Supporting Information:

In search of a photoswitchable drug for serotonin receptor: A molecular dynamics simulation study

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June 10, 2025

S1:Lipid structure used for the preparation of the membrane

POPC lipid membrane model was used to construct a lipid membrane around the 5-HT_{1B} receptor in each initial docked structures of the CAS-receptor and TAS-receptor complexes. The structure of POPC lipid is shown in Fig. S1.

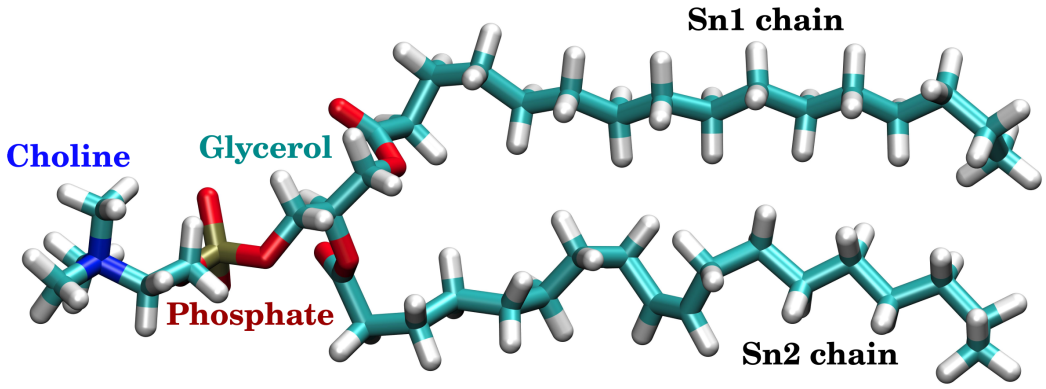

FIG. S1: Chemical structure of 1-palmitoyl-2-oleoylphosphatidylcholine (POPC).

S2: Results and analysis from independent simulations

0.1 RMSD

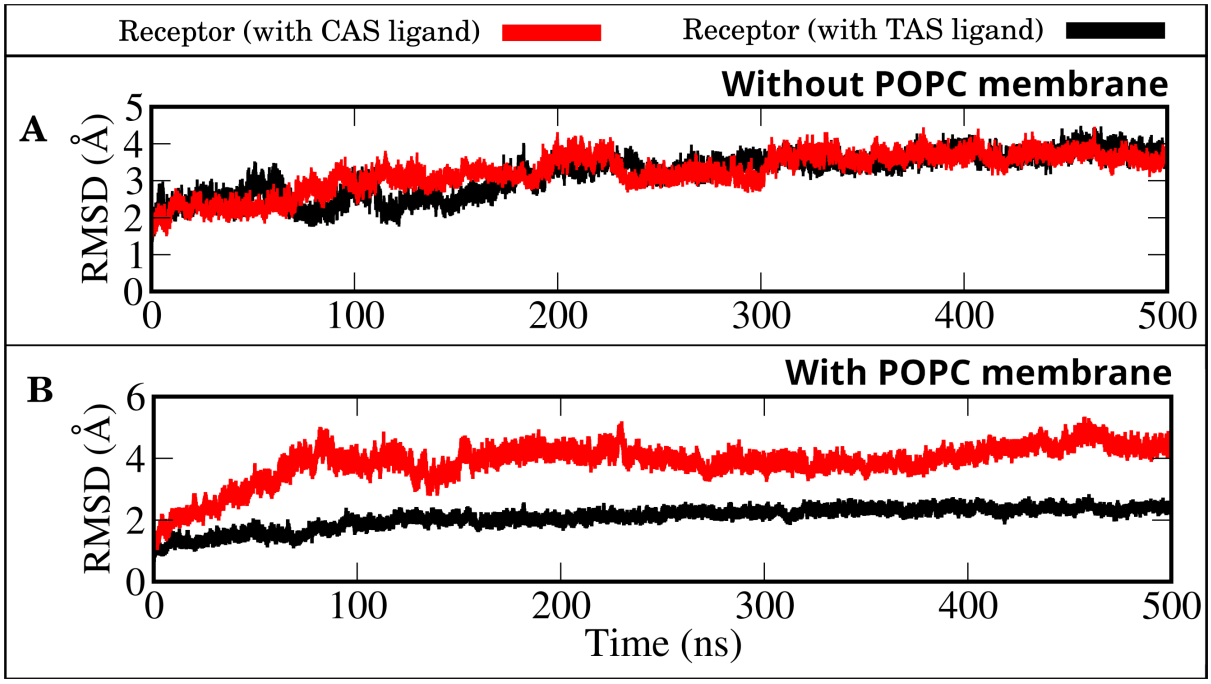

FIG. S2: Root mean square deviations (RMSDs) of receptor's C-alpha carbon atoms plotted as a function of simulation time (ns).

S2.1: Ligand clustering analysis

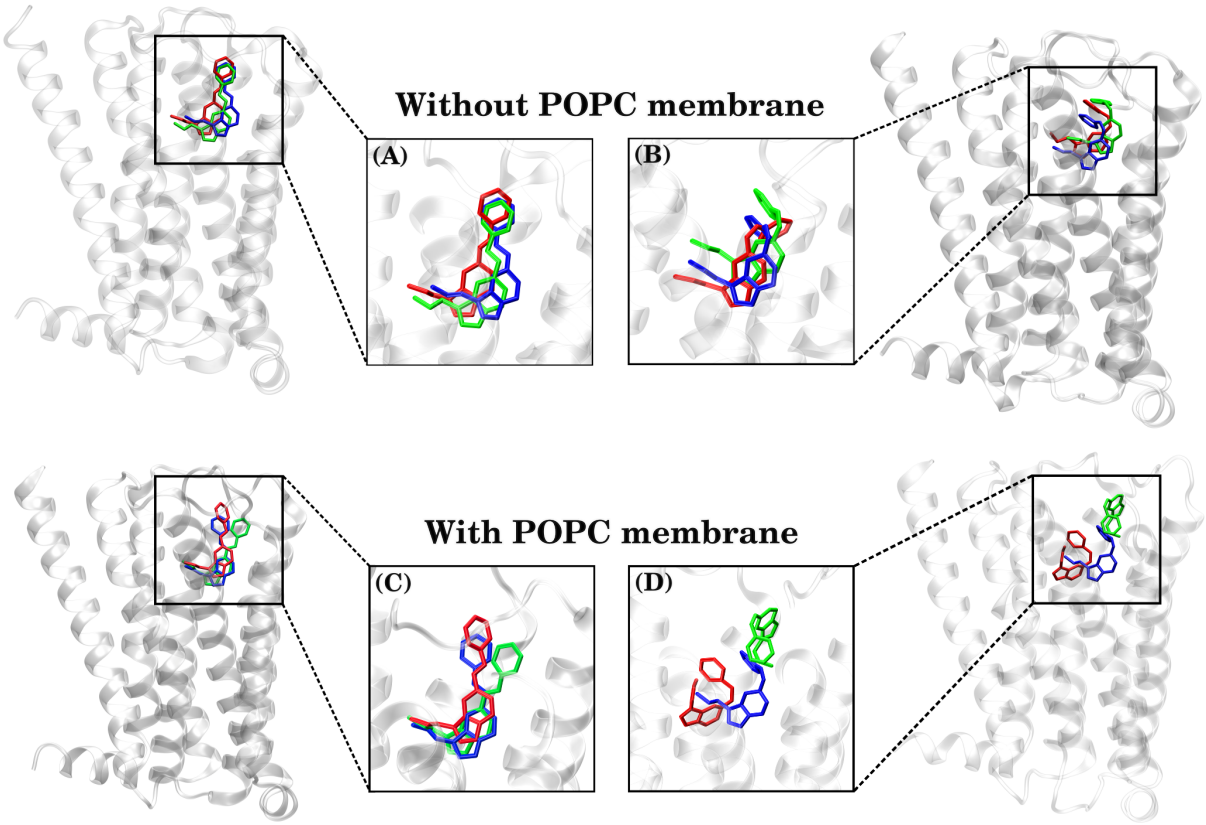

FIG. S3: Comparison of MD simulated conformations of (A), (C) TAS ligand and (B), (D) CAS ligand, representing the clusters as obtained VMD clustering analysis.

S2.2: Binding free energies results from the independent simulation (simulation 2)

System	Enthalpy (kcal/mol)	Entropy (kcal/mol)	$\Delta G_{\mathrm{MM/GBSA}}$(kcal/mol)
Without POPC Membrane			
CAS-Receptor	-32.80	19.29	-13.51
TAS-Receptor	-37.49	10.69	-26.8
With POPC Membrane			
CAS-Receptor	-27.26	26.89	-0.37
TAS-Receptor	-36.99	8.69	-28.30

Table S1: Thermodynamic Properties: Binding free energy results incorporating enthalpy and entropy contributions for both systems without and with POPC membrane.

S3: Binding free energies with error bars from simulation 1

System	Enthalpy (kcal/mol)	Entropy (kcal/mol)	$\Delta G_{\mathrm{MM/GBSA}}$(kcal/mol)
Without POPC Membrane			
CAS-Receptor	-32.06 ± 2.59	20.36 ± 4.45	-11.70 ± 5.15
TAS-Receptor	-37.64 ± 2.42	11.47 ± 2.49	-26.17 ± 3.47
With POPC Membrane			
CAS-Receptor	-31.06 ± 5.24	26.95 ± 12.59	-4.11 ± 13.63
TAS-Receptor	-37.95 ± 2.77	7.66 ± 1.57	-30.29 ± 3.19

Table S2: Thermodynamic Properties: Binding free energy results incorporating enthalpy and entropy contributions for both systems without and with POPC membrane.

S4: Receptor structures clustering analysis

Figure S4 shows the superimposed highest populated structures of receptors from all simulation systems. This analysis corroborates the quantitative data obtained from the calculations of the binding pocket volumes. Notably, receptor structures possessing the CAS ligand have a larger binding pocket volume compared to that of the TAS ligand.

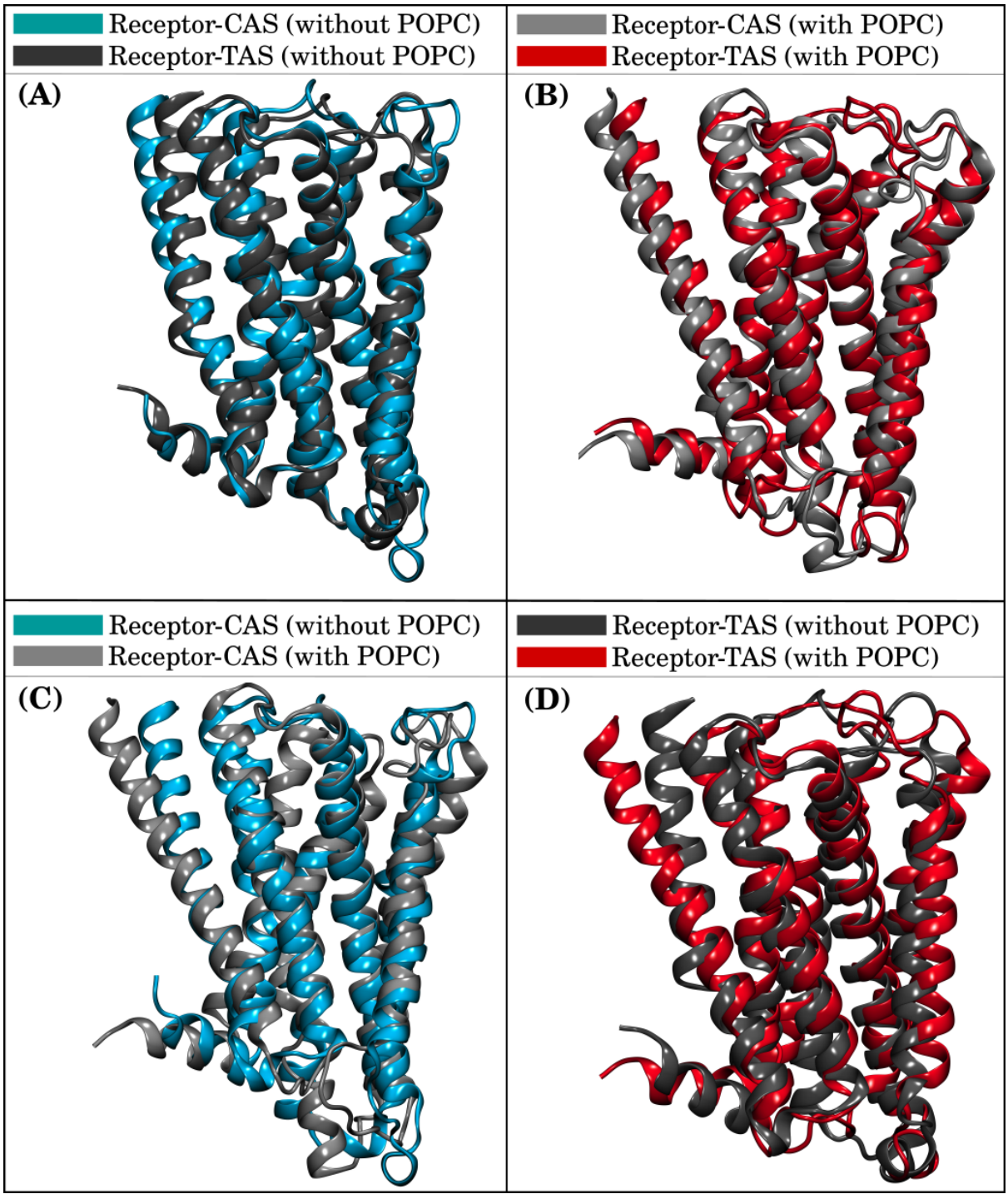

FIG. S4: Comparison of receptor structures bound to TAS and CAS with and without POPC membrane. Each structure represents the conformation of the most populated cluster from the 450 ns trajectories obtained by VMD clustering analysis.

S5: Qualitative stacking interactions

S5.1: Ligand decomposition

As discussed in previous sections, the azobenzene and serotonin were fused to make the photoswitchable azo-sero ligand. The primary objective of conjugating serotonin with azobenzene is to enhance targeted drug delivery. Hence, it became necessary to evaluate how each aromatic moiety of the ligands interacts with the aromatic residues of interest inside the binding pocket of proteins. Figure S5 shows how the aromatic moieties of photoswitchable ligands were decomposed as two aromatic parts for detailed analysis: the azo part and the sero part. The purpose of analyzing the ligands in two parts was to separately evaluate and deeply understand the stability and type of stacking interactions formed between the ligands and the main aromatic residues of interest.

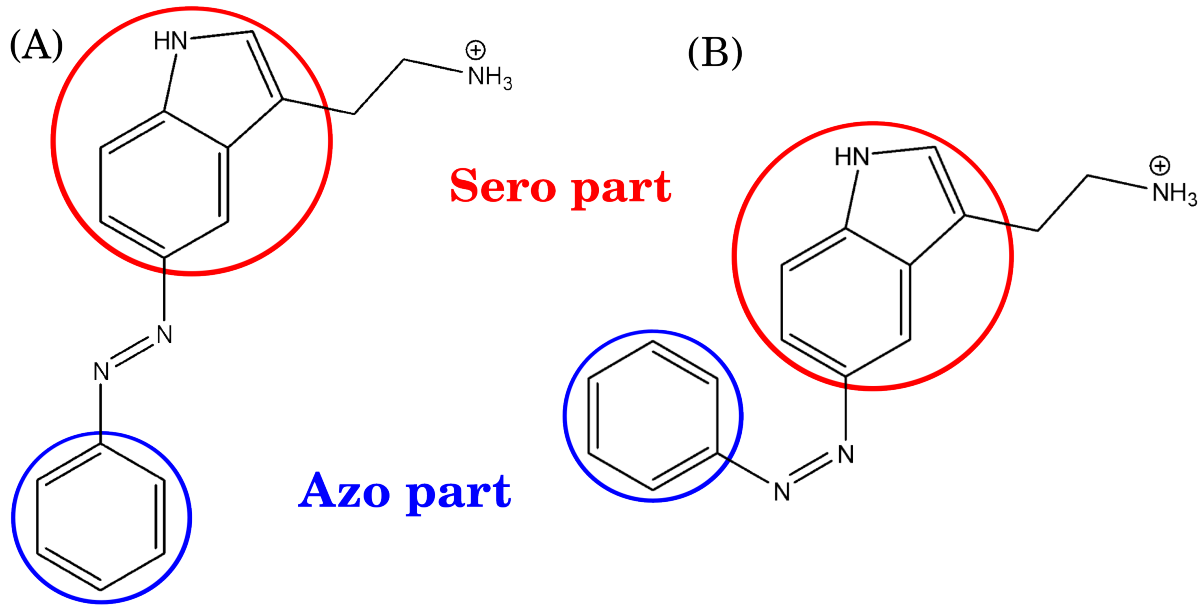

FIG. S5: The photoswitchable ligands divided in two parts for detailed analysis: the azo part and sero part.

S5.2: Qualitative stacking interaction plots for systems with the POPC membrane

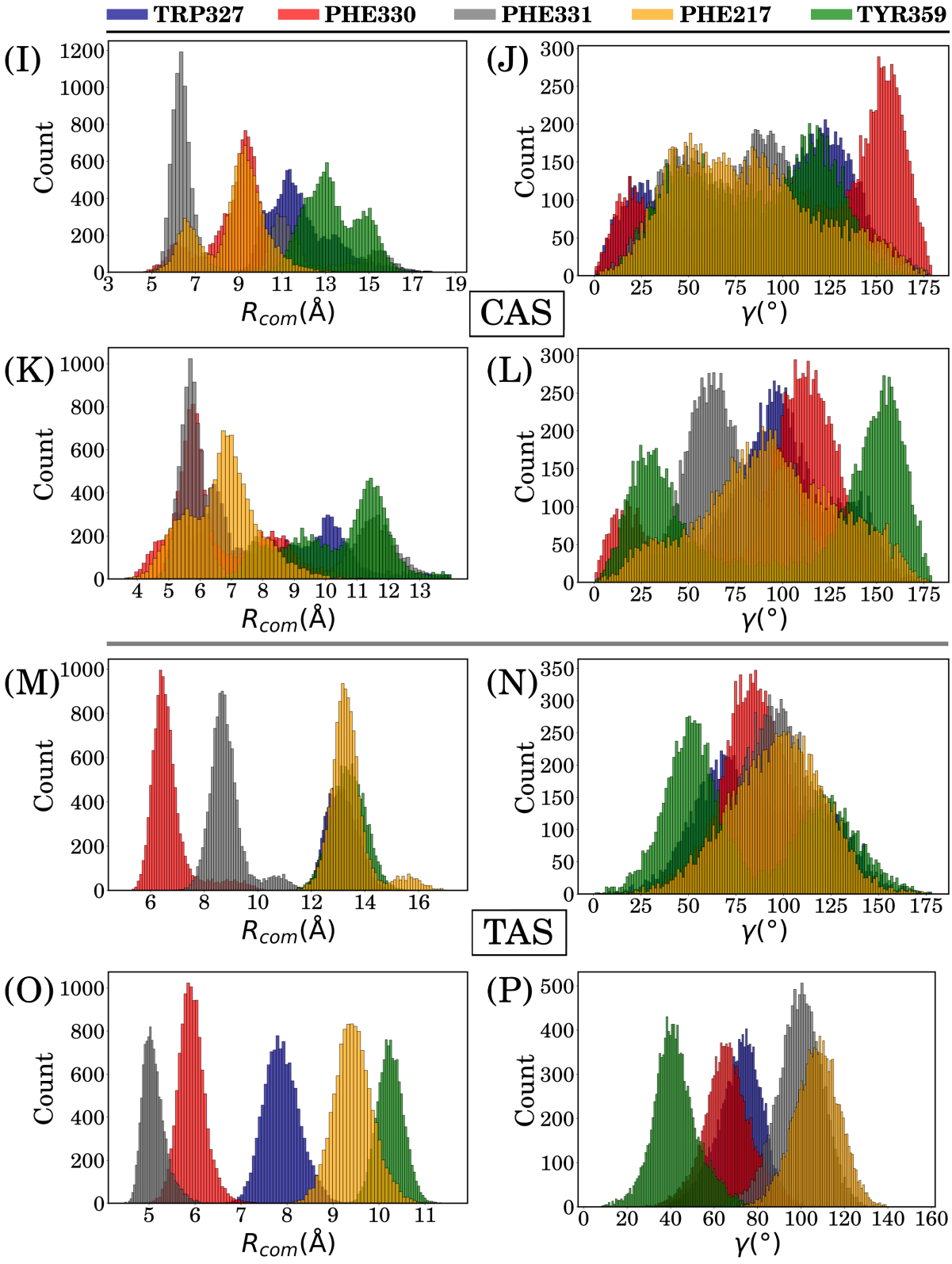

FIG. S6: Qualitative stacking interaction plots for the both complexes (embedded within the POPC membrane). Panels (I), (J) and (M), (N) represents the R_{com} and γ, respectively for the azo part; While panels (K), (L) and (O), (P) are corresponding plots for the sero part.

S6:MM interaction energy between aromatic residues of interest and ligands

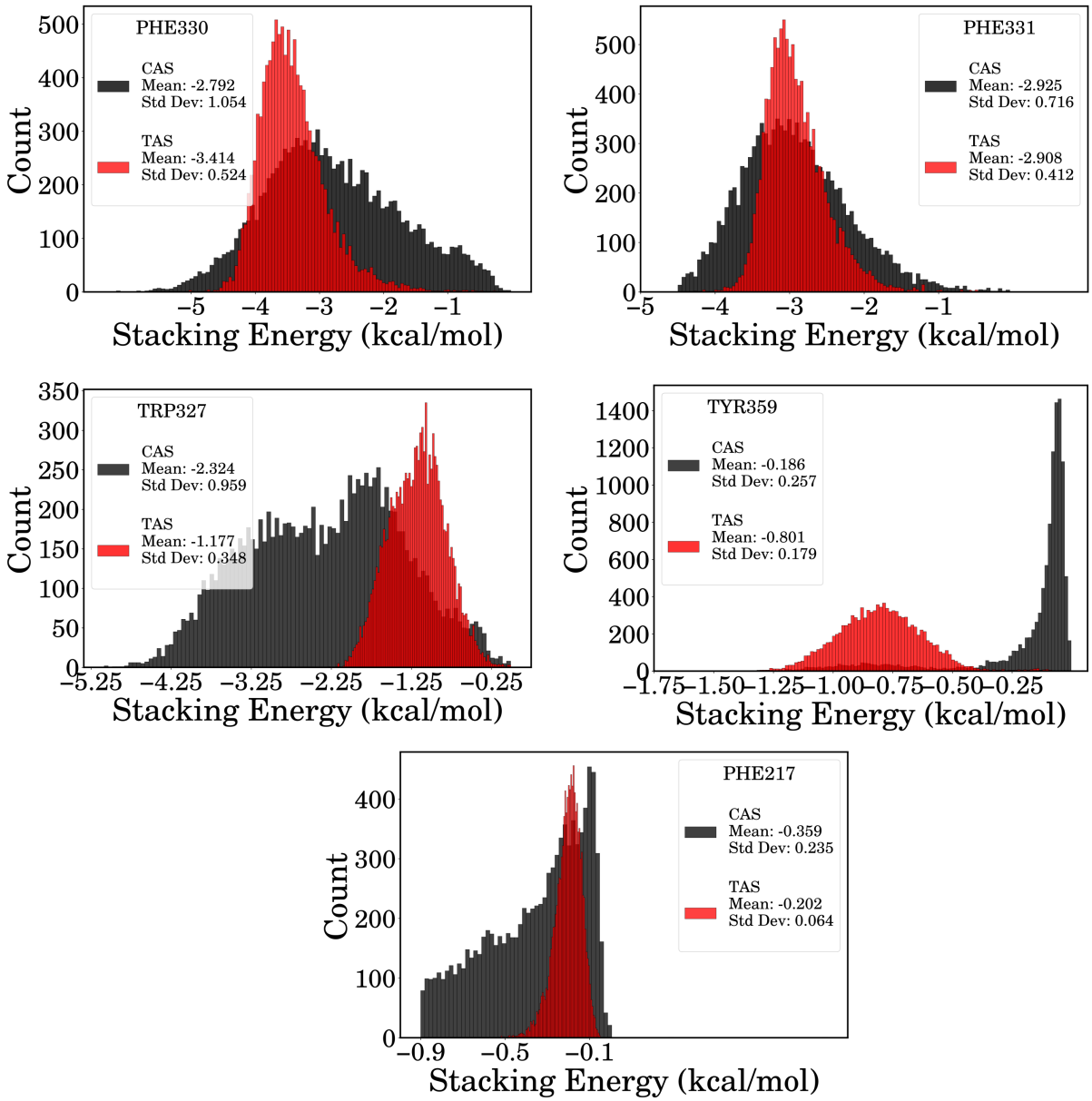

FIG. S7: MM non-bonded interaction energy plots of key residues with TAS and CAS ligands in protein without the POPC membrane.

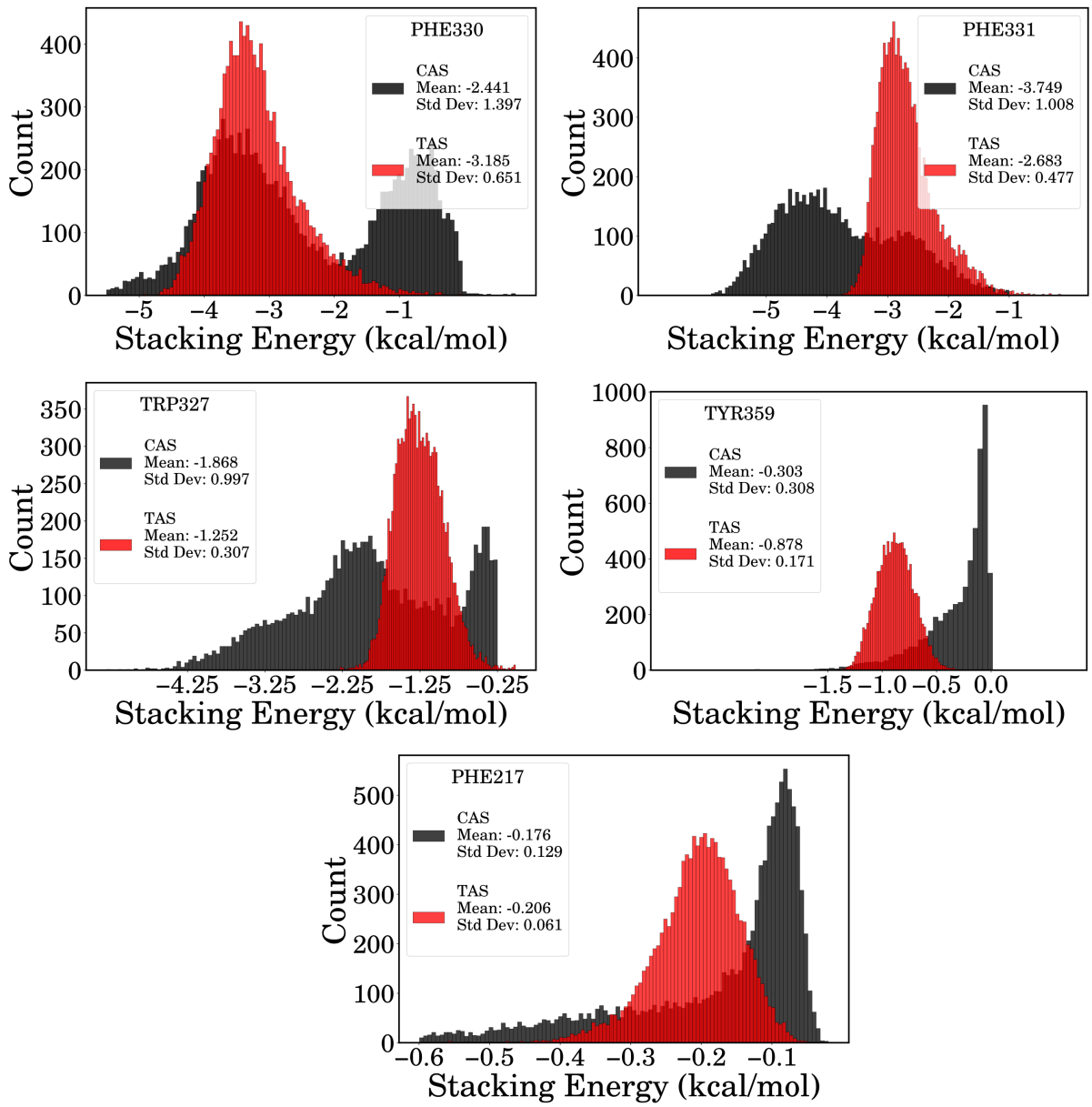

FIG. S8: MM non-bonded interaction energy plots of key residues with TAS and CAS ligands in protein with the POPC membrane.

The larger standard deviation value of MM interaction energy between aromatic residues of interest and the CAS ligand compared to that of the TAS ligand implies the higher fluctuation and lesser stability of the CAS-receptor complex (as also evident from all other analyses). It should be noted that the whole TAS/CAS ligand is taken as a single moiety while calculating the MM interaction energy.

S7: Difference dynamic cross correlation (DDCC) between CAS-receptor and TAS-receptor

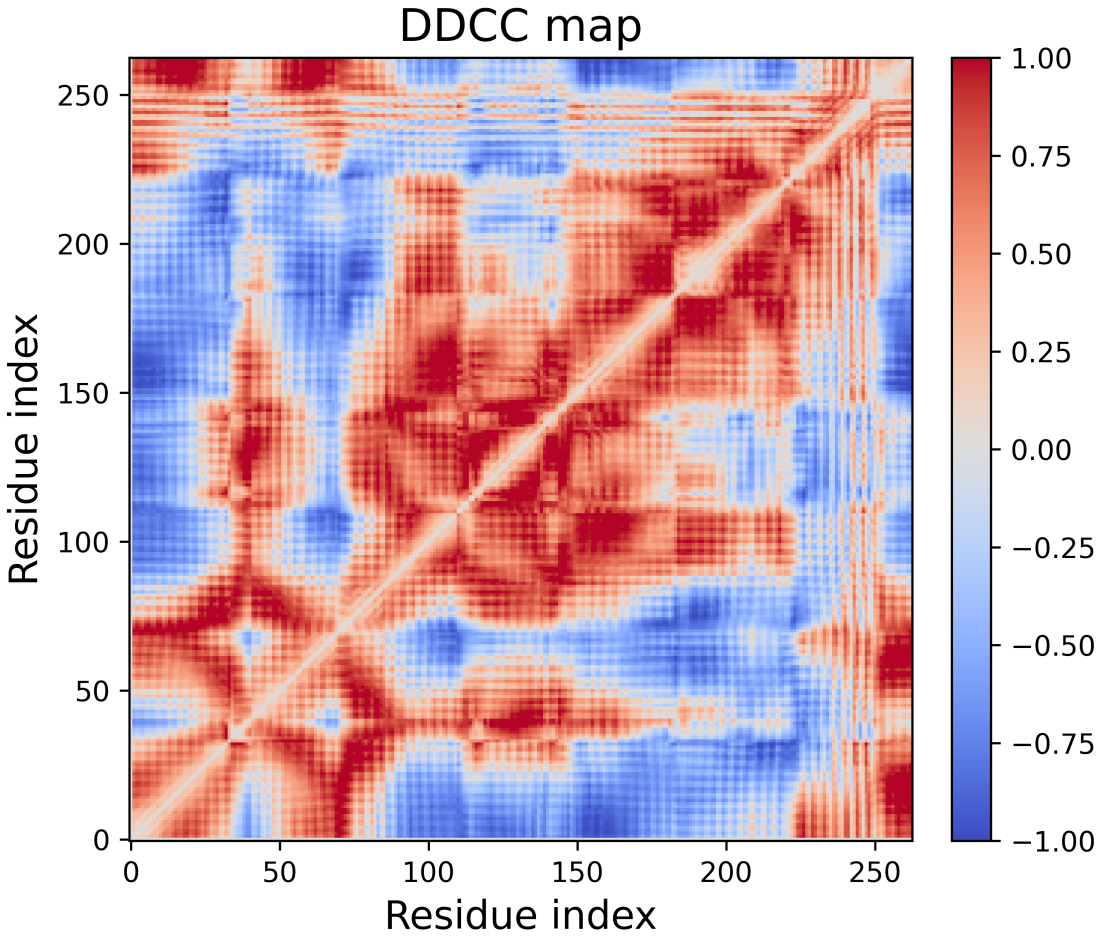

FIG. S9: Difference dynamic cross correlation (DDCC) map between CAS-receptor complex and TAS-receptor complex

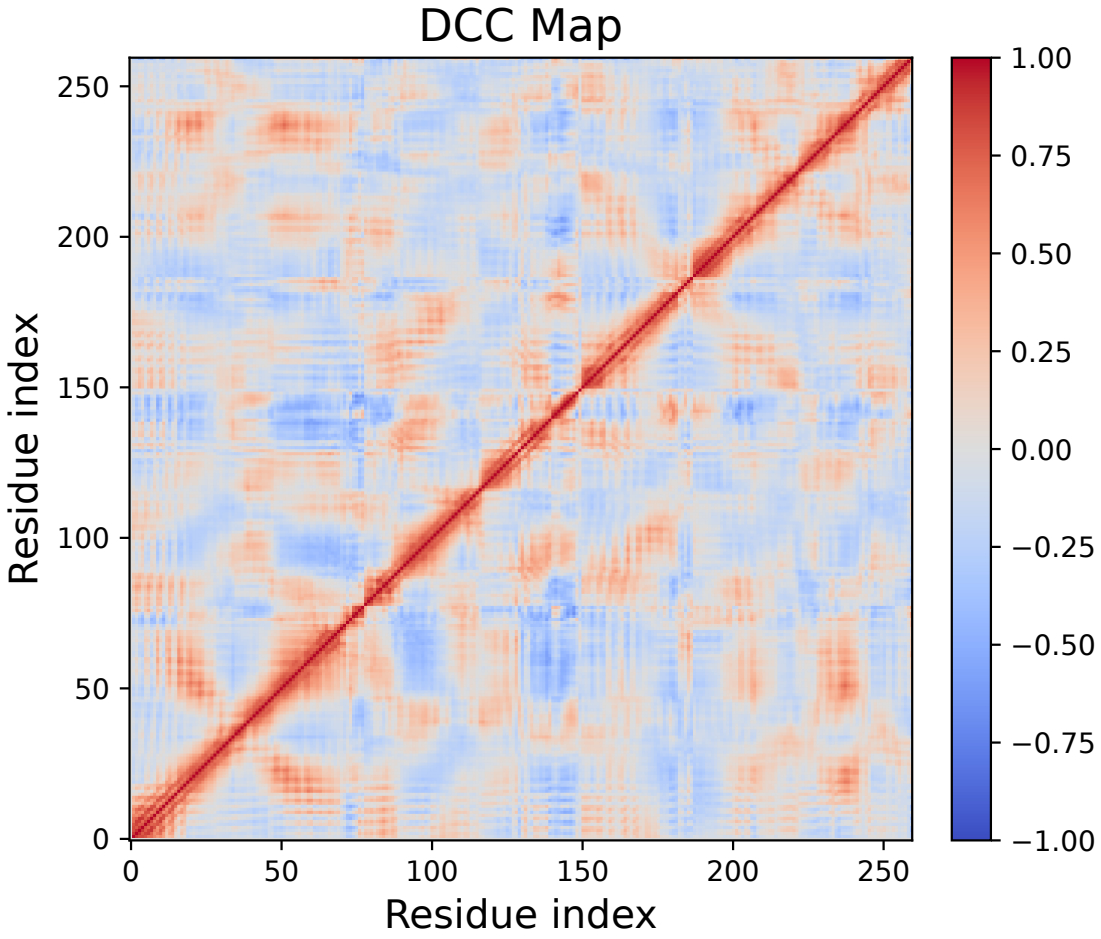

FIG. S10: Dynamic cross correlation (DCC) map for the apo-receptor (without any ligand)