Title: The 3D structure prediction of TAS2R38 bitter receptors bound to agonists phenylthiocarbamide (PTC) and 6-n-Propylthiouracil (PROP)

Supplementary Information

Methods of Molecular Dynamics Simulation

We performed molecular dynamics (MD) simulations of the predicted structure of bitter taste receptor with and without ligand for 10 ns in explicit lipid bilayer and water. We carried out MD simulations using NAMD including explicit water and a periodically infinite lipid to determine the interactions of the protein with lipid and water. We used the CHARMM22 force field parameters for the protein, the TIP3 model for water, and the CHARMM27 force field parameters for the lipids. Quantum charges from DFT/6311G** method were used for these ligands. We started with the predicted protein structure, stripped away the lipid molecules, and inserted it in a periodic structure of 1-palmytoil-2-oleoylsn-glycero-3-phosphatidylcholine (POPC). In this process, we eliminated lipid molecules within 5 Å of the protein. Then, we inserted this in a box of water molecules and eliminated waters within 5 Å of the lipid and protein. Chloride ions were added to neutralize the charge of the system. The membrane and water molecules were minimized with the protein fixed, and then equilibrated for 500 ps in an NPT simulation. Finally, the entire system was minimized, and then 10 ns of NPT simulation was run. All NPT simulations were run using Langevin dynamics with a damping coefficient of 1 ps^{-1} and a bath temperature of 310 K. The pressure was kept constant by Nosé-Hoover Langevin piston pressure control, with a target pressure of 1 atm and barostats oscillation and damping times of 200 fs. The step size was 1 fs, with periodic boundary conditions applied. The full system (Figure S4) contains the predicted protein, 101 lipid molecules, 7528 water molecules, and 19 chlorine ions for a total of 41570 atoms per periodic cell for apo-

PAV protein. That of apo-AVI protein contains the predicted protein, 102 lipid molecules, 7498 water molecules, and 19 chlorine ions for a total of 41619 atoms per periodic cell. That of PAV protein bound to PTC contains the predicted protein, 104 lipid molecules, 5626 water molecules, and 19 chlorine ions for a total of 36284 atoms per periodic cell. That of AVI protein bound to PTC contains the predicted protein, 105 lipid molecules, 7387 water molecules, and 19 chlorine ions for a total of 41706 atoms per periodic cell. The box size is 75 Å by 75 Å by 85 Å. We then used the NAMD program to carry out 10 ns of NPT MD with a bath temperature of 310 K.

Table I. BiHelix and ComBiHelix results for the PAV variation of bitter taste receptors in the different receptor templates.

Receptor Templates	**Rotational Angle**							**Total Energy (Kcal/mol)**
	H1	***H2***	***H3***	***H4***	***H5***	***H6***	***H7***	
tβ1AR	30	330	60	90	180	**270**	30	598.1
hβ2AR	30	330	60	120	330	**90**	270	754.5
BovR	0	0	60	150	330	**30**	330	997.3
$hAA_{2A}R$	0	330	30	180	0	**30**	0	932.8

Figure S1 Sequence alignment against tβ1AR, hβ2AR, Rhodopsin and hAA2AR for TAS2R38 bitter taste receptor variants PAV.

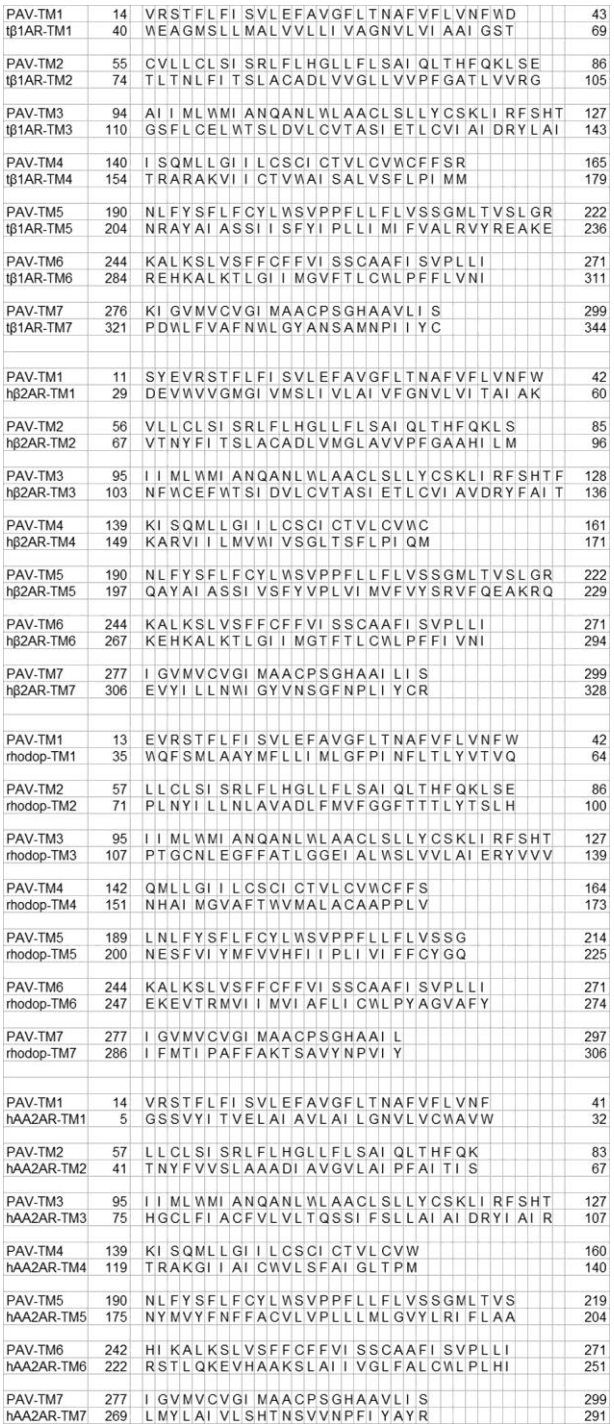


Figure S2. The prediction of 7 hydrophobic regions from PredicTM

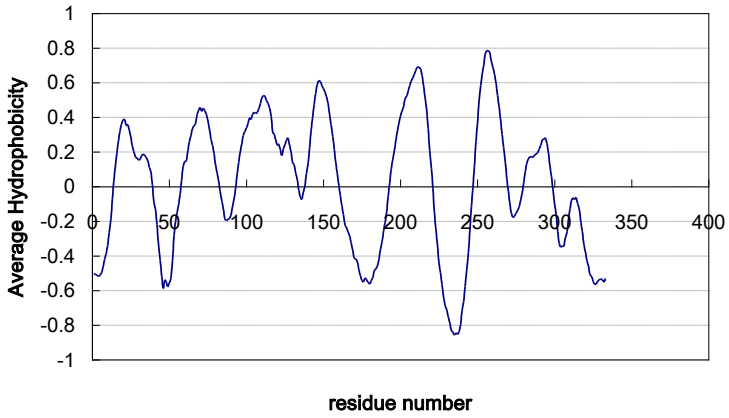


Figure S3 Predicted 3D structures of bitter taste receptors PAV based on the four templates (a) tβ1AR, (b) hβ2AR, (c) Rhodopsin and (d) $hAA_{2A}R$ from BiHelix. (Residue A262 in the TM6 are highlighted here)

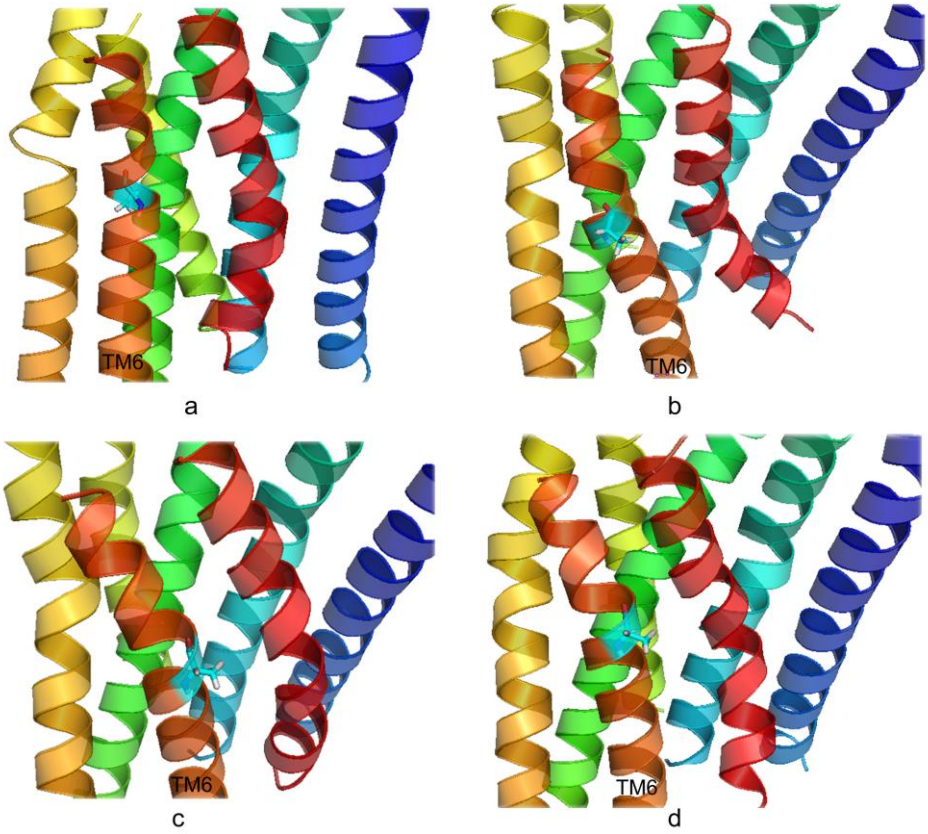


Figure S4. The molecular dynamics simulation box of TAR2S38 bitter receptor with lipid and water. The EC region is at the top.

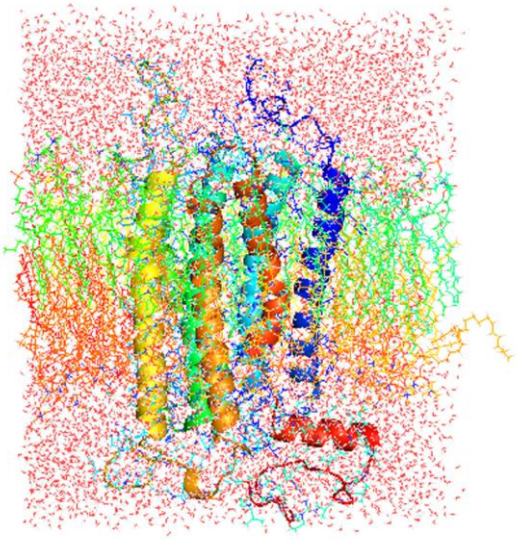
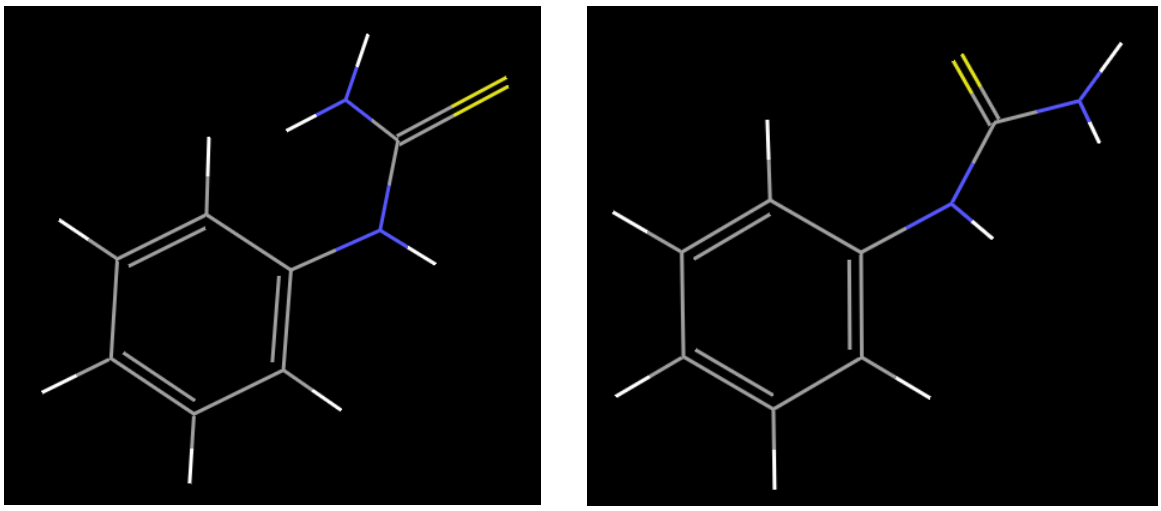
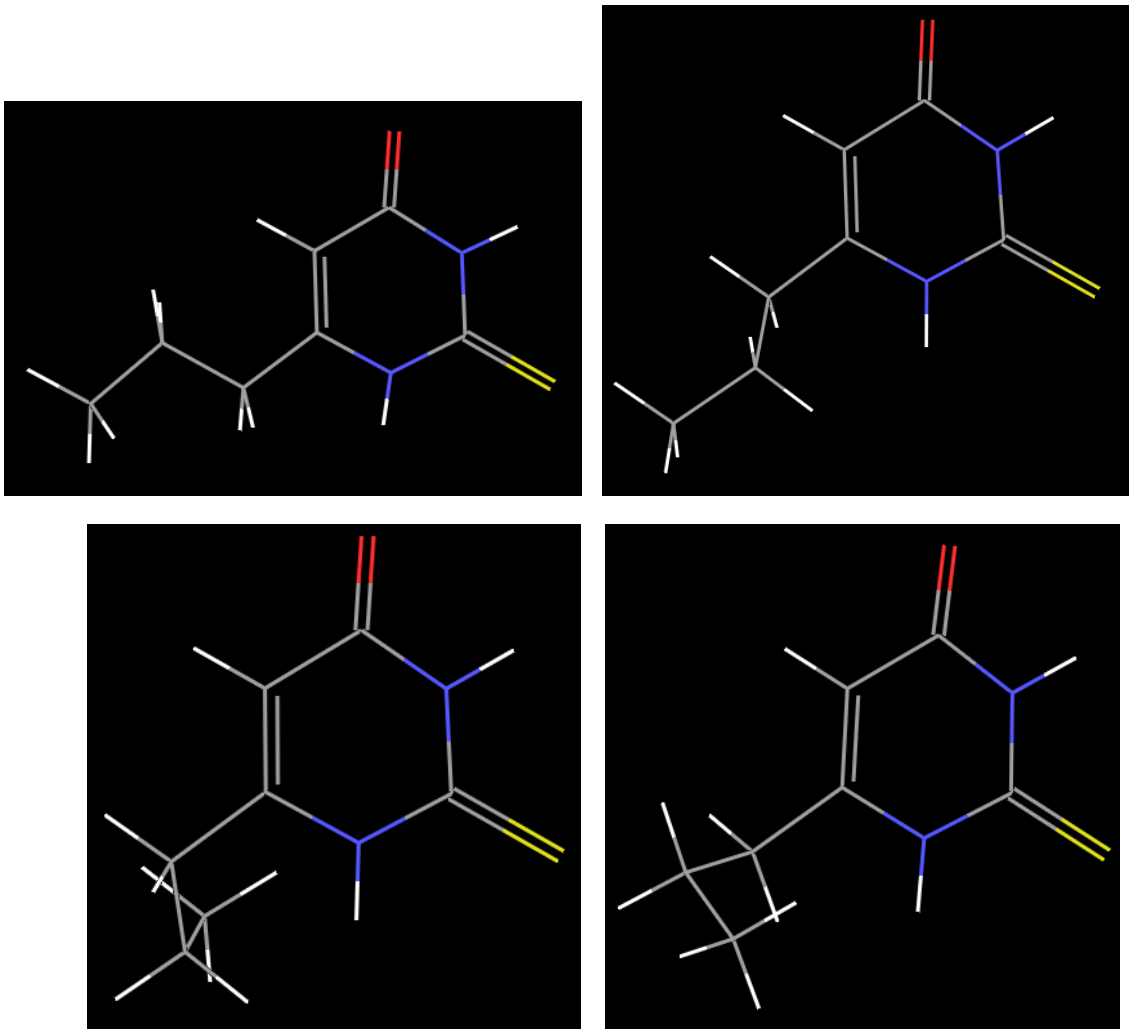


Figure S5 The 2 conformations of PTC and 4 of PROP docked to bitter taste receptor hTAS2R38.

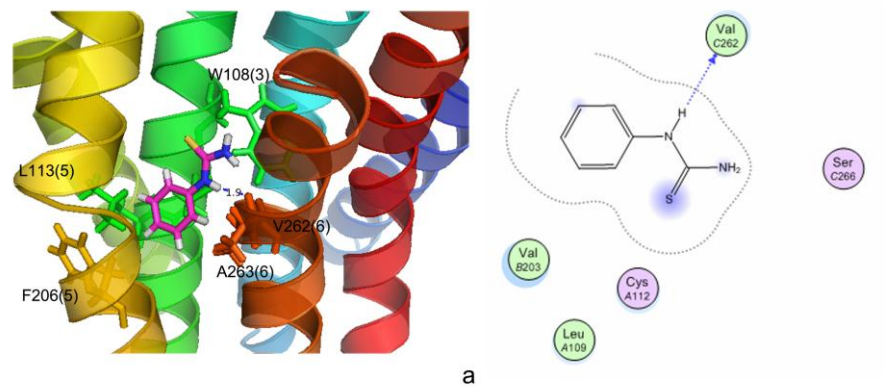


a

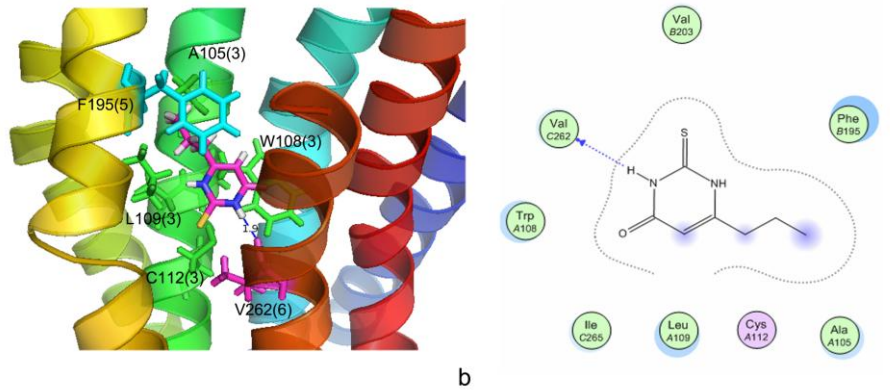


b

Figure S6 Predicted binding sites of agonists in bitter taste receptors. (a) PTC in hTAS2R38$_{PVV}$, (b) PROP in hTAS2R38$_{PVV}$, (c) PTC in hTAS2R38$_{AAI}$, (d) PROP in hTAS2R38$_{AAI}$.



a



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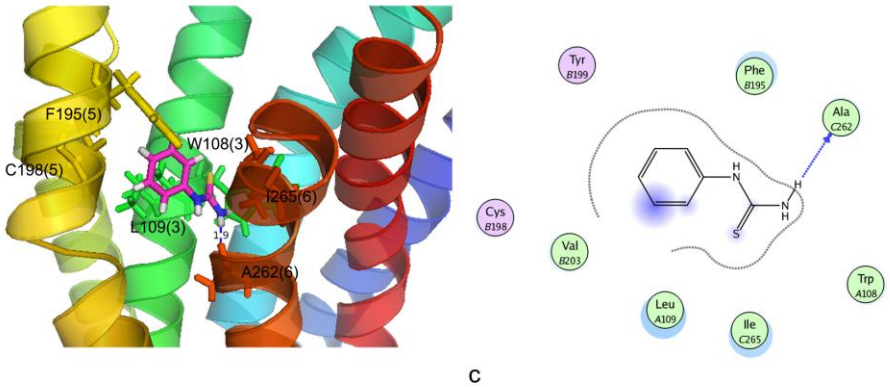

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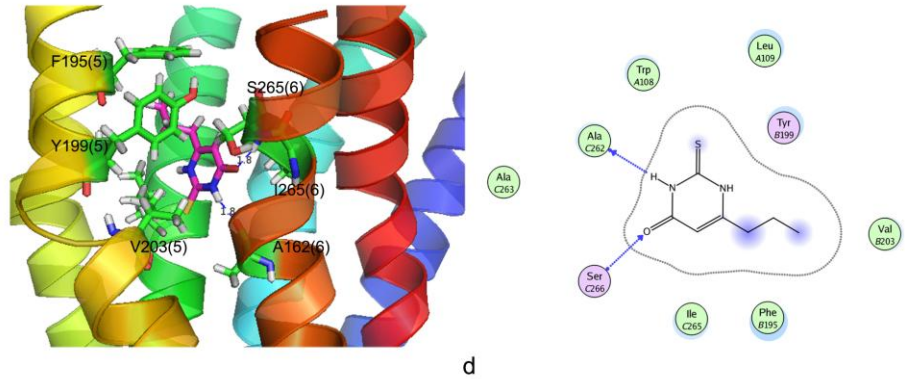

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