Elucidating Structural Determinants of Biased Signaling at the 5-HT$_{1A}$ G Protein-Coupled Receptor through Molecular Dynamics Simulations

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G Protein-Coupled Receptors (GPCRs) represent a class of structurally conserved membrane proteins characterized by seven transmembrane helices, playing pivotal roles in diverse physiological functions. With over 800 coding genes attributed to this protein class, and nearly 30-40% of FDA-approved drugs targeting them, their significance in drug development is paramount. Notably, the myriad signaling pathways mediated by distinct G proteins and effector proteins like β-arrestin underscore the immense pharmacological potential of GPCRs.

In particular, the 5-HT$_{1A}$ receptor emerges as a compelling target for pain management. This study unveils the discovery of ST171, a novel compound exhibiting functional selectivity towards the G_i protein while displaying minimal recruitment of β-arrestin. Furthermore, whereas serotonin manifests a bell-shaped inhibition of cAMP formation—indicative of G_s protein recruitment at higher concentrations—ST171 demonstrates a sigmoidal inhibition curve, signifying exclusive G_i recruitment even at elevated concentrations. Molecular dynamics (MD) simulations elucidate that the interaction between the benzoxazinone moiety of ST171 and Tyr96$^{2.64}$ induces a notable impact on the TM2-TM3 distance, potentially accounting for ST171's preference for G_i over G_s. Additionally, the benzoxazinone moiety fosters hydrogen bond formation between Gln97$^{2.65}$ and Trp387$^{7.40}$, providing a mechanistic basis for ST171's selectivity towards G_i protein over β-arrestin.

Lastly, comparative simulations between the ternary and binary complex models reveal that the ST171-bound binary complex maintains its conformation consistently throughout the simulation, distinguishing it from other ligand-bound complexes. In summation, these findings hold promise for ushering in a new era of secure and efficacious analgesics.