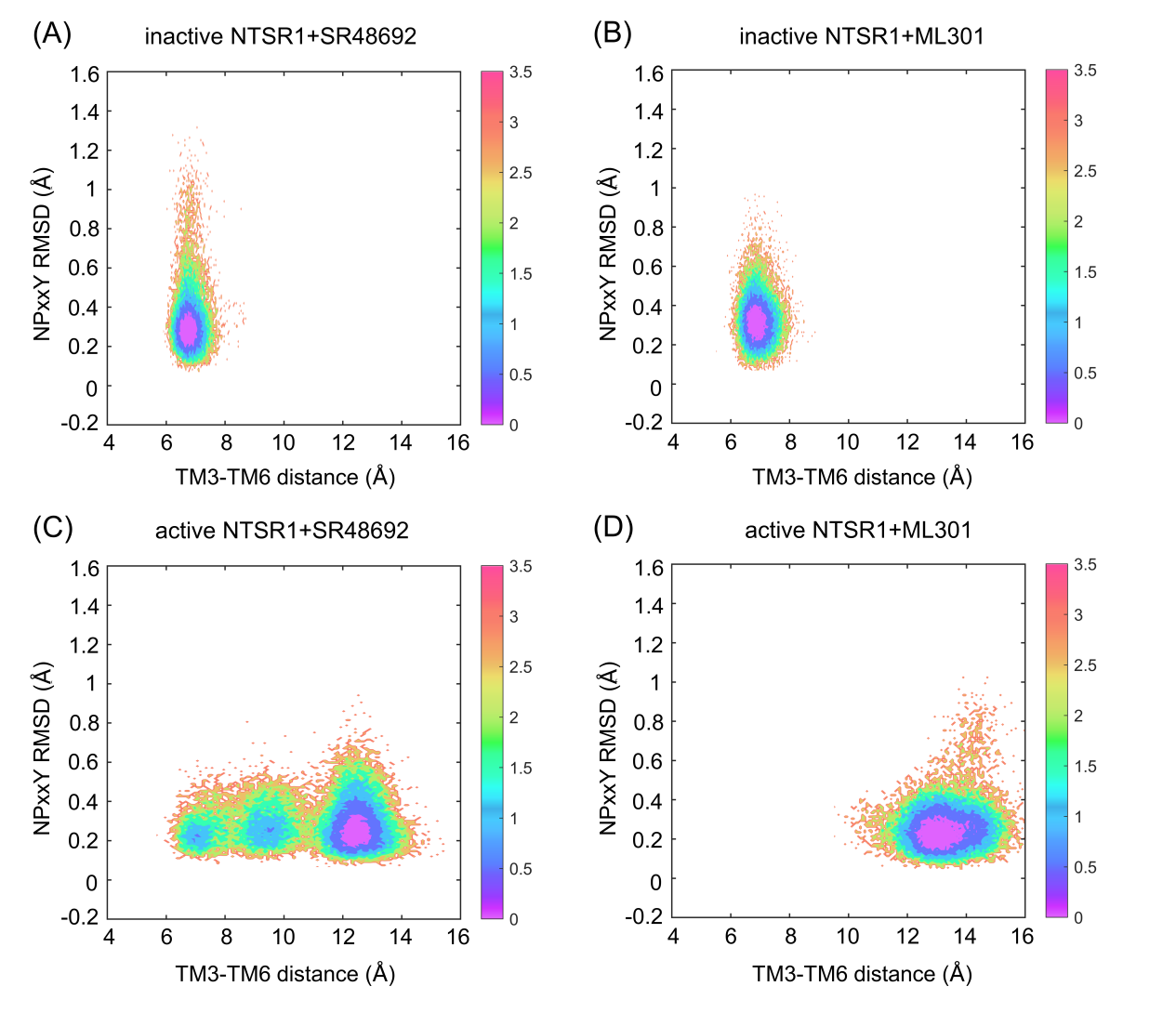
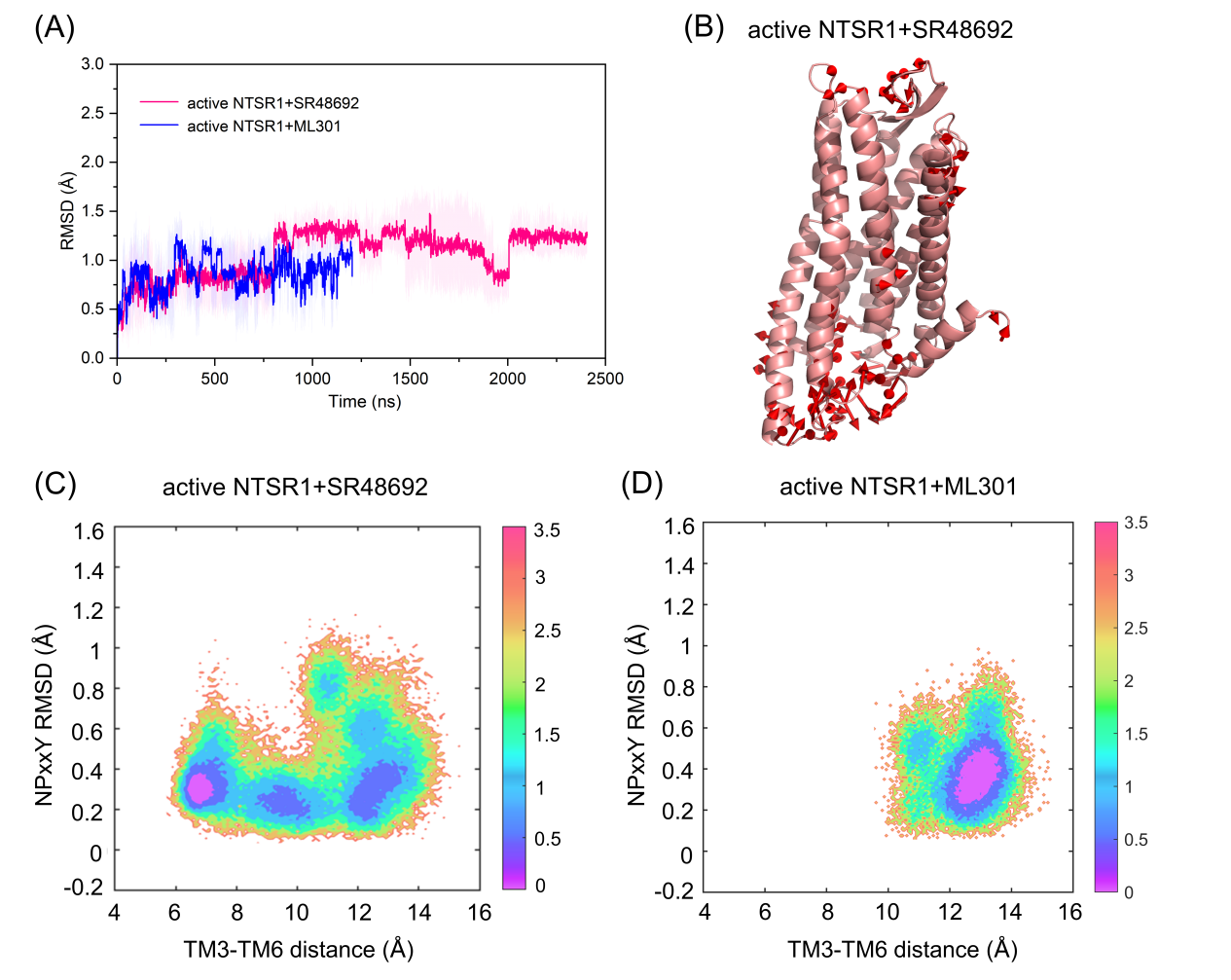
**Supplemental Information**

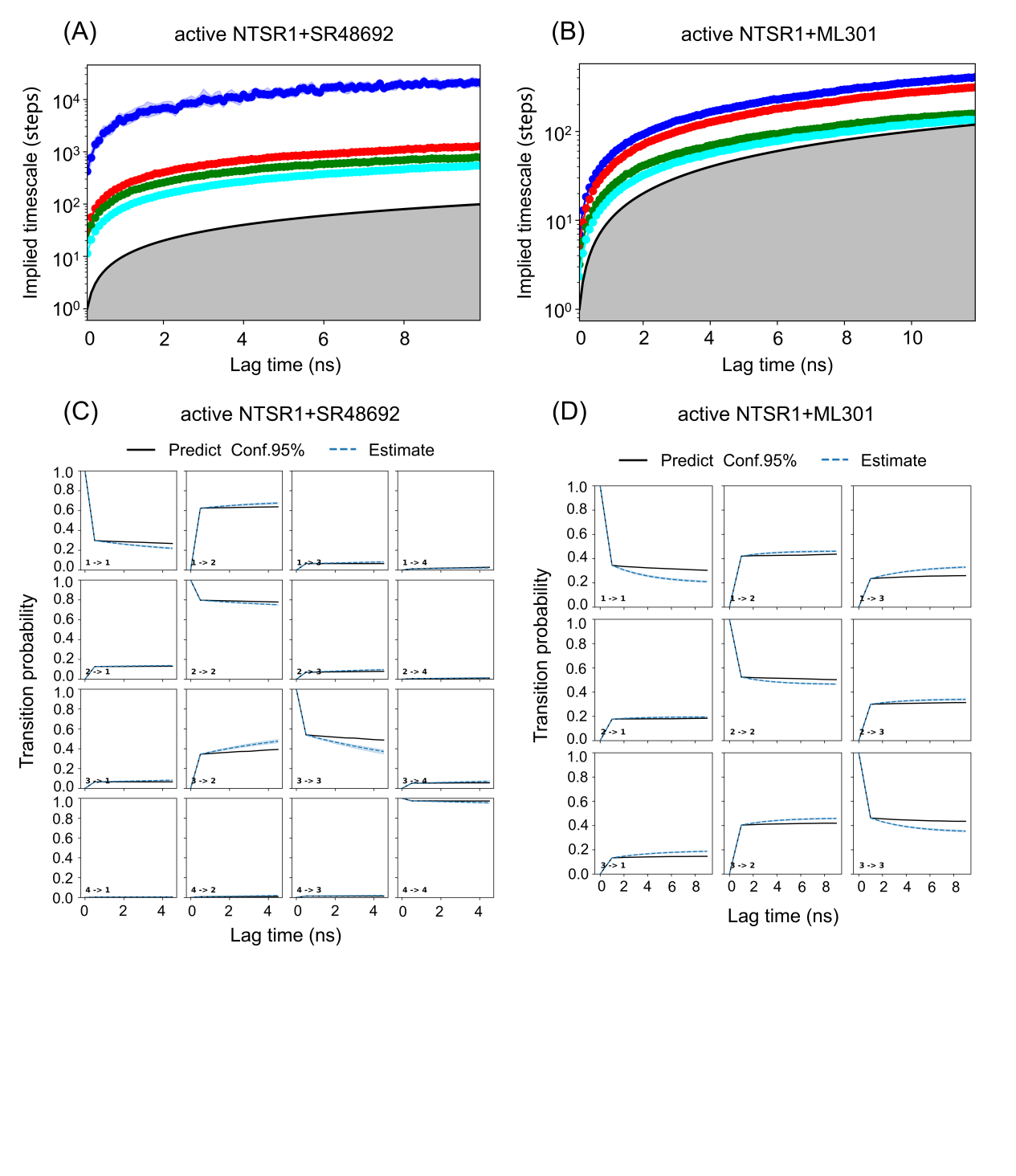
**Mechanistic Elucidation of Activation or Deactivation Signal Transduction within Neurotensin Receptor 1 (NTSR1) Triggered by ‘Driver Chemical Group’: A Comparative Molecular Dynamics Simulation**



**Figure S1.** The analogical free energy landscape of the inactive NTSR1+SR48692 system (**A**), the inactive NTSR1+ML301 system (**B**), the active NTSR1+SR48692 system (**C**) and the active NTSR1+ML301 system (**D**) are shown by simulation trajectory projection. CV1: TM3-TM6 distance (evaluated by the distance between the center of mass of R1663.50 in TM3 and V3026.34 in TM6), CV2: NPxxY RMSD (evaluated by RMSD of non-symmetric side-chain atoms of residues N3607.49 to Y3647.53). Color scale on the right is evaluated through density.



**Figure S2.** (**A**) The RMSD value of ligands in all simulations in the active NTSR1+SR48692 system (pink curve) and the active NTSR1+ML301 system (blue curve). (**B**) The principal pattern of motion of the active NTSR1+SR48692 system. The sizes and lengths of the red arrows are proportional to the amplitude of motions. The free energy landscapes of the active NTSR1+SR48692 system (**C**) and the active NTSR1+ML301 system (**D**) in cMD simulation. Collective variable 1 (CV1): TM3-TM6 distance (evaluated by the distance between the center of mass of R1663.50 in TM3 and V3026.34 in TM6), CV2: NPxxY RMSD (evaluated by RMSD of non-symmetric side-chain atoms of residues N3607.49 to Y3647.53). The unit of free energy values is kcal/mol. Color scale on the right is evaluated through free energy.



**Figure S3.** Implied timescale test for MSMs in the active NTSR1+SR48692 system (**A**) and the active NTSR1+ML301 system (**B**) at different lag times. Blue, red, green, and cyan lines show the timescale τ1, τ2, τ3 and τ4. Black line represents x=y in logarithmic coordinates, which separates the area where the dynamics of the processes is resolvable (white) from the non-resolvable area (grey). Chapman-Kolmogorov test of metastable states for the active NTSR1+SR48692 system (**C**) and the active NTSR1+ML301 system (**D**). The black solid estimate lines are the transition probability predicted by MSMs, while the blue dotted predict lines are practical transition probability observed in trajectories.

Table S1. Frequency of Y3196.51-F3537.42 and F3537.42-R1483.32 interaction in the representative trajectories in the active NTSR1+SR48692 system and the active NTSR1+ML301 system.

