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Identification of small aromatic ligands to GABA-A receptor associated protein GABARAP

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Type-A receptors for the neurotransmitter GABA (gamma-aminobutyric acid) are ligand-gated chloride channels that mediate inhibitory neuro-transmission. The 14 kDa GABA-A receptor associated protein GABARAP interacts with the gamma2 subunit of GABA-A receptor and modulates channel kinetics and promotes channel clustering. GABARAP is involved in receptor trafficking and targeting to GABAergic synapses.

With Phage Display methods we identified peptides with micromolar affinity for GABARAP. Although exhibiting great sequence diversity, the most prominent common feature of the selected peptides was a tryptophan residue occurring in all peptides. This lead us to further investigate the role of this tryptophan residue in GABARAP-ligand interactions.

We used saturation transfer difference NMR (STDNMR) in order to identify tryptophan-derived small aromatic molecules which interact with GABARAP. Chemical shift perturbation and J-surface analysis allowed for mapping of the indole moiety's binding site to GABARAP.