Supporting Information

A molecular dynamics investigation of CDK8/CycC and ligand binding: conformational flexibility and implication in drug discovery

Timothy Cholko[#], Wei Chen[#], Zhiye Tang[#], and Chia-en A. Chang*

Department of Chemistry, University of California, Riverside, Riverside, CA 92521

*Corresponding author: Chia-en Chang

Telephone: (951) 827-7263

Email: chiaenc@ucr.edu

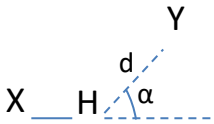

Figure S1. Definition of hydrogen bonds. X and Y stand for the donor and the acceptor respectively. d is the distance between the acceptor Y and the hydrogen, and α is the complimentary angle of X-H Y. A hydrogen bond is formed if d is smaller than 2.5 Å and α is smaller than 30º in this study.

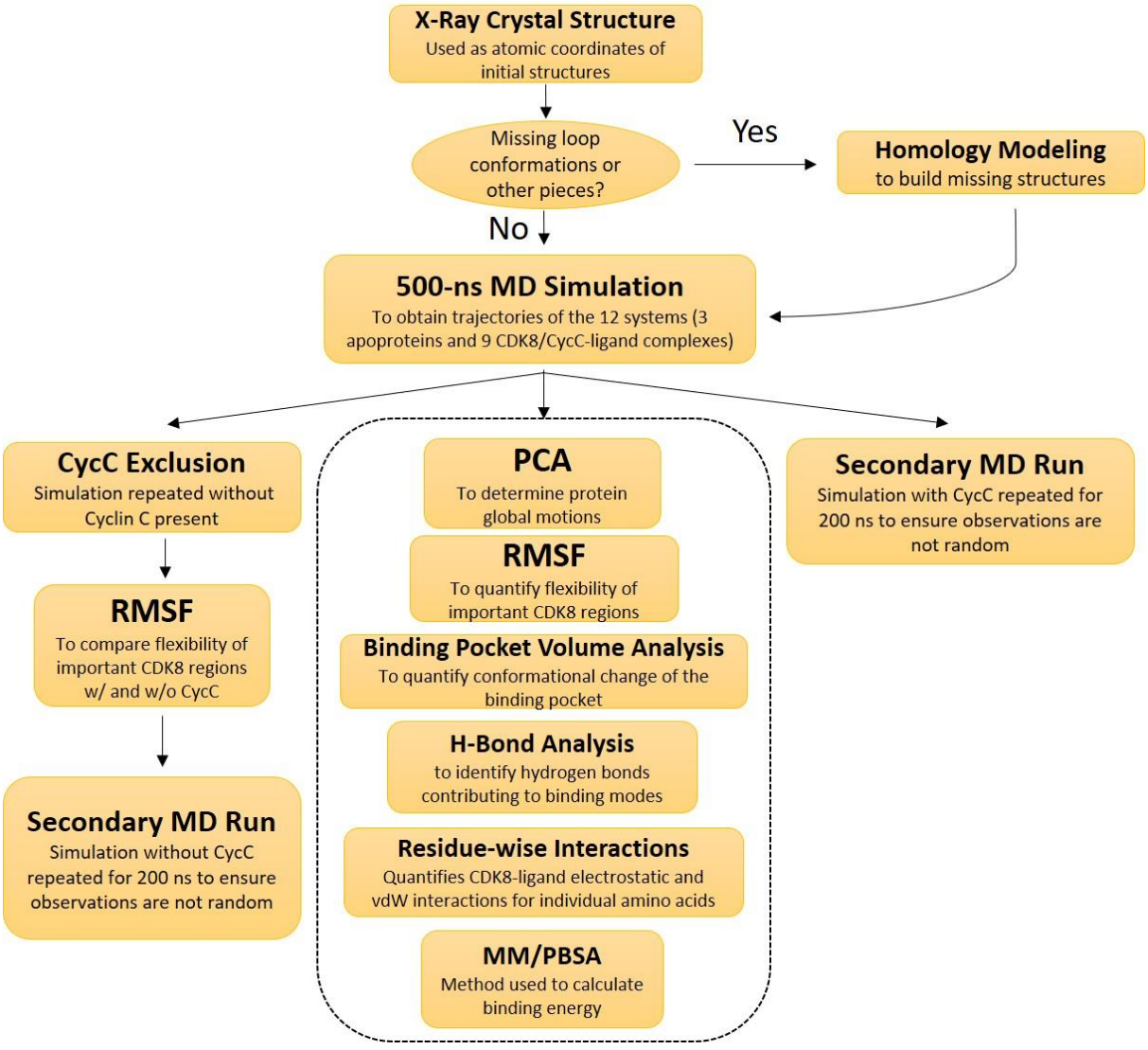

Figure S2. A flow chart showing the entire process from simulation set-up to post-production analysis

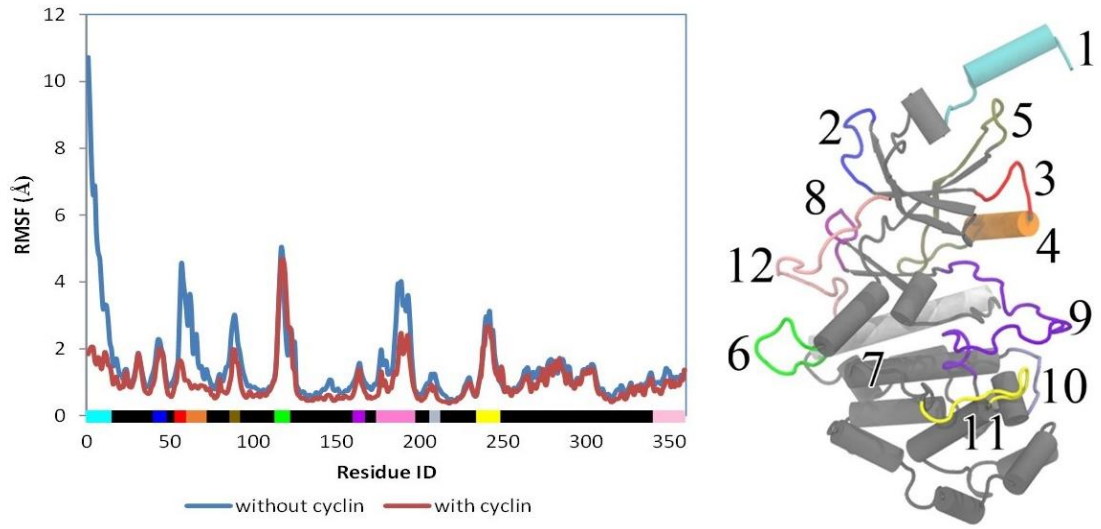

Figure S3. Comparison of RMSF of the complex of CDK8 and 50R with and without CycC. Color bar on x-axis corresponds to the colored regions on the image of CDK8 to the right.

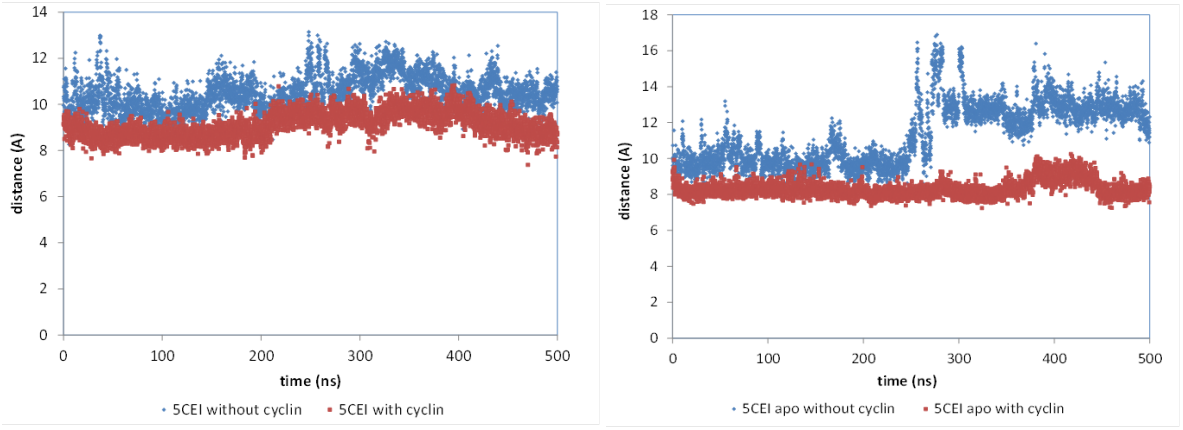

Figure S4. DMG-αC-helix distance changes throughout the trajectory with and without CycC in the CDK8-ligand complex (left) and apoprotein (right).

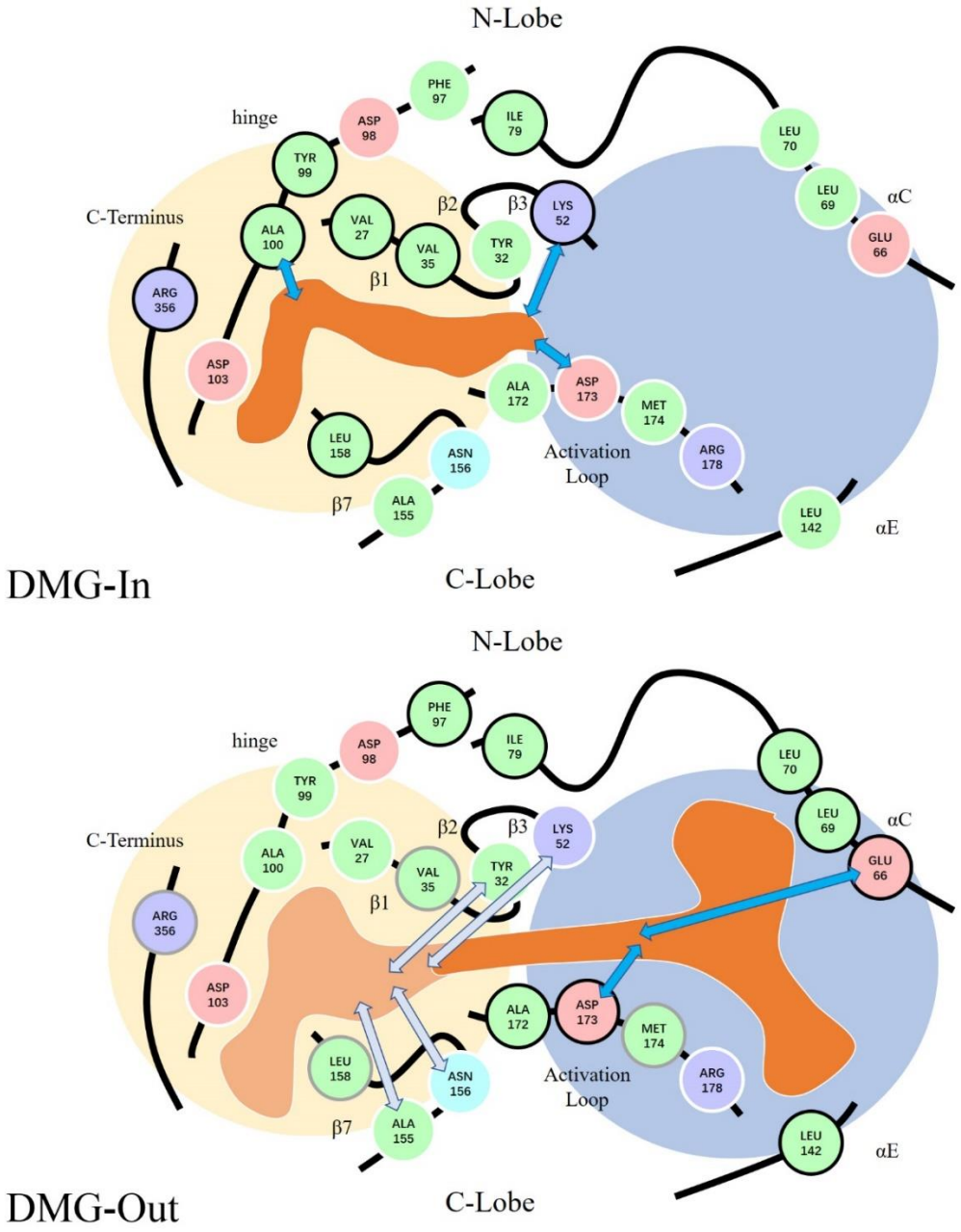

Figure S5. Illustration of ligand binding modes in DMG-in and DMG-out conformations. The regions of CDK8 are indicated by black lines, and labeled correspondingly. Important residues are shown by spheres, where non-polar residues are in green, polar and neutral residues are in cyan, positive charged residues are in blue and negatively charged residues are in red. Residues with interactions stronger than -1 kcal/mol with DMG-in/DMG-out ligands are black-bordered. Residues with interaction stronger than -1 kcal/mol with SKR1 are gray bordered. Other residues are white-bordered. Important hydrogen bonds between residues and ligands are indicated by deep cyan arrows, while hydrogen bonds with type II ligands are indicated by light cyan arrows. Ligand binding modes are shown by orange areas, and light orange area indicates additional binding area by SKR1. The two big circles indicate the ATP binding site (light orange) and the allosteric binding site (light blue).

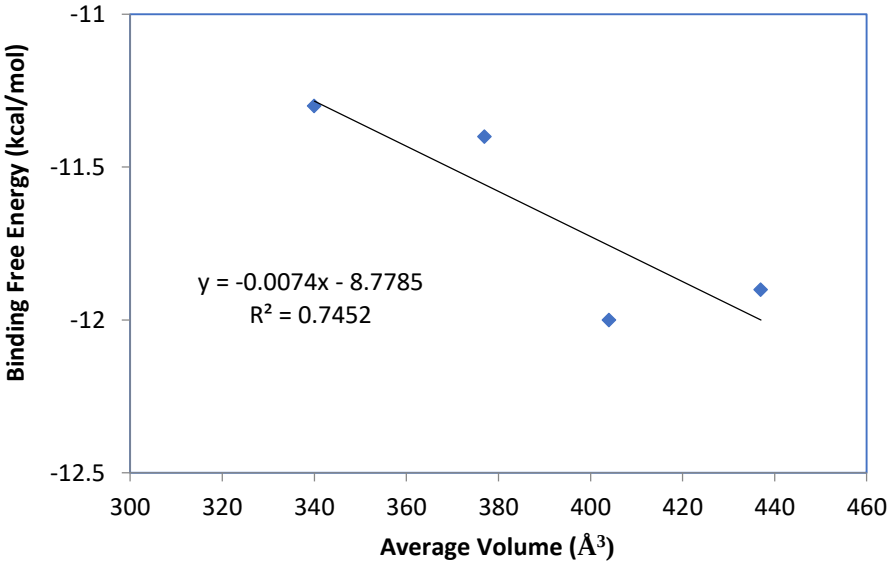

Figure S6. Relationship between the average volume of the ATP binding site and the experimental binding free energies for type-I ligands.

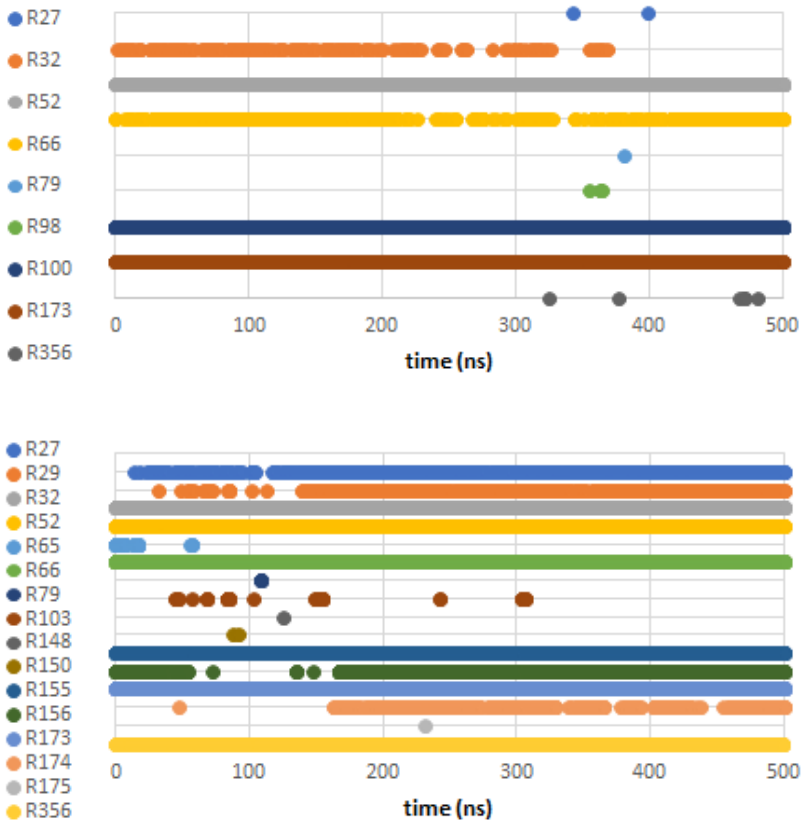

Figure S7. Breaking and reforming of hydrogen bonds between residues and ligands are observed throughout the trajectories. A colored dot means an H-bond is present with that residue at a given time. “R27” stands for residue 27, and so on. Top: type-I ligand 50R; Bottom: type-II ligand SKR1.