Supplemental Materials

Force field parameters for naproxen

To parameterize naproxen we used standard CHARMM19 atom types. The charges were assigned consistent with the standard charges in the CHARMM19 force field and SASA implicit solvent model. Charges in the methoxy group were assigned using the parameterization of trimethoprim molecule [1]. The bond length and bond angle terms were autogenerated. The dihedral and improper angle potentials were transferred from structurally analogous amino acids Glu and Val (for carboxylate group in naproxen), Phe and Trp (for naphthalene ring), and Tyr (for methoxy group). Additional improper angle for C14 atom (Fig. 1c in the paper) was introduced as in branched side chain of Ile. The topology description of naproxen molecule in CHARMM19 force field is given below:

```
RESI NPXN    0.00000  ! naproxen

!             C7    C12    C14
!           //  \  /  \\    |
!          C8    C6    C11-C13-C15--O16
!          |     ||    |         |
!          C3    C5    C10     O17
!         / \\  /  \  //
!   C1--O2   C4    C9

GROUP
ATOM C1   CH3E    0.15
ATOM O2   OS     -0.30
ATOM C3   CR      0.15
GROUP
ATOM C4   CR1E    0.00
ATOM C5   CR      0.00
ATOM C6   CR      0.00
ATOM C7   CR1E    0.00
ATOM C8   CR1E    0.00
ATOM C9   CR1E    0.00
ATOM C10  CR1E    0.00
ATOM C11  CR      0.00
ATOM C12  CR1E    0.00
GROUP
ATOM C13  CH1E   -0.15
ATOM C14  CH3E    0.00
ATOM C15  C       1.35
ATOM O16  OC     -0.60
ATOM O17  OC     -0.60
```

```
BOND C1   O2        O2   C3        C3   C4        C4   C5        C5   C6
BOND C6   C7        C7   C8        C8   C3        C5   C9        C9   C10
BOND C10  C11       C11  C12       C12  C6        C11  C13       C13  C14
BOND C13  C15       C15  O16       C15  O17

DIHE C4   C3   O2   C1
DIHE C11  C13  C15  O17       C12  C11  C13  C15
DIHE C4   C5   C6   C12       C7   C6   C5   C9
DIHE C8   C6   C5   C10       C8   C5   C6   C11

IMPH C3   C4   C8   O2        C13  C15  C14  C11
IMPH C15  O16  O17  C13       C11  C10  C12  C13
IMPH C3   C4   C5   C6        C4   C5   C6   C7        C5   C6   C7   C8
IMPH C6   C7   C8   C3        C7   C8   C3   C4        C8   C3   C4   C5
IMPH C5   C9   C10  C11       C9   C10  C11  C12       C10  C11  C12  C6
IMPH C11  C12  C6   C5        C12  C6   C5   C9        C6   C5   C9   C10

IC  C1   O2   C3   C4     0.0000  000.00  180.00  000.00   0.0000
IC  O2   C4  *C3   C8     0.0000  000.00  180.00  000.00   0.0000
IC  C3   C4   C5   C6     0.0000  000.00    0.00  000.00   0.0000
IC  C4   C5   C6   C7     0.0000  000.00    0.00  000.00   0.0000
IC  C5   C6   C7   C8     0.0000  000.00    0.00  000.00   0.0000
IC  C10  C9   C5   C6     0.0000  000.00    0.00  000.00   0.0000
IC  C9   C5   C6   C12    0.0000  000.00    0.00  000.00   0.0000
IC  C5   C6   C12  C11    0.0000  000.00    0.00  000.00   0.0000
IC  C6   C4  *C5   C9     0.0000  000.00  180.00  000.00   0.0000
IC  C5   C7  *C6   C12    0.0000  000.00  180.00  000.00   0.0000
IC  C10  C12 *C11  C13    0.0000  000.00  180.00  000.00   0.0000
IC  C12  C11  C13  C15    0.0000  000.00    0.00  000.00   0.0000
IC  C11  C15 *C13  C14    0.0000  000.00 -120.00  000.00   0.0000
IC  C11  C13  C15  O16    0.0000  000.00    0.00  000.00   0.0000
IC  C13  O16 *C15  O17    0.0000  000.00  120.00  000.00   0.0000
```

The following parameters for bond, dihedral and improper angle potentials were added:

```
ANGLES
CR1E CR   CH1E    70.0     121.5
CR   CH1E C       70.0     112.5
CR   CH1E CH3E    70.0     106.5
CR   CR1E CR      90.0     119.0
CR   OS   CH3E    46.5     120.5
CR1E CR   OS      65.0     119.0

DIHE
CR1E CR   CH1E C        1.6       3       0.0
CR1E CR   OS   CH3E     1.8       2     180.0

IMPHI
CR   CR1E CR1E CH1E    90.0    0    0.0
CH1E C    CH3E CR      55.0    0   35.26439
CR   CR1E CR1E OS     150.0    0    0.0
```

The solvation parameters for ester OS atom were set equal to those of hydroxyl oxygen. The transferred intramolecular terms in CHARMM19 were checked by building the naproxen molecule by analogy in the all-atom CHARMM general force field [2]. The energy minimized structures in both force fields were very similar (RMSD ~ 0.35 Å).

Convergence of REMD simulations

The convergence of REMD sampling of Aβ-naproxen interactions was tested using the number N_s of the unique states (E_{eff} ,L_e) sampled at least once in the course of simulations. Each state (E_{eff},L_e) is defined by the effective energy of the simulation system, E_{eff}, which includes the potential and solvation energies, and by the number of ligands L_e bound to the fibril edge e=CX or CV (Fig. 1b). Fig. S1 shows N_s as a function of the cumulative equilibrium simulation time τ_{sim}. As τ_{sim} exceeds roughly 10 μs N_s levels off suggesting the onset of approximate convergence of REMD simulations. The convergence of Aβ-naproxen simulations is very similar to that observed in our previous simulations of binding ibuprofen molecules to Aβ fibril (ref. [35] in the paper).

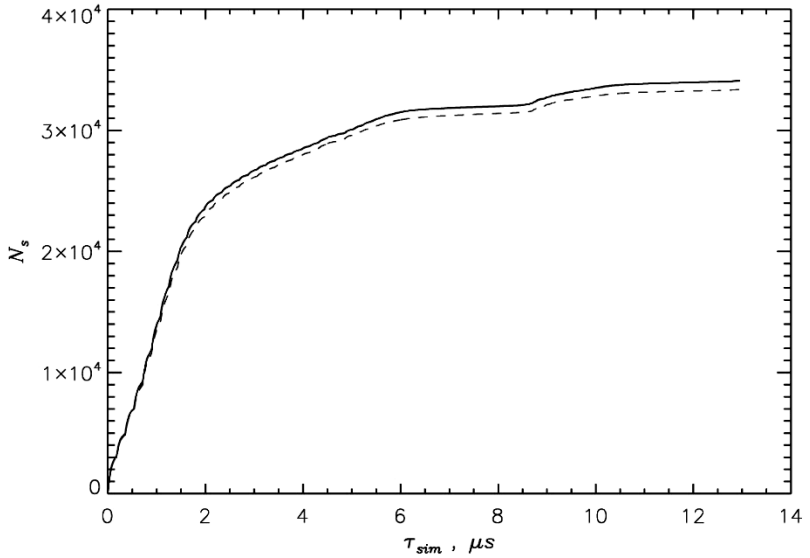

Fig. S1 The numbers of unique states N_s sampled in the course of REMD simulations as a function of cumulative equilibrium simulation time τ_{sim}. The solid and dashed lines correspond to N_s computed for the naproxen molecules bound to different edges of Aβ fibril.

To further test the reliability of REMD sampling we divided the simulation data into two equal subsets and analyzed them independently. The thermodynamic quantities from the two subsets related to naproxen interactions with Aβ fibril differed by no more than 8% from the averages computed using the entire dataset. The quantities related to naproxen-naproxen interactions have the errors not exceeding 10%. The convergence of Aβ-ibuprofen REMD simulations is reported in ref. [35] in the paper.

Testing force field parameterization of naproxen

Bednarek *et al* have performed the conformational analysis of naproxen using *ab initio* methods and NMR technique at 300K (ref. [52] in the paper). Among the quantities considered were the distributions of two dihedral angles ϕ and χ. These angles are defined by the atoms C12-C11-C13-C15 and C1-O2-C3-C4 in Fig. 1c. Theoretical analysis of naproxen revealed three peaks in the distribution of ϕ at ≈-116˚, ≈-43˚ and ≈126˚ with the populations of 0.11, 0.18, and 0.70. The distribution of χ dihedral angle has a single maximum at ≈-3˚ with the population of 0.8. The existence of three states in the distribution of ϕ dihedral angle was supported by NMR data. To test naproxen parameterization in CHARMM19 force field we computed the probability distributions $P(\phi)$ and $P(\chi)$ at 330K, i.e., at the lowest temperature at which conformational states were collected in REMD. Fig. S2 shows that $P(\phi)$ has three maxima, at ≈-175˚ and ≈-43˚, and ≈58°. The populations of these states are 0.06, 0.14, and 0.80, respectively. According to Fig. S2 the distribution $P(\chi)$ has two peaks of equal amplitude at ≈-180° and ≈-6°.

When compared against *ab initio* data CHARMM19 force field reproduces the number of peaks in $P(\phi)$ and approximately their location. Our parameterization of naproxen also correctly predicts the statistical weights of the three peaks. The largest discrepancy between our and *ab initio* results is the location of the dominant peak #3. The impact of this difference on ligand binding can be assessed using our previous simulations of ibuprofen binding to Aβ fibril (ref. [35] in the paper and unpublished data). Ibuprofen has chemically identical group G3 (Fig. 1c) with the equivalent dihedral angle ϕ formed by C3-C4-C7-C8. For ϕ we have tested two versions of dihedral angle potential, first with zero amplitude (which facilitates free rotation around ϕ) and the second identical to the one used in naproxen. These potentials result in sharply different distributions $P(\phi)$ at 330K. The first leads to the appearance of two peaks of equal height at ≈-120° and ≈60°. The second results in the distribution almost identical to that in Fig. S2. Interestingly, differences in the parameterizations have negligible impact on binding to Aβ fibril. For example, the numbers of ligands bound to the fibril CX and CV edges vary between the parameterizations by 4 and 1%, respectively. The difference in the free energy of binding is less than 1%. These findings suggest that the exact location of the maximum #3 in $P(\phi)$ should not significantly affect naproxen binding to Aβ fibril.

The peak #1in the distribution $P(\chi)$ computed from our simulations (Fig. S2) coincides with that obtained from *ab initio* calculations (ref. [52] in the paper). However, CHARMM19 simulations predict the existence of the second maximum of equal amplitude that is at variance with the *ab initio* data. It is worth noting that our energetics analysis (see Results) suggests that the group G2 plays minor role in naproxen binding compared to G1 or G3. Therefore, the specific form of the distribution $P(\chi)$ is not likely to be important for naproxen binding to Aβ fibril. A reasonable agreement between the conformational ensembles obtained from *ab initio* calculations and our simulations supports the CHARMM19 parameterization of naproxen.

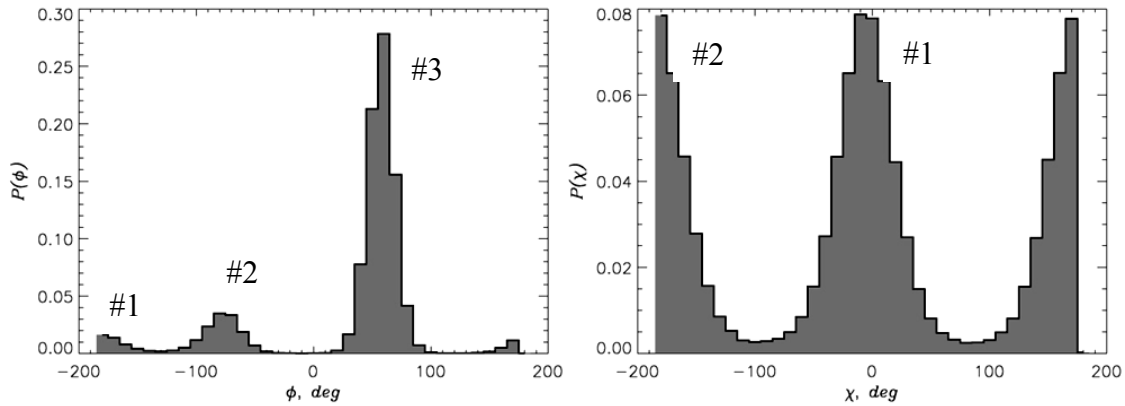

Fig. S2 Probability distributions, $P(\phi)$ and $P(\chi)$, of naproxen dihedral angles ϕ and χ (Fig. 1c) computed at 330K. $P(\phi)$ and $P(\chi)$ serve as tests of the naproxen parameterization. The distributions $P(\phi)$ and $P(\chi)$ are computed for all naproxen molecules irrespective of their binding state. We checked that binding has a minor impact on these distributions that allows us to directly compare them with the ab *initio* dihedral angle distributions computed for a single molecule.

Distribution of ibuprofen on the fibril edges

To compare binding of naproxen and ibuprofen we computed the distributions of bound ibuprofen molecules $<L(S_c)>$ at 360K (Fig. S3). In contrast to naproxen (Fig. 4b) ibuprofen tends to form small clusters upon binding to Aβ fibril. The numbers of ligands bound to the CV and CX edges are $<L_{CV}>\approx 13.5$ and $<L_{CX}>\approx 12.1$, of which 5.8 and 3.0 are included in large clusters. Therefore, the fractions of ibuprofen molecules forming large clusters are $\phi_{CV}=0.43$ and $\phi_{CX}=0.25$.

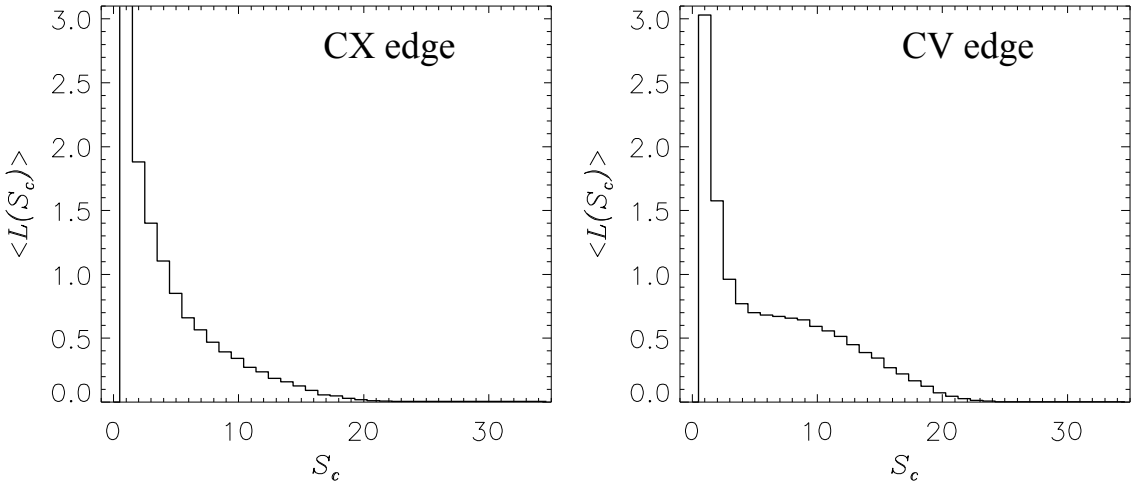

Fig. S3 Distributions of the numbers of bound ibuprofen ligands $<L(S_c)>$ with respect to cluster size S_c on the CX and CV edges.

Binding mechanism for modified naproxen

To provide direct test of the importance of interligand interactions for binding we performed simulations of modified naproxen. We used the same simulation system as described in Materials and Methods with the exception that all non-bonded interactions between naproxen molecules were switched off. This modification of energy function radically changes naproxen binding. The binding temperature is reduced from 398K to <330K and the difference in edge binding affinities is eliminated. Fig. S4 compares the numbers of ligands bound to the CV and CX edges, $<L_{CV}>$ and $<L_{CX}>$, for the original and modified naproxen ligands. It is seen that cancelation of non-bonded interligand interactions erases the difference between $<L_{CV}>$ and $<L_{CX}>$ in the entire temperature range. For example, at 360K $<L_{CV}>\approx 8.6$ and $<L_{CX}>\approx 8.5$. Furthermore, the cluster distributions $<L(S_c)>$ for the modified naproxen become unimodal, because the formation of large clusters is completely blocked ($\phi_{CV}=\phi_{CX}\approx 0$). These findings strengthen our conclusion that the interligand interactions are one of the two key factors controlling binding.

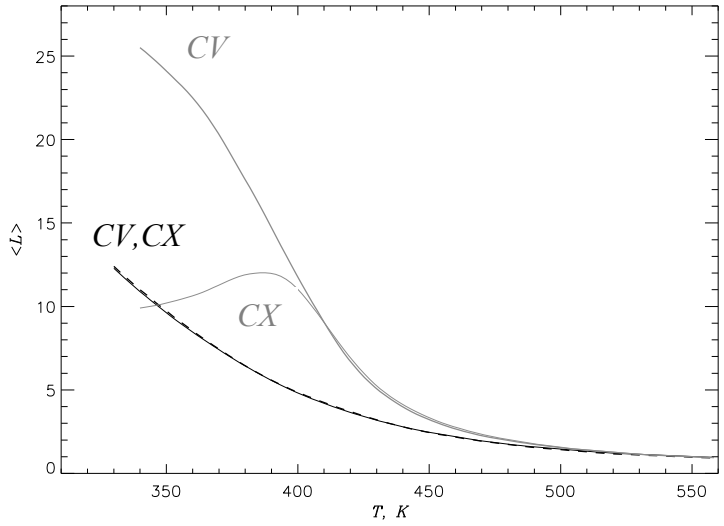

Fig. S4 The numbers of naproxen molecules $<L>$ bound to the CV and CX edges vs temperature. The data for the naproxen ligands, in which non-bonded interligand interactions are switched off, are shown in black: thin and dashed lines represent $<L>$ computed for the CV and CX. The data in grey represent the "original" naproxen simulations (as shown in Fig. 3a): thick and thin lines mark binding to the CV and CX edges. The plot suggests that cancelation of interligand interactions makes binding affinities of the edges equal.

Ordering of bound naproxen molecules

To check mutual ordering of naproxen ligands, which may occur upon binding to the fibril, we computed the probability distribution $P(\cos(\phi))$ of the angles ϕ formed by naphthalene rings. To this end, for each bound naproxen molecule we define a vector $\vec{n}$, which is the cross product of the vectors $\vec{r}_1 = \vec{R}(\text{C11})\text{-}\vec{R}(\text{C3})$ and $\vec{r}_2 = \vec{R}(\text{C10})\text{-}\vec{R}(\text{C8})$,

where $\vec{R}$ are the radius vectors of naproxen carbon atoms (Fig. 1c). Due to planarity of naphthalene ring $\vec{n}$ describes its orientation. The angle ϕ is then obtained from the scalar product of the vectors $\vec{n}_i$ and $\vec{n}_j$ computed for the bound naproxen molecules *i* and *j*, which are in contact with each other. The distribution *P(cos(ϕ))* is plotted in Fig. S5.

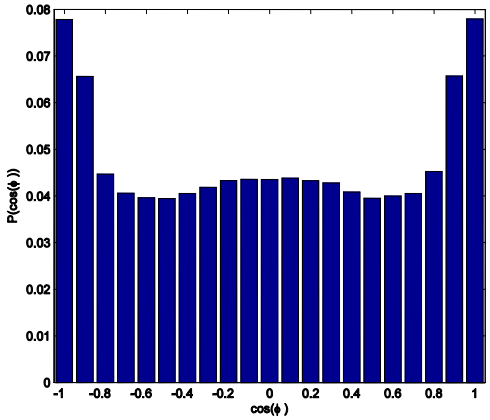

Fig. S5 Probability distribution *P(cos(ϕ))* of the angles ϕ for the pairs of interacting naproxen molecules bound to the fibril. The plot suggests that parallel alignment of naproxen molecules is preferred.

References

[1] Fleischman, S. H. and Brooks, C. L, 1990. Protein-Drug interactions: Characterization of inhibitor binding in complexes of DHFR with trimethoprim and related derivatives. *Proteins Struct. Funct. Bioinform*. **7**, 52-61.

[2] Vanommeslaeghe, K., Hatcher, E., Acharya, C., Kundu, S., Zhong, S., Shim, J., Darian, E., Guvench, O., Lopes, P., Vorobyov, I., MacKerell, A. D., Jr., 2010. CHARMM General Force Field (CGenFF): A force field for drug-like molecules compatible with the CHARMM all-atom additive biological force fields. *J. Comp. Chem.* **31**, 671-690.