

CSIC researchers develop photocontrolable drugs that enable the control of the heart rate by light

- This work, tested on zebrafish, shows the potential of photopharmacology in future more precise heart therapies with fewer side effects
- This study is published in the journal *Angewandte Chemie International Edition*, highlighted as *Hot Paper*



Zebrafish larvae. / Demetrio Raldúa.

Madrid / Barcelona, June 21, 2022. Researchers at the [Institute for Advanced Chemistry of Catalonia \(IQAC\)](#), in collaboration with the [Institute of Environmental Assessment and Water Research \(IDAEA\)](#) from the [Spanish National Research Council \(CSIC\)](#), have developed molecules that allow the control the activity of beta adrenoceptors located in cardiomyocytes, heart muscle cells, by the use of light . This research, published in the

journal *Angewandte Chemie International Edition* and tested in the zebrafish animal model, shows the potential of photopharmacology (drugs controlled by light) for the study and control of cardiac physiology, and its applicability in living beings. Besides, the results of this work point to the generation of future more precise therapies with reduced side effects.

Adrenoceptors, located on the surface of cells, are activated by substances called catecholamines (adrenaline and noradrenaline) and their regulation is essential for the proper functioning of the heart and many other physiological processes. One of these receptors is the so-called β -adrenoceptor, which is found in the heart, arteries, and lungs. With the arrival of catecholamines, these receptors are stimulated, raising heart rate and bronchodilation, among many other effects. These receptors are the main therapeutic target of first-line drugs such as anti-asthmatics or beta-blockers.

Beta-blockers are among the most prescribed drugs worldwide and are used to treat various cardiac pathologies, in particular for the treatment of heart rhythm disorders and in cardioprotection after a heart attack. These drugs block β -adrenoceptors, in such a way that it prevents the union of catecholamines and their stimulation, thus improving the function of the heart. However, some patients with respiratory problems may develop side effects.

In this study, several photocontrolable drugs with beta-blocking activity were designed, produced and pharmacologically tested. "This work presents a new strategy for the control with a high level of precision of the β 1-adrenoceptor by means of photosensitive drugs", explains **Xavier Rovira**, researcher of the Medicinal Chemistry group at the IQAC. "Light-controlled drugs can be activated and inactivated by light with great control at the site of action and during the desired time, thus opening new paths towards highly specific therapies with fewer unwanted effects that arise from the action of drugs in other organs", explains the researcher.

Remarkably, this work demonstrates that with these photocontrolable drugs, which have potencies and selectivities similar to that of approved beta-blockers, it is possible to increase and decrease heart rate by using light of different colors. These molecules were tested in *in vitro* assays, and in live zebrafish larvae. "This study confirms the enormous potential of zebrafish as a vertebrate model in cardiac photopharmacology studies," says **Demetrio Raldúa**, a researcher in the Environmental Toxicology group at the IDAEA.

This work provides the first proof of concept of the potential of photopharmacology for the study and control of cardiac physiology in native environments without the need for genetic modification, where the β 1-adrenergic receptor plays a fundamental role. These types of molecules could meet the procedures and requirements of conventional drugs developed by pharmaceutical companies.

"In the future, molecules with different light-control capabilities will be developed for future research applications, and it is hoped that this and future work will inspire the development of much more efficient treatments for heart diseases with fewer side effects for patients," concludes **Rovira**.

Anna Duran-Corbera, Melissa Faria, Yuanyuan Ma, Eva Prats, André Dias, Juanlo Catena, Karen L. Martinez, Demetrio Raldua, Amadeu Llebaria, Xavier Rovira. **A Photoswitchable Ligand Targering the β 1-Adrenoceptor Enables Light-Control of the Cardiac Rhythm**. *Angewandte Chemie. Int. Ed.* DOI: 10.1002/anie.202203449

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