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Screening for new GABA$_B$ receptor compounds

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The main inhibtorial transmitter in the CNS is γ-aminobutyric acid (GABA), which exerts its function by binding to GABA$_A$, GABA$_B$ and GABA$_C$ receptors. The 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. The receptor is a functional heterodimer consisting of the GABA$_{B1}$ and GABA$_{B2}$ subunits. 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 is 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 structure of the allosteric 7TM is not known. In the present study, we have been 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, β$_2$-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.