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Screening for $GABA_B$ receptor compounds

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γ-aminobutyric acid (GABA) is the main inhibtorial transmitter in the CNS. GABA exerts its function by binding to $GABA_A$, $GABA_B$ and $GABA_C$ receptors. $GABA_A$ and $GABA_C$ receptors are pentameric ligand gated ion channels, while the $GABA_B$ receptor is a family C GPCR. The $GABA_B$ receptor is implicated in a variety of psychiatric and neurological conditions including depression, anxiety, schizophrenia, epilepsy, addiction, pain and obsessive compulsive disorder, and is a functional heterodimer consisting of two subunits ($GABA_{B1}$ and $GABA_{B2}$). Each subunit consists of an N-terminal extracellular Venus flytrap (VFT) domain, a seven transmembrane (TM) helical domain and a C-terminal tail. The orthosteric binding site recognized by agonists (including GABA) and antagonists are located within the VFT domain of the $GABA_{B1}$ subunit, while an allosteric binding site is located within the 7TM of the $GABA_{B2}$ subunit. The structure of the orthosteric VFT domain is known, while the structures of the the $GABA_{B1}$ subunit and the allosteric $GABA_{B2}$ subunit are not known.

In the present study, we are using a combination of ligand based and structure based virtual screening to identify new compounds for the $GABA_B$ receptor. 2D fingerprints and pharmacophore models were generated based on known $GABA_B$ compounds, and used to screen available databases. Hits from the ligand based approach were used for docking. Homology modeling was used to construct models of the allosteric $GABA_{B2}$ subunit using structural templates from family A (rhodopsin, β2-adrenergic), family B (corticothropin releasing factor, glucagon receptor) and family C (mGlu1 and mGlu5). The different models were evaluated by docking of 74 known positive allosteric modulators and decoys, and the best performing models were used for docking hits from the ligand based approach. The most promising hits from the docking were purchased and tested experimentally. Preliminary experimental testing indicates that we have identified novel $GABA_B$ receptor compounds.

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