Two Approaches towards new in-depth Investigations of Monoamine Neurotransmitter Transporters

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The three monoamine neurotransmitters serotonin, norepinephrine and dopamine play a major role in our bodies' everyday functions. Malfunctions of their respective transporters SERT (serotonin transporter), NET (norepinephrine transporter) and DAT (dopamine transporter) are associated with diseases like depression, epilepsy, anxiety, ADHD and Parkinson's disease [1]. This makes in-depth understanding of SERT, NET and DAT indispensable for the design of novel drugs.

Our first approach towards control and investigation of SERT, NET and DAT utilizes methods and principles of photopharmacology. Photopharmacology enables light-induced, highly precise temporal and spatial control of e.g. ion channels and transporters [2]. By introduction of photoswitchable azo-handles into the known NET-selective substrate Reboxetine, we obtained photoswitchable inhibitors for NET.

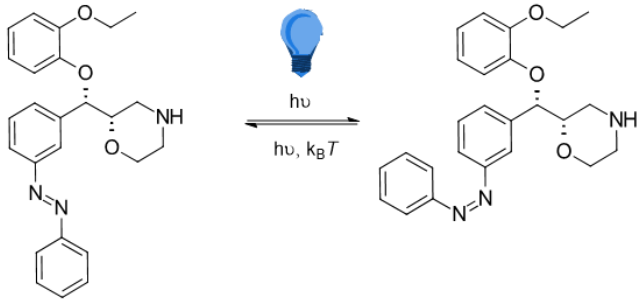

Fig. 1: Photoswitchable modified Reboxetine as its *E*- and *Z*-isomer

Investigating the SERT transport cycle, serotonin derivatives with different sidechain lengths were synthesized. Biological tests revealed that minor changes of only one or two carbons can lead to severely different binding behavior. This supports new hypotheses regarding the SERT transport cycle.

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[1] A. S. Kristensen, J. Andersen, T. N. Jørgensen, L. Sørensen, J. Eriksen, C. J. Loland, K. Strømgaard, U. Gether, *Pharmacol Rev* **2011**, *63*, 585-640.

[2] K. Hüll, J. Morstein, D. Trauner, *Chem Rev* **2018**, *118*, 10710-10747.