Naphthoquinone-dopamine hybrid disrupts α-Synuclein fibril by their intramolecular snergistic interactions with the fibril and display a better effect on fibril disruption

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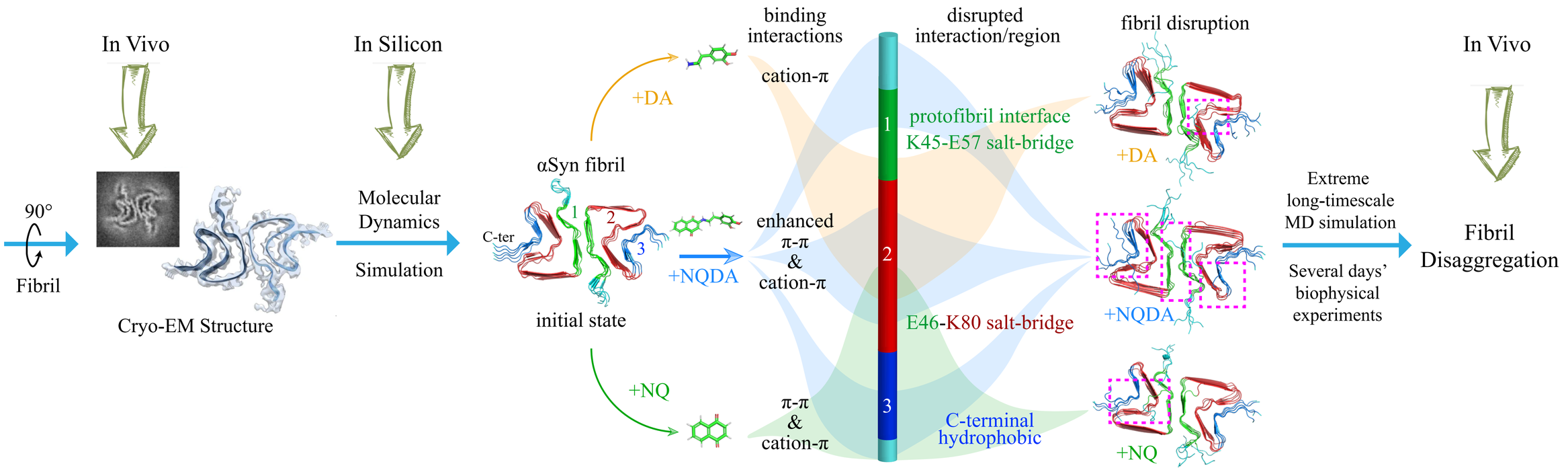
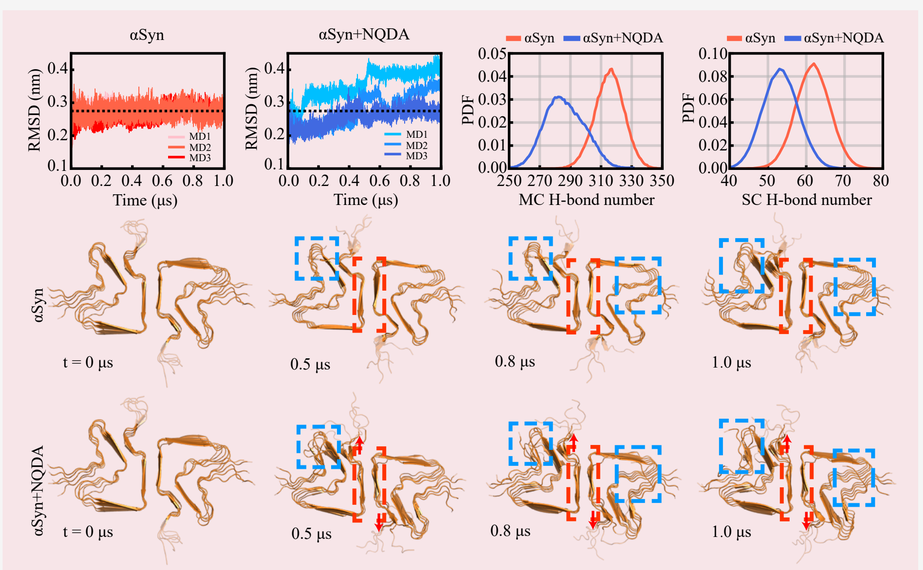
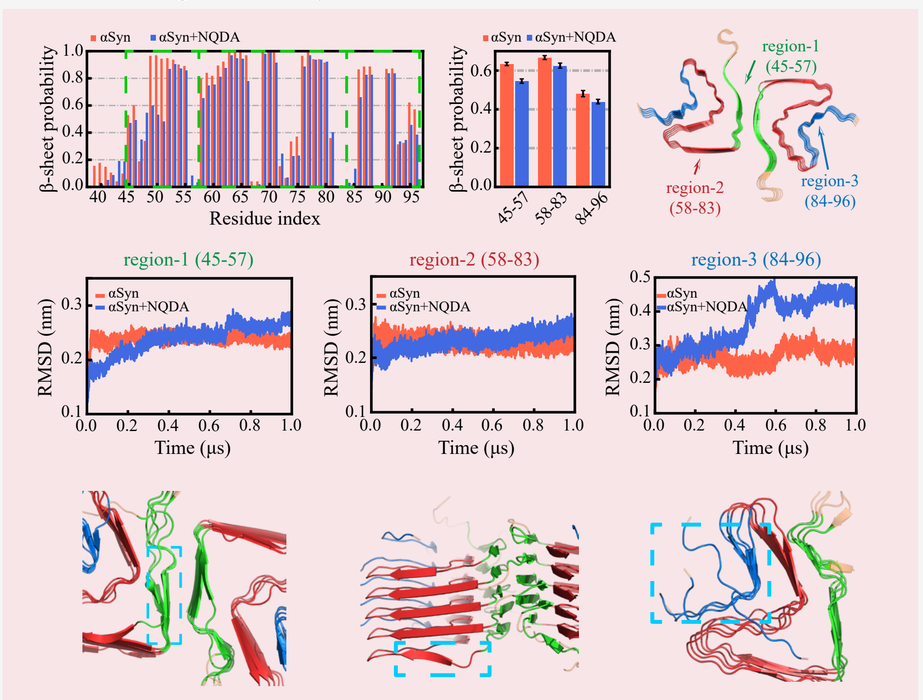


Results

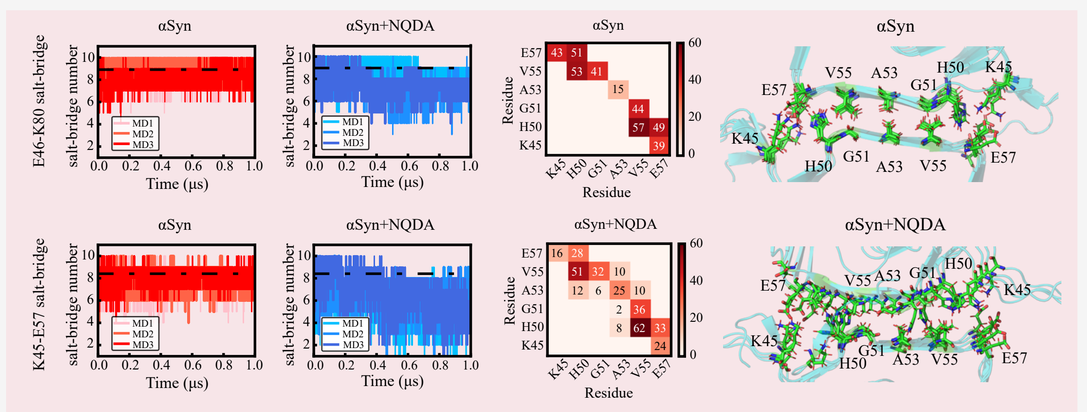
■ The influence of NQDA on the global structure of αSyn fibril.



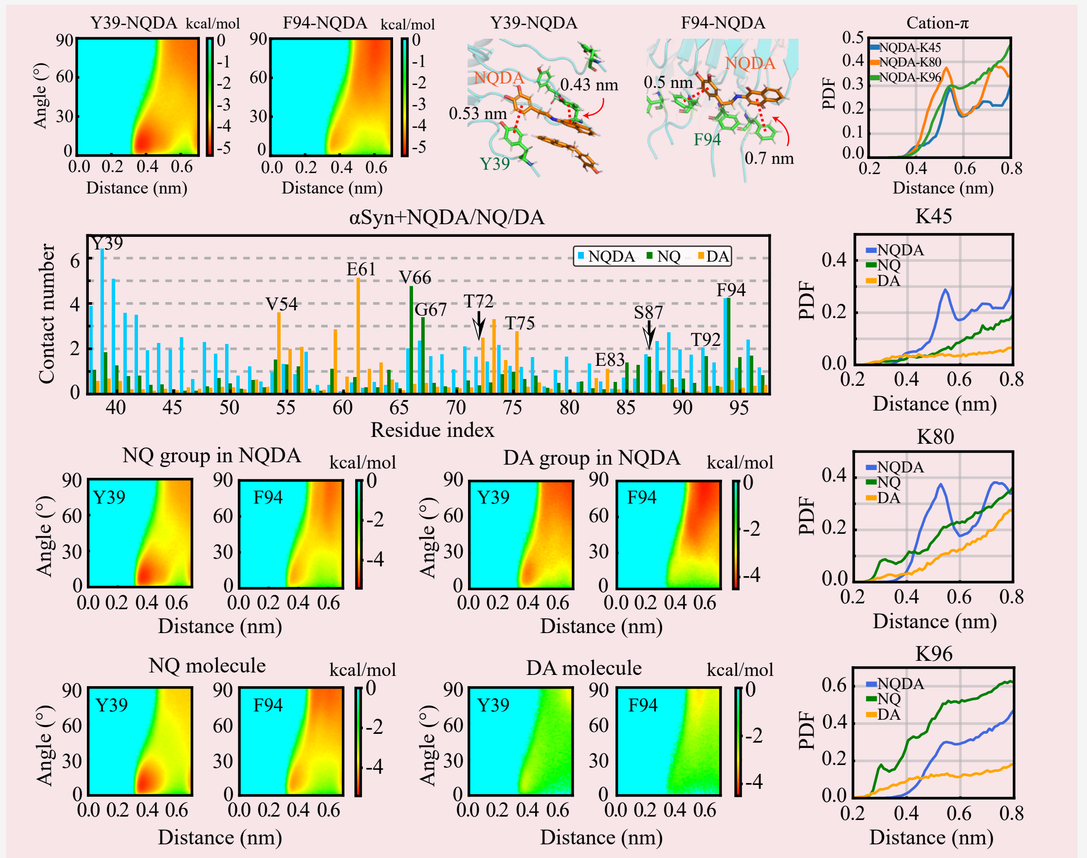
■ Disruptive effects of NQDA on the β-sheets and structures of three different regions of αSyn fibril.



■ Influences of NQDA on E46-K80 / K45-E57 salt-bridges and protofibril interface.



■ Analysis of binding interactions between NQDA and αSyn fibril and comparisons of the binding mechanisms of NQDA, NQ and DA molecules with αSyn fibril.



Conclusions

Our simulations show that NQDA hybrids can destroy the structure of αSyn fibril and NQDA exhibits a better performance than both NQ and DA molecules. NQDA has the ability to disrupt the protofibril interface and the β-sheet structures of αSyn fibril by forming cation-π, H-bonding, π-π stacking and hydrophobic interactions. By comparing the interaction modes between NQDA, NQ, or DA and αSyn fibril, we find that NQ has a preference to bind with residues in region-3, while DA mainly binds with residues in region-2. Intriguingly, NQDA can bind to both region-2 and region-3, as well as region-1. This synergistic interaction effect leads to a better fibril destabilization effect of NQDA than both NQ and DA molecules.

Materials and Methods

α-Synuclein PDB ID: 6CU7

Force Field: amber99sb-ildn Water Model: TIP3P

Systems: α-Syn, α-Syn+NQDA, α-Syn+NQ, α-Syn+DA

Method: molecular dynamics simulations at 310K and 1 bar

Simulation Number: three independent MD runs for each system

Simulation Time: 1000 ns for each MD runs

Packages: Gromacs-2018, python and PyMOL

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