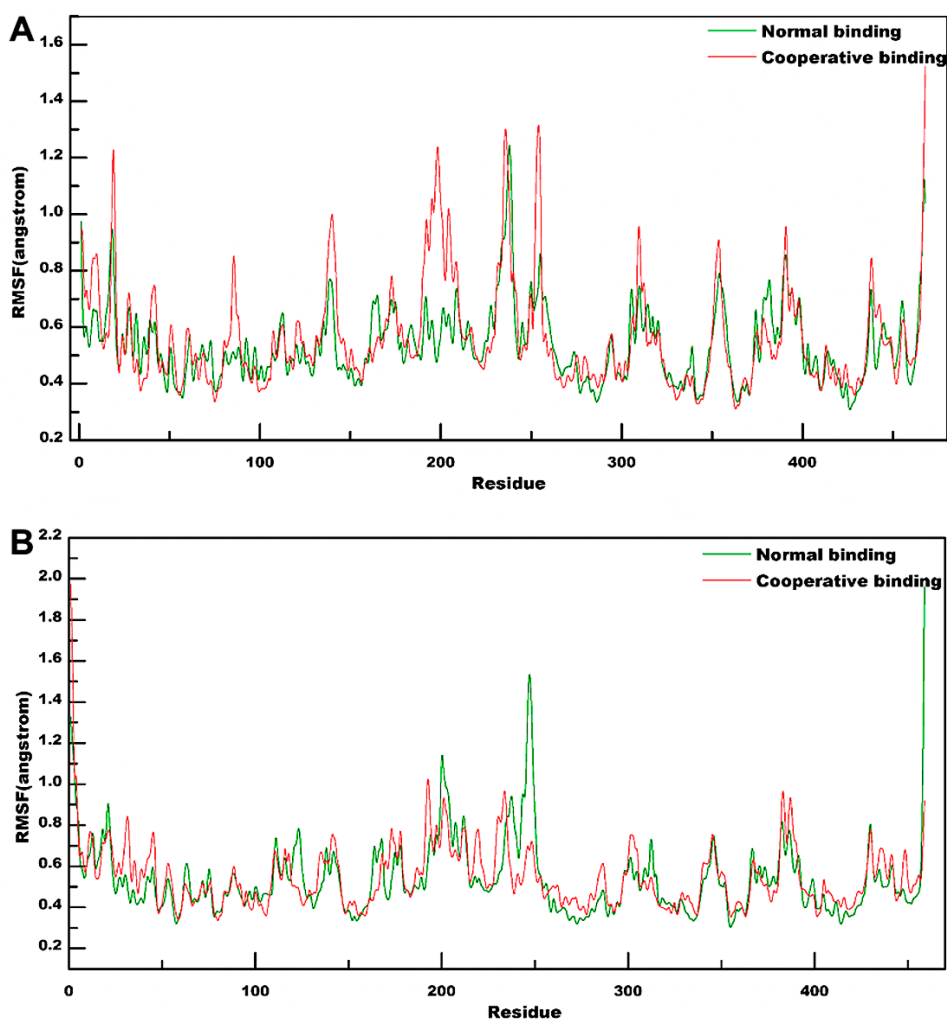


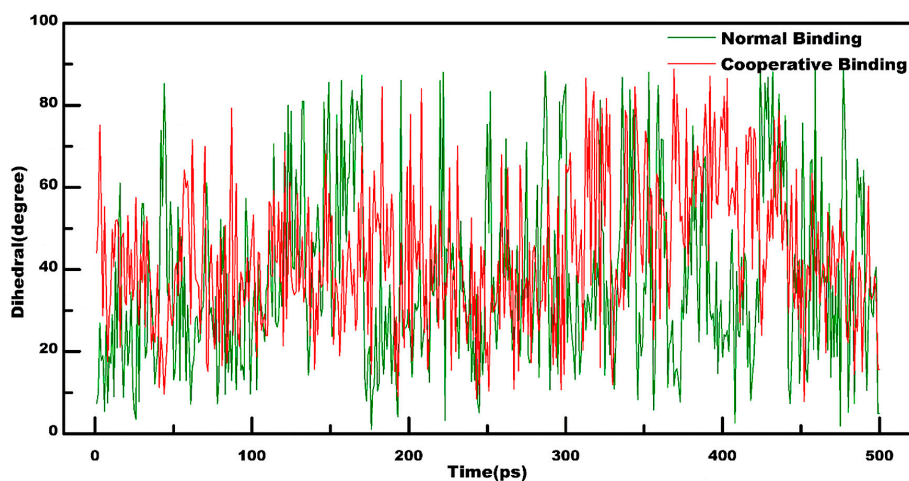
## Supplementary Materials

**Table S1.** The detailed information for the computational models involved in the current study. The crystal structures 1tqn.pdb and 1w0f.pdb were used to construct the normal (Model 1 and Model 3) and cooperative (Model 2 and Model 4) binding models.

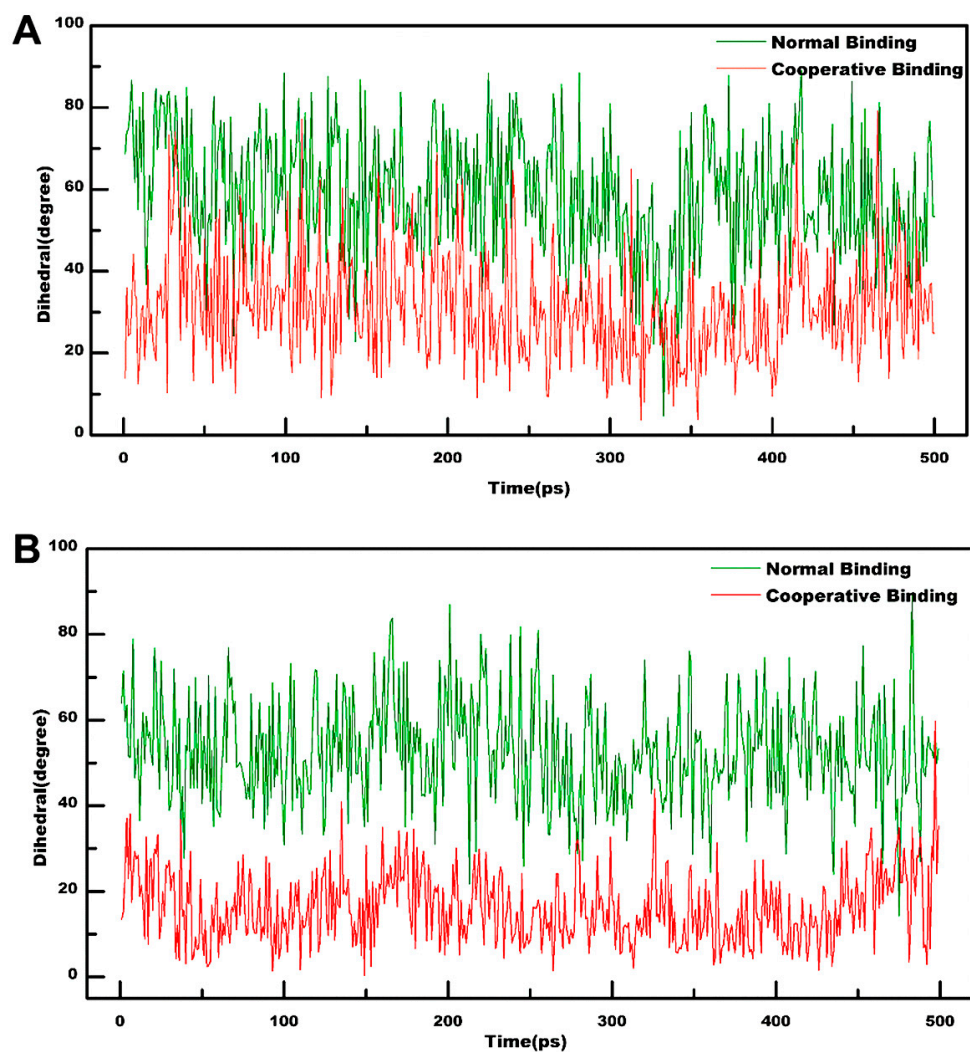
| Model | Protein Structure | Heme | 1st KLN | 2nd KLN | No. of Waters |
|-------|-------------------|------|---------|---------|---------------|
| 1     | 1tqn.pdb          | +    | +       | —       | 6421          |
| 2     | 1w0f.pdb          | +    | +       | —       | 5976          |
| 3     | 1tqn.pdb          | +    | —       | +       | 6403          |
| 4     | 1w0f.pdb          | +    | —       | +       | 5987          |



**Figure S1.** RMS fluctuations for protein backbone structure of (A) CYP3A4t structure and (B) CYP3A4w structure.



**Figure S2.** Dihedral angles between the phenyl rings of the first KLN and Phe215 for both normal and cooperative binding models in CYP3A4t structure.



**Figure S3.** Dihedral angles between Phe304 and dioxolan moiety of the first KLN in (A) CYP3A4t structure and (B) CYP3A4w structure.