A novel $GABA_A$ receptor ligand derivative that photoswitches with red light

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A balance between excitatory and inhibitory neurotransmission occurs in the central nervous system of mammals. Inhibition is mediated by two fast transmitters, glycine and gamma-aminobutyric acid (GABA). GABA released from presynaptic terminals activates ligand-gated ion channel receptors ($GABA_AR$), which are present in all organisms with a neurons system. $GABA_ARs$ constitute a key target for pharmacology since many neurodegenerative and age-related diseases result in changes in pre- and post-synaptic GABAergic and glycinergic inhibitory neurotransmission.

Drugs acting as positive allosteric modulators (PAM) or agonists of $GABA_AR$ have been effectively used as sedatives, anxiolytics, hypnotics and anticonvulsants to treat the symptoms of epilepsy, migraines and used for anesthesia during surgery. However, when applied systemically, these drugs give rise to numerous side effects and cause addiction.

The possibility to spatiotemporally control neuronal activity with light-regulated drugs is a powerful capacity of photopharmacology. This emerging field of pharmacology allows mimicking the complex activity patterns of cell-to-cell communication thanks to the use of photoswitchable drugs and controlled light stimulation.

A key step forward in the field is the possibility to address the photochromic conversion in the drug molecule with a low energy light, which is less scattered in tissue and can penetrate deeper in the body, and in the brain in particular. In this regard, a proper molecular structure should be designed to ensure a photoconversion with light in the region of red and infrared light, that effectively enabling remote photoswitching by non-invasive illumination. Here, we will present the molecular design of a novel $GABA_AR$ ligand derivative displaying photochromic properties with red light, and will discuss the synthetic procedure, the characterization of its chemical and photoisomerization properties in polar and aqueous solvents, and its photopharmacological properties.