Supporting Information

Small-molecule targeted $A\beta_{42}$ aggregate degradation-Negatively charged small molecules are more promising than the neutral ones

Jinfei Mei, Huijuan Yang, Bo Sun, Chengqiang Liu, Hongqi Ai*

School of Chemistry and Chemical Engineering, University of Jinan, Jinan 250022, PR China

*Corresponding Authors

Dr. Hongqi Ai (E-mail: chm_aihq@ujn.edu.cn)

Contents

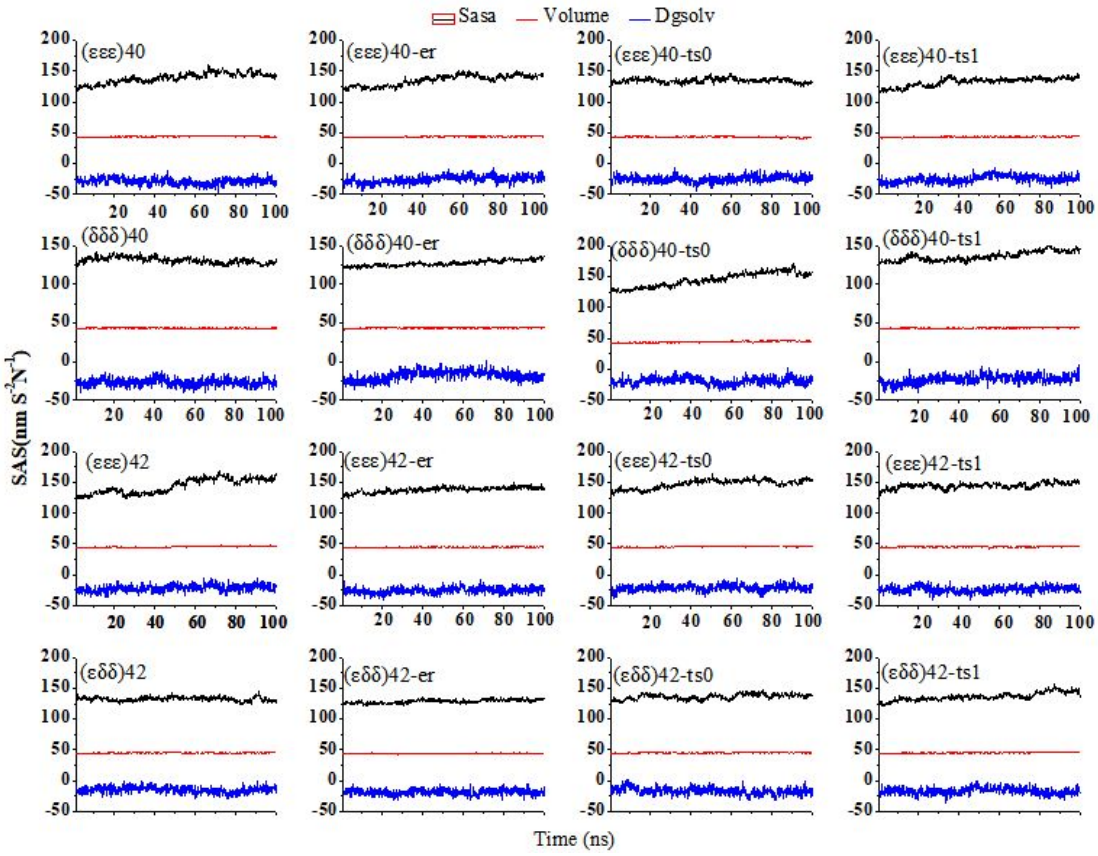


Figure S1. SASA of each system (in black) and the corresponding volume (in red) and estimated solvation free energy (in blue)

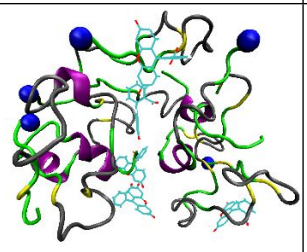
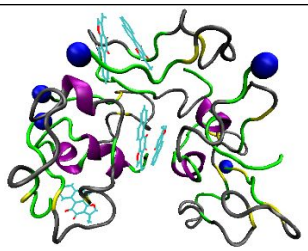
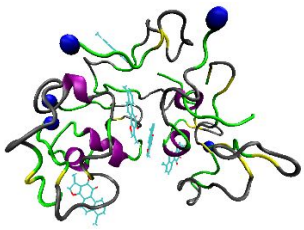
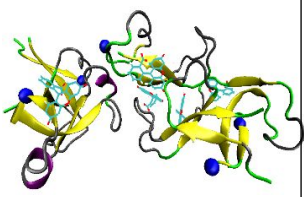
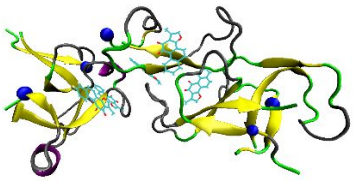
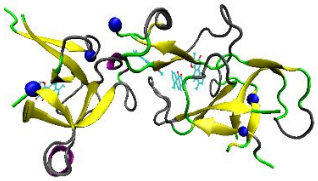
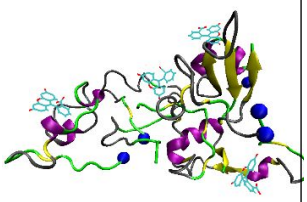
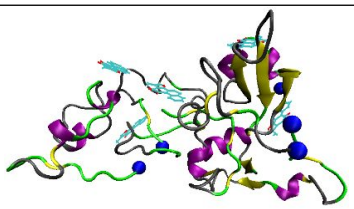
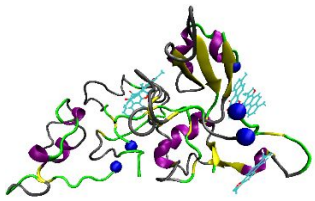
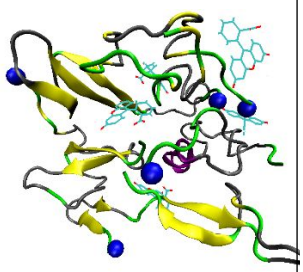
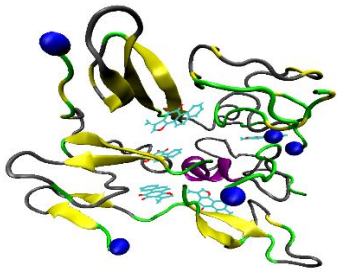
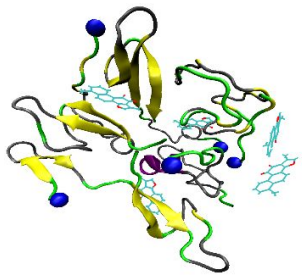
	ER	TS0	TS1
$(\varepsilon\varepsilon\varepsilon)_{40}$			
$(\delta\delta\delta)_{40}$			
$(\varepsilon\varepsilon\varepsilon)_{42}$			
$(\varepsilon\delta\delta)_{42}$			

Figure S2. The initial distribution of inhibitors in oligomer by docking. Helix/β/turn/coil contents are shown in purple/yellow/gray/green, respectively, with blue ball as N-terminal N atom.

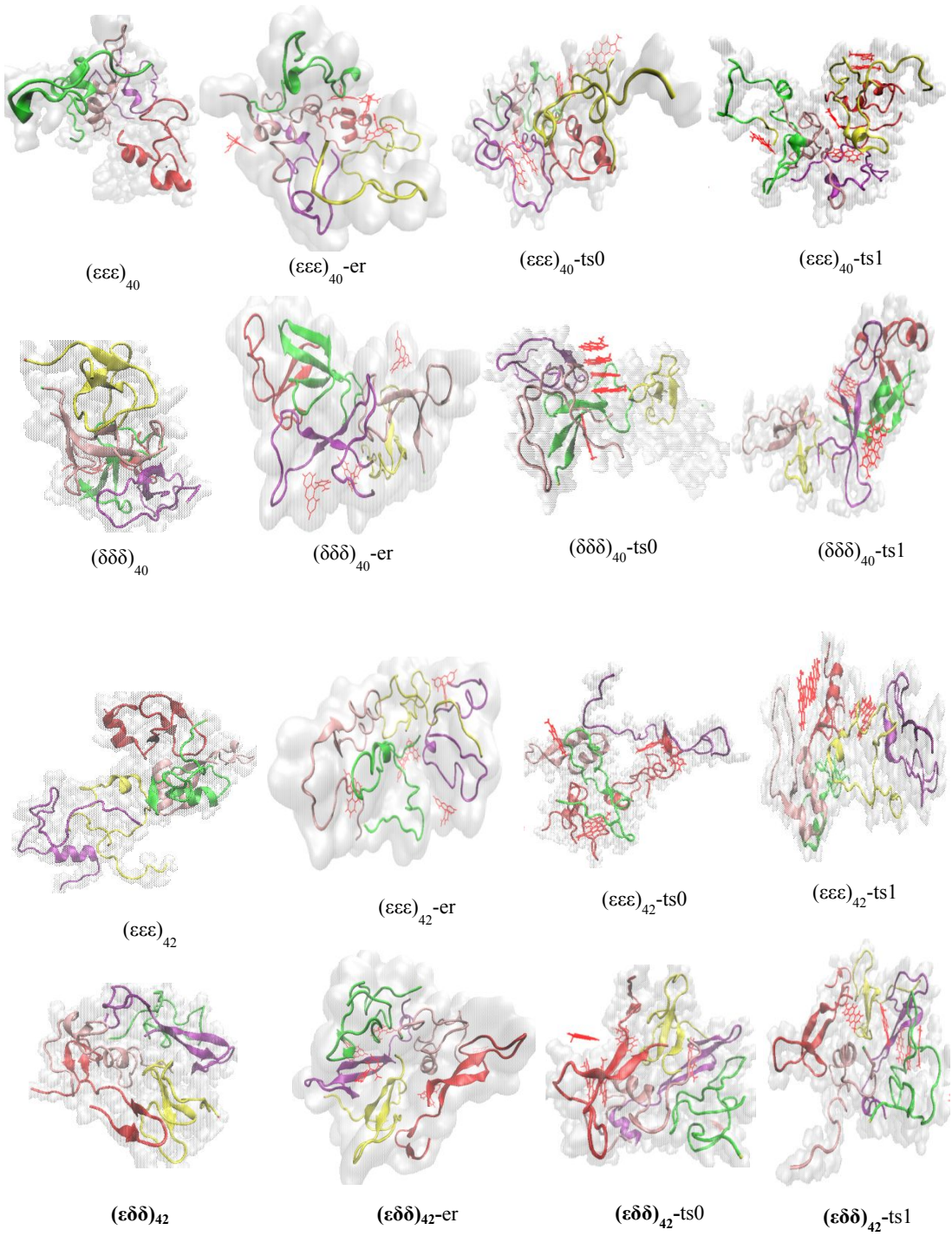


Figure S3 Conformations of pentameric oligomers and their inhibitor-involved complexes after MD. Five Aβ chains in each oligomer are shown in purple, brown, orange, yellow and green, respectively. Inhibitors are shown in stick.

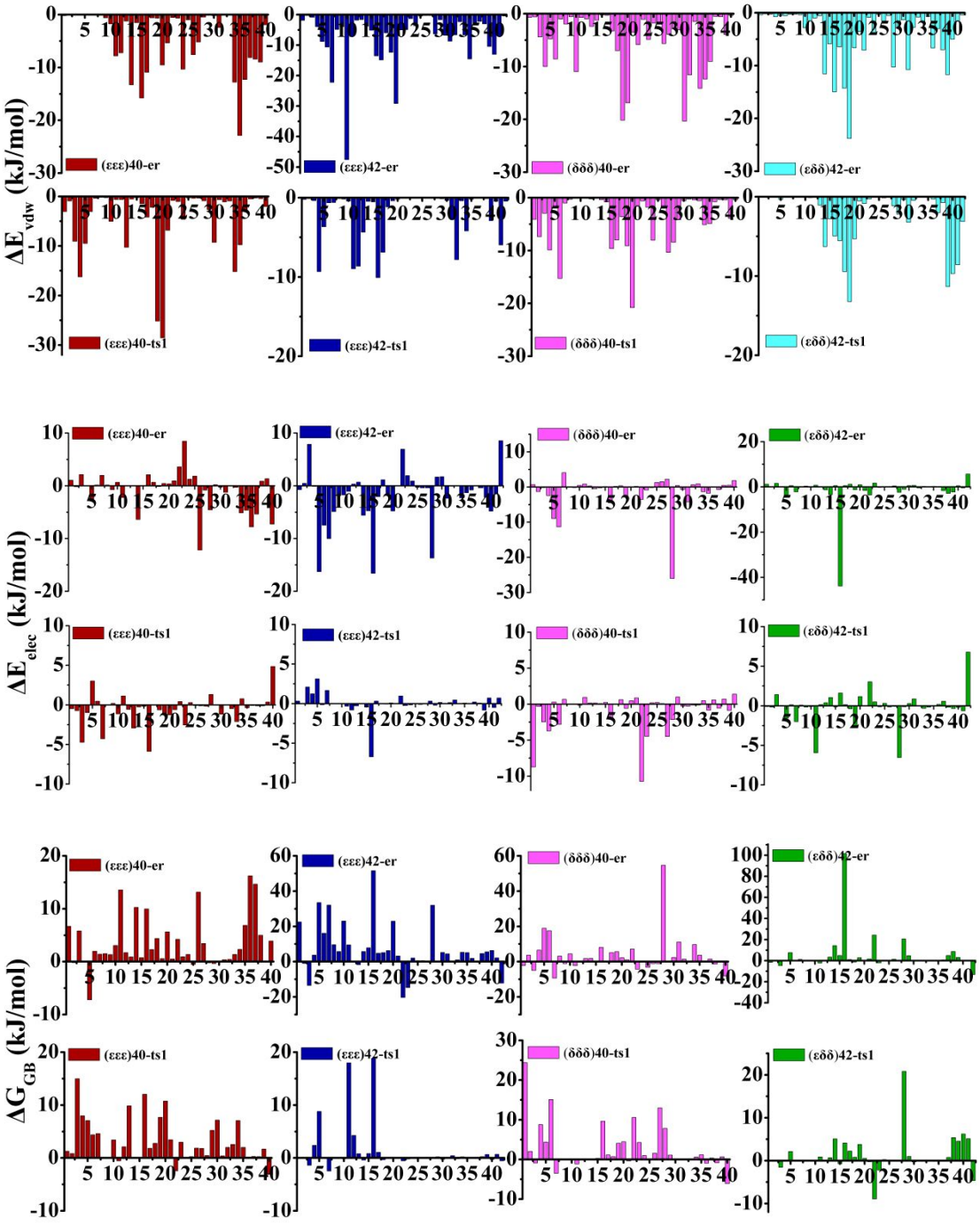


Figure S4. Normalized contributions of residues to the ΔE_{vdw} (top panel), ΔE_{elec} (middle panel) and ΔE_{GB} (bottom panel)

Table S1 Number of H-bond in **total** pentameric oligomers, only in intramolecular main chain of five separate Aβ monomers **(a)**, and between intermolecular main chains **(e)** and between intermolecular **sidechain**s of Aβ monomers (same to Figure 3).

Complex	**Total**	Main chain**(e)**	**Side chain**	Main chain**(a)**
(εεε)40	88	8	18	45
(εεε)40-er	88	5	13	41
(εεε)40-ts0	90	7	15	41
(εεε)40-ts1	92	7	14	33
(δδδ)40	77	14	30	45
(δδδ)40-er	85	6	14	42
(δδδ)40-ts0	77	9	17	42
(δδδ)40-ts1	85	6	15	44
(εεε)42	95	4	15	58
(εεε)42-er	104	3	13	51
(εεε)42-ts0	94	4	14	51
(εεε)42-ts1	99	4	11	52
(εδδ)42	78	9	35	49
(εδδ)42-er	99	4	20	46
(εδδ)42-ts0	90	5	25	48
(εδδ)42-ts1	82	5	22	42

Table S2 Salt bridges and H-bonds

	Monomer	Peptide	Salt bridge/H-bond	Distance/Å
$(\varepsilon\varepsilon\varepsilon)_{40}$-er	S26-C	ER-2	(Side chain)H -O (2)	1.65
$(\varepsilon\varepsilon\varepsilon)_{42}$-er	H14-A	ER-2	(Side chain)H-O (1)	2.18
	I32-C	ER-3	(Main chain)H-O (2)	2.36
	K16-C	ER-4	(Side chain)H-O(1)	2.80
	H6-B	ER-5	(Side chain)H-O(1)	2.05
	Y10-B	ER-5	π-π	2.60
$(\delta\delta\delta)_{40}$-er	K28-D	ER-2	(Side chain)H-O(2)	2.08
	F4-E	ER-1	(Main chain)H-O (2)	1.80
	H6-E	ER-4	(Main chain)H-O (2)	1.92
$(\varepsilon\delta\delta)_{42}$-er	V39-B	ER-1	(Main chain)H-O (2)	1.88
	K16-B	ER-2	(Side chain)H-O(2)	1.79
	K16-E	ER-3	(Side chain)H-O(2)	1.68

A strong π-π interaction between residue Y10 and ER in $(\varepsilon\varepsilon\varepsilon)_{42}$-er is presented additionally. Note that the suffix letter followed residue name denotes the chain label of five Aβ chains of these complexes. For example, S26-C stands for the S26 at the third Aβ chain of pentamer. The label after the ER denotes the numbering of the ER. (Side chain)H -O(2) signifies that the interaction between a hydrogen at the side chain of residue and the second oxygen on ER (see the label in Figure 1)