Design and Molecular Modeling of D_2R/NTS_1R Heterodimer-Selective Ligands

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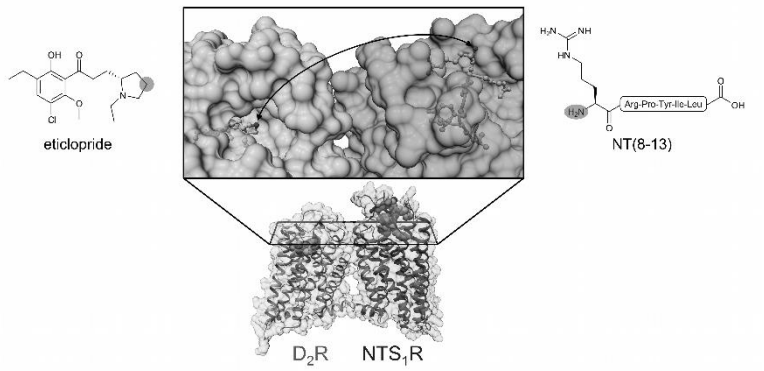
Dopamine D_2 receptors (D_2Rs) regulate a large number of physiological functions and are involved in a number of neuropsychiatric disorders including schizophrenia and Parkinson's disease. Along with numerous other GPCRs, dopamine D_2Rs have been proven to form both homodimers [1] and heterodimers [2]. Among receptors interacting with D_2Rs in the CNS, the neurotensin receptor subtype 1 (NTS_1R) has gained substantial interest. Both GPCRs are closely associated and highly co-localized in vivo [3].

A powerful tool to address GPCR dimers are bivalent ligands bridging the two neighbored orthosteric binding sites, of which the design can be quite challenging. However, high resolution crystal structures of GPCRs revealing a dimeric orientation opened new opportunities to design bivalent ligands in a rational way.



We made use of the crystal structure of the β_1-adrenergic receptor [4] and build a D_2R/NTS_1 heterodimer model, with the dimer protomers based on a D_2R homology model (based on D_3R [5]) and a crystal structures of NTS_1R [6]. The crystal structure revealed a dimer interface involving transmembrane helix 1 (TM1), TM2 and helix 8. The dimer model could be used to select linker attachment points for both D_2R and NTS_1R pharmacophores as well as to determine suitable linker lengths. Molecular dynamics simulations with 3 representative ligands, performed to validate ligand design, showed stable receptor-ligand complexes supplying a good basis for further experimental evaluation.

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