Supplementary Information (SI)

12-crown-4 ether disrupts the Patient Brain-derived Amyloid-βeta Fibril Trimer: Insight from All-atom Molecular Dynamics Simulations

Nikhil Agrawal[1], Adam A. Skelton*[1]

[1]School of Pharmacy and Pharmacology, University of KwaZulu-Natal, Durban, 4001, South Africa

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Control simulations

In all the control simulations no opening event of Amyloid fibril was observed. The U-shaped structure of Aβ fibril remained quite intact. Figure 1S A) shows the opening of Aβ40 fibril in three control simulations (500ns); in all three control simulations the opening value always fluctuated between 20-22, and RMSD value also remained stable.

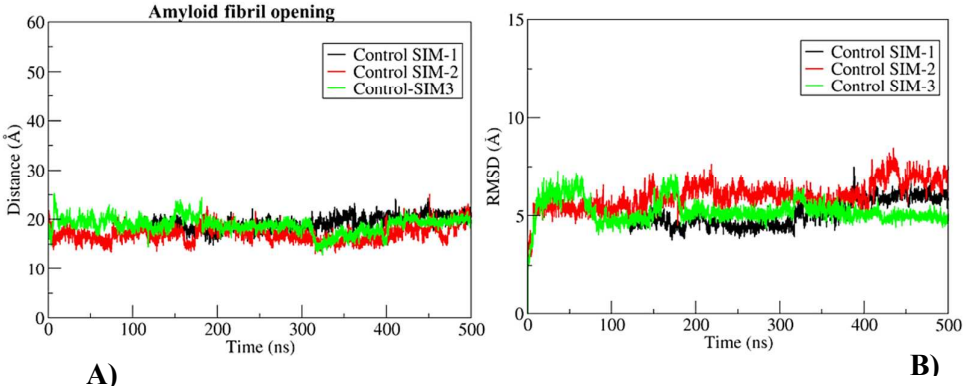


Figure 1S: A) Amyloid fibril opening in three control simulations (500 ns). B) RMSD change for the three control simulations (500ns).

Figure: 2S and Figure: 3S shows the "opening" of amyloid fibril and conformational change in two trajectories. This is to prove that the opening of the U-Shaped structure is reproducible and statistically significant. Figure: 2S A shows entering of first 12-crown-4 molecule around ~9 ns in core region (red line) and consecutive opening of U-shaped topology of Aβ40 fibril (black line). A second 12-crown-4 molecule entered into the core region at ~21 ns, which leads to the further opening of Aβ40 fibril. Figure: 2S B shows the

time evolution of conformational change in Aβ40 fibril; that is, the conformation of Aβ40 fibril drastically changed as U-shaped topology starts to open.

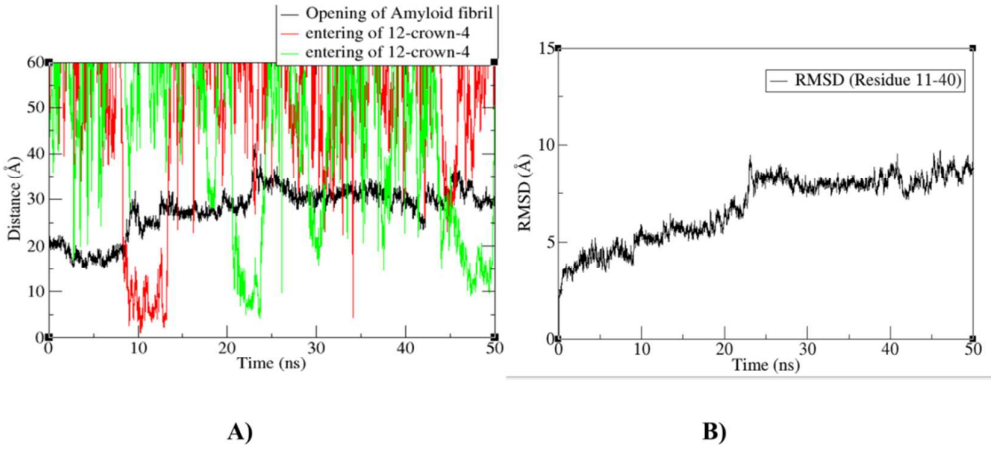


Figure 2S: A) shows time evolution of entering of 12-crown-4 in core region (red line) and opening of U-shaped structure of Aβ40 fibril (black line). B) shows time evolution of RMSD in Aβ40 fibril.

Figure: 3S A) shows "entering" of 12-crown-4 in core region (red line) and subsequent "opening" of Aβ40 fibril. In this simulation, 12-crown-4 entered into the core region ~12 ns and subsequent "opening" of U-shaped structure occurred (black line); meanwhile a drastic conformation change was observed in Aβ40 fibril, Figure: 3S B).

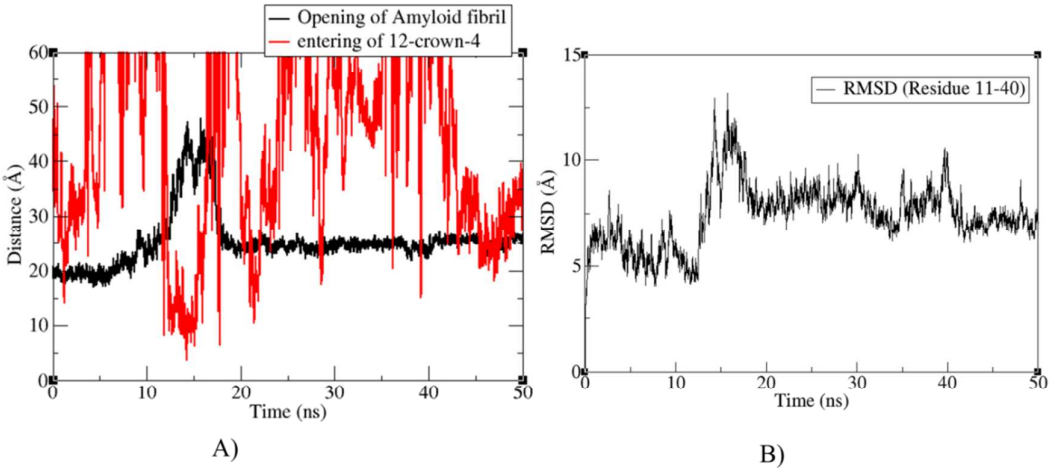
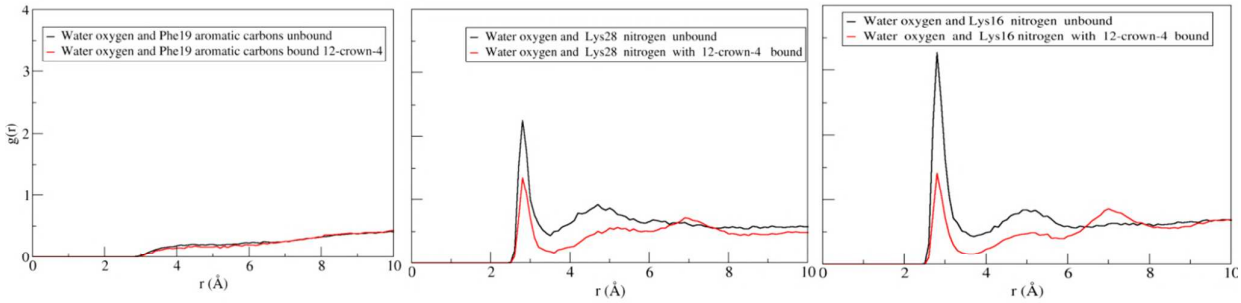


Figure 3S: A) shows time evolution of entering of 12-crown-4 in core region (red line) and opening of U-shaped structure of Aβ40 fibril (black line). B) shows time evolution of conformational change in Aβ40 fibril.

Displacement of water molecules



A) **B)** **C)**

Figure 4S A) RDF of water oxygen atoms and Phe19 (Chain B) phenyl ring C-atoms in presence and absence of 12-crown-4. B) RDF of water oxygen atoms with Lys28 (Chain C) amine nitrogen atom in presence and absence of 12-crown-4. C) RDF of Lys28 (Chain B) amine nitrogen in presence and absence of 12-crown-4.

The RDF of water oxygen atoms and Phe19 (Figure 4S A) shows that the presence of the 12-crown-4 does not affect the distribution of water molecules around Phe19. The RDF is undefined showing little water structure and the amount of water molecules is less than bulk water. The RDFs for water oxygen atoms with Lys28 and with Lys16 are quite similar; there is a considerable amount of water structuring with first shell water oxygen atoms at ~3 Å and the second solvation shell at ~4.4 Å. For profiles for Lys during binding of 12-crown-4, there is an extra peak at ~ 7 Å, which is related to the water molecules that are hydrogen bonding to the 12-crown-4. The RDFs for Lys28 and Lys16 are similar in the presence of 12-crown-4 but the height of the first peak is lower for Lys28 than Lys16 because of the competition of the Lys28-Asp23 salt-bridge.

Table: 1S the number of water molecules around hydrophobic and charged residues (side chain atoms) wit in 3.5 Å in presence and absence of 12-crown-4.

Residue Name and Number	Number of water molecules in absence of 12-crown-4	Number of water molecules in presence of 12-crown-4	Water displacement due to 12-crown-4
Leu34 (Chain B)	0.23	0.04	0.19
Phe19 (Chain B)	0.20	0.16	0.04
Lys16 (Chain B)	4.62	1.88	2.74
Lys28 (Chain C)	3.27	1.78	1.50

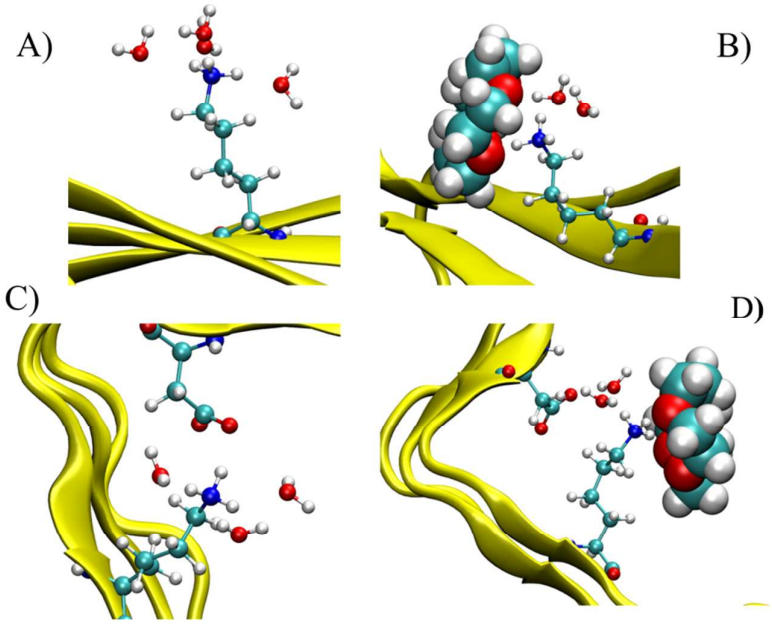


Figure: 5S A) Water molecules within 3.5 Å of Lys16 (Chain B) in absence of 12-cown-4. B) Water molecules within 3.5 Å of Lys16 (Chain B) during binding of 12-crown-4. C) Water molecules around Lys28 with in 3.5 Å of Lys28 (Chain C) in absence of 12-crown-4. D) Water molecules around Lys28 with in 3.5 Å of Lys28 (Chain C) during binding of 12-crown-4.

Non Bonded parameters for 12-crown-4 derived from charm ether force field

Supplementary table: 2S shows the Van der Waals parameters for 12-crowm-4

Name of atom	**Charge**	**Sigma**	**Epsilon**
CC325B (C)	0.02	0.3599230	0.25104
OC305A (O)	-0.4	0.29399657698	0.41840
HCA25A (H)	0.09	0.2316336061760	0.1406350