EFMC-ISMC
International Symposium
on Medicinal Chemistry
Nice, France
September 4-8, 2022

BOOK OF ABSTRACTS

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Nice, France
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EFMC-ISMC
International Symposium
on Medicinal Chemistry
Rome, Italy
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Content

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2

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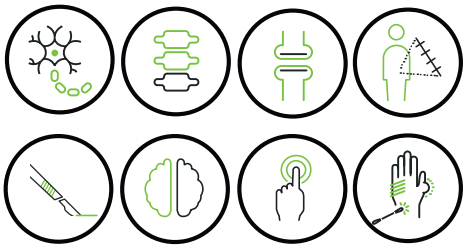

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APPLICATIONS OF MOLECULAR PHOTOSWITCHES IN CHEMICAL BIOLOGY

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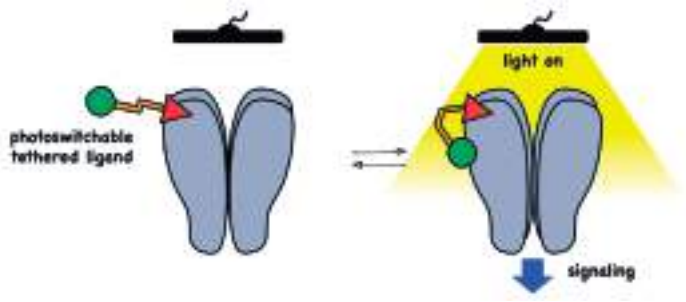
Light-controllable tools provide powerful means to manipulate and interrogate biological functions with high spatiotemporal precision and low invasiveness. Photopharmacology, which relies on the use of synthetic molecular photoswitches to establish photocontrol over the action of bioactive molecules, has recently emerged and found broad application in reversible modulation across various biological targets. Our research efforts in the field have focused on the design of reversible light-modulated bioactive compounds to photocontrol enzymes, GPCRs, and ion channels. Over the last few years we have developed **phototrexate**, the first photoswitchable inhibitor of the human dihydrofolate reductase with demonstrated cytotoxicity in vitro and in zebrafish larvae,[1] **PAI**, a light-controlled dualsteric agonist of muscarinic M2 receptors that enabled the photomodulation of cardiac function in tadpoles and of brain states in mice,[2,3] and **azodopa**, a photoswitchable dopamine D1 receptor agonist that was used to photocontrol swimming behavior in zebrafish larvae and neural activity in mouse cortex.[4] More recently, we have designed a fast photoswitchable tethered ligand of ionotropic glutamate receptors to enable neuronal control in the auditory system. This compound, named **TCP$_{fast}$**, induced photocurrents in untransfected neurons upon covalently tethering to endogenous glutamate receptors and activating them reversibly with visible light pulses of few milliseconds. As a proof of concept, we applied it to the ultrafast synapses of auditory neurons of the cochlea that encode sound and provide auditory input to the brain. TCP$_{fast}$ functions as a molecular prosthesis that bypasses the neurotransmitter-encoded signal with a photonic signal. Photosensitization of cochlear spiral ganglion neurons (SGNs) by locally administered TCP$_{fast}$ enabled temporally precise light-evoked SGN firing up to a rate of approximately 1 kHz, thus matching the fastest optogenetic SGN stimulation. Hence, TCP$_{fast}$-mediated photopharmacology might serve as an interesting alternative to the optogenetic approach for the development of an optical cochlear implant for hearing restoration.[5] The results of these studies will be presented and discussed.



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ANALOGUES OF INCADRONATE - PROBING OF HYDROPHOBIC FRAGMENT OF THE MOLECULE

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28 analogues of a promising antiosteoporetic drug – incandronate, have been synthesized and evaluated for their antiproliferative activity against mouse, macrophage-like J774E cells originating from the same precursors as osteoclasts.Two of the most active compounds *n*-heptyl- and *n*-octyl-aminomethylenebispohosphonic acids were selected for medication of sheep with induced osteoporesis. They appeared to exert mild antiosteoporetic activity as documented by bone histopathology. Unfortunately, severe side-effects are accompanying this medication. Animals lose their fleece and their weight loss was observed in the initial period of treatment and caseous lymphadenitis, which led to outcomes ranging from skin injury to animal death. This is most likely the effect of the decreased immunological response towards *Corynebacterium pseudotuberculosis*, the causal agent of this infectious disease.