, and black is uncharged.

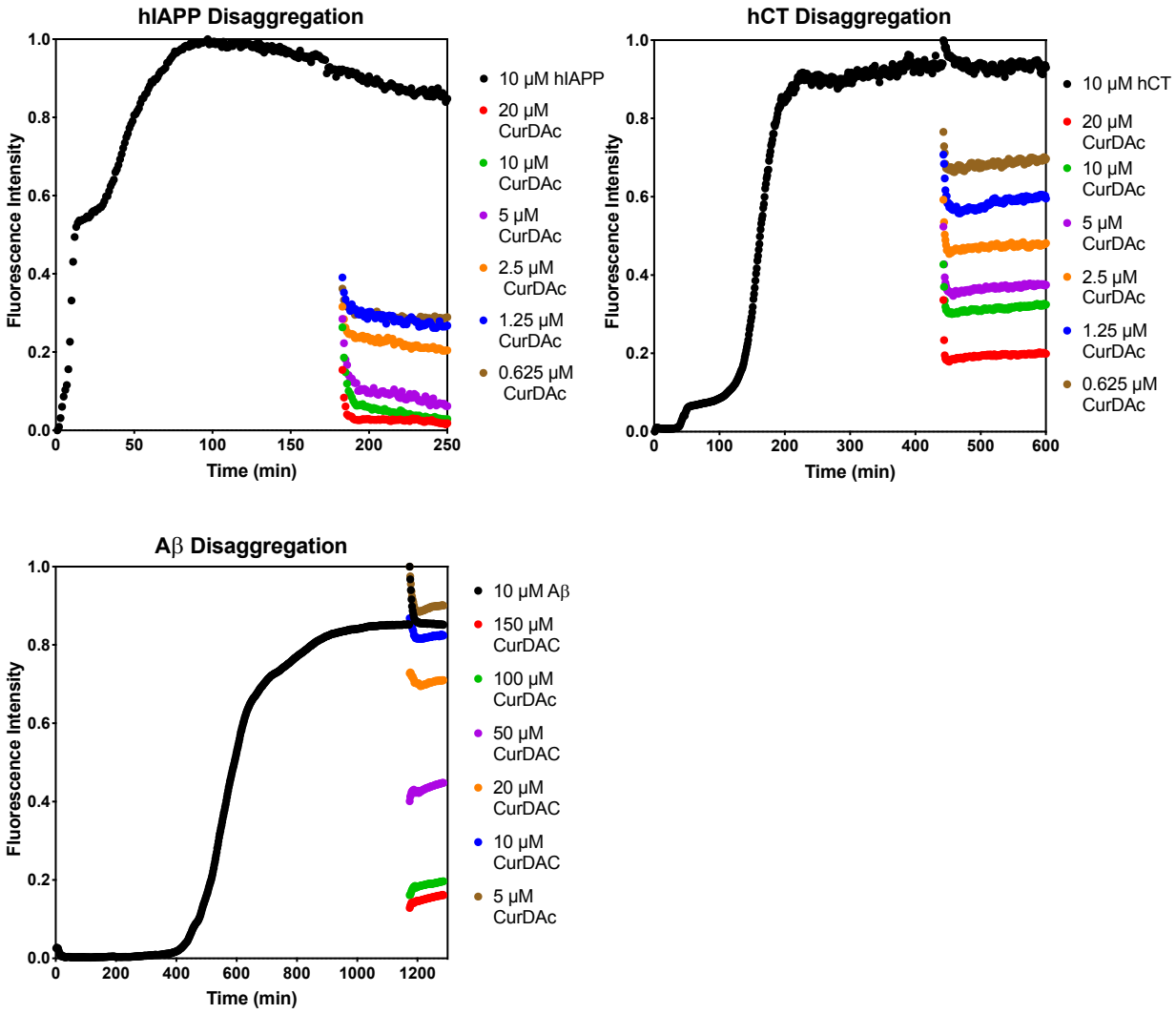


Figure S3. Kinetic amyloid disaggregation curves obtained using 4 equivalents of ThT. 10 μM peptide (hIAPP, hCT or Aβ) was allowed to aggregate to form amyloid fibers, as shown in the black trace in each figure, with 40 μM ThT to monitor the peptide aggregation. Wells were then treated with the indicated concentrations of the peptide and CurDAc.

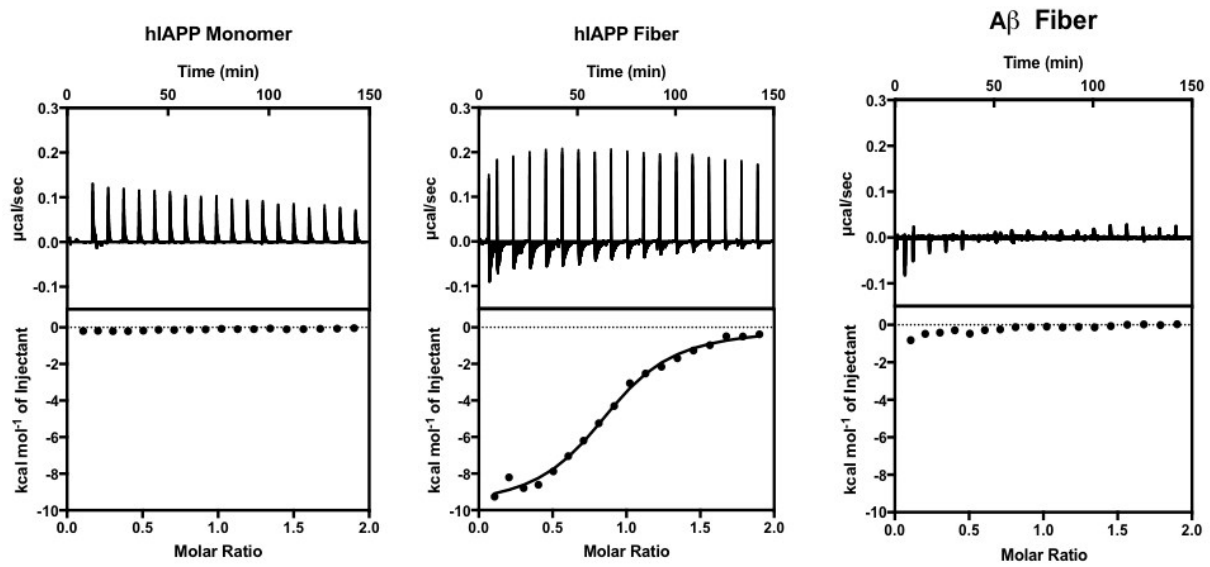


Figure S4. Isothermal titration calorimetry (ITC) experimental traces showing the binding of CurDAc with the indicated peptide over time. hIAPP monomers and Aβ fibers show no thermodynamic binding. hIAPP fibers show an endothermic interaction with CurDAc.

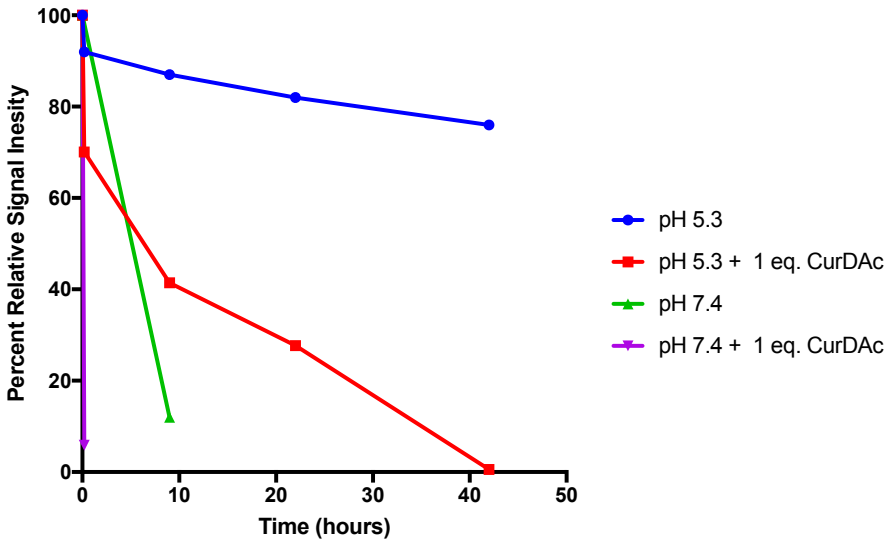


Figure S5. NMR aggregation kinetics of hIAPP in the presence and absence of CurDAc at two different pH values (5.3 and 7.4) as measured by 1D ^{1}H NMR signal intensity. proton NMR spectra were acquired from 100 μM hIAPP dissolved in phosphate (pH 7.4) or acetate (pH 5.3) buffer with and without CurDAc. Experimentally measured proton NMR signal intensities of the amide-NH region (6.0-8.5 ppm) are plotted over time. Zero-time point corresponds to the spectra acquired immediately after the addition of CurDAc to hIAPP monomers, and subsequent spectra were obtained at the indicated time points.

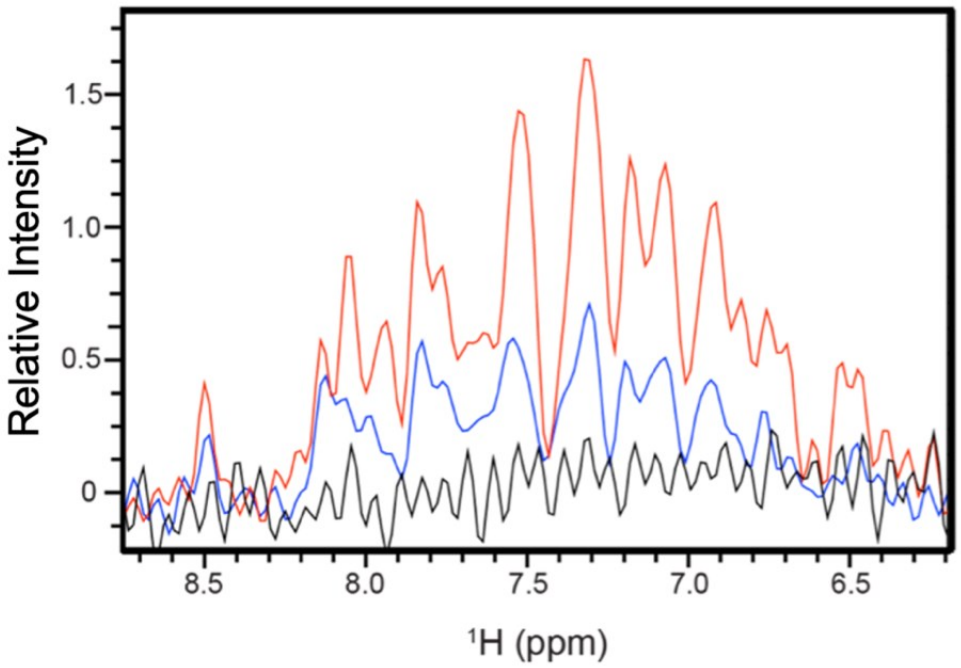


Figure S6. The amide-NH region of ^{1}H NMR spectra of hIAPP monomers in the presence of 1 equivalent of CurDAc over time. Spectra were acquired using an 850 MHz NMR spectrometer at 25 °C. NMR spectra were acquired from 80 μM hIAPP and 80 μM CurDAc in acetate buffer (pH 5.3) at 0 (red), 9 (blue), and 40 (black) hours.

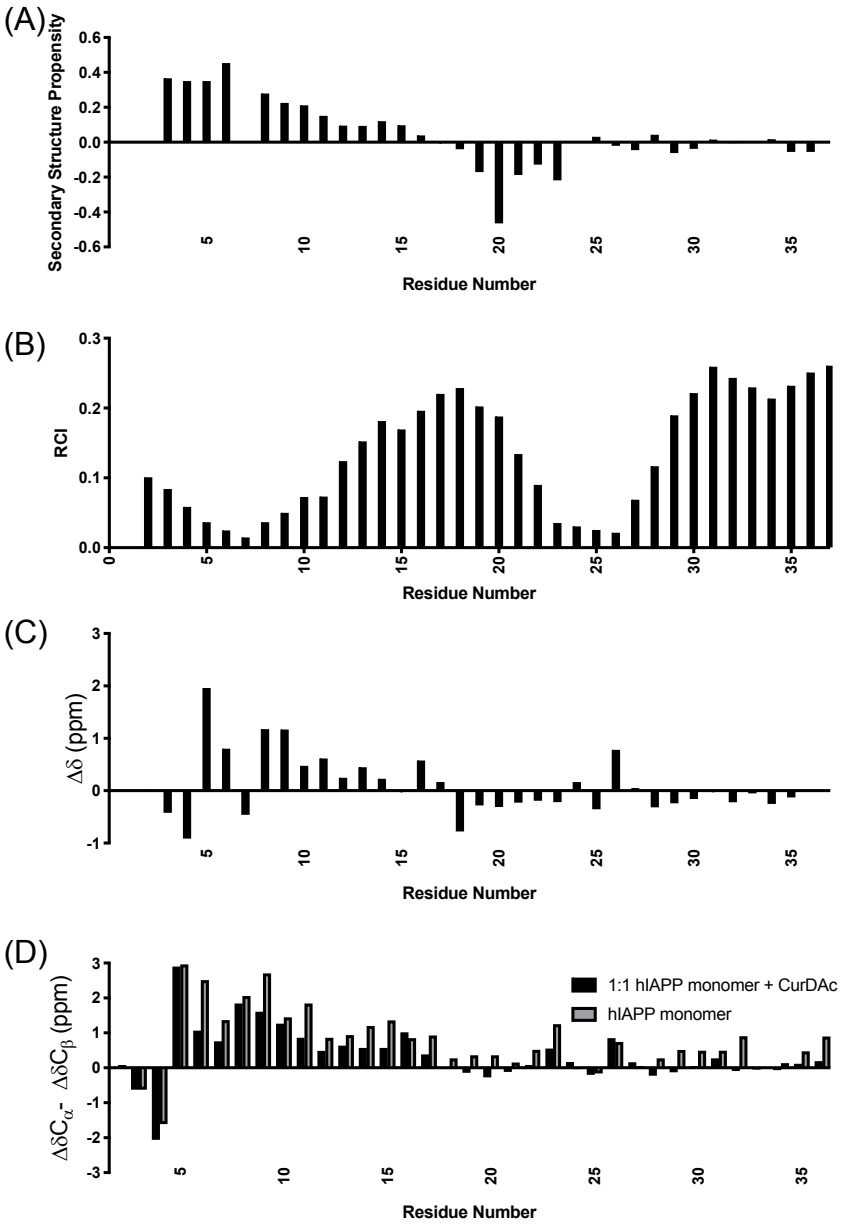


Figure S7. Secondary structure prediction of hIAPP monomers in the presence of CurDAc using $^{13}C_\alpha$, $^{13}C_\beta$, ^{1}HN and ^{15}N chemical shift values measured from 3D HNCACB experiments. (A) Secondary structure propensities obtained using the Forman-Kay group approach[1], (B) Random-Coil Index obtained using the Wishart et al approach[2], and (C) the Δδ for $^{13}C_\alpha$ chemical shifts. (D) Differences in the random-coil chemical shifts for C_α and C_β of the hIAPP monomer (grey) and 1:1 hIAPP + CurDAc (black). All three predictions show a tendency of an alpha-helical structure at the N-terminus, a small portion of a beta-sheet conformation near the amyloidogenic core (residues 20-27), and then a random-coil for the rest of the peptide. This structure of hIAPP is similar to the hIAPP monomer structures determined from solution and membrane by NMR spectroscopy.[3]

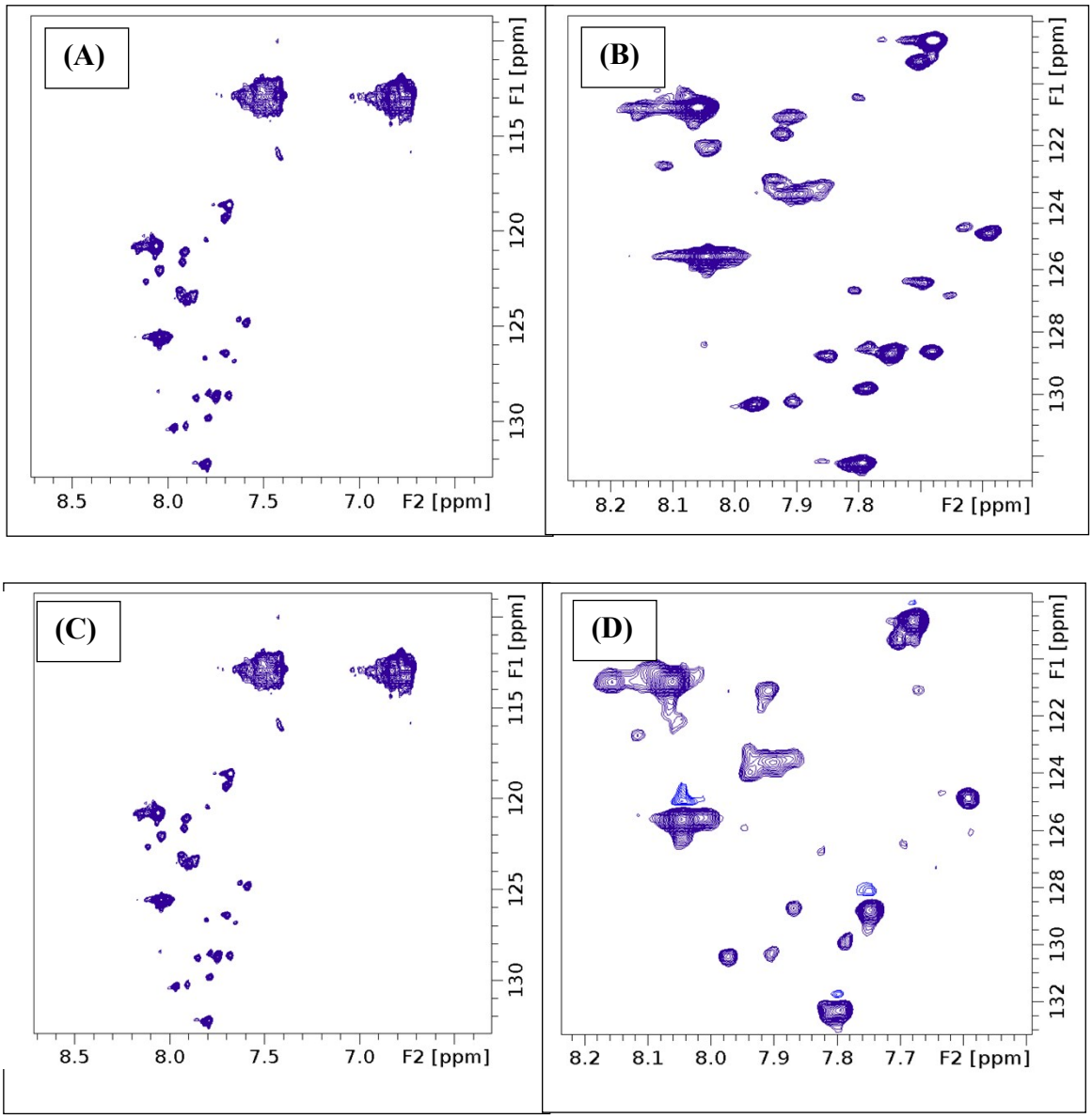


Figure S8. 2D-^{15}N/^{1}H SOFAST-HMQC spectra of hIAPP fibril sample 72 hours after the addition of CurDAc. Spectra obtained before ((A) and (B); same as Figure 3C (red) in the main text, but plotted in a different contour level to clearly show the observation of most resonances) and after ((C) and (D)) the measurements of 3D NMR spectra (shown in Figures S9 and S10).

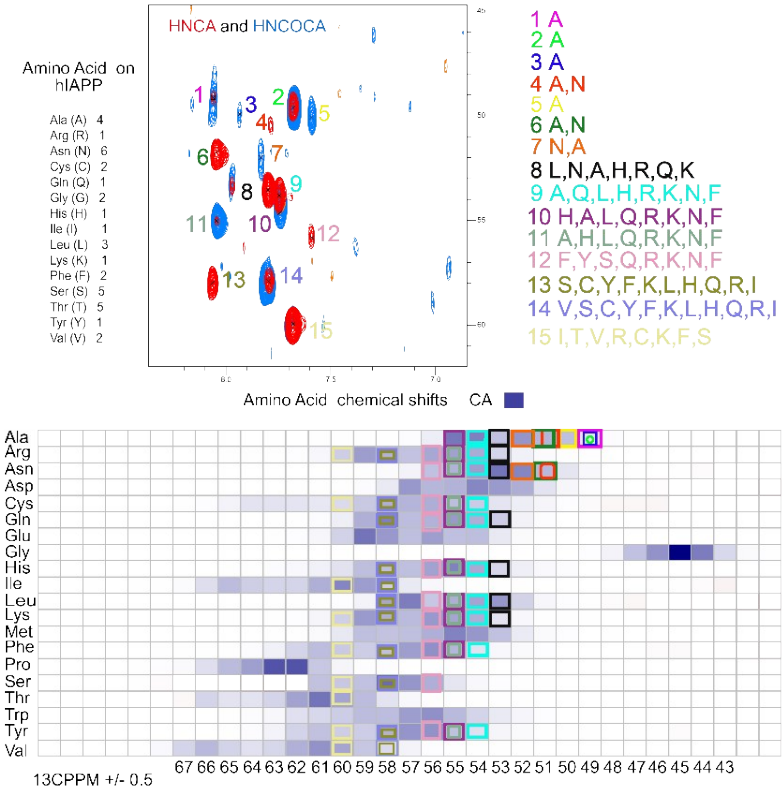
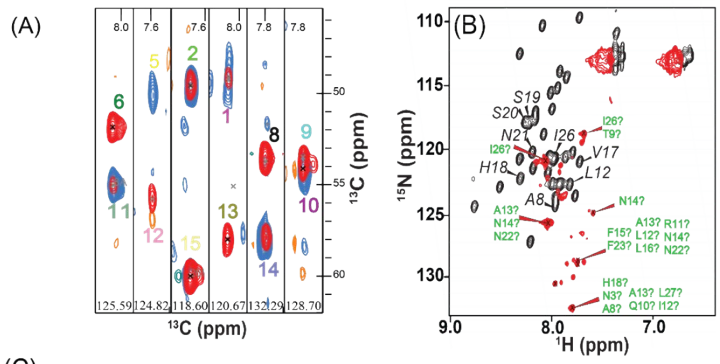


Figure S9. Tentative identification of amino acid residues affected by the interaction of CurDAc with hIAPP fibers using the projections of 3D HNCA and 3D HNCOCA spectra and the statistics of CA chemical shifts from CcpNmr Analysis software. (Top, left) List of amino acids that are present in the hIAPP sequence and number of their occurrences in hIAPP. (Top, center) Overlay of HNCA (red) and HNCOCA (blue) spectra. (Top, right) labels of peaks in spectra that correspond to boxes on the bottom figure by color. (Bottom) Graphical representation of CA chemical shift statistics for the 20 amino acids adapted from CcpNmr. Intensity of the square (light to dark) indicates the probability of the peak to be assigned to that residue given by CcpNmr. Although 15 distinct peaks appear in the projections of HNCA and HNCACO spectra, it was only possible to analyze 6 of them by the residue (i.e. residue-(i)) and its neighboring residue (i.e., residue-(i-1)) using the strips of these two spectra (as shown in Figure S10). Additional details can be found in Figure S10C.



(C)

KCNTATCATQRLANFLVHSSNNFGAILSSTNVGSNTY

Peak number in the HNCA and HNCOCA and amino acids posibilities	Possible combinations based on the seq of the peptide by analyzing the neighboring-1 residue: exist / non-exist	Tentative assignment
6 A,N = i 11 A,H,L,Q,R,K,N,F = i-1	AA, HA,LA,QA,RA,KA,NA,FA AN,HN,LN,QN,RN,KN,NN,FN	A13? or N14? or N22?
5 A = i-1 12 F,Y,S,Q,R,K,N,F = i	AF, AY,AS,AQ,AR,AK,AN,AF	N14?
2 A = i-1 15 I,T,V,R,C,K,F,S = i	AI, AT,AV,AR,AC,AK,AF,AS	I26? OR T9?
1 A = i-1 13 S,C,Y,F,K,L,H,Q,R,I = i	AS, AC,AY,AF,AK,AL,AH,AQ,AR,AI	I26?
8 L,N,A,H,R,Q,K = i 14 V,S,C,Y,F,K,L,H,Q,R,I = i-1	VL, SL,CL,YL,FL,KL,LL,HL,QL,RL,IL VN, SN,CN,YN,FN,KN,LN,HN,QN,RN,IN VA, SA,CA,YA,FA,KA,LA,HA,QA,RA,IA VH, SH,CH,YH,FH,KH,LH,HH,QH,RH,IH VQ, SQ,CQ,YQ,FQ,KQ,LQ,HQ,QQ,RQ,IQ VR, SR,CR,YR,FR,KR,LR,HR,QR,RR,IR VI, SI,CI,YI,FI,KI,LI,HI,QI,RI,II	H18? or N3? or A8? or A13? or Q10? or L27? or I12?
9 A,Q,L,H,R,K,N,F = i 10 H,A,L,Q,R,K,N,F = i-1	HA,AA,LA,QA,RA,KA,NA,FA HQ,AQ,LQ,QQ,RQ,KQ,NQ,FQ HL,AL,LL,QL,RL,KL,NL,FL HH,AH,LH,QH,RH,KH,NH,FH HR,AR,LR,QR,RR,KR,NR,FR HK,AK,LK,QK,RK,KK,NK,FK HN,AN,LN,QN,RN,KN,NN,FN HF,AF,LF,QF,RF,KF,NF,FF	A13? or L12? or L16? or R11? or N14? or N22? F15? or F23

Figure S10. (A) 2D strips obtained from 3D HNCA and 3D HNCOCA spectra with high intensity in the spectrum and number correlated to the numbers of each peak shown in Figure S9. (B) ^{15}N SOFAST- HMQC spectra of the dissolved fibrils (red) with the possible assignment (in green) compared to the monomeric hIAPP (in black) (Figure 3C from the main text is reproduced). (C) Explanation of how the tentative assignment was performed using the possible combinations of amino acids and the order in the sequence of the peptide. As a criterion for choosing the peak that corresponds to the residue-(i), we took the intensity of the peak that appeared with strong intensity in the HNCA experiment (the red peaks with high intensity are 6,12,15,13,8 and 9). Then the peak arising from the neighboring (i-1)th-residue (shown in blue: 11,5,2,1,14 and 10) from the HNCOCA spectrum is shown. These peaks from HNCA and HNCOCA spectra and the possible amino acids are listed in the table (1st column of C). The 2nd column of the table list the possibilities based on the amino acid sequence of the peptide. The 3rd column of the table is the tentative assignments of peaks shown in Figure S10B.

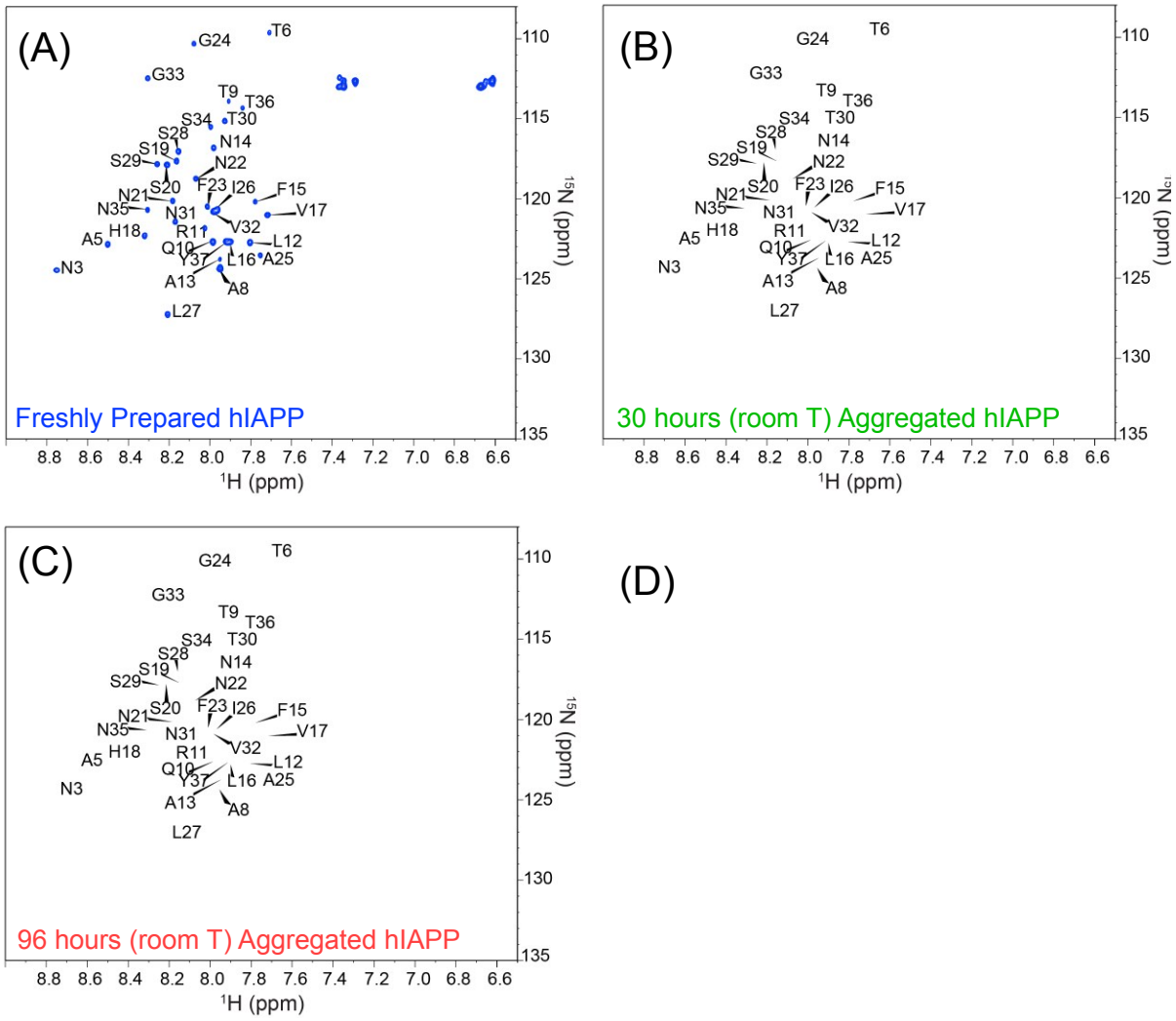


Figure S11. NMR spectra of 100 μM hIAPP acquired at different time points of aggregation. 2D ^{1}H-^{15}N SOFAST-HMQC (A, B, and C) and 1D ^{1}H (D) NMR spectra of hIAPP acquired at pH 7.4 at 25 °C using an 800 MHz NMR spectrometer: 0 (blue), 30 hours (green) and 96 hours (red). The loss of signal at 30 and 96 hours is indicative of amyloid aggregation of the peptide, which resulted in the complete loss of monomers. No appearance of peaks in the 7.5-8.0 ppm ^{1}H /125-135 ppm ^{15}N region, after extending the incubation period up to 96 hours, indicates that there is no degradation of hIAPP; otherwise, resonances from the degraded peptide fragments could have been observed. Therefore, these observations indicate that CurDAc induced appearance of signals from hIAPP fibers (as shown in Figure 3A) is not due to peptide degradation.

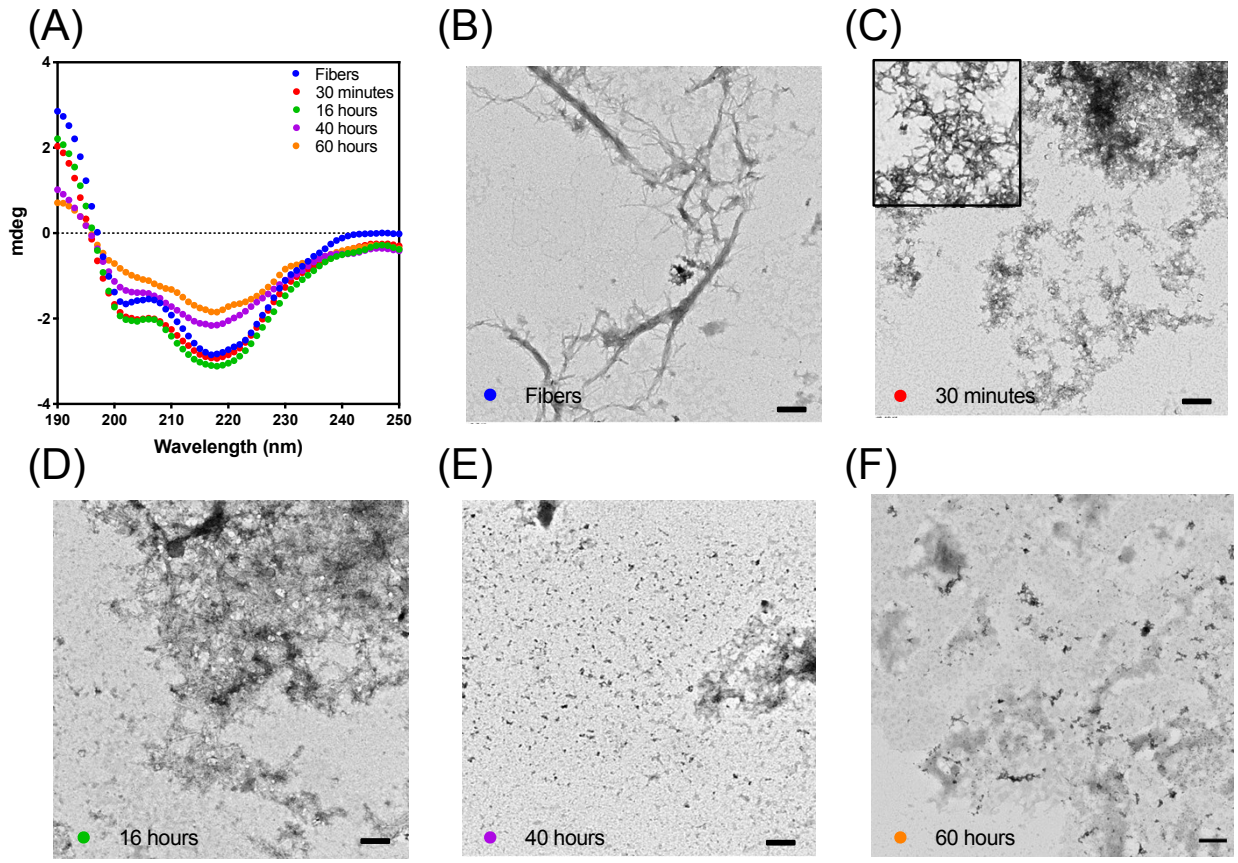


Figure S12. Circular dichroism (CD) and TEM of hIAPP fibers before and after CurDAc treatment. (A) CD spectra of hIAPP fibers in the presence of one molar equivalent of CurDAc over a course of 60 hours in phosphate buffer at pH 7.4. TEM images of hIAPP fibers (B) and hIAPP fibers incubated with CurDAc at the indicated times (C-F); the scale bar is 200 nm. Selective portions of TEM images from B, C and F are shown in Figure 3F in the main text.

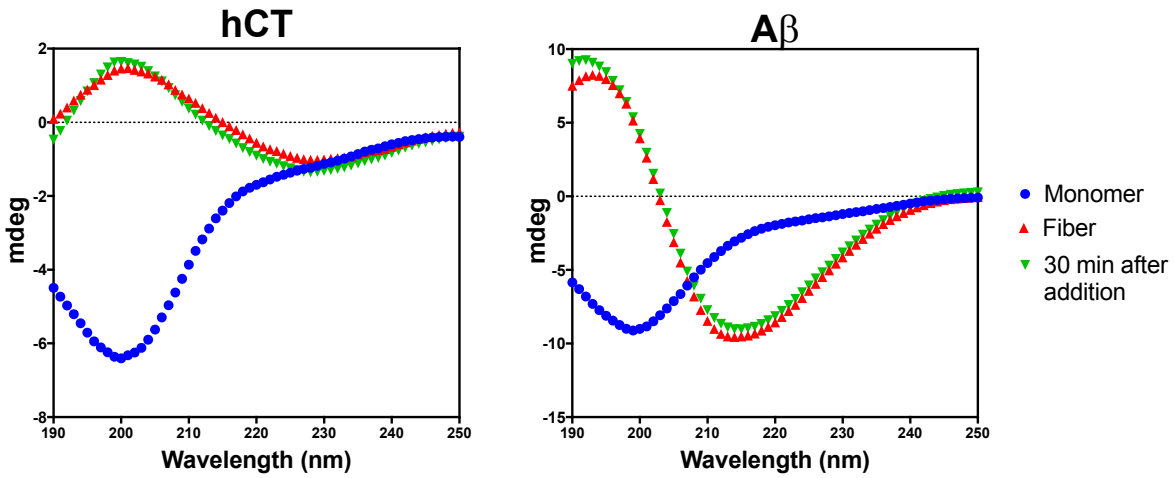


Figure S13. CD spectra of hCT and Aβ before (as monomers (blue) or fibers (red)) and after treatment with CurDAc (green). 40 μM peptide monomers in pH 7.4 phosphate buffer show random-coil monomers at time zero (blue), and a beta-sheet conformation for fibers formed from monomers after 24 hours (red). hCT fibers was treated with 2 equivalents of CurDAc, and Aβ fibers were treated with 10 equivalents of CurDAc, and then CD spectra were obtained after 30 minutes of incubation (green).

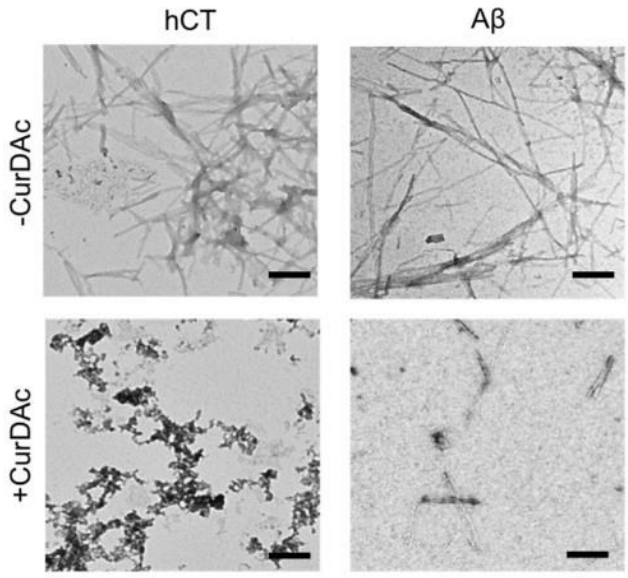


Figure S14. TEM images hCT and Aβ fiber samples before (indicated as -CurDAc, top row) and after (indicated as +CurDAc, bottom row) the treatment with CurDAc. Top: 40 μM hCT (left) and Aβ (right) after 24 hours shaking at pH 7.4 phosphate buffer at 25°C and 37°C, respectively. Bottom: TEM images obtained from the fiber samples after 30 minutes incubation with CurDAc. 2 equivalents of CurDAc were added to hCT and 10 Equivalents were added to Aβ. The scale bar is 100 nm.

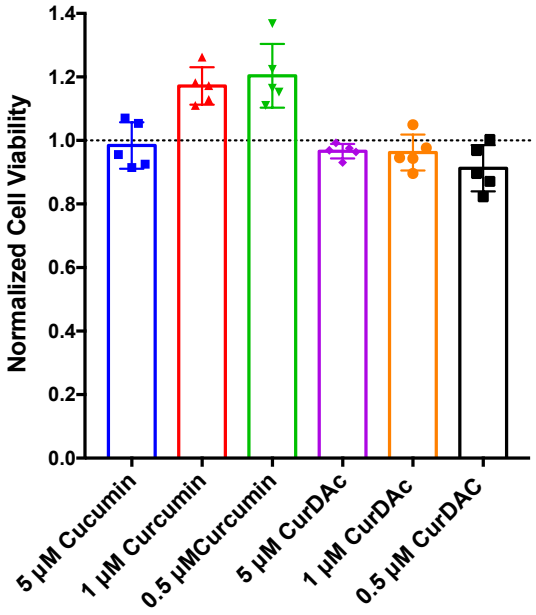


Figure S15. **MTT cell toxicity assay of curcumin and CurDAc.** RIN-5F cells were treated with varying amounts of curcumin or CurDAc. MTT reduction was measured after 24 hours. These control samples were used to evaluate the toxicity of hIAPP monomers, fibers and samples treated with CurDAc as shown in Figure S15.

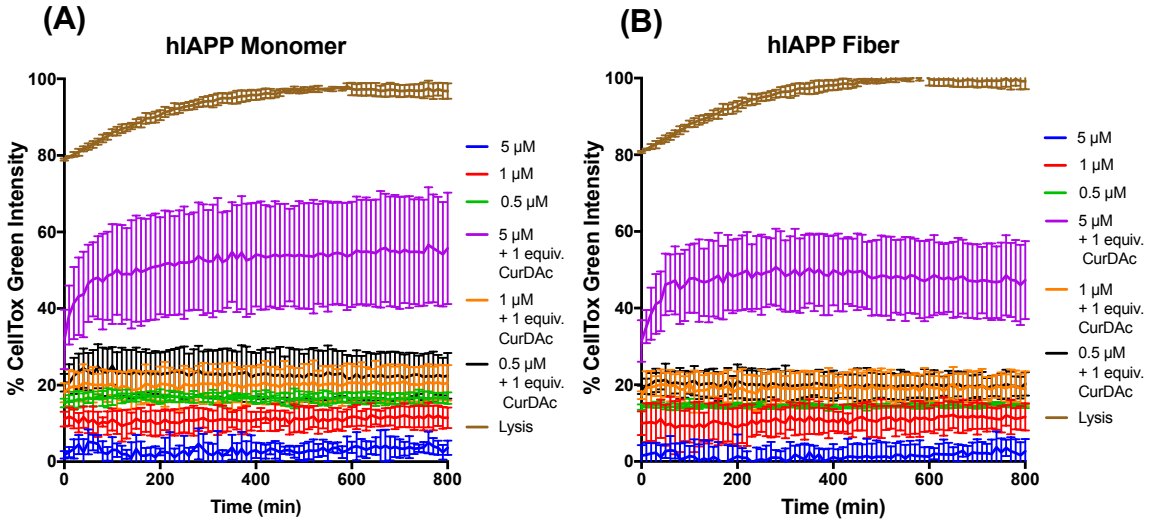


Figure S16. **Cell toxicity of hIAPP.** RIN-5F cell death monitored every 10 minutes for 13 hours by CellTox Green fluorescence in the presence of hIAPP monomers (A) or fibers (B) with varying amounts of CurDAc as indicated.

Table S1. Thermodynamic parameters determined from isothermal titration calorimetry (ITC) experiments carried out to measure the interaction of hIAPP fibers with CurDAc. Experimental data are shown in **Figure S4**. Dissociation constant (K_d), ΔH_{bind} and n value were obtained by fitting with a one site binding model. ΔG_{bind} was calculated using $\Delta G_{bind} = -RT\ln K_a = RT\ln K_d$. $(-)T\Delta S_{bind}$ was finally obtained using $\Delta G_{bind} = \Delta H_{bind} - T\Delta S_{bind}$.

hIAPP Fibers + CurDAc	
ΔG_{bind} (kcal mol^{-1})	-7.3
ΔH_{bind} (kcal mol^{-1})	-9.9
$-T\Delta S_{bind}$ (kcal mol^{-1})	2.6
K_d (μM)	6.8
n (value)	0.88

Table S2. Isotropic chemical shift values, measured from 3D HNCACB NMR spectra of a sample containing hIAPP monomers and CurDAc. These values were used to for secondary structure predictions shown in **Figure S7**.

Number	Residue	C_β ppm	C_α ppm	N ppm	HN ppm
2	CYS			122.11	8.77
3	ASN	39.08	52.67	124.29	8.77
4	THR	70.75	61.11	110.66	7.35
5	ALA	18.17	54.58	122.71	8.51
6	THR	69.22	62.92	109.54	7.72
7	CYS	40.87	56.13	120.40	7.86
8	ALA	18.53	53.64	124.17	7.96
9	THR	69.22	63.15	113.71	7.91
10	GLN	28.68	56.20	122.51	7.99
11	ARG	30.32	56.64	107.93	8.04
12	LEU	41.94	55.34	122.54	7.81
13	ALA	18.76	53.05	123.63	7.95
14	ASN	38.33	53.37	116.67	7.99
15	PHE	38.79	58.00	120.03	7.79
16	LEU	41.86	55.45	122.38	7.91
17	VAL	32.35	62.34	120.76	7.71
18	HIS	28.88	55.11	122.07	8.31
19	SER	63.61	57.98	117.51	8.16
20	SER	63.55	58.12	117.73	8.22
21	ASN	38.51	53.09	120.01	8.19
22	ASN	38.33	53.08	118.65	8.07
23	PHE	38.67	53.21	120.38	8.02
24	GLY		45.05	110.13	8.09
25	ALA	19.04	52.11	123.43	7.76
26	ILE	38.30	53.45	120.40	7.96
27	LEU	42.07	55.06	127.03	8.21
28	SER	63.61	57.96	117.08	8.16
29	SER	63.58	58.13	117.67	8.26
30	THR	69.41	61.85	115.01	7.94
31	ASN	38.45	53.12	121.26	8.18
32	VAL	32.34	62.41	120.73	7.96
33	GLY		45.10	112.36	8.30
34	SER	63.56	58.02	115.41	8.01
35	ASN	38.47	53.12	120.54	8.31
36	THR	69.41	62.06	114.20	7.85
37	TYR	38.43	57.70	122.66	7.93

Table S3. Parameters obtained by fitting the circular dichroism spectra of hIAPP fibers sample time course disaggregation with CurDAc using BeStSEL. CD spectra for hIAPP fibers without CurDAc and 30 minutes incubation with CurDAc are shown in **Figure S13**. Values are shown in percentage of total content.

Sample	Helix 1	Helix 2	Total Helix	Anti 1	Anti 2	Anti 3	Para	Turn	Total β-sheet	others	NRMSD
hIAPP Fiber	0	0	0	7.1	7.46	19.93	9.32	10.23	54.04	45.97	0.0215
30 Minutes	9.14	0	9.14	0	0	19.46	20.12	8.66	48.24	42.63	0.0334
16 Hours	10.49	1.83	12.32	0	0	16.6	19.67	7.48	43.75	43.93	0.0366
40 Hours	0	2.69	2.69	0	0	14.23	23.63	13.73	51.59	45.72	0.0529
60 Hours	0	0	0	0	1.87	10.25	21.36	15.85	49.33	50.68	0.0535

Table S4. Statistical significance calculated by one-way ANOVA using Tukey's multiple comparison tests. Comparisons were done between cells treated with hIAPP with and without CurDAc; see the toxicity results shown in **Figure S16**.

Samples Compared	Significant?	Summary	Adjusted P Value
hIAPP monomer MTT Experiments			
5 μM vs. 5 μM + 1 equiv. CurDAc	Yes	****	<0.0001
1 μM vs. 1 μM + 1 equiv. CurDAc	Yes	****	<0.0001
0.5 μM vs. 0.5 μM + 1 equiv. CurDAc	Yes	****	<0.0001
5 μM + 1 equiv. CurDAc vs. 1 μM + 1 equiv. CurDAc	Yes	**	0.0034
5 μM + 1 equiv. CurDAc vs. 0.5 μM + 1 equiv. CurDAc	Yes	****	<0.0001
1 μM + 1 equiv. CurDAc vs. 0.5 μM + 1 equiv. CurDAc	No	ns	0.0855
hIAPP Fiber MTT Experiments			
5 μM vs. 5 μM + 1 equiv. CurDAc	No	ns	0.9985
1 μM vs. 1 μM + 1 equiv. CurDAc	Yes	****	<0.0001
0.5 μM vs. 0.5 μM + 1 equiv. CurDAc	Yes	****	<0.0001
5 μM + 1 equiv. CurDAc vs. 1 μM + 1 equiv. CurDAc	Yes	****	<0.0001
5 μM + 1 equiv. CurDAc vs. 0.5 μM + 1 equiv. CurDAc	Yes	****	<0.0001
1 μM + 1 equiv. CurDAc vs. 0.5 μM + 1 equiv. CurDAc	No	ns	0.1464
hIAPP Monomer CellTox Green Experiments			
5 μM vs. 5 μM + 1 equiv. CurDAc	Yes	****	<0.0001
1 μM vs. 1 μM + 1 equiv. CurDAc	No	ns	0.5995
0.5 μM vs. 0.5 μM + 1 equiv. CurDAc	No	ns	0.9128
5 μM + 1 equiv. CurDAc vs. 1 μM + 1 equiv. CurDAc	Yes	***	0.0002
5 μM + 1 equiv. CurDAc vs. 0.5 μM + 1 equiv. CurDAc	Yes	***	0.0003
1 μM + 1 equiv. CurDAc vs. 0.5 μM + 1 equiv. CurDAc	No	ns	0.9998
hIAPP Fiber CellTox Green Experiments			
5 μM vs. 5 μM + 1 equiv. CurDAc	Yes	****	<0.0001
1 μM vs. 1 μM + 1 equiv. CurDAc	No	ns	0.5284
0.5 μM vs. 0.5 μM + 1 equiv. CurDAc	No	ns	0.7522
5 μM + 1 equiv. CurDAc vs. 1 μM + 1 equiv. CurDAc	Yes	****	<0.0001
5 μM + 1 equiv. CurDAc vs. 0.5 μM + 1 equiv. CurDAc	Yes	***	0.0001
1 μM + 1 equiv. CurDAc vs. 0.5 μM + 1 equiv. CurDAc	No	ns	0.9999

Materials and Methods

Materials and Reagents:

All reagents were purchased from commercial suppliers and used as received unless noted otherwise. Aβ was purchased from BioBasic (Markham, ON, Canada) at >95% purity and used without further purification. hIAPP was purchased from AnaSpec (Fermont, CA, USA) at >95% purity and used without further purification unless otherwise noted. Human calcitonin peptide was synthesized via FMOC chemistry as described previously.[4] To ensure consistent monomeric starting conditions, peptides were dissolved in hexafluoroisopropanol (HFIP) at a concentration of 1 mg/ml and then lyophilized for 48 hours. Powders were kept at -80 °C until needed for experiments. CurDAc was synthesized in the same way as previously described[5]. All other reagents were purchased from Sigma-Aldrich (St. Louis, MO, U.S.A).

Thioflavin-T Assay:

Monomer samples were prepared by dissolving the lyophilized peptide in either dilute HCl at pH 4 (hIAPP) or in buffer (hCT and Aβ) to stock concentrations between 150 – 200 μM, kept at 0 °C (ice), vortexed for 15 s and bath sonicated at 0 °C for 1 min. Monomer samples were diluted into phosphate buffer (pH 7.4) containing 50 mM NaCl for each subsequent experiment. The kinetics of amyloid formation were monitored by the fluorescent, amyloid-specific dye ThT. All samples were prepared by diluting the stock solution to a final concentration of 10 μM in the presence of 20 μM ThT. Samples were plated in triplicate on Corning 96- well plates, maintained at 25 °C (hCT and hIAPP) or 37 °C (Aβ), and subjected to continuous, slow orbital shaking. Fluorescence readings were taken on a Biotek Synergy 2 microplate reader and were read from the bottom with an excitation wavelength of 440 nm (30 nm bandwidth) and an emission wavelength of 485 nm (20 nm bandwidth) at three-minute intervals. For studies exploring fibril remodeling, fibrils were initially formed in the 96-well plate for 24 h. After mature fibrils were formed CurDAc was added directly to wells at varying concentrations, diluting the volume by less than 1% to maintain the signal intensity. The experiment was then restarted under identical conditions to those used to monitor fibril formation. After data acquisition, raw fluorescence values were background subtracted and then normalized.

Circular Dichroism:

Single point CD measurements were carried out at a concentration of 40 μM peptide in the absence or presence of varying concentrations of CurDAc. CD measurements were performed on a JASCO J- 1500 CD spectrometer using a 0.1 cm path length cell. Spectra were acquired at 25 °C using a bandwidth of 2 nm, a scan rate of 200 nm/min, and averaging spectra over 20 scans. Measurements were taken immediately after mixing the sample (t = 0 h) and after various time points at 25 °C (hIAPP and hCT) or 37 °C (Aβ) under slow orbital shaking (conditions mimicking those used in ThT kinetic assays). hIAPP time course disaggregation experiment was analyzed using BeStSel [6] using the multiple spectra analysis tool with a scaling factor of 10.

Transmission Electron Microscopy:

Samples used in TEM analysis were taken directly from the time course CD experiments after 24h incubation (both for the modulation of fiber formation and the remodeling of preformed fibrils). Glow discharged grids (Formar/carbon 200 mesh, Electron Microscopy Sciences, Hatfield, PA, U.S.A.) were treated with samples (7 μL) for 2 min at room temperature. Excess buffer was removed via blotting and then washed three times with ddH_2O. Each grid was then incubated with

uranyl acetate staining solution (1% w/v in ddH_2O, 7 μL) for 1 min, and excess stain was blotted away. Images were taken on a JEOL 1400-plus TEM (80 kV) at 12,000x magnification.

Cell Toxicity Experiments:
RIN-5F(ATCC# CRL-2058 batch number 61465080) cells were grown in RPMI-1640 media with 2 mM L-glutamine supplemented with 10% fetal bovine serum in a humidified incubator at 37 °C with an environment of 5% CO_2. Cells were kept between passage numbers below 25. 10-cm cell culture dishes were used for culturing, and 96 flat-bottom well trays for the MTT assays. Cells were plated at 50,000 cells per well in 90 μL and were allowed to adhere for 24 hours. To prepare hIAPP fibrils to be used in cell toxicity experiments, lyophilized hIAPP monomers were solubilized in Milli-Q water brought to pH 4 using HCl and diluted to appropriate concentration using 20 mM Phosphate buffer (pH 7.4) containing 50 mM NaCl. Peptide was then treated with 1 equivalent of CurDAc. Peptide was incubated for 24 hours at room temperature with shaking at 750 rpm to form fibrils. Monomers were freshly dissolved in the same manner and then diluted in buffer. 10 fold stocks of peptide were added to each well at 10 μL for a final volume of 100 μL. After 24-h incubation of cells with aggregates, the MTT cell proliferation assay (Promega, G4000) was used to determine the toxicity of samples following the manufacturer protocol. 10 μL of the MTT dye solution was added to each well and set to incubate at 37 °C for 3-3.5 hours. 100 μL of stop solution was added and set to incubate for 12 hours. The absorbance of each well was then measured at both 570 nm and 700 nm (700 nm for the background correction). All cellular viability values were normalized to cells treated with buffer. Values reported are the average of five independent trials and the error is reported as the standard deviation of these averages. CellTox Green Cytotoxicity experiments were performed as per the manufacturer's suggestions (Promega G8741). Cells were plated at 50,000 cells per well in a 96 well plate. Peptide and compounds were prepared and added in the same manner as the MTT assay above. Immediately after the addition, the plate was put in a FLUOstar omega plate reader equipped with an atmospheric control unit kept at 37 °C with 5% CO_2 and 20%O_2. The plate was read every 10 minuets at 485ex/520em. All cellular toxicity values were normalized to cells treated with buffer. Values reported are the average of three independent trials and the error is reported as the standard deviation of these averages. Ordinary one-way ANOVA tests with Tukey's multiple comparisons were performed.

NMR Sample preparation:
Lyophilized powder of recombinant human-IAPP(1-37)(hIAPP) was produced as using the published protocol[7] and was dissolved into buffer to yield a final peptide concentration of maximal 100 μM. To study the hIAPP monomer, 30 mM deuterated acetic acid buffer (at pH 5.3) was used to decrease the rate of peptide aggregation so that it can be studied at the NMR timescale. Alternatively, for the experiments involving fibers, the peptide fiber-powder was dissolved in 100 μL of the acetate buffer pH 5.3 (to help disassemble the aggregates) and then diluted to 500 μL with 50 mM phosphate buffer and 50mM sodium chloride at pH 7.4. The solutions were supplemented with 10 % D_2O. The samples were measured and stored at 25 °C. For the NMR sample of fibrils, the peptide was dissolved into phosphate buffer and the sample was incubated for approximately 12 hours at room temperature to create amyloid fibers. The CurDAc solution was prepared in water to a high concentration of 10 mM and diluted, and then mixed with the hIAPP as required. The sample was transferred to an NMR tube for solution NMR measurements. For control experiments of the fiber disaggregation (Figure S11), freshly prepared ^{15}N hIAPP monomer was used to acquire spectra were obtained at 0, 30, and 96 hours. Between recordings the sample was incubated at room temperature.

NMR Experiments:

All NMR experiments were performed at 25 °C, employing Bruker Avance 500 and 850 MHz spectrometers, equipped with cryogenic probes. For the control experiments to rule out the degradation of hIAPP, we performed ^{1}H-^{15}N SOFAST HMQC experiments at 3 different time points at 25 °C on a Bruker Ascend 800 MHz NMR spectrometer equipped with a triple-channel cryogenic probe (spectra are shown in Figure S11). Proton chemical shifts are referenced relative to water resonance frequency, whereas the ^{15}N and ^{13}C shifts were referenced indirectly. Backbone assignments were accomplished using triple-resonance assignment experiments by employing the Non Uniform Sampling approach for experiments on monomers with CurDAC (Figures 2A and S7).[8,9] NMR spectra were processed using TopSpin (Bruker). Spectra were analyzed using ccpNMR analysis.[10] 3D NMR experiments on disaggregated fibers were also performed using Non Uniform Sampling (Figures S9 and S10). The low signal-to-noise ratio and the absence of some of the resonances made the assignment extremely difficult. Therefore, the observed peaks are tentatively identified based on the CSPs measured from 3D HNCA and 3D HN(CO)CA spectra (Figures S9 and S10). Signal intensities to monitor the depletion of hIAPP monomers were extracted from the amide region of proton NMR spectra (6.0-8.5 ppm) (Figure S5).

2D ^{1}H-^{15}N SOFAST HMQC spectra were acquired with 128 scans, a recycle delay of 0.2 s, and 128 t_1 increments. 3D HN(CO)CA spectra were acquired with 152 scans, with 15% NUS sampling (with 40 t_1 and 60 t_2 points) and a recycle delay of 1s. 3D HNCA spectra were acquired with 128 scans, with 20% NUS sampling (with 40 t_1 and 60 t_2 points) and a recycle delay of 1s. 3D HNCACB spectra were acquired with 24 scans, with 25% NUS sampling (with 200 t_1 and 50 t_2 points) and a recycle delay of 1s. The increase in the observed signal intensity from the disaggregation of hIAPP amyloid fibers was obtained from the FIDs of the SOFAST-HMQC spectra.

Secondary structure propensities were calculated using the methods from Forman-Kay, Wishart and change in chemical shifts from the random-coil index.[1,2,11] CSPs were calculated using the equation given below.[12]

$$d = \sqrt{\frac{1}{2}\left[\delta_H^2 + \left(\alpha \cdot \delta_N^2\right)\right]}$$

Isothermal Titration Calorimetry (ITC):

ITC experiments were performed using a VP-ITC instrument (Marvern Instrument, UK). The concentrations of CurDAc in the ITC syringe were 1 mM for fiber experiments or 500 μM for monomer experiments. The concentration hIAPP was 30 μM and Aβ was 100 μM in the ITC cell. 10 mM phosphate buffer (pH 7.4) with 100 mM NaCl was used. Titration experiments consisted of 19 injections spaced at 300/600 s intervals for fibers and 100 s interval for monomers. Injection volume and injection duration was 0.2 μl for 0.4 s and 2 μl for 4 s. Fibers were stirred at 1000 rpm and monomer at 750 rpm with a reference power of 5 μcal/s.

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