**Development of subtype-selective photoswitchable positive allosteric modulators for mGlu receptors**

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Positive allosteric modulators (PAMs) for metabotropic glutamate receptors have been postulated to treat neuropsychiatric diseases. Besides, obtaining a reversible and efficient spatiotemporal control of mGlu activity would be therapeutically advantageous. Photopharmacology may provide a solution on this topic, since it is based on the use of light and photoswitchable ligands to modulate a protein activity. This approach offers new perspectives for drug discovery and promises a better drug action control reducing side effects to unattained levels.

Optogluram is active as a PAM of mGlu4 and mGlu6 in its trans configuration and loses activity with 380 nm illumination in its trans configuration and loses activity with 380 nm illumination. The active isomer was recovered upon illumination with 500 nm light. Here, we present a new series of 6 different analogues of Optogluram, from which Optogluram-2 emerges as a new more selective photoswitchable PAM of mGlu4 receptor. The potency of Optogluram-2 in mGlu4 is slightly lower than that for Optogluram. However, the selectivity versus mGlu6 is higher.

We have also developed photoswitchable PAMs for mGlu1 and mGlu4 in order to precisely switch on/off the activity of the receptor with light. Replacing the phtalimide moiety of a known mGlu1 PAM with a N=N bond led to azobenzene candidates. Subsequent in vitro assays revealed that Photoglurax-2 is a mGlu1 PAM ligand in the dark, whereas it loses activity under 380 nm light. It derived from the equipotent mGlu1/4 PAM Photoglurax-1 converted into a highly selective mGlu1 PAM.

Overall, we are offering to the scientific community tool compounds to fine control the activity of a mGlu subtype with light and with a high selectivity. This will allow to study pharmacological and physiological implications those mGlu subtypes with an unprecedented precision, which may lead to unexpected findings in neuroscience.