

Supporting Information

Identification of Selective and Cell Active Inhibitors of Protein Arginine Methyltransferase 5 (PRMT5) through Structure-Based Virtual Screening and Biological Assays

Fei Ye,^{†,*} Weiyao Zhang,[†] Xiaoqing Ye,[†] Jia Jin,[†] Zhengbing Lv,[†] Cheng Luo^{‡,*}

[†]College of Life Sciences, Zhejiang Sci-Tech University, Hangzhou 310018, China

[‡]Drug Discovery and Design Center, State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy, Shanghai 201203, China

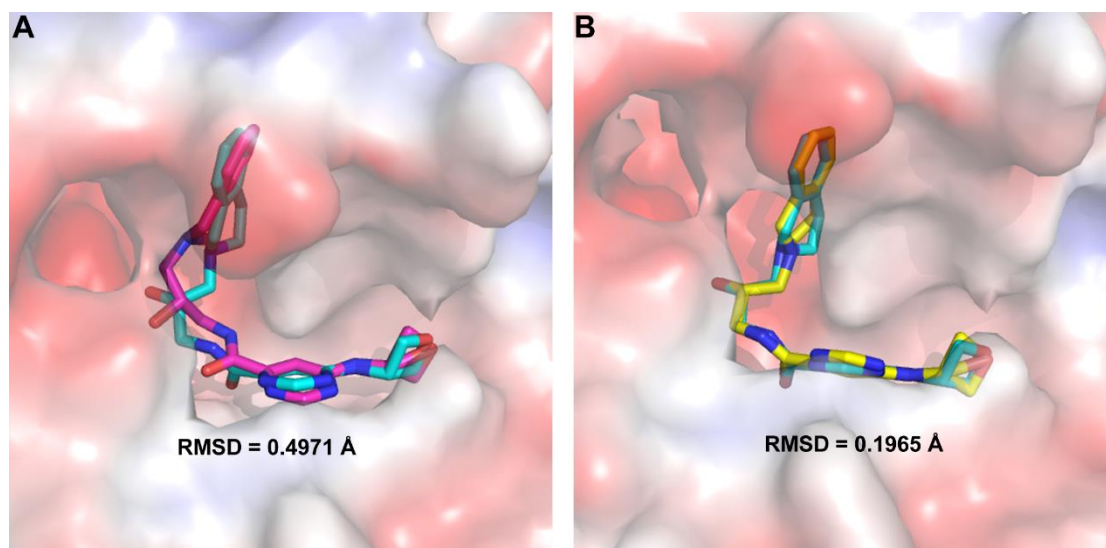


Figure S1. The re-docking validation results of compound EPZ015666. (A) Glide SP mode can reproduce the bioactive conformation of EPZ015666 with the RMSD value of 0.4971 Å. The original EPZ015666 structure extracted from the X-ray crystal structure of PRMT5 PDB ID 4X61)¹ is depicted as cyan sticks, and the re-docked result is depicted as magenta sticks. (B) Glide XP mode can reproduce the bioactive binding conformation of EPZ015666 with the RMSD value of 0.1965 Å. The re-docked EPZ015666 is shown as yellow sticks.

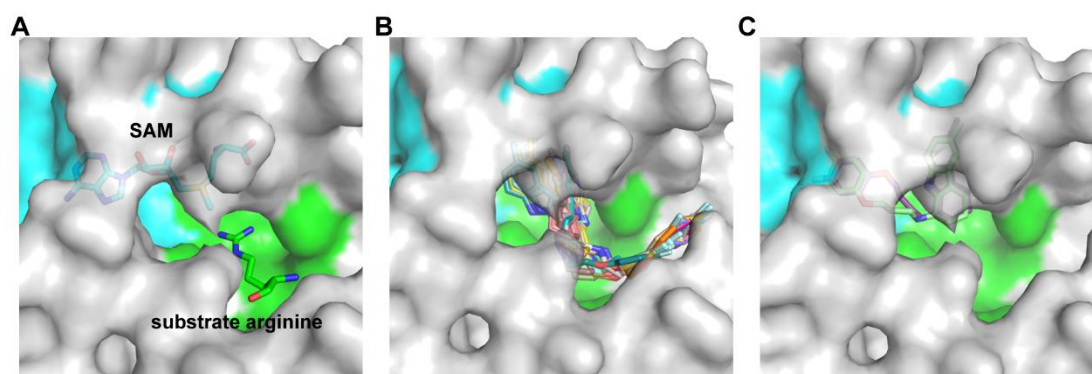


Figure S2. Docking poses of DC_Y134 binding to PRMT5. (A) Surface representative cofactor and substrate binding at active pocket in PRMT5 crystal structure (PDB code 4GQB).² The SAM-binding region is colored in cyan, and the binding site of substrate arginine is colored in green. (B) 18 of top 20 blind docking poses are located at the binding site of substrate arginine. (C) 2 of top 20 blind docking poses are located at the SAM-binding region.

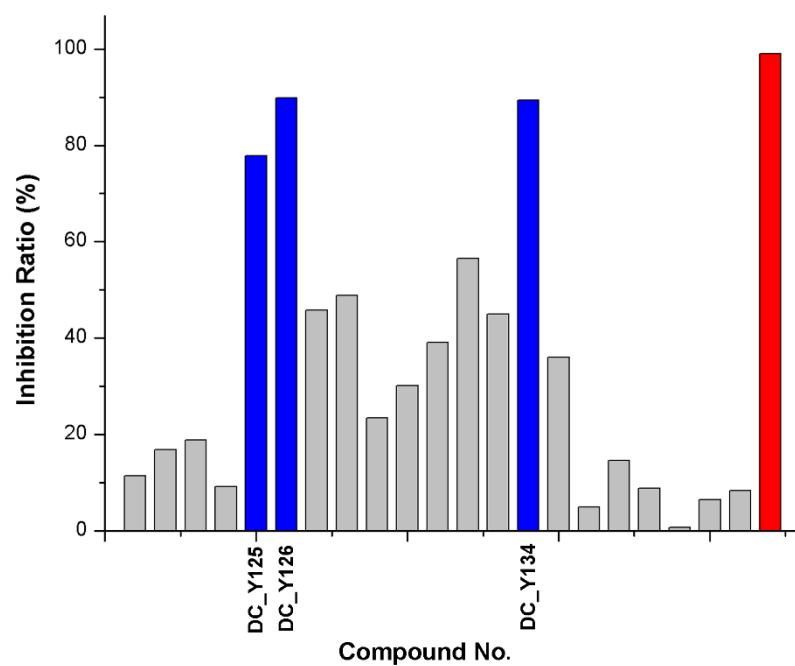


Figure S3. Inhibitory activity of the 21 analogues of DC_Y53 selected from the similarity search, in which the inhibition rate was determined at 100 μ M. The red columnar bar represents the activity of the reference compound SAH.

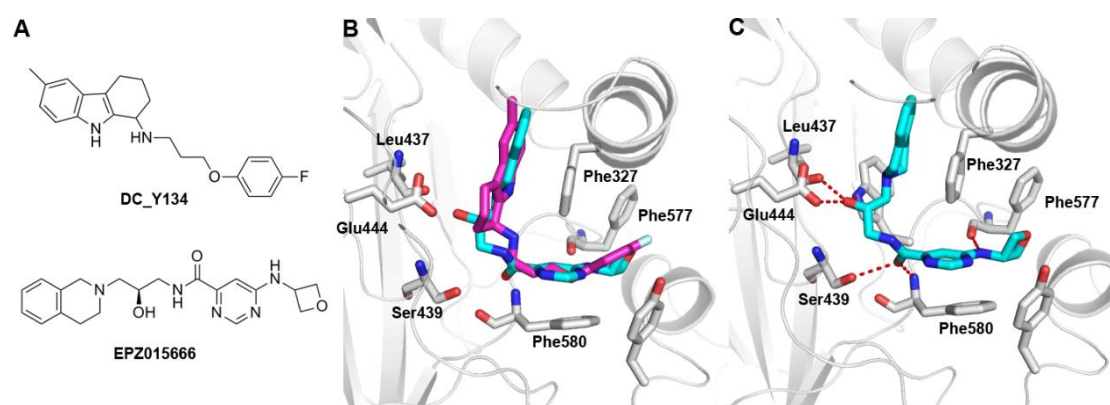


Figure S4. A comparison of DC_Y134 with PRMT5 inhibitor EPZ015666. (A) Chemical structures of DC_Y134 and EPZ015666. (B) Superimposition of the binding modes of DC_Y134 and EPZ015666. Compound DC_Y134 is shown as magenta sticks, and EPZ015666 is shown as cyan sticks. (C) Binding mode of EPZ015666.

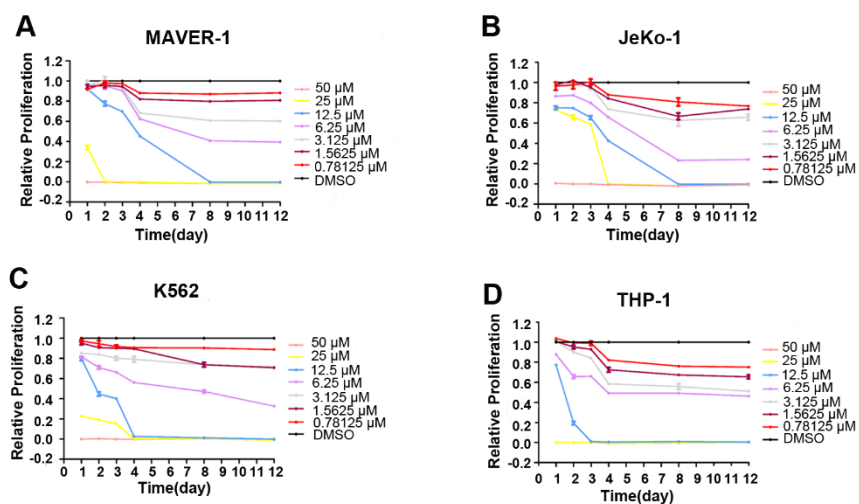


Figure S6. Cell activity. (A-D) Relative proliferation rates of MAVER-1, JeKo-1, K562 and THP-1 after treatment with DC_Y134 over 12 days.

Table S1. IC₅₀ Values of Active Compounds Identified in Virtual Screening

Compound No.	SPECS ID	IC ₅₀ (μM)
DC_Y1	AH-487/36443030	>200
DC_Y8	AK-968/15360328	111
DC_Y53	AH-262/34398047	5.7
DC_Y84	AG-664/42673766	127
DC_Y109	AT-051/43410102	32

Table S2. List of poses in blind docking of DC_Y134 targeting PRMT5. The top 20 binding modes are listed. # indicates that the ligand binds to the substrate-binding site.

Poses	Docking Score
1	-10.582 #
2	-9.631 #
3	-9.353 #
4	-9.250 #
5	-9.016 #
6	-8.398
7	-8.134 #
8	-7.971 #
9	-7.80 #
10	-7.774
11	-7.621 #
12	-7.519 #
13	-7.488 #
14	-7.412 #
15	-7.287 #
16	-7.027 #
17	-6.783 #
18	-6.506 #
19	-6.478 #
20	-6.114 #

Supplementary Reference:

1. Chan-Penebre, E.; Kuplast, K. G.; Majer, C. R.; Boriack-Sjodin, P. A.; Wigle, T. J.; Johnston, L. D.; Rioux, N.; Munchhof, M. J.; Jin, L.; Jacques, S. L., A Selective Inhibitor of PRMT5 with in Vivo and in Vitro Potency in MCL Models. *Nat. Chem. Biol.* **2015**, *11*, 432-437, DOI:10.1038/nchembio.1810.
2. Antonyamy, S.; Bonday, Z.; Campbell, R. M.; Doyle, B.; Druzina, Z.; Gheyi, T.; Han, B.; Jungheim, L. N.; Qian, Y.; Rauch, C.; Russell, M.; Sauder, J. M.; Wasserman, S. R.; Weichert, K.; Willard, F. S.; Zhang, A.; Emtage, S., Crystal Structure of the Human PRMT5:MEP50 Complex. *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 17960-17965, DOI:10.1073/pnas.1209814109.