Supporting Information

Dihydrochalcone molecules destabilize Alzheimer’s amyloid-β protofibrils through binding to the protofibril cavity

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This material contains seven supplementary figures and a movie. The movie is used to show the dynamic process of a Dih molecule entering the cavity and dissociate the edge strand at the even end from the Aβ17-42 protofibril.

![Residue-based Cα-root-mean-square fluctuations (Cα-RMSFs) of the Aβ17-42 protofibril in Aβ (A) and Aβ+Dih (B) systems.](image1)

**Figure S1.** Residue-based Cα-root-mean-square fluctuations (Cα-RMSFs) of the Aβ17-42 protofibril in Aβ (A) and Aβ+Dih (B) systems.

![The K28 Cα-Cα distance between each two nearest neighboring chains of the Aβ17-42 protofibril in each of the Aβ (A, B, C) and Aβ+Dih (D, E, F) systems as a function of simulation time.](image2)

**Figure S2.** The K28 Cα-Cα distance between each two nearest neighboring chains of the Aβ17-42 protofibril in each of the Aβ (A, B, C) and Aβ+Dih (D, E, F) systems as a function of simulation time.
Figure S3. Secondary structure analysis of the Aβ17-42 protofibril in each MD run of the Aβ and Aβ+Dih systems. (A) Secondary structure probabilities of β1 region (residues 18-26). (B) Residue-based β-sheet probabilities of the protofibril (residue 17-42).

Figure S4. Probability density function (PDF) of the intra-chain (A, C, E) and inter-chain (B, D, F) D23-K28 distance of the Aβ17-42 protofibril in each of the MD run of the Aβ+Dih system compared with the three MD runs of Aβ system.
Figure S5. Snapshots taken at nine different time points in a representative trajectory showing the dynamic process of Dih molecules entering the cavity and dissociating the edge strand at the even end of the Aβ17-42 protofibril.

Figure S6. The initial structure of U-shaped Aβ42/Aβ40 protofibrils and S-shaped Aβ42 protofibril in the absence (A, C, E) or presence of ten Dih molecules (B, D, F).
Figure S7. Snapshots taken at 12 different time points in a representative trajectory showing the dynamic process of Dih molecules entering the cavity and remodeling the S-shaped Aβ_{42} protofibril.