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Defensio: 08.08.2018

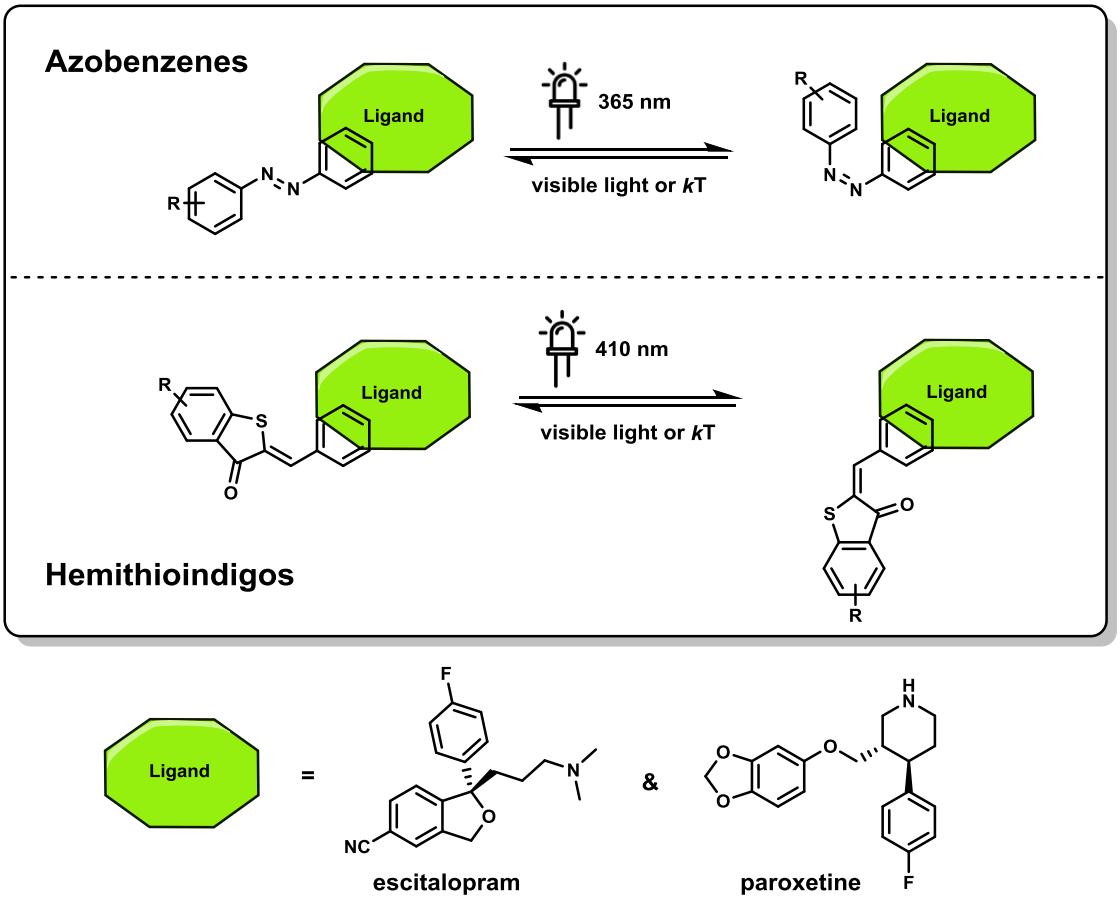
Title: Synthesis and Evaluation of Photoswitchable Monoamine Transporter Inhibitors

Abstract in English:

The monoamine transporters SERT (serotonin transporter), DAT (dopamine transporter) and NET (norepinephrine transporter) are essential regulatory features in neurotransmission. These transmembrane proteins are responsible for the reuptake of released neurotransmitters (serotonin, dopamine and norepinephrine) from the synaptic cleft and thereby terminate synaptic signaling. In consequence, transporters influence important neurological processes like mood, sleep, aggression behavior and hunger. A malfunction is linked to many serious diseases like depression, anxiety, ADHD and Parkinson's disease. Over the last decades a rich collection of pharmacologically active compounds was developed to inhibit reuptake. Many reuptake inhibitors are in clinical use best known as antidepressants. Severe side effects remain a great challenge and further insights into the functionality of transporter proteins would have tremendous implications for drug discovery and a deeper understanding of brain related processes.

The precise and reversible mode of action of photoswitchable bioactives poses a great opportunity for novel tool compounds. The research field of photopharmacology has attracted enormous interest and tremendous progress was made in the past years. In this work we sought to develop photoswitchable SERT inhibitors as novel photoswitchable tool compounds to study this important transporter with light as an accurate inhibitory stimulus.

Based on well-studied SERT inhibitors escitalopram and paroxetine we rationally designed and synthesized azobenzene and hemithioindigo analogs. The compound's photophysical parameters were thoroughly investigated. For the light-dependent biological evaluation, we developed (UV) LED well plates which allowed robust and reliable photocontrolled measurements in in-vitro assays.



From all the assessed derivatives paroxetine based azobenzene analog **DD-482** emerged as a promising lead compound. In a cell-based uptake inhibition assay the photoswitched inhibitor displayed an 11-fold higher activity compared to its thermodynamically stable configuration when 365 nm light was used for irradiation. In electrophysiological experiments, the photo-activated form was able to block the serotonin-induced current while the natural form remained ineffective. We were able to rationalize the activity difference of the two photo-isomers by computational studies on the hSERT crystal structure. When the azobenzene moiety is isomerized with UV light, the sterical bulk in an important area of the compound decreases which otherwise hinders binding and the (*Z*)-isomer can bind to the transporter in a similar fashion as the parent compound paroxetine.