SERINE 242$^{5.46}$ AND ALANINE 222$^{5.46}$ AS DETERMINANTS OF 5-HT$_{2A/2C}$ SELECTIVITY

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The human 5-HT$_2$ receptor family consists of three subtypes, 5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$, that have high sequence identity in their orthosteric ligand-binding domain. Nevertheless, activation of each of these subtypes is associated with different pharmacological outcomes. 5-HT$_{2A}$ agonists are generally viewed as potential psychedelic drugs, the 5-HT$_{2B}$ receptor is considered an "antitarget" that leads to cardiac valvulopathy, and the 5-HT$_{2C}$ receptor currently attracts interest as a target for appetite inhibitors. The simpler tryptamine and phenethylamine agonists of these receptors usually show little subtype selectivity, which is understandable considering the near-identity of their orthosteric binding pocket.

We have synthesized a small collection of phenethylamine analogs in which the benzene ring is replaced by a bulky dibenzo[*b,d*]furan moiety. Radioligand displacement and calcium mobilization studies indicated that our compounds had worse than micromolar affinity as 5-HT$_{2A}$ receptor agonists, while their affinities at the 5-HT$_{2C}$ receptor were at least an order of magnitude better and in one case a K_i = 35 nM was achieved, with full agonism and EC_{50} = 222 nM. Molecular docking studies of this compound at both receptor subtypes revealed the structural basis of its selectivity. In the 5-HT$_{2C}$ receptor, the dibenzofuran ring system interacts strongly with the conserved Phe$^{6.51}$ and Phe$^{6.52}$ residues (the latter forming part of the toggle switch believed to initiate activation of monoamine GPCRs) and forms a hydrogen bond with Ser$^{5.43}$. In the 5-HT$_{2A}$ receptor the replacement of Ala$^{5.46}$ by the bulkier Ser$^{5.46}$ obliges the dibenzofuran to adopt a slightly different pose where its interaction with Phe$^{6.52}$ is considerably weakened and the hydrogen bond is broken. We feel that this difference is a likely explanation of the 70-fold ratio of the affinities and potencies of this compound for both 5-HT$_2$ receptor subtypes, and that it should be exploited for the design, synthesis and assay of further potentially 5-HT$_{2C}$-selective ligands.