Optical Control of Cardiac Function with a Photoswitchable Ligand

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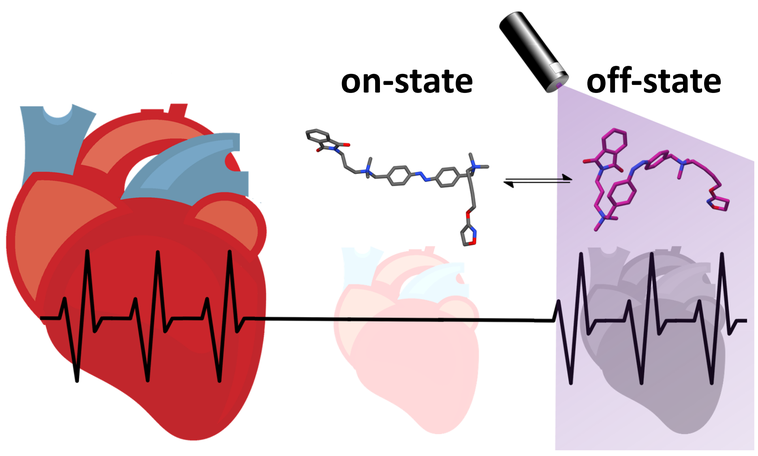
INTRODUCTION

Light-triggered reversible modulation of physiological functions offers the promise of enabling on-demand spatiotemporally controlled therapeutic interventions.

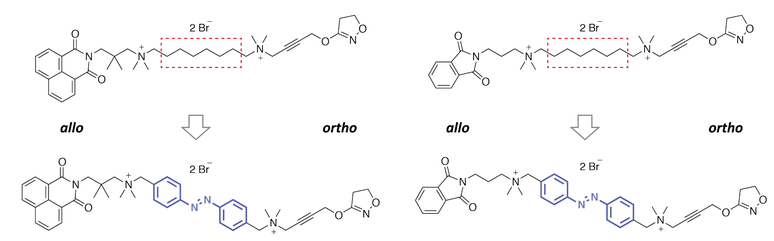
Optogenetics has been successfully implemented in the heart, but significant barriers to its use in the clinic remain, such as the need for genetic transfection. Herein, we present a method to modulate cardiac function with light through a photoswitchable compound and without genetic manipulation.



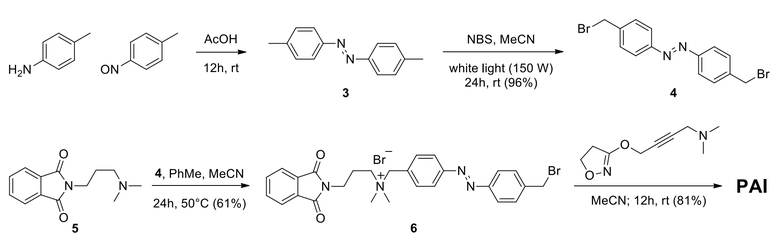
DESIGN

We designed two photoswitchable ligands, NAI and PAI, by introduction of an azobenzene into the molecular structure of M2 mAChR dualsteric agonists.

The incorporation of a photoisomerizable unit into the structure of such dualsteric agonists should enable controlling with light the mutual position of the orthosteric and allosteric moieties, leading to differences between the two isomers in receptor affinity and efficacy.

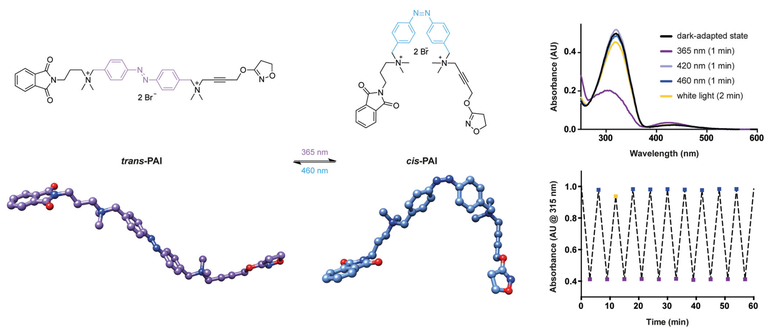


SYNTHESIS



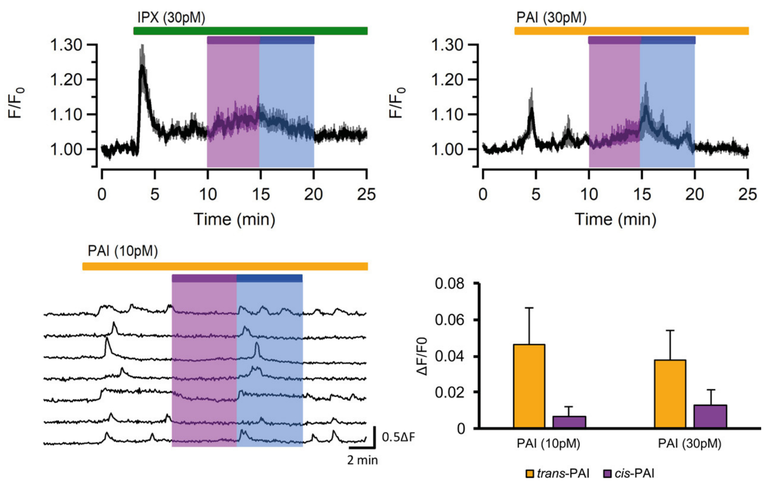
PHOTOCHEMISTRY

Photochromic behavior and fatigue resistance of PAI. NAI showed low photoisomerization yield and was discarded from further studies.



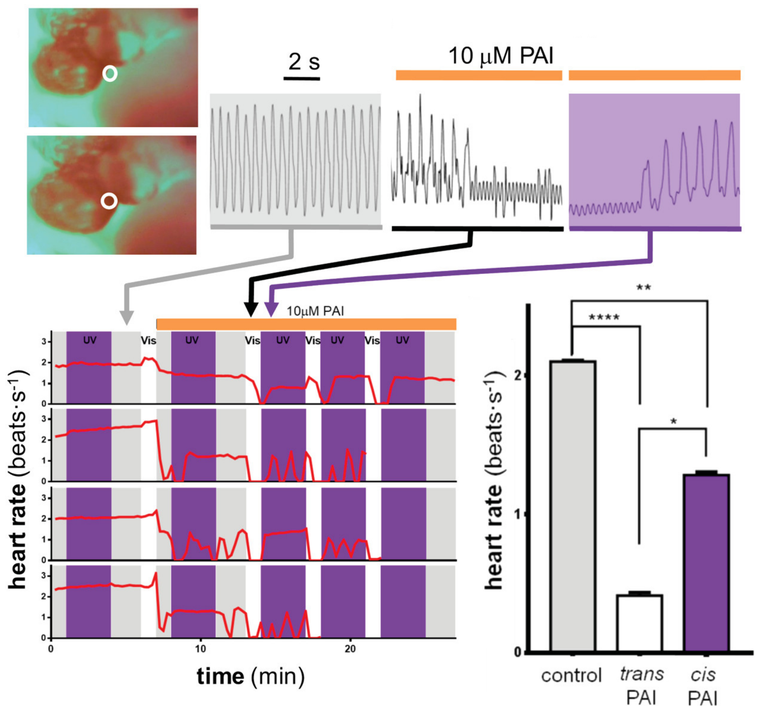
M_2 mAChR ACTIVATION

PAI can reversibly photocontrol M2 mAChR activity in real-time Ca^{2+} imaging assays.



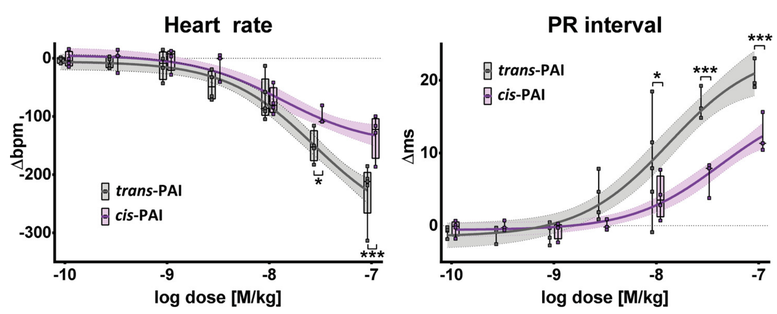
PHOTOCONTROL OF CARDIAC ACTIVITY

PAI enables reversible control of heart rate with light in translucent *Xenopus tropicalis* tadpoles.



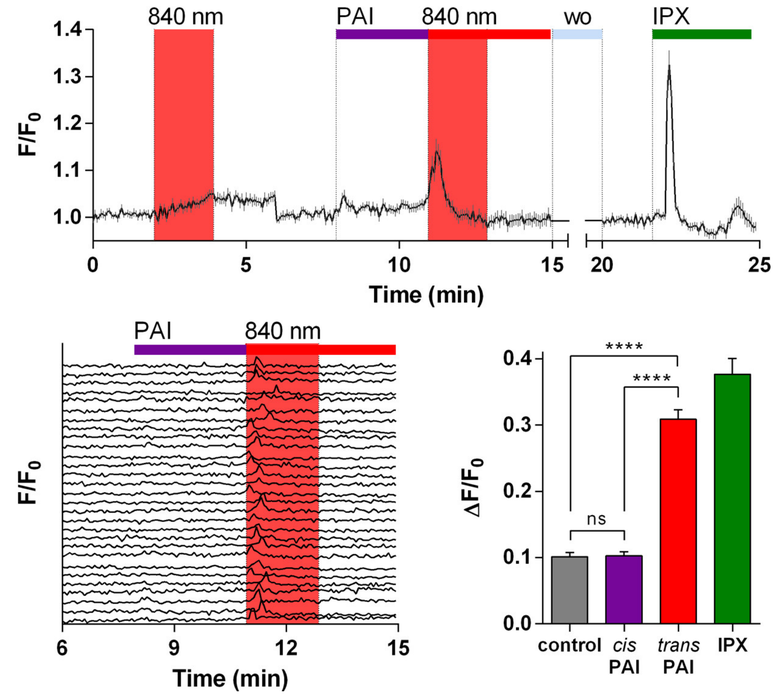
EFFICACY IN RATS

Trans-PAI is more effective than *cis*-PAI at inducing bradycardia and PR lengthening in rats (IP injection). These results confirmed also in mammals our findings in cells and tadpoles.



2-PHOTON PHARMACOLOGY

PAI can activate M2 mAChRs under two-photon excitation with NIR light in Ca^{2+} imaging assays.



REMARKS

- PAI is the first photoswitchable ligand used to photocontrol cardiac activity in translucent wildtype animals without genetic manipulation.
- Future experiments will be addressed to demonstrate that PAI enables precise spatiotemporal control of cardiac function in mammals under 2PE with NIR light.

REFERENCE

Riefolo F, Matera C, et al. Optical Control of Cardiac Function with a Photoswitchable Muscarinic Agonist. J Am Chem Soc. 2019 May 8;141(18):7628-7636. doi: 10.1021/jacs.9b03505

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