Supporting Information

Binding selectivity of inhibitors toward the first over the second bromodomain of BRD4: theoretical insights from free energy calculations and multiple short molecular dynamics simulations

Yan Wang[a], Shiliang Wu[a], Lifei Wang[a*], Zhiyong Yang[b*], Juan Zhao[a] , and Lulu Zhang[a]

[a]School of Science, Shandong Jiaotong University, Jinan, China

[b]Department of Physics, Jiangxi Agricultural University, Nanchang, China

Corresponding Authors

*E-mail: wanglf@sdjtu.edu.cn (L.W.).

*E-mail: zhiyongyang2009@163.com (Z.Y.)

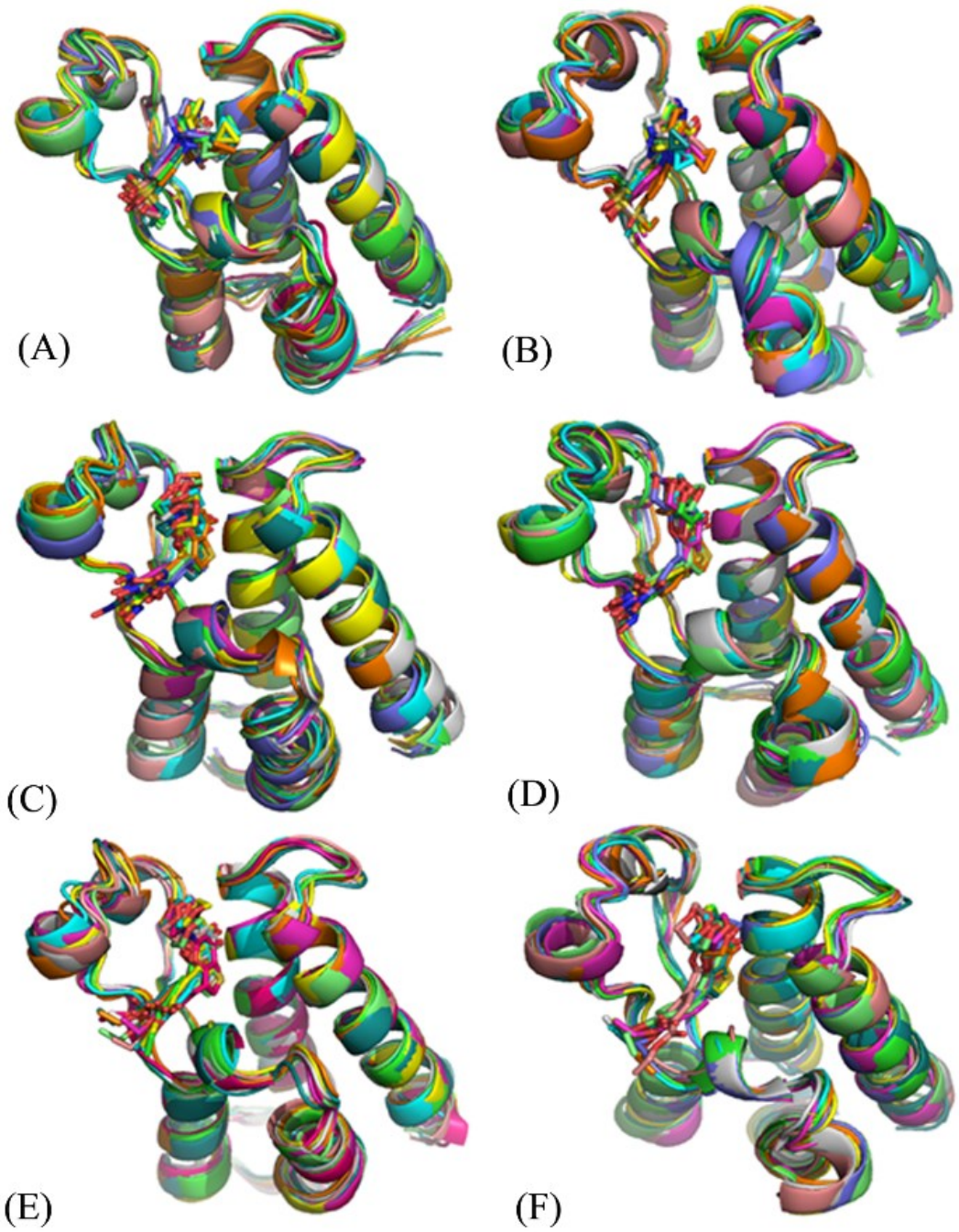

Figure S1. Superimpositions of ten initial conformations extracted from the first 100-ns MD simulations: (A) the 8NS-BD1 complex, (B) the 8NS-BD2 complex, (C) the 82Y-BD1 complex, (D) the 82Y-BD2 complex, (E) the 837-BD1 complex, (F) the 837-BD2 complex.

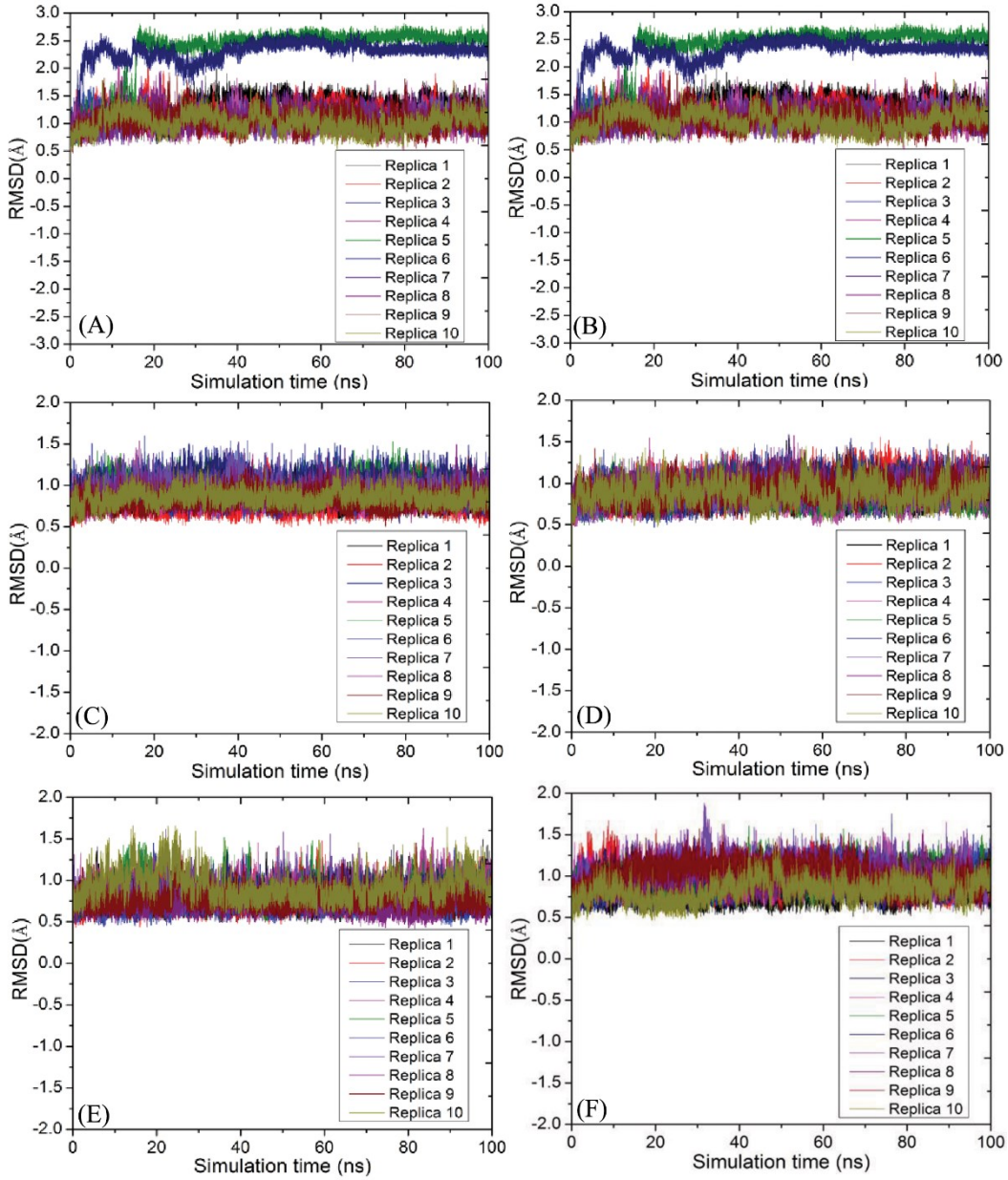

Figure S2. Root-mean-square deviations (RMSDs) of backbone atoms in six systems calculated by using MSMD trajectories of ten replicas: (A) the 8NS-BD1 complex, (B) the 8NS-BD2 complex, (C) the 82Y-BD1 complex, (D) the 82Y-BD2 complex, (E) the 837-BD1 complex, (F) the 837-BD2 complex.

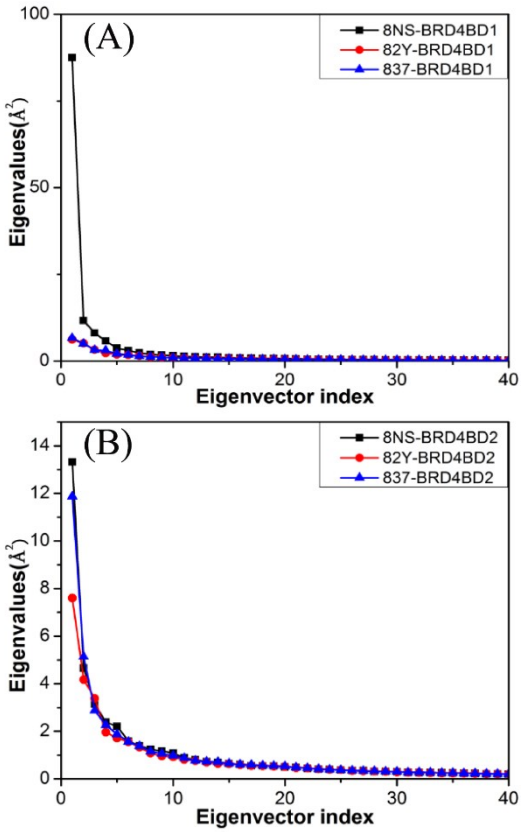

Figure S3. The function of eigenvalues versus eigenvector index stemming from PC analysis on the single joined MSMD trajectory: (A) BD1 and (B) BD2 complexed with three inhibitors 8NS, 82Y, and 837.

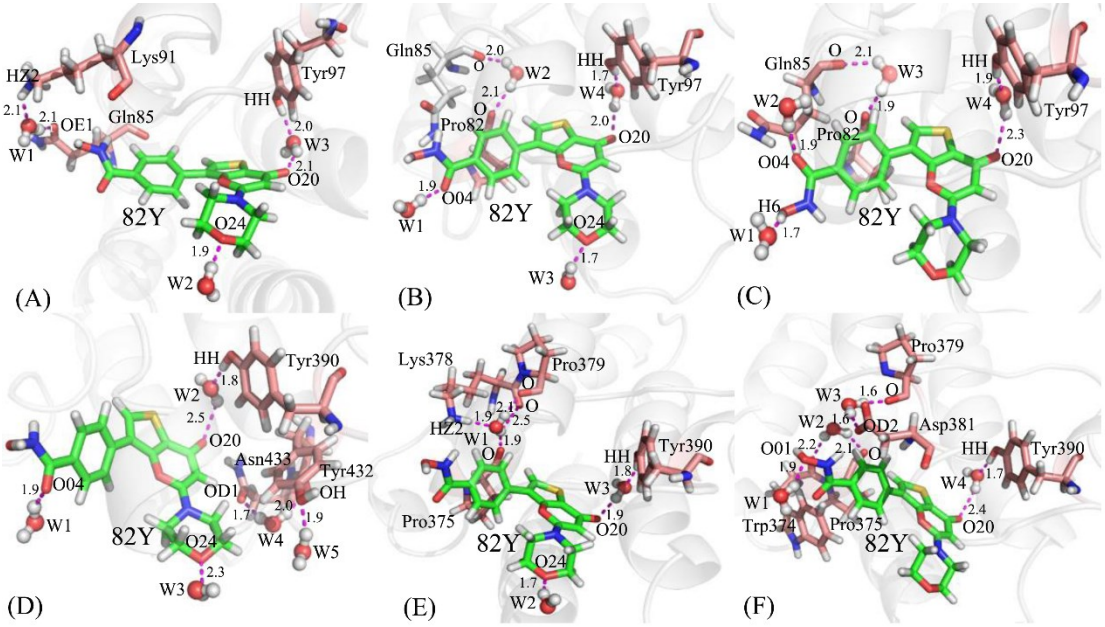

Figure S4. Snapshots of hydrogen bonds formed between important waters and inhibitor 82Y and residues of BD1 or BD2 at different times: (A) the 82Y-BD1 complex at 200 ns, (B) the 82Y-BD1 complex at 300 ns, (C) the 82Y-BD1 complex at 500 ns, (D) the 82Y-BD2 complex at 200 ns, (E) the 82Y-BD2 complex at 300 ns, (F) the 82Y-BD2 complex at 500 ns. Inhibitor 82Y and residues are shown in stick representation, and waters are displayed with the sphere mode.

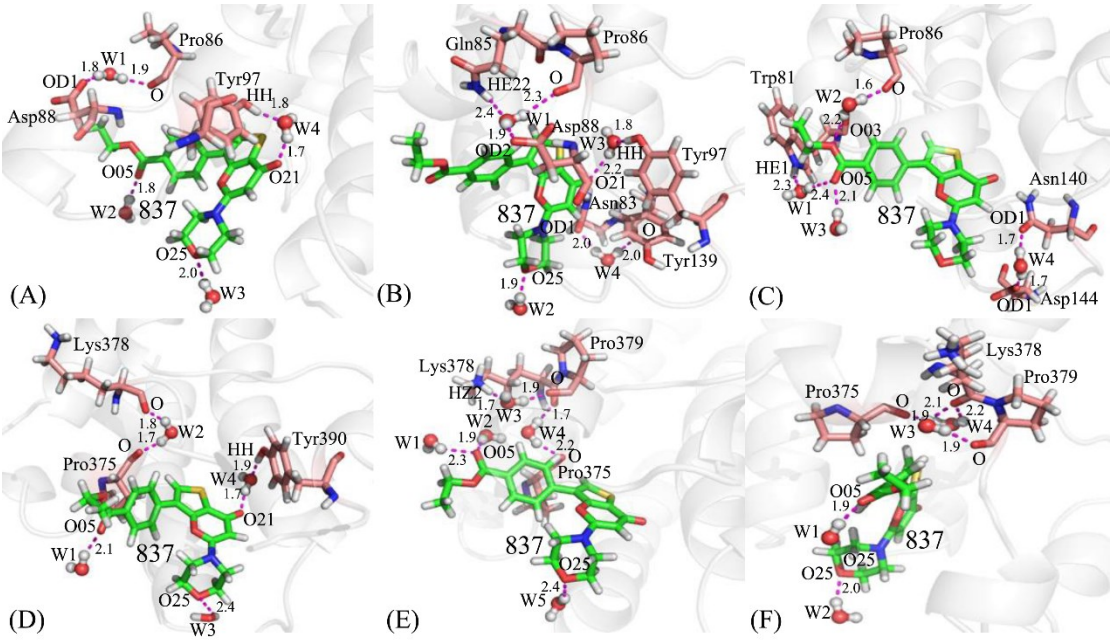

Figure S5. Snapshots of hydrogen bonds formed between important waters and inhibitor 837 and residues of BD1 or BD2 at different times: (A) the 837-BD1 complex at 200 ns, (B) the 837-BD1 complex at 300 ns, (C) the 837-BD1 complex at 500 ns, (D) the 837-BD2 complex at 200 ns, (E) the 837-BD2 complex at 300 ns, (F) the 837-BD2 complex at 500 ns. Inhibitor 82Y and residues are shown in stick representation, and waters are displayed with the sphere mode.