Supporting Information

List of PDB used to retrieve the SAM binding conformation. The Protein Data Bank (www.rcsb.org/pdb) was interrogated at the time of experiments (May 2015). All human proteins binding to the SAM methyl donor were downloaded and used to the aims of this research work. In detail, following PDBs were used:

1NC6,[1] 1ZQ9, 2B9E, 2G72,[2] 2NYU, 2P02, 2R3A,[3] 3A7E, 3CKK, 3G07, 3O7W,[4] 3OOI,[5] 3OPE,[6] 3QOW,[7] 3QWP, 3QXY,[8] 3RC0,[8] 3S8P,[9] 3SMT, 3TG4,[10] 4A6D,[11] 4A6E,[11] 4IJ8, 4JLG,[12] 4KTT,[13] 4N49,[14] 4NDN,[13] 4PCU,[15] 4UUU,[16] 4XUD,[17] 4XUE,[17] 4YZ8.

Self-Docking of S-adenosyl-L-homocysteine (SAH) into G9a. To monitor the efficacy of the programs selected for conformational analysis and molecular docking (OMEGA and FRED from OpenEye, respectively)[18-22] the crystallographic ligand SAH was self-docked into the PDB structure 3K5K, after removing all crystallographic small molecules and water molecules. To strengthen the reliability of the self-docking procedure, the conformation of SAH was generated *de novo* and not taken from the X-ray structure. Overall, docking was able to reproduce the crystallographic pose with a good precision (RMS = 2.42 Å). Notably, a high accuracy was found in docking the adenine aromatic portion (RMSD = 0.35 Å), whereas a higher variation was observed in the docking pose of the homocysteine tail, as shown in the figure S1. This difference may be attributed to the larger flexibility of the homocysteine moiety than the adenine ring, as well as to the lack of histone tail or small molecule inhibitors complexed with G9a in our exercise. Indeed, as reported above, these molecules were removed from the PDB structure to eliminate any possible bias.

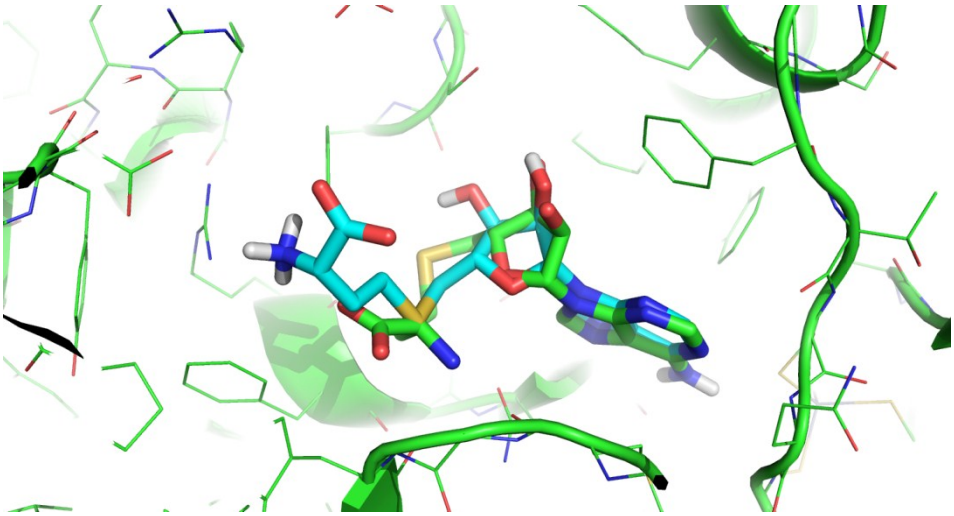

Figure S1. Self-docking of SAH into the crystallographic structure of G9a. The protein is shown as green lines and cartoon, crystallographic SAH is shown as green sticks, docked SAH as cyan sticks.

REFERENCES

1. M. J. Costanzo, S. C. Yabut, H. R. Almond, Jr., P. Andrade-Gordon, T. W. Corcoran, L. De Garavilla, J. A. Kauffman, W. M. Abraham, R. Recacha, D. Chattopadhyay and B. E. Maryanoff, *J. Med. Chem.*, 2003, **46**, 3865-3876.
2. C. L. Gee, N. Drinkwater, J. D. Tyndall, G. L. Grunewald, Q. Wu, M. J. McLeish and J. L. Martin, *J. Med. Chem.*, 2007, **50**, 4845-4853.
3. H. Wu, J. Min, V. V. Lunin, T. Antoshenko, L. Dombrovski, H. Zeng, A. Allali-Hassani, V. Campagna-Slater, M. Vedadi, C. H. Arrowsmith, A. N. Plotnikov and M. Schapira, *PLoS ONE*, 2010, **5**, e8570.
4. M. L. Tsai, N. Cronin and S. Djordjevic, *Acta Crystallogr. D Biol. Crystallogr.*, 2011, **67**, 14-24.
5. Q. Qiao, Y. Li, Z. Chen, M. Wang, D. Reinberg and R. M. Xu, *J. Biol. Chem.*, 2011, **286**, 8361-8368.
6. S. An, K. J. Yeo, Y. H. Jeon and J. J. Song, *J. Biol. Chem.*, 2011, **286**, 8369-8374.
7. V. M. Richon, D. Johnston, C. J. Sneeringer, L. Jin, C. R. Majer, K. Elliston, L. F. Jerva, M. P. Scott and R. A. Copeland, *Chem. Biol. Drug Des.*, 2011, **78**, 199-210.
8. Y. Chang, D. Levy, J. R. Horton, J. Peng, X. Zhang, O. Gozani and X. Cheng, *Nucleic Acids Res.*, 2011, **39**, 6380-6389.
9. H. Wu, A. Siarheyeva, H. Zeng, R. Lam, A. Dong, X. H. Wu, Y. Li, M. Schapira, M. Vedadi and J. Min, *FEBS Lett.*, 2013, **587**, 3859-3868.
10. L. Wang, L. Li, H. Zhang, X. Luo, J. Dai, S. Zhou, J. Gu, J. Zhu, P. Atadja, C. Lu, E. Li and K. Zhao, *J. Biol. Chem.*, 2011, **286**, 38725-38737.
11. H. G. Botros, P. Legrand, C. Pagan, V. Bondet, P. Weber, M. Ben-Abdallah, N. Lemiere, G. Huguet, J. Bellalou, E. Maronde, P. Beguin, A. Haouz, W. Shepard and T. Bourgeron, *J. Pineal Res.*, 2013, **54**, 46-57.
12. D. Barsyte-Lovejoy, F. Li, M. J. Oudhoff, J. H. Tatlock, A. Dong, H. Zeng, H. Wu, S. A. Freeman, M. Schapira, G. A. Senisterra, E. Kuznetsova, R. Marcellus, A. Allali-Hassani, S. Kennedy, J. P. Lambert, A. L. Couzens, A. Aman, A. C. Gingras, R. Al-Awar, P. V. Fish, B. S. Gerstenberger, L. Roberts, C. L. Benn, R. L. Grimley, M. J. Braam, F. M. Rossi, M. Sudol, P. J. Brown, M. E. Bunnage, D. R. Owen, C. Zaph, M. Vedadi and C. H. Arrowsmith, *Proc. Natl. Acad. Sci. U. S. A.*, 2014, **111**, 12853-12858.
13. B. Murray, B. V. Antonyuk, A. Marina, S. M. Van Liempd, S. C. Lu, J. M. Mato, S. S. Hasnain and A. L. Rojas, *IUCrJ*, 2014, **1**, 240-242.
14. M. Smietanski, M. Werner, E. Purta, K. H. Kaminska, J. Stepinski, E. Darzynkiewicz, M. Nowotny and J. M. Bujnicki, *Nat. Commun.*, 2014, **5**, 3004.
15. J. Ereno-Orbea, T. Majtan, I. Oyenarte, J. P. Kraus and L. A. Martinez-Cruz, *Proc. Natl. Acad. Sci. U. S. A.*, 2014, **111**, E3845-3852.
16. T. J. McCorvie, J. Kopec, S. J. Hyung, F. Fitzpatrick, X. Feng, D. Termine, C. Strain-Damerell, M. Vollmar, J. Fleming, J. M. Janz, C. Bulawa and W. W. Yue, *J. Biol. Chem.*, 2014, **289**, 36018-36030.
17. S. T. Harrison, M. S. Poslusney, J. J. Mulhearn, Z. Zhao, N. R. Kett, J. W. Schubert, J. Y. Melamed, T. J. Allison, S. B. Patel, J. M. Sanders, S. Sharma, R. F. Smith, D. L. Hall, R. G. Robinson, N. A. Sachs, P. H. Hutson, S. E. Wolkenberg and J. C. Barrow, *ACS Med Chem Lett*, 2015, **6**, 318-323.
18. M. McGann, *J. Chem. Inf. Model.*, 2011, **51**, 578-596.
19. M. McGann, *J. Comput. Aided Mol. Des.*, 2012, **26**, 897-906.
20. FRED 3.0.1 OpenEye Scientific Software, Santa Fe, NM. http://www.eyesopen.com.
21. P. C. Hawkins, A. G. Skillman, G. L. Warren, B. A. Ellingson and M. T. Stahl, *J. Chem. Inf. Model.*, 2010, **50**, 572-584.
22. OMEGA 2.5.1.4: OpenEye Scientific Software, Santa Fe, NM. http://www.eyesopen.com.