Synthesis of Substrates for the Investigation 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.

Utilizing principles of photopharmacology, we synthesized a photoswitchable inhibitor for NET by introduction of photoswitchable azo-handles into the known NET-selective substrate Reboxetine. Photopharmacology enables light-induced, highly precise temporal and spatial control of e.g. ion channels and transporters [2].
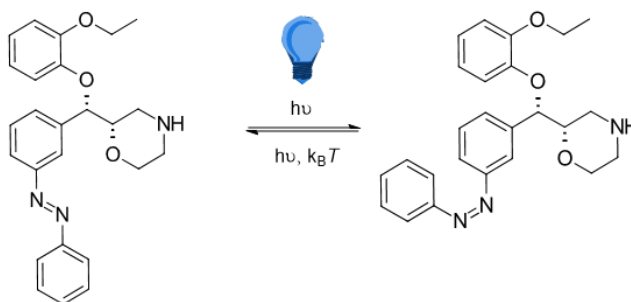
Fig. 1: Photoswitchable modified Reboxetine as its *E*- and *Z*-isomer

Investigating the SERT transport cycle, serotonin derivatives with different sidechain lengths were synthesized. Biological tests revealed that such alterations lead to severely different binding behavior, supporting new hypotheses about 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.