Supporting Information

Mechanism for Cocaine Blocking the Transport of Dopamine: Insights from Molecular Modeling and Dynamics Simulations

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Supporting Information Available. Four figures for molecular structures of dopamine, cocaine, β-CFT, β-CIT, 3β-benzoyltropine, (2β,3α)-allococaine, and clomipramine; the conformational clusters of the docked results for the docking of cocaine into the binding site of DAT-DA; the energy-minimized DAT-DA-cocaine complex superimposed with the X-ray structure of $LeuT_{Aa}$ bound with antidepressant clomipramine (PDB entry 2Q6H); and plots of the time-dependence of internuclear distances related to some important hydrogen bonds in the MD-simulated DAT-DA complex, and DAT-DA-cocaine complex. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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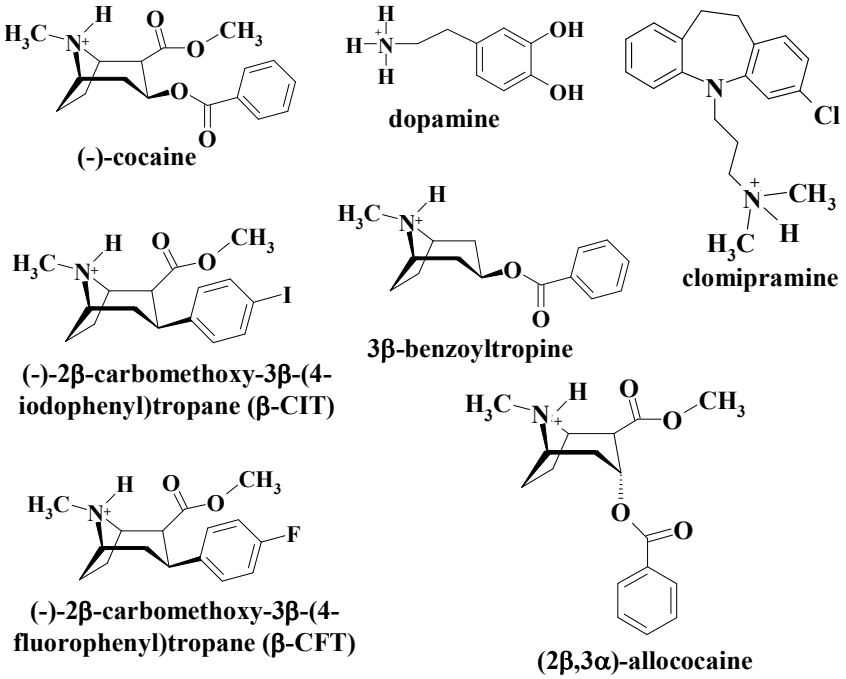

Figure S1. Molecular structures of dopamine, cocaine, cocaine analogs, and antidepressant drug clomipramine

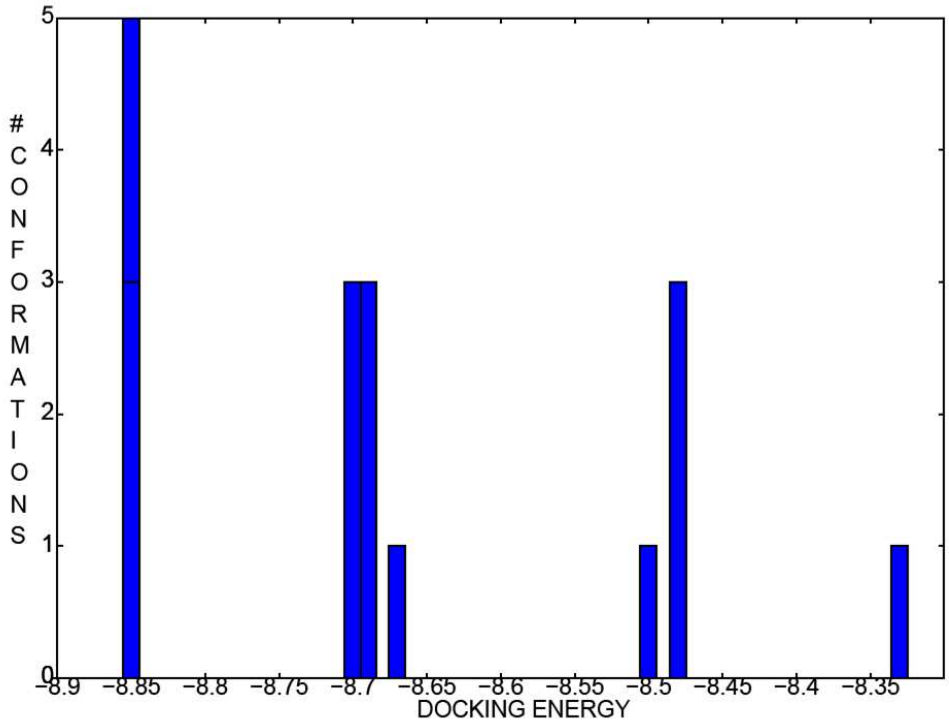

Figure S2. Conformational clusters of the docked results for the docking of cocaine into the binding site in the vestibule formed by helices 1, 3, 6, 8, and 10 of DAT-DA. The x axis represents the averaged binding energy (kcal/mol) for each cluster and the y axis for the number of conformations in each cluster.

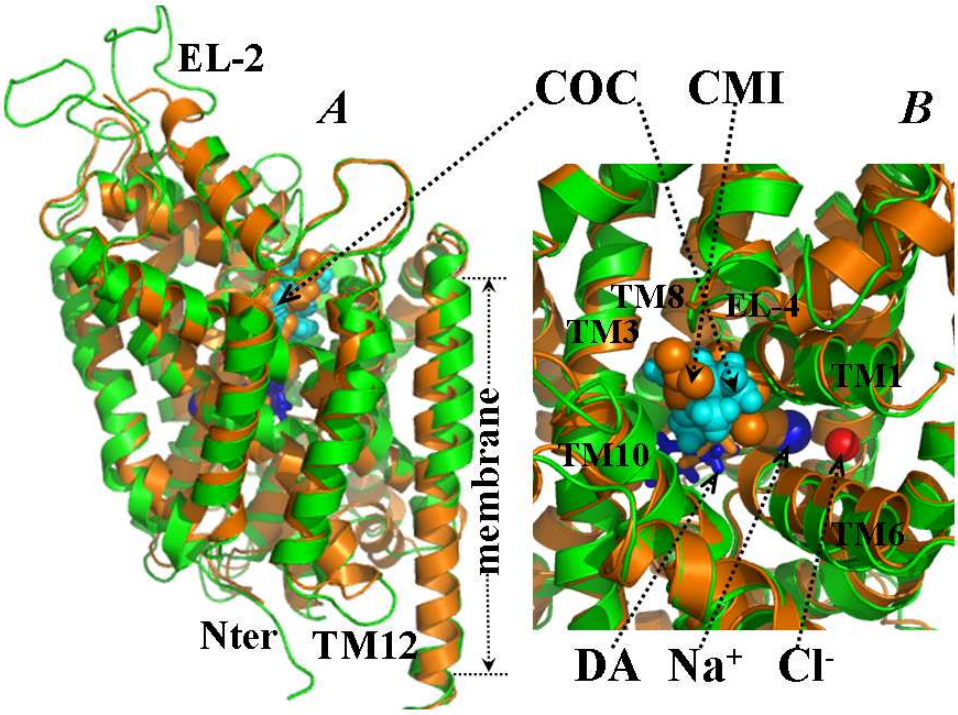

Figure S3. The energy-minimized DAT-DA-cocaine complex structure (represented as green ribbon) superimposed with X-ray structure of $LeuT_{Aa}$ in complex with antidepressant clomipramine (CMI)[1] (orange ribbon). (A) Side view along the normal of the membrane. (B) Local view of the complex structure along the vertical vestibule between helices 1, 3, 6, 8, and 10 of DAT-DA. Na^+ ions are shown in blue spheres, and Cl^- ion in red sphere. Dopamine (DA) is shown in space-filled spheres and colored in blue. Cocaine molecule (COC) in the complex is shown in space-filled spheres and colored in cyan, and CMI is also shown in space-filled spheres and colored in orange. Also labeled are the EL-2, TM1, TM3, TM6, TM8, TM10, and TM12, and the membrane position. This figure is generated by using PyMol (DeLano Scientific LLC, San Carlos, California, USA).

[1] Singh, S. K.; Yamashita, A.; Gouaux, E. Antidepressant binding site in a bacterial homologue of neurotransmitter transporters. *Nature* **2007**, *448*, 952-956.

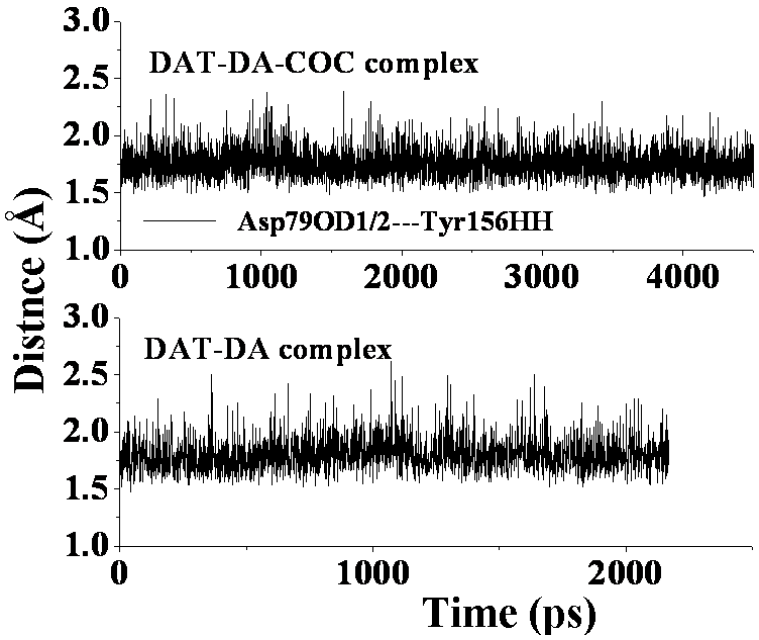

Figure S4. Hydrogen bonding distance between the side chain of Asp79 and the hydroxyl group at the side chain of Tyr156 as tracked from the molecular dynamics (MD) simulations on DAT-DA-cocaine complex and MD simulations on DAT-dopamine in our previous study (Huang, X.; Zhan, C.-G.. How dopamine transporter interacts with dopamine: insights from molecular modeling and simulation. *Biophys. J.* **2007**, *93*, 3627-3639).