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## PhD Thesis title: "Structural basis of allosteric $GABA_A$ receptor modulation"


**ABSTRACT**

$GABA_A$ receptors constitute prominent ionotropic receptors in the central nervous system (CNS), as well as important elements in peripheral tissues. They are important therapeutic targets modulated by multiple drugs such as benzodiazepines, barbiturates and neurosteroids that mediate among others anticonvulsant activity and general anesthesia. A staggering variety of receptor subtypes and thus binding sites exists, resulting in an intrinsically complex pharmacological profile. The atomic resolution structures of several receptors of the cys-loop family, including $GABA_A$ receptors, and their homology models can give insights into the structural features of different subtypes. The aim of this thesis was to improve the understanding of the molecular and structural rules which underlie allosteric modulation of $GABA_A$ receptors, in part also applied to subtype selective ligands.

Structure-activity data drives the finetuning of ligand/ protein interactions both for known and unknown binding sites. In this work, I present the development and characterization of subtype selective pyrazoloquinolinone ligands with optimized selectivity profiles towards two sites of interest and reduced off-target activities.

Based on structural hypotheses and mutational analysis we report that compounds of the same, clinically important, benzodiazepine class can in fact assume distinct binding modes. This finding represents one of the most crucial contributions of this thesis to the required knowledge for future optimization of the development of benzodiazepine ligands that target specific subtypes. To the same end, an interesting compound of the triazoloquinazolinedione class is introduced as a potential benzodiazepine antagonist.

Existing structural data was utilized and led to the identification of a novel binding site. This study shows that both chlorpromazine and the antipsychotic clozapine exert negative allosteric modulation on $GABA_A$ receptors and proposes this novel intra-subunit binding site as the site of action of these drugs.

In the course of this thesis I also collected and evaluated structure-activity data for synthetic natural compounds with so far unrecognized binding sites.

On the whole, the work involved in this thesis gives to a considerable extent a structural basis of allosteric $GABA_A$ receptor modulation that can serve as an invaluable foundation for future rational development of $GABA_A$ receptor ligands and contributes towards a better understanding of allosteric modulation.