Electronic Supplementary Material (ESI) for RSC Advances.

Electronic Supplementary Materials

Curcumin-Like Compounds Designed to Modify Amyloid Beta Peptide Aggregation Pattern

Docking

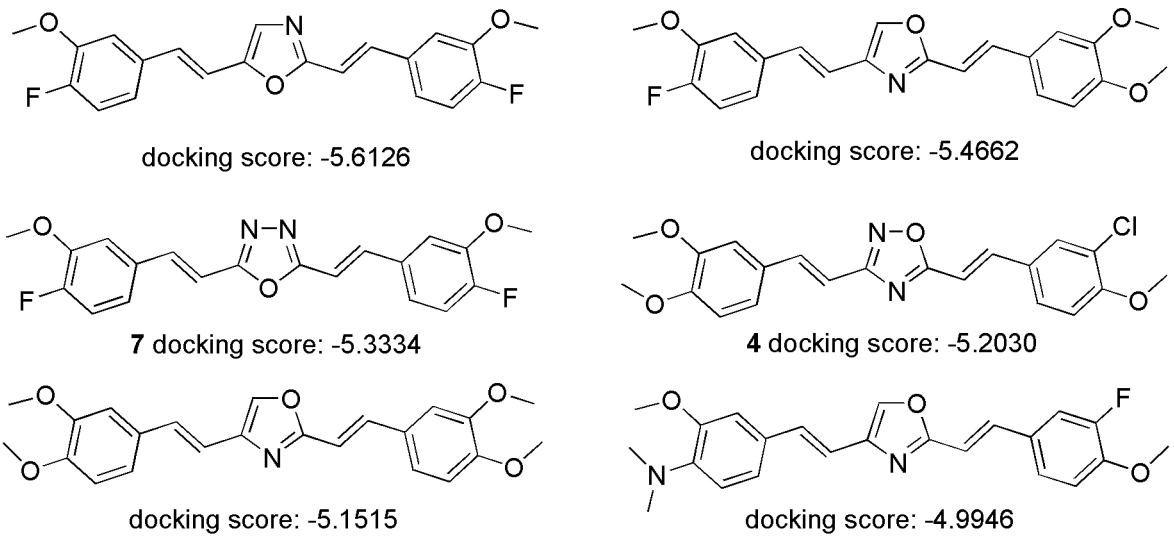

Figure S1. Structures of selected curcumin-like compounds. Docking score for curcumin was -3.92.

Entry Name	docking score	Prime Energy	IFDScore		Entry Name	docking score	Prime Energy	IFDScore
	average	average	average			best	best	best
7	-7.064	-2846.4	-149.384		**7**	-8.026	-2849.3	-150.491
4	-6.741	-2795.9	-146.536		**4**	-7.325	-2794.7	-147.06

Table 1. Summary of IFD results.

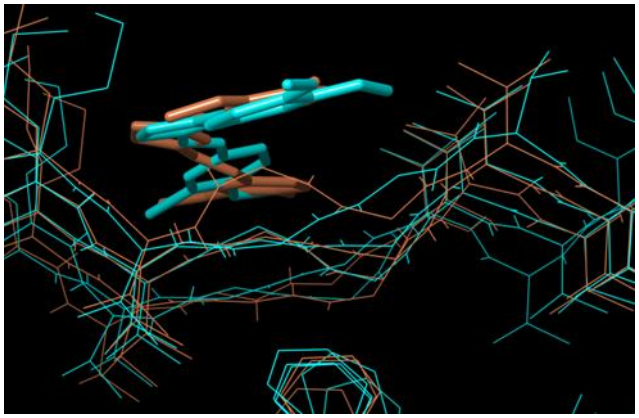

Figure S2. IFD poses for compound 4 (turquoise) and 7 (orange) bound to Aβ pentamer (PDB: 2BEG). In the presence of 7, the pristine zigzag conformation of Gly37-Gly38 is partially preserved.

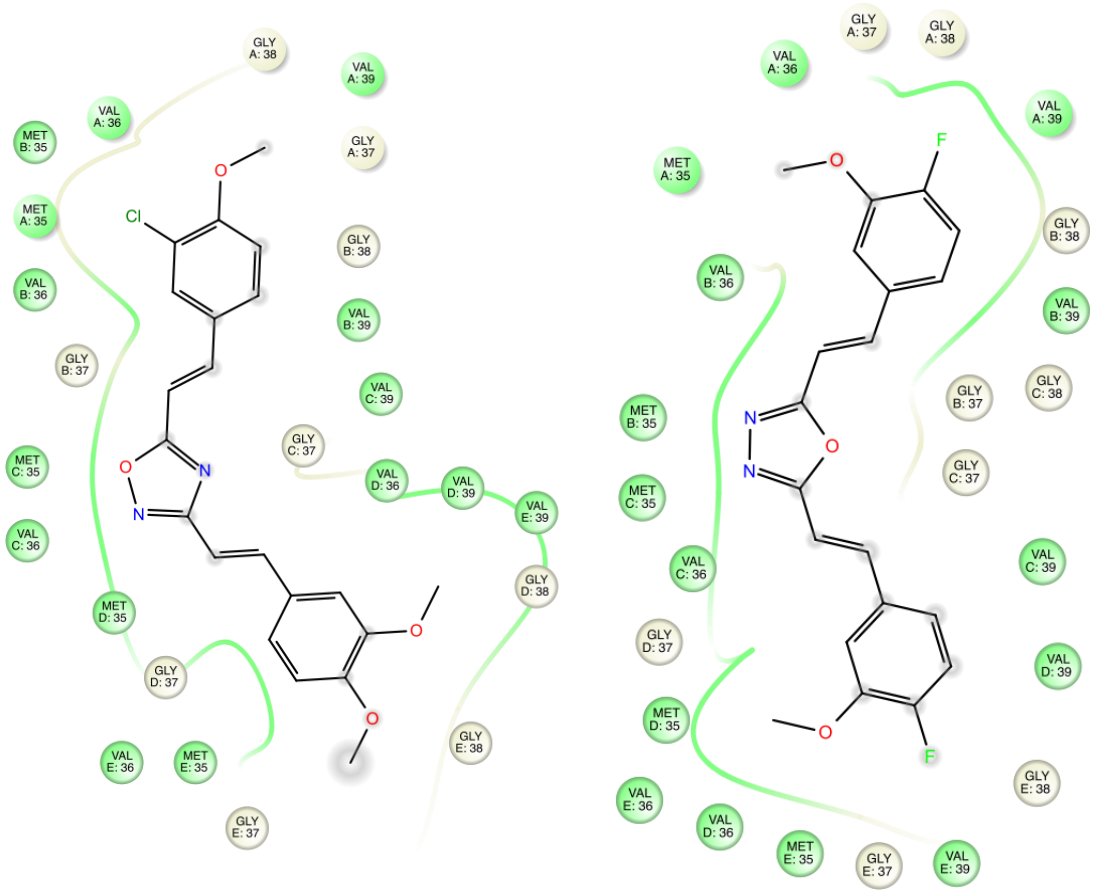

*Figure S3. Interaction maps derived from IFD poses for compound **4** (left) and compound **7** (right) bound to A (PDB: 2BEG).*

Small Angle X-ray Scattering

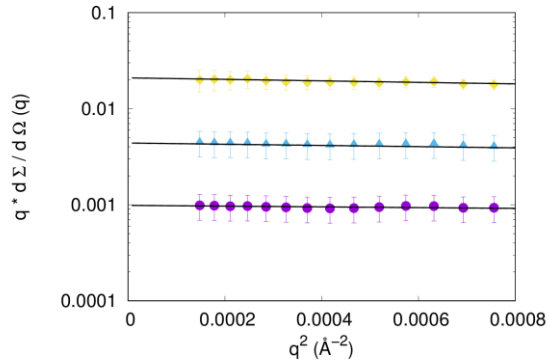

Figure S4. Guiner plots for rod-like particles of SAXS data corresponding to Aβ in absence of the compounds, after 100, 150, and 200 minutes. Curves at increasing time are shifted for clarity by a factor 5^i (with i=0 for time 100, i=1 for the measurement after 150 minutes, and so on). Continuous lines are the theoretical fitting corresponding to Guinier approximation for rod-like particles.

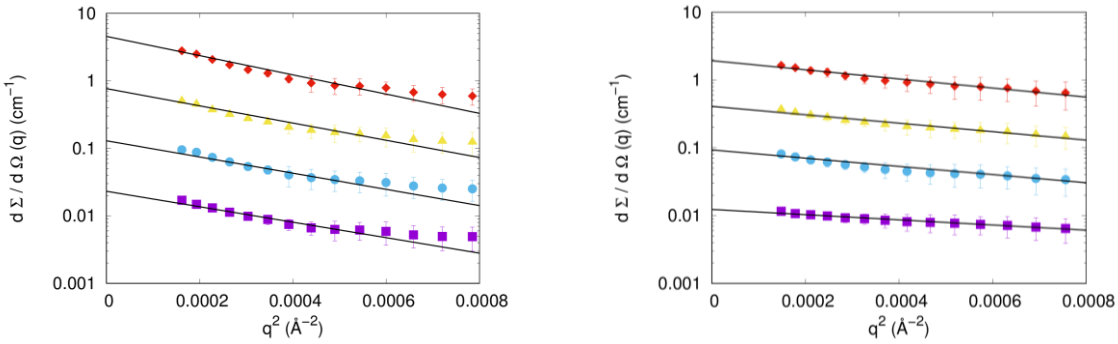

*Figure S5. Guinier plots of SAXS curves corresponding to Aβ aggregation in presence of compound **4** (right) and **7** (left) (ratio 1:1), obtained at time 0 (violet squares), and after 100 (blue circles), 150 (yellow triangles), and 200 (red diamonds) minutes. Curves at increasing time are shifted for clarity by a factor5^i (with i=0 for time 100, i=1 for the measurement after 150 minutes, and so on). Continuous lines are the theoretical fitting corresponding to Guinier approximation for spherical particles.*

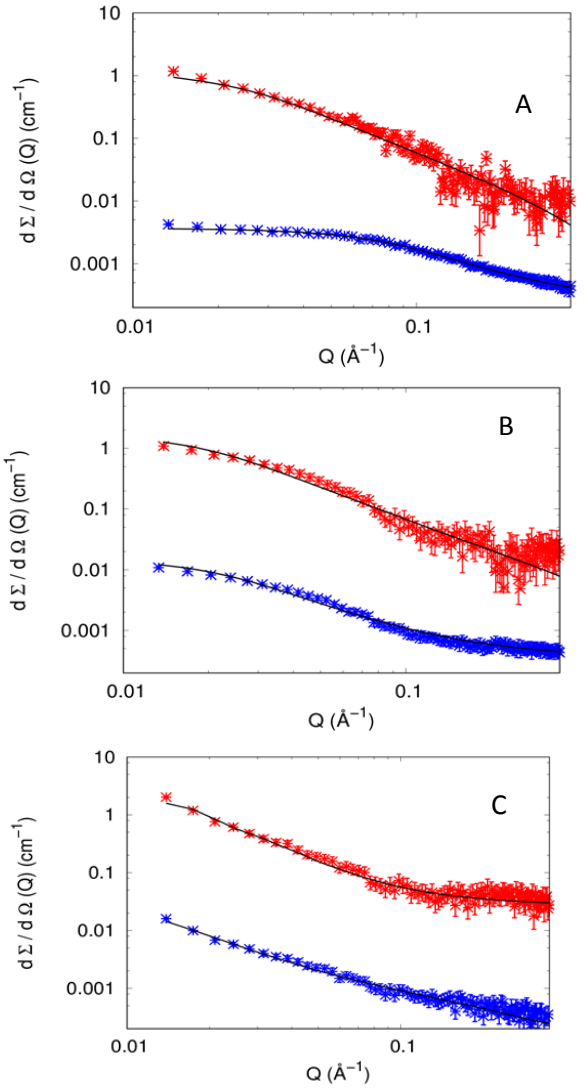

Figure S6: Starting (blue) and final (red) stages of Aβ alone (A), Aβ in presence of compound 4 (B), Aβ in presence of compound 7 (C). Black lines represent the fitting obtained with worm like model (one population

with aggregation number 1 for Aβ alone and two population for Aβ with compounds 4 and 7) and cylinders. Curves are scaled for sake of clarity (10^2 factor) to evidence the fitting in the whole range of Q.

	Aβ40	Compound 7 + Aβ40	Compound 4 + Aβ40
start	1 worm like: n_{agg}=1	2 worm like: 25±2% n_{agg}=2±1 75±8% n_{agg}=13±2	2 worm like: 0,10±0,03% n_{agg}=2±1 99,8±0,5% n_{agg}=13±3
end	3±1% worm like: n_{agg}=16±5 97±8% cylinder: r=23±4Å h>1500Å	31±4% worm like: n_{agg}=17±5 69±7% cylinder: r=28±6Å h>1500Å	95±9% worm like: n_{agg}=16±5 5±1% cylinder: r=28±4Å h>1500Å

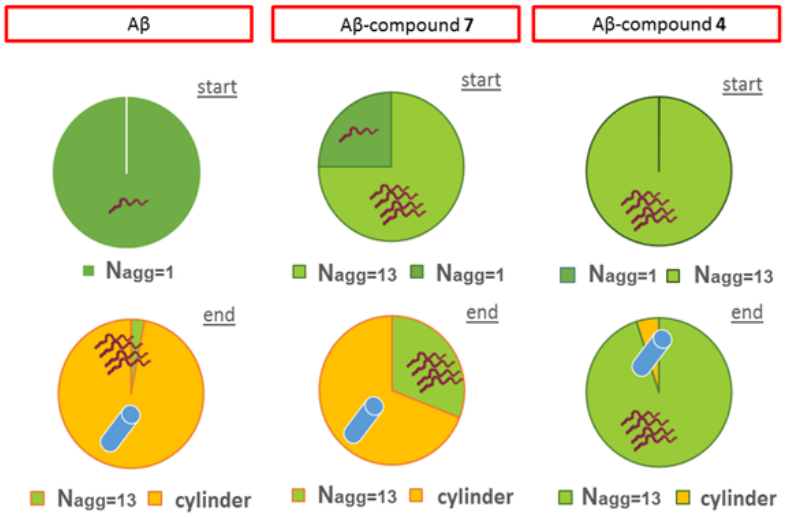

*Figure S7. Table (top) of remarkable parameters and schematic representation (bottom) of SAXS fitting analysis on starting and final data of Aβ and Aβ in presence of compound **7** and compound **4**. SAXS curves were analysed considering the macroscopic differential scattering cross section written as a combination of the form factors corresponding to the fibril-like cylinders states and unfolded species to describe respectively final and initial stages. In table are reported the percentage of each species obtained from the fitting, for the worm like model the aggregation number of segments(n_{agg}) and for cylinder model the radii (r) and the cylinders length (h). As can be seen, for Aβ alone, the starting point is nicely fitted by a worm like model with aggregation number equal to one, indicating the presence of monomers in solution (see details in the text). The final stage is instead fitted by cylinders and worm like with a higher aggregation number. The presence of the two compounds lead to a different behaviour in the final stages, where the fraction of cylinders in solution decrease from Aβ alone for both compounds, more noticeably in presence of compound **4** , thus confirming microscopy results.*

SAXS analysis

To analyse SAXS curves for the starting and final stages of Aβ in absence and in presence of compounds, it was considered the macroscopic differential scattering cross section as a combination of the form factors corresponding to the fibril-like cylinders (*lng*) states and unfolded species (*unf*) for final stages and unfolded species alone for the starting states:

$$\frac{d\Sigma}{d\Omega}(Q) = \frac{cN_A}{M_1}\left[x_{unf}P_{unf}(Q) + \frac{x_{lng}}{N_{lng}}P_{lng}(Q)\right]$$

where c is the protein mass concentration, N_A is Avogadro's number, M_1 is the monomer molecular weight, x_i is the fraction of monomers involved in the formation of the i-species, $P_i\ (Q)$ its form factor and N_i is the aggregation number of that species (which is 1 for unfolded monomers). The structure factor $S(q)$ was approximated to unity due to the low protein concentration of the experiment.

The unfolded or intrinsically disordered state of the protein monomer was described by statistical chains, such as the so-called worm-like model, based on the Kratky-Porod statistics. The corresponding form factor $P_{wlk}\ (Q)$, which includes the effect of excluded volume, has been obtained by Pedersen and Schurtenberger through Montecarlo simulations, whose results have been given in terms of numerical approximations (50). As reported in the manuscript, $P_{wlk}\ (Q)$ is multiplied by a two-density level cylindrical cross section (51). The unfolding protein form factor thus results:

$$P_{unf}(Q) = (2\pi L)^2 P_{wlk}(Q)\left[(\rho_s - \rho_0)(Rc+\delta)^2\frac{J_1[Q(R_c+\delta)]}{Q(R_c+\delta)} + (\rho_1 - \rho_s)R_c^2\,\frac{J_1(QR_c)}{QR_c}\right]^2$$

where L is the contour length of the chain, representative of the its extended length, R_c is the inner radius of the cross section that represents the mean half of the thickness of the protein chain, δ is the thickness of the solvation layer and $J_1\ (x)$ is the first order Bessel function. The parameters ρ_1 , ρ_s and ρ_0 are the scattering length densities of the dry protein, of the hydration layer and of the bulk solvent, respectively.

The worm-like form factor $P_{wlk}\ (Q)$ depends on L and on the statistical segment (Kuhn) length b, the average separation between two subsequent segments. The number of segments is simply given by the ratio $n_b = L/b$.

The shape of early protofibrils, representing the first fibrillation states, and of the fibril-like aggregates, were adequately described by monodisperse cylinders. The form factor of a cylinder is written as:

$$P_{cyl}(Q) = \left(2\pi R_{cyl}^2\, H_{cyl}\right)^2\left(\rho_{cyl} - \rho_0\right)^2\int_0^{\frac{\pi}{2}} d\beta\,\sin\beta\left\{\frac{\sin\left(\frac{1}{2}QH_{cyl}cos\beta\right)}{\frac{1}{2}QH_{cyl}cos\beta}\,\frac{J_1(QR_{cyl}\sin\beta)}{QR_{cyl}\sin\beta}\right\}^2$$

where R_{cyl} and H_{cyl} are the cylinder radius and length. The average scattering length density of the cylinder, ρ_{cyl} , is fixed to the average electron density of a protein, and the monomer aggregation number, N_{cyl}, is calculated from $N_{cyl} = \frac{\pi R_{cyl}^2 H_{cyl}}{V_1}$.