

Andreas JURIK

Thesis Supervisor: Gerhard F. ECKER

Department of Pharmaceutical Chemistry, University of Vienna.

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Title: In Silico Evaluation of Inhibitor Binding Modes in the Gamma-Aminobutyric Acid Transporter System

Abstract in English

Fast and selective reuptake of gamma-aminobutyric acid (GABA) from the synaptic cleft is an essential process during neurotransmission. Likewise, selective inhibition of its reuptake carriers is a strategy for the pharmacotherapy of central nervous diseases. Emergence of crystallographic data for remotely related transport proteins allowed vital insights into the structural arrangement of the four GABA transporter (GAT) subtypes, albeit at low template-target sequence identity. This rendered potential comparative modeling processes risky without data providing experimental backup.

This thesis focuses on investigating the molecular basis of GAT inhibition with an emphasis on computational methods. Three independent studies exemplify specific challenges associated with the target family. At first, known GAT inhibitors from the literature were collected in order to exploit available knowledge about activity-determining structural properties on the ligand side, and quantify their respective contributions. Subsequent docking studies were able to reflect activity trends by the topology of the modeled hGAT-1 substrate binding site. Further support for a comparative modeling approach came from a virtual screening campaign, successfully extrapolating the binding mode of tiagabine to pharmacologically relevant chemical space.

Encouraged by the results from the first subtype, docking studies for differentiating mGAT1 and mGAT2-selective binding modes were carried out. Sound binding hypotheses could be generated, although overall low potency of the available compounds made it clear that the results have to be used with caution. Taken together, application of structure based methods strictly scrutinized by biological data helped to gain validated insights into the molecular mechanisms of GAT inhibition, but many questions remain to be answered in order to achieve true selective GABA uptake inhibition for all subtypes.