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TAKEDA G-PROTEIN RECEPTOR (TGR)-5 EVOLVES CLASSICAL ACTIVE-STATE CONFORMATIONAL SIGNATURES IN COMPLEX WITH CHROMOLAENA ODORATA FLAVONOID

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Chromolaena Odorata-derived flavonoid-5, 7-dihydroxy-6-4-dimethoxyflavanone (COF) has been identified as a major anti-diabetic agent targeting Takeda G-protein receptor 5 (TGR5) activation resulting in glucagon-like peptide-1 stimulation. This study provides structural and dynamic insights into COF/TGR5 interaction by investigating classical GPCR activation signatures (TMIII-TMVI ionic lock, toggle switches, internal water pathway) in comparison with known agonist (INT-777), antagonist (triamterene, TRX) and apo-state using MD simulation. $Y89^{3.29}$, $N93^{3.33}$ and $S270^{7.42}$ are key residues involved in ligand binding. Continuous internal water pathway connects the hydrophilic substituents of the ligand to the TMIII-TMVI interface in COF and INT-777 bound TGR5 but not TRX-bound TGR5. TMIII-TMVI ionic locks are ruptured in COF and INT-777 bound TGR5 but not TRX-bound, ionic lock rupture is associated with evolution of active-state "VPVAM" (analogous to NPxxY) conformation. Dihedral angles (x^2) calculated along the trajectory strongly suggest $W237^{6.48}$ as a ligand-dependent but not agonist-dependent toggle switch. In conclusion, TGR5 evolves active state conformation from a starting intermediate state conformation when bound to COF and INT-777, which further explains their underlying anti-diabetic activities.

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