**Table S1.** Overview of the simulation systems and their simulated time scales.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Ligand | Initial His3936.55 conformation | Total number  of atoms | Simulation time |
| A | Dopamine | D2DownR | 224,760 | 1000 nsa  + 500 ns |
| B | Dopamine | D2UpR | 227,641 | 1000 nsa |
| C | Aripiprazole | D2UpR | 227,577 | 800 ns |
| D | FAUC350 | D2UpR | 227,571 | 500 ns |

apreviously published simulation: Kling RC, et al. (2013), PLoS One 8: e67244.