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Pairwise structural comparison of tiagabine analogs gives new insights into their protein binding modes

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Tiagabine (Gabitril®) is a selective inhibitor of the human gamma-aminobutyric acid (GABA) transporter 1 (hGAT-1), a transport protein belonging to the family of neurotransmitter-sodium-symporters (NSS). It is a marketed drug, used for treatment of epilepsy. However, the molecular basis of protein-ligand interaction remains obscure due to the lack of a 3D structure of the target protein.

In order to identify activity-determining structural features of a series of tiagabine analogs taken from literature [1-3], we chose an approach combining traditional methods of molecular modeling with exhaustive sampling of docking poses, and a pairwise comparison of structural features and their respective bioactivity values.

We determined a common binding mode of tiagabine analogs, which is in nice agreement with literature [4]. Further, we were able to trace back considerable differences in inhibitory activities to distinct molecular attributes of the analogs.

Our study revealed the molecular explanation for the importance of a polar linker region and thus paves the way for subsequent screening efforts in the search for novel GAT-1 inhibitors.

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References

1. Andersen KE, *et al*: **The synthesis of novel GABA uptake inhibitors. 1. Elucidation of the structure-activity studies leading to the choice of (R)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid (tiagabine) as an anticonvulsant drug candidate.** *J Med Chem* 1993, **36**:1716-1725.
2. Knutsen LJ, *et al*: **Synthesis of novel GABA uptake inhibitors. 3. Diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine as anticonvulsant agents.** *J Med Chem* 1999, **42**:3447-3462.
3. Andersen KE, *et al*: **Synthesis of novel GABA uptake inhibitors. 4. Bioisosteric transformation and successive optimization of known GABA uptake inhibitors leading to a series of potent anticonvulsant drug candidates.** *J Med Chem* 1999, **42**:4281-4291.
4. Skovstrup , *et al*: **Homology modelling of the GABA transporter and analysis of tiagabine binding.** *Chem Med Chem* 2010, **5**:986-1000.

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