Photoswitchable carbamazepine analogs for non-invasive neuroinhibition *in vivo*

Luisa Camerin,[1,2,3] Galyna Maleeva,[1,2,+] Alexandre M. J. Gomila,[1,2,+] Irene Suárez-Pereira,[4,5,6] Carlo Matera,[1,2,7] Davia Prischich,[1,2,^] Ekin Opar,[1,2] Fabio Riefolo,[1,2,#] Esther Berrocoso,[4,5,6] and Pau Gorostiza[1,2,8,*]

1. Institute for Bioengineering of Catalonia (IBEC), The Barcelona Institute for Science and Technology
2. Networking Biomedical Center in Bioengineering, Biomaterials, and Nanomedicine (CIBER-BBN), ISCIII
3. Doctorate program in organic chemistry, University of Barcelona.
4. Neuropsychopharmacology & Psychobiology Research Group, Department of Neuroscience, University of Cádiz, Cádiz, Spain.
5. Networking Biomedical Center in Mental Health (CIBER-SAM), ISCIII, Madrid, Spain.
6. Institute for Research and Innovation in Biomedical Sciences of Cádiz, INiBICA, University Hospital Puerta del Mar, Cádiz, Spain.
7. Department of Pharmaceutical Sciences, University of Milan, Milan, Italy
8. Catalan Institution of Research and Advanced Studies (ICREA)
^. Current address: Imperial College London
#. Current address: Teamit Institute, Partnerships, Barcelona Health Hub
+. Equivalent contribution.
**. Correspondence. E-mail: pau@icrea.cat*

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Abstract

A problem of systemic pharmacotherapy is off-target activity, which causes adverse effects. Outstanding examples include neuroinhibitory medications like antiseizure drugs, which are used against epilepsy and neuropathic pain but cause systemic side effects. There is a need for drugs that inhibit nerve signals locally and on-demand without affecting other regions of the body. Photopharmacology aims to address this problem with light-activated drugs and localized illumination in the target organ. Here, we have developed photoswitchable derivatives of the widely prescribed antiseizure drug carbamazepine. For that purpose, we expanded our method of *ortho* azologization of tricyclic drugs to *meta*/*para* and to N-bridged diazocine. Our results validate the concept of *ortho* cryptoazologs (uniquely exemplified by Carbazopine-**1**) and bring to light Carbadiazocine (**8**), which can be photoswitched between 400-590 nm light (using halogen lamps and violet LEDs) and shows good drug-likeness and predicted safety. Both compounds display photoswitchable activity *in vitro* and in translucent zebrafish larvae. Carbadiazocine (**8**) also offers *in vivo* analgesic efficacy (mechanical and thermal stimulus) in a rat model of neuropathic pain and a simple and compelling treatment demonstration with non-invasive illumination.