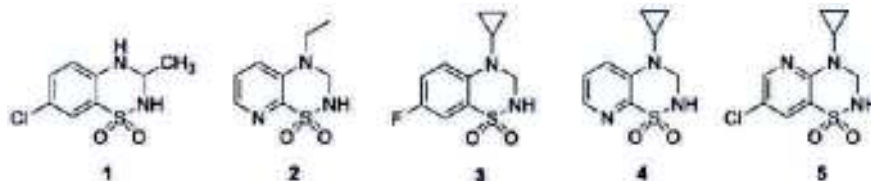


(PTDs) and BTDs. The first series of PTDs isosters of the reference compound IDRA-21 (**1**) allowed the establishment of coherent structure–activity relationships and led to the identification of **2** as one of the most potent PTD-type AMPA potentiators. Further improvement of the pharmacokinetic properties as well as of the biological activity was reached in the benzenic series by introducing a cyclopropyl side chain at the 4-position, leading to BTD compounds such as **3**. Several of these newly synthesized BTBs were co-crystallized with the ligand-binding domain (LBD) of the GluA2 subunit of AMPA receptors.<sup>[2]</sup>

The present work aimed at exploring the interaction of representative PTD-type AMPApams (such as **2**) with the GluA2 LBD in order to study the impact of the position of the nitrogen atom on their binding mode and affinity for the AMPA receptors. This study was completed by the synthesis and biological evaluation of new pyridothiadiazines belonging to the different heterocyclic subclasses and bearing the cyclopropyl group at the 4-position (i.e. compounds **4** and **5**). 4-Cyclopropyl-substituted compound **4** was found to provoke a much more pronounced potentiation of AMPARs than the corresponding 4-ethyl-substituted PTD (**2**).



#### References:

- [1] B. Pirotte, P. Francotte, E. Goffin, P. de Tullio, *Expert Opin. Ther. Pat.* **2013**, *23*, 615–628.  
[2] A.B. Nørholm, P. Francotte, L. Olsen, C. Krintel, K. Frydenvang, E. Goffin, S. Challal, L. Danober, I. Botez-Pop, P. Lestage, B. Pirotte, J.S. Kastrup, *J. Med. Chem.* **2013**, *56*, 8736–8745.

#### A010 | Scaffold Optimization of the GABA<sub>A</sub> Receptor Ligand Valerenic Acid

Gerit Pototschnig,<sup>(1)</sup> Max Haider,<sup>(1)</sup> Denise Luger,<sup>(2)</sup> Steffen Hering,<sup>(2)</sup> Marko D. Mihovilovic<sup>(1)</sup>

1) Vienna University of Technology, Getreidemarkt 9 / 163, 1060 Vienna, Austria

2) University of Vienna, Althanstraße 14, 1090 Vienna, Austria

Anxiety and panic disorders are amongst the most common mental diseases worldwide. Most effectively, these diseases are treated with benzodiazepines. However, these compounds are known to cause severe side effects like confusion, fatigue and drug addiction. Valerenic acid, a sesquiterpenoidal compound isolated from roots of *Valeriana officinalis*, acts as subtype selective allosteric ligand on the GABA<sub>A</sub> receptor.<sup>[1]</sup> The highly pronounced selectivity for  $\beta_{2/3}$  over  $\beta_1$  subunits allows for addressing anxiety rather than sedation in animal models.<sup>[2]</sup> Therefore, Valerenic acid could serve as alternative for benzodiazepines for the treatment of anxiety.

To gain insight into the so far unknown binding mode and mode of action of Valerenic acid derived GABA<sub>A</sub> receptor ligands different regions of the complex original structure were modified (see Figure 1). Based on the total synthesis of Valerenic acid,<sup>[3]</sup> a set of compounds was synthesized and biologically evaluated via electrophysiology. Results from the above mentioned structural alterations, in regions and functionalities, could give insight in the ligand–receptor interaction and elucidate structural motifs necessary for binding. We plan to further optimize the structure in terms of synthetic feasibility and biological activity.



Figure 1. Modifications of the original Valerenic acid structure.

#### References:

- [1] S. Khom, I. Baburin, E. Timin, A. Hohaus, G. Trauner, B. Kopp, S. Hering, *Neuropharmacology* **2007**, *53*, 178–187.  
[2] S. Khom, B. Strommer, J. Ramharter, T. Schwarz, C. Schwarzer, T. Erker, G. F. Ecker, J. Mulzer, S. Hering, *Br. J. Pharmacol.* **2010**, *161*, 65–78.  
[3] J. Ramharter, J. Mulzer, *Org. Lett.* **2009**, *11*, 1151–1153.