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Title: Towards Selective Ligands for the $GABA_A$ Receptor α+/β - Interface

Abstract in English:

The neurotransmitter γ - aminobutyric acid (GABA) occurs ubiquitously in our central nervous system (CNS) and binds, *inter alia*, to a class of ligand-gated ion channels called $GABA_A$ receptors. These pentameric receptors are targets of many clinically relevant drugs (e.g. benzodiazepines). The family contains many different subunits which are further classified into isoforms (e.g. α1-6, β1-3, γ1-3, etc). Thus, there exists an enormous number of possible different subunit assemblies (receptor subtypes) which results in a very complex pharmacology of these receptors. Hence, the exploration of selective pharmacological tool compounds to study $GABA_A$ receptors is of great importance.

The compound class of pyrazoloquinolinones (PQs) is known to interact with the high affinity α+/γ2− interface (benzodiazepine binding site) and the low affinity modulatory site at the α+/β−interface. Therefore, PQs represent a suitable starting point to study the molecular determinants which influence the mechanism of allosteric modulation at the two homologous binding sites.

In this thesis we focused on the synthesis of a systematic library of differently substituted PQs to examine molecular determinants which trigger potency and efficacy at the α+/β− and the α+/γ2− sites. Based on this library we were able to identify two subtype selective prototypes which served as proof of concept in the development of urgently required subtype selective tool compounds. Furthermore, we identified one compound which represents a lead towards subtype selective ligands for the α+/β− interface exclusively.

Moreover, different homology models were generated to improve the understanding of the structural requirements of allosteric modulation. Experimentally, we studied a quadruple mutant to study different benzodiazepine ligands. Interestingly, we revealed that the allosteric modulation at both sites seemingly follows a quite conserved mechanism and that similar benzodiazepine ligands can have different binding poses.

Ultimately, we elucidated the binding mode of PQs at the α1+/γ2- site by establishing a novel docking protocol which assesses SAR data during the scoring process. The combination of these findings led to innovative ligand designs which should exclusively interact with the α+/β− interfaces and will be investigated in future studies.