Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.


# Supplementary Information

**Table S1**. MM/GBSA free energy calculation for the 26 complexes based on the 5 ns MD simulations

| No. | Protein | Ligand | Ligand source | PDB entry | Docking score | $\Delta G_{bind}$ (kcal/mol) |
|---|---|---|---|---|---|---|
| 1 | DNMT1 | SFG | PDB:3SWR | 3SWR | / | -53.31 |
| 2 | | | Glide XP top1 | 3SWR | -8.01 | -38.97 |
| 3 | | | Glide XP top2 | 3SWR | -7.19 | -38.65 |
| 4 | DNMT1 | DC_05 | Glide XP top3 | 3SWR | -6.89 | -48.96 |
| 5 | | | Glide XP top4 | 3SWR | -6.50 | -33.77 |
| 6 | | | Glide XP top5 | 3SWR | -5.13 | -35.99 |
| 7 | | | Glide XP top1 | 3SWR | -7.91 | -45.61 |
| 8 | | | Glide XP top2 | 3SWR | -7.82 | -43.24 |
| 9 | DNMT1 | GSKex1 | Glide XP top3 | 3SWR | -7.70 | -34.28 |
| 10 | | | from complex no.22 | 3SWR | / | -47.67 |
| 11 | | | Glide SP top1 | 3SWR | -6.25 | -37.44 |
| 12 | | | Glide XP top1 | 4U7T/A | -6.65 | -50.08 |
| 13 | | | Glide XP top2 | 4U7T/A | -6.57 | -50.90 |
| 14 | DNMT3A | SFG | Glide XP top3 | 4U7T/A | -6.54 | -53.75 |
| 15 | | | Glide XP top4 | 4U7T/A | -5.88 | -57.10 |
| 16 | | | Glide XP top5 | 4U7T/A | -5.47 | -51.60 |
| 17 | | | Glide XP top1 | 4U7T/A | -7.04 | -26.39 |
| 18 | | | Glide XP top2 | 4U7T/A | -6.85 | -14.25 |
| 19 | DNMT3A | DC_05 | Glide XP top3 | 4U7T/A | -6.51 | -41.29 |
| 20 | | | Glide XP top4 | 4U7T/A | -6.41 | -37.18 |
| 21 | | | Glide XP top5 | 4U7T/A | -6.38 | -39.62 |
| 22 | | | Glide XP top1 | 4U7T/A | -9.52 | -59.60 |
| 23 | | | Glide XP top2 | 4U7T/A | -9.30 | -56.43 |
| 24 | DNMT3A | GSKex1 | Glide XP top3 | 4U7T/A | -8.22 | -56.15 |
| 25 | | | Glide XP top4 | 4U7T/A | -8.19 | -55.15 |
| 26 | | | Glide XP top5 | 4U7T/A | -7.36 | -56.63 |

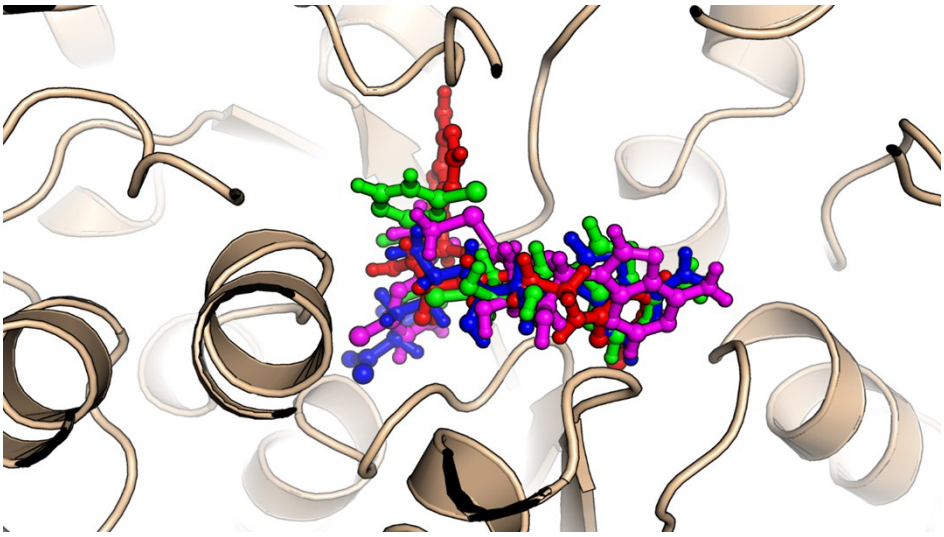

**Figure S1.** The best binding poses of GSKex1 predicted by the Glide SP/XP docking compared with that of DNMT1/SFG (PDB entry: 3SWR) . SFG is colored blue, and the best binding poses of GSKex1 predicted by the Glide XP and SP are colored red and green, respectively. The binding pose of GSKex1 on DNMT3A predicted by the Glide XP is colored magenta.

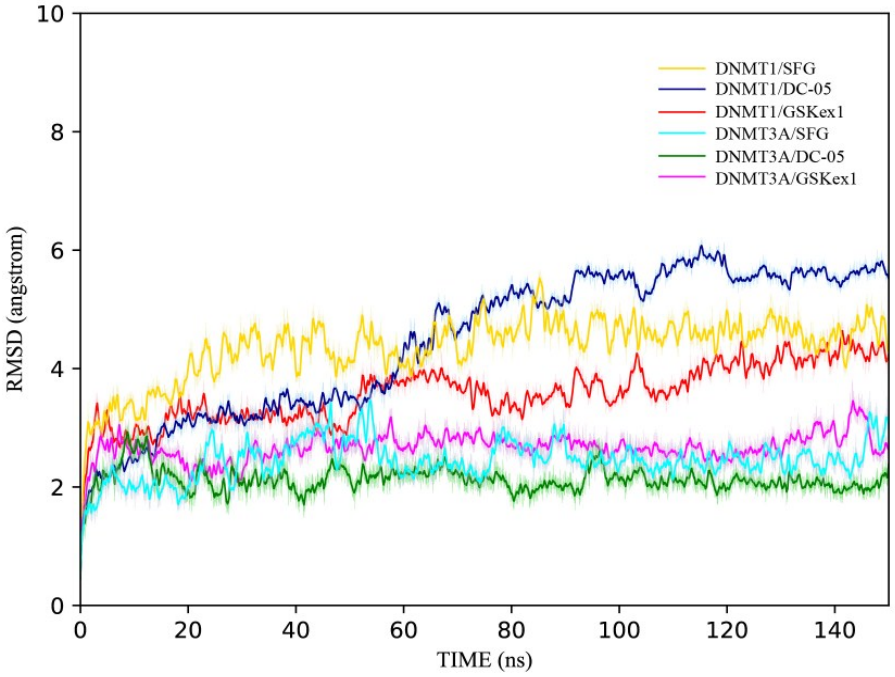


**Figure S2.** RMSDs of $C_\alpha$ atoms of the protein in the six studied complexes as a function of simulation time.

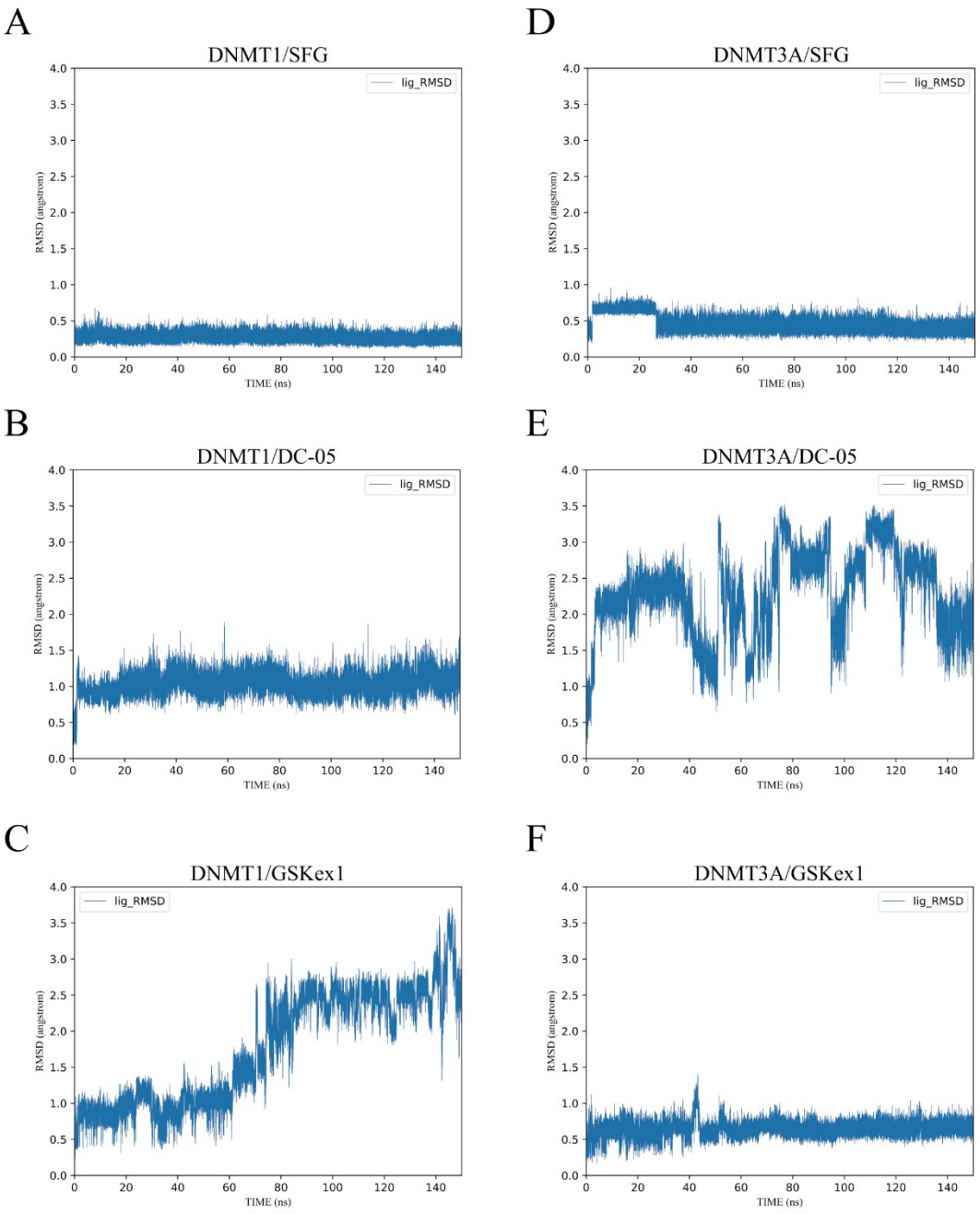


**Figure S3.** RMSDs of the heavy atoms of the ligands in the six studied complexes as a function of simulation time.

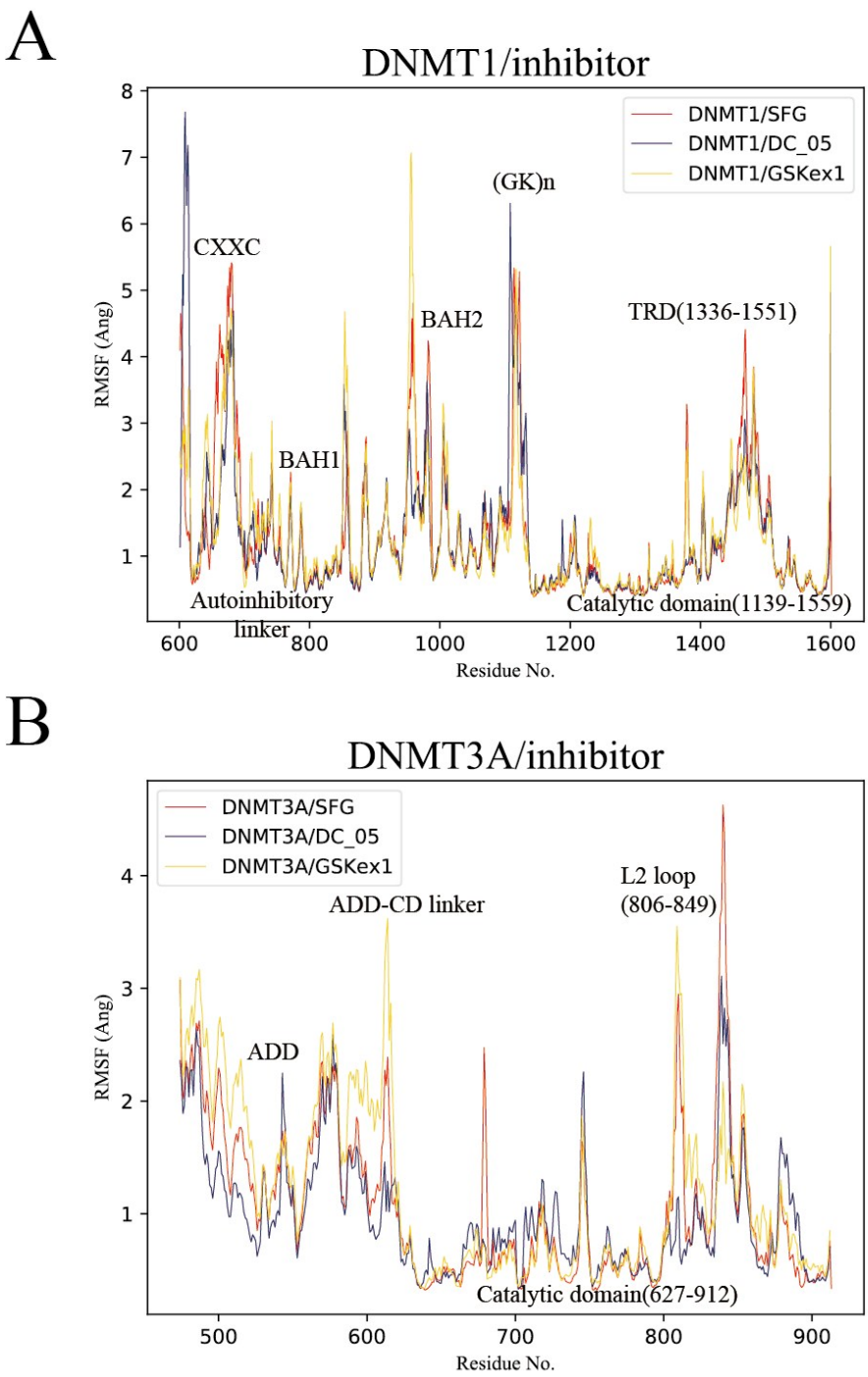


**Figure S4.** Residue-based RMSFs relative to the initial structure during the 150 ns MD simulations.

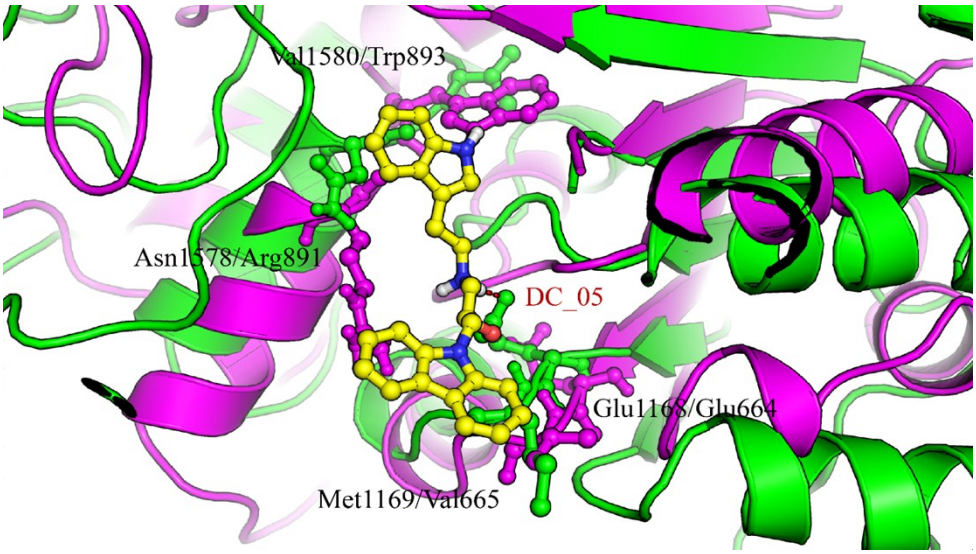


**Figure S5.** Comparison of the representative structures of DNMT1/DC_05 and DNMT3A/GSKex1 with the lowest RMSDs relative to the averaged structures extracted from the 150 ns MD trajectories. DNMT1 is colored green, and DNMT3A is colored magenta. The Carbon backbone of DC_05 is colored yellow.

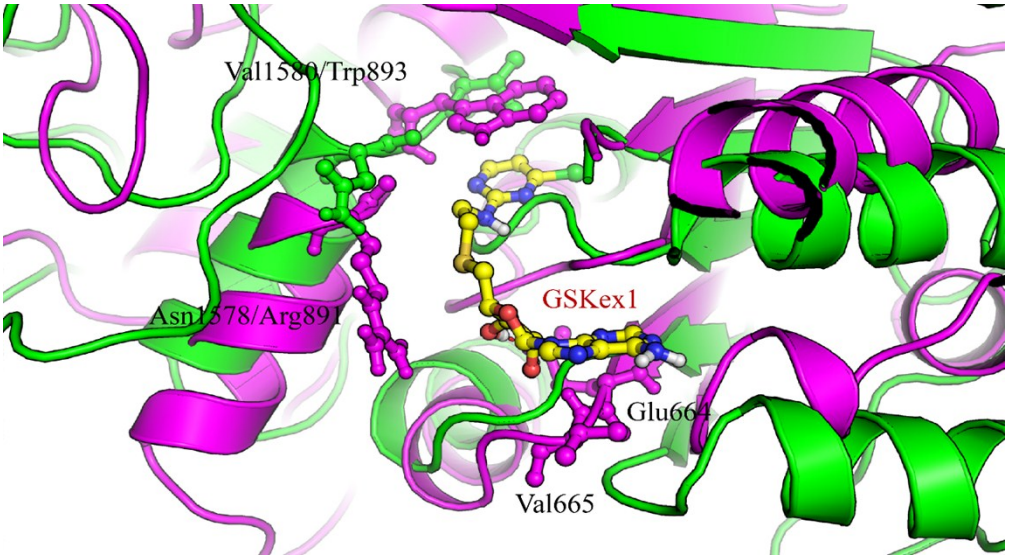


**Figure S6.** Comparison of the representative structures of DNMT1/DC_05 and DNMT3A/GSKex1 with the lowest RMSDs relative to the averaged structures extracted from the 150 ns MD trajectories. DNMT1 is colored green, and DNMT3A is colored magenta. The Carbon backbone of GSKex1 is colored yellow.

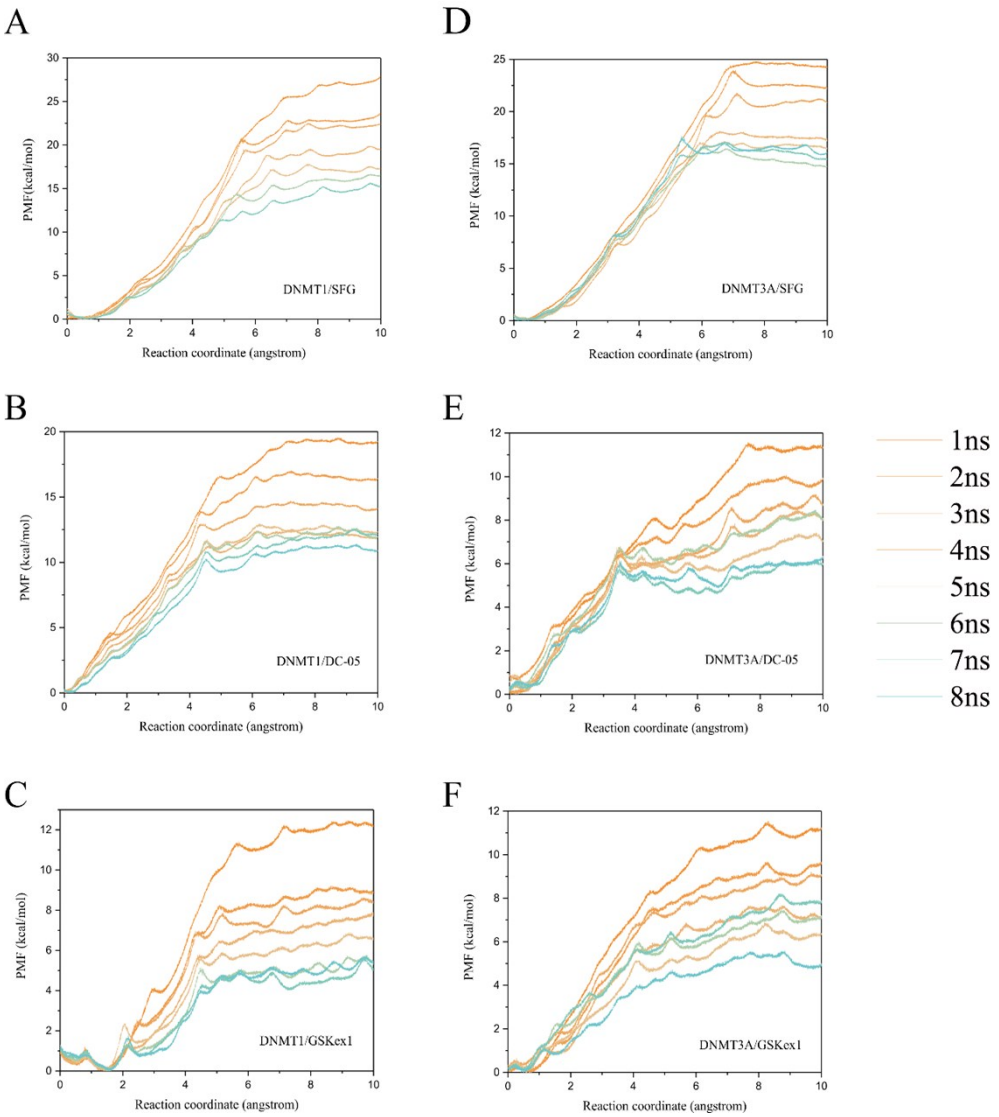


**Figure S7.** Convergence of the PMFs given by the US simulations for (A) DNMT1/SFG, (B) DNMT1/DC_05, (C) DNMT1/GSKex1, (D) DNMT3A/SFG, (E) DNMT3A/DC_05, and (F) DNMT3A/GSKex1.