Electronic Supplementary Material (ESI) for Molecular BioSystems.
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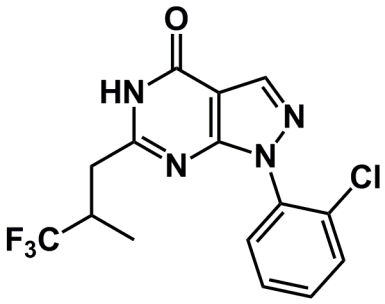
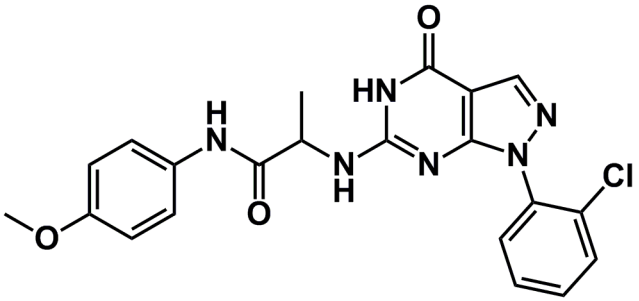
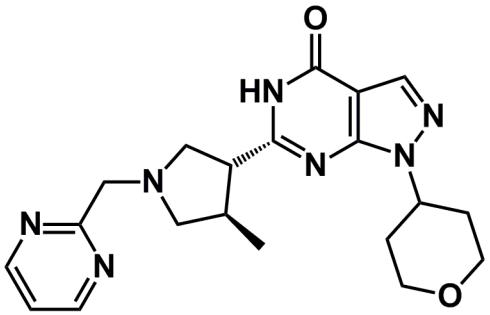


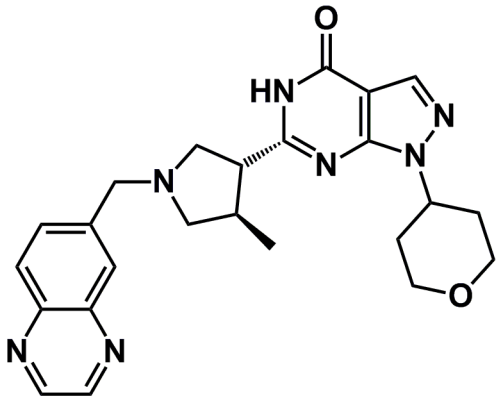
BAY73-6691



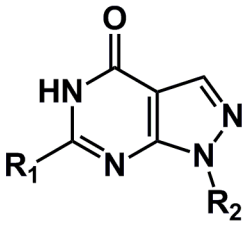
28s



PF-04447943



PF4181366



pyrazolopyrimidinone scaffold

Figure S1. Figure S1.Chemical structures of classical PDE9 inhibitors (**BAY73-6691**,[13] **28s**,[28] **PF-04447943**,[26] and **PF-4181366**[27]) with a same scaffold of pyrazolopyrimidinone. Their scaffolds are shown in the bottom.

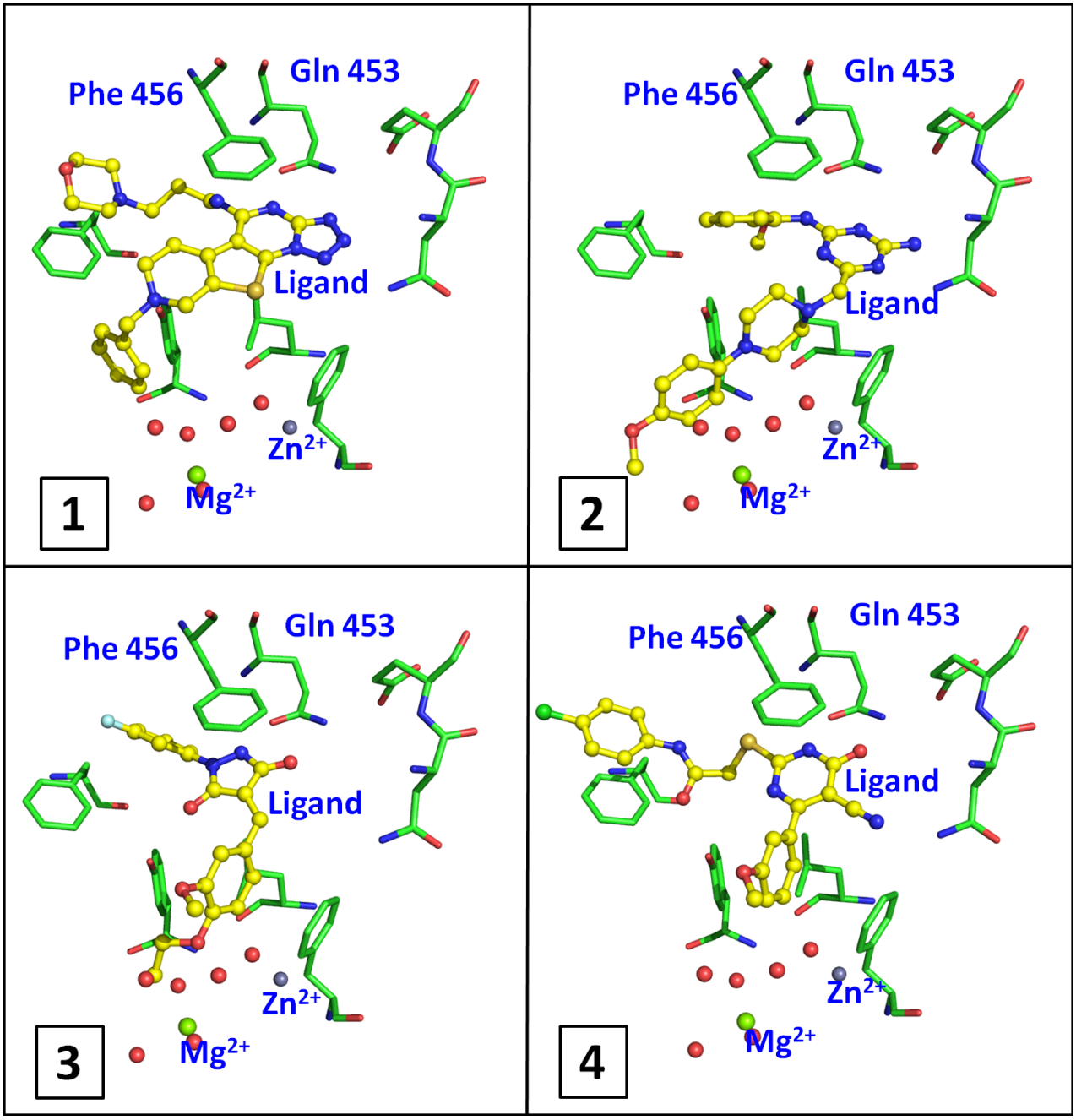


Figure S2. Compounds with "appropriate" binding modes with PDE9. Phe 456 and Gln 453 are the two most important residues in PDE9. In the present study, only molecules interacting with the two residues were retained as potent PDE9 inhibitors.

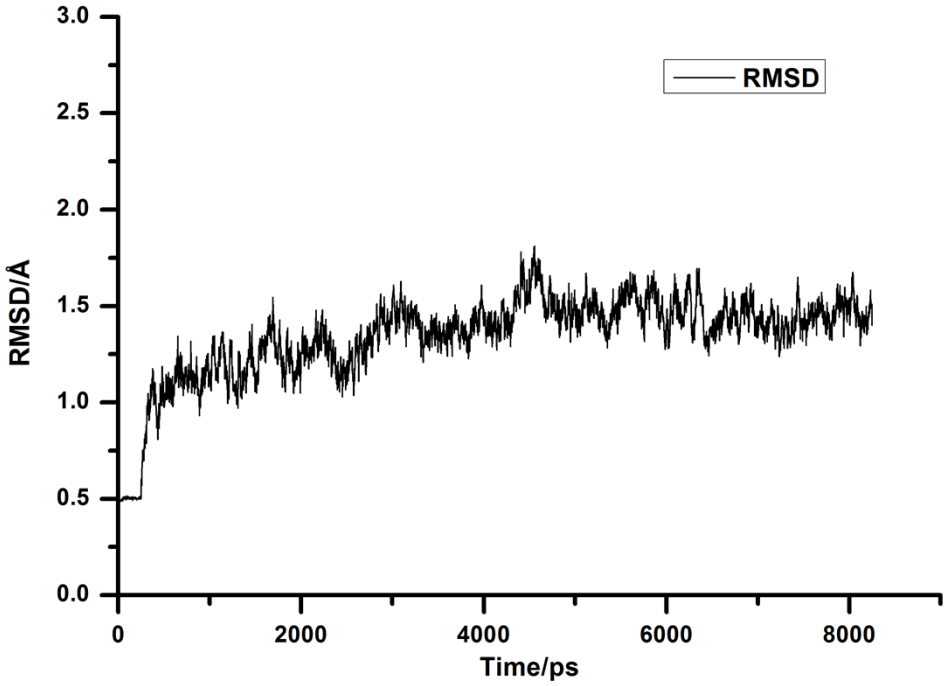


Figure S3. The RMSD curve of the PDE9A crystal structure (PDB ID: 4GH6) which was used in our MD- augmented virtual screening.

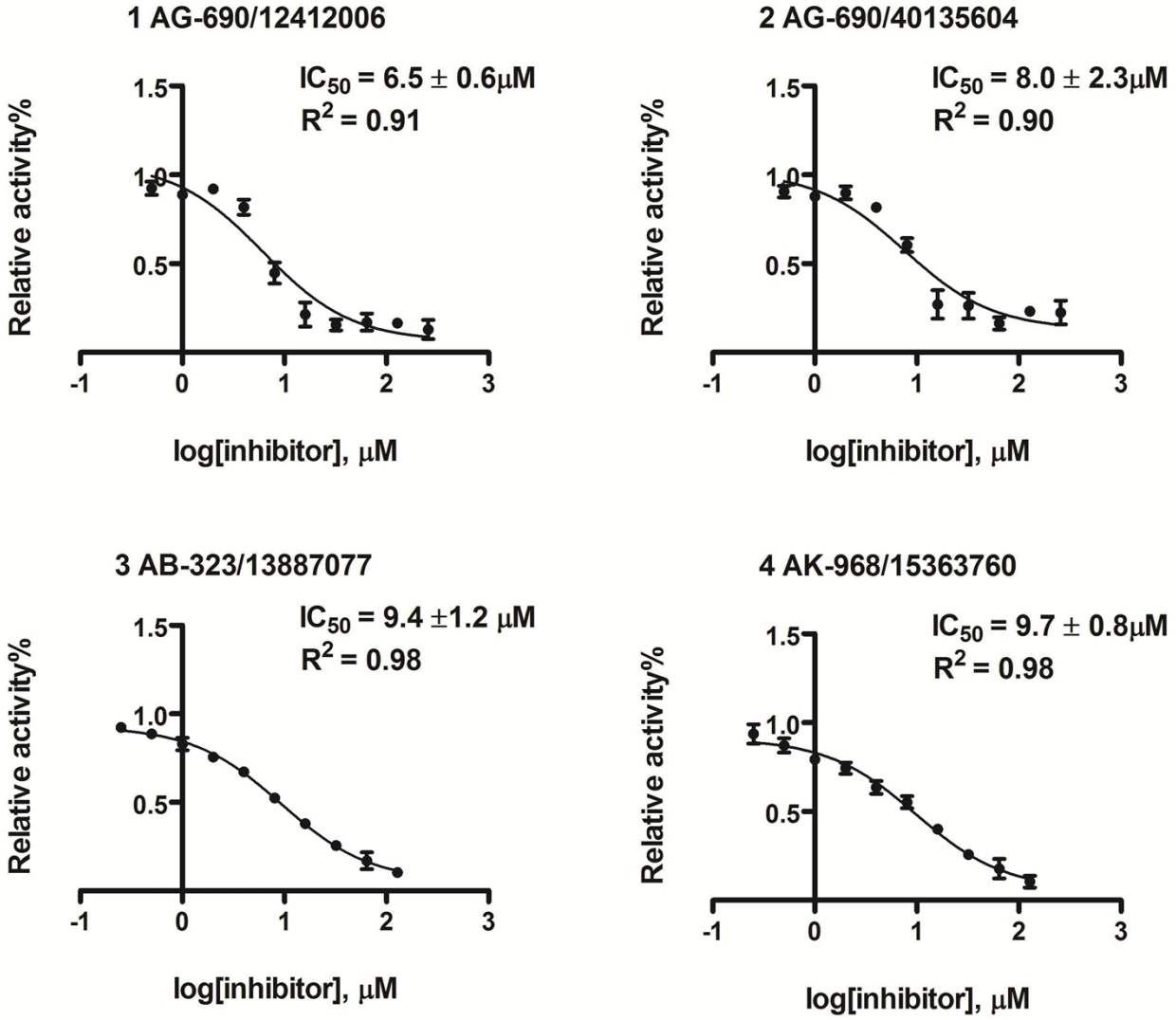


Figure S4. Inhibitory curves of the four most potent compounds towards PDE9A.

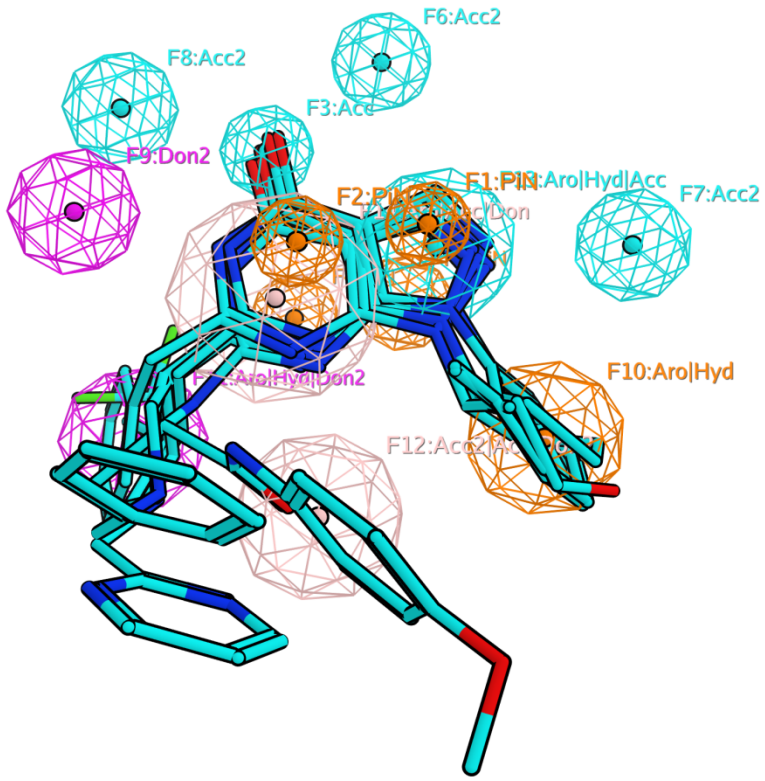


Figure S5. The pharmacophore model generated automatically by MOE 2008.10. Due to the similarity between the ligands in the training set, there are a lot of common features shared by all the ligands, resulting in a pharmacophore model with 14 features. It is an over-fitting model, thus can't be used for the purpose of screening.