

## Supporting Information

### Mechanisms of Melatonin Binding and Destabilizing Protofilament and Filament of Tau R3-R4 Domains Revealed by Molecular Dynamics Simulation

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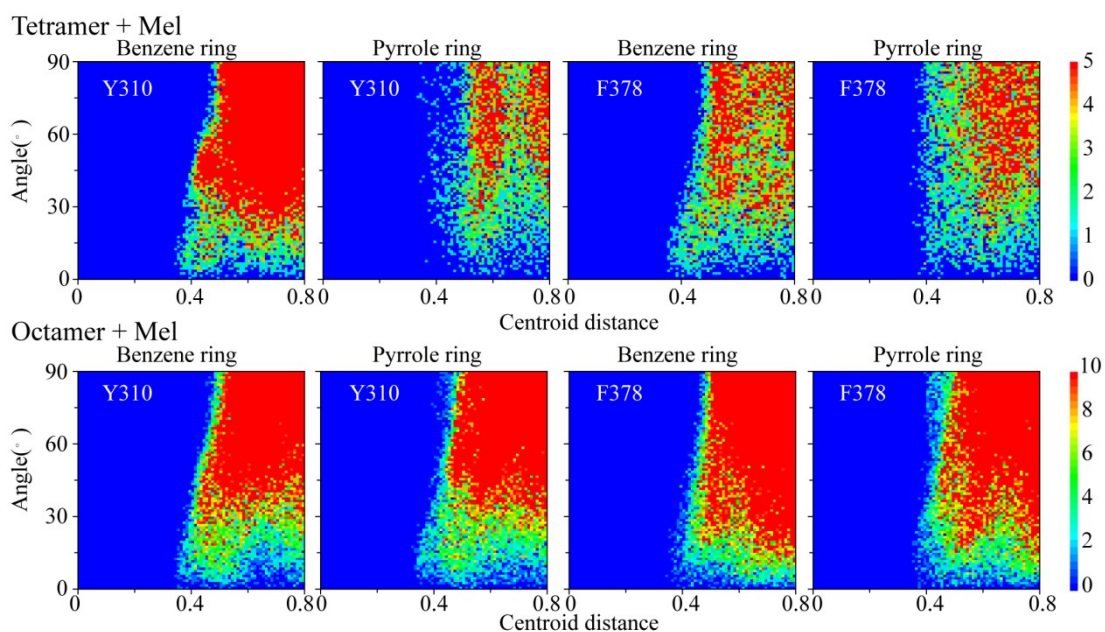
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The H-bond number with D-H-A angle set to 120 degrees is shown in Table S1. The weakening of the angle geometry criterion increases the number of H-bonds. Still, the numerical relationship of different systems remains unchanged, and the ratio of H-bond number between the systems using 120 or 150 degrees is very close.

The 2D frequency diagram as a function of centroid distance and dihedral of paired rings in  $\pi$ - $\pi$  stacking is shown in Fig. S1. It reveals that Y310 has a higher frequency to form  $\pi$ - $\pi$  stacking with benzene ring of Mel compared with pyrrole ring in Tetramer+Mel system, and has almost the same frequency to stack with benzene or pyrrole ring in Octamer+Mel system. As for F378, the frequency to form  $\pi$ - $\pi$  stacking with pyrrole ring are higher than benzene ring in both tetramer and octamer, especially for the ring pairs with a smaller centroid distance. The increase of dihedral angle will greatly reduce the strength of  $\pi$ - $\pi$  stacking interaction, and the strict distance constraint in the main text already implies the restricted orientation range of the stacking ring pairs.

**Table S1** The comparison of H-bond numbers with different D-H-A angles

| System       | D-H-A angle | MC-MC | SC-SC | Tau-Mel |
|--------------|-------------|-------|-------|---------|
| Tetramer     | 120°        | 226.8 | 68.7  |         |
|              | 150°        | 144.2 | 49.4  |         |
| Tetramer+Mel | 120°        | 225.7 | 71.4  | 55.9    |
|              | 150°        | 147.5 | 52.0  | 43.2    |
| Octamer      | 120°        | 450.2 | 149.9 |         |
|              | 150°        | 286.5 | 111.6 |         |
| Octamer+Mel  | 120°        | 449.7 | 150.5 | 90.3    |
|              | 150°        | 296.4 | 111.9 | 68.8    |

**Fig. S1** 2D frequency diagram as a function of centroid distance and dihedral of paired rings in  $\pi$ - $\pi$  stacking.