

**EFMC-ISM**

International Symposium  
on Medicinal Chemistry

Nice, France

September 4-8, 2022

# BOOK OF ABSTRACTS



Organised by



Service de Chimie Thérapeutique

On behalf of



Nice, France  
September 4-8, 2022  
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**EFMC-ISM**

International Symposium  
on Medicinal Chemistry

Rome, Italy

September 1-5, 2024

[www.efmc-ismc2024.org](http://www.efmc-ismc2024.org)



**See you in Rome 2024!**



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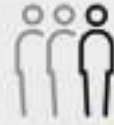
years in pain research



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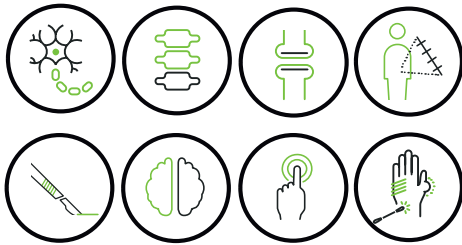


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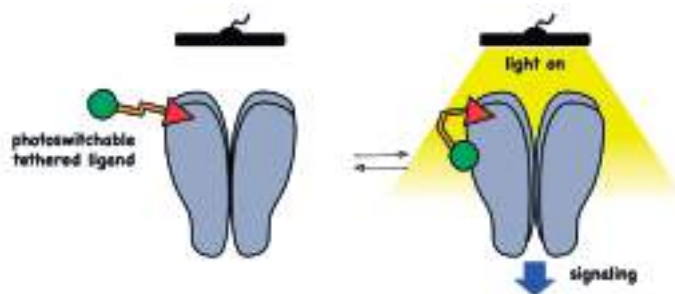
- To know more about research in the DDE unit: [mauro.marigo@grunenthal.com](mailto:mauro.marigo@grunenthal.com)
- For job opportunities please visit: <https://careers.grunenthal.com/>

## 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,<sup>1</sup> **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,<sup>2,3</sup> and **azodopa**, a photoswitchable dopamine D1 receptor agonist that was used to photocontrol swimming behavior in zebrafish larvae and neural activity in mouse cortex.<sup>4</sup> 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<sub>fast</sub>**, 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<sub>fast</sub> 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<sub>fast</sub> enabled temporally precise light-evoked SGN firing up to a rate of approximately 1 kHz, thus matching the fastest optogenetic SGN stimulation. Hence, TCP<sub>fast</sub>-mediated photopharmacology might serve as an interesting alternative to the optogenetic approach for the development of an optical cochlear implant for hearing restoration.<sup>5</sup> The results of these studies will be presented and discussed.



### References

- 1) Matera C et al. Journal of the American Chemical Society 2018, 140 (46), 15764–15773
- 2) Riefolo, F, Matera C et al. Journal of the American Chemical Society 2019, 141 (18), 7628–7636
- 3) Barbero-Castillo A, Riefolo F et al. Advanced Science 2021, 8 (14), 2005027
- 4) Matera C et al., manuscript in preparation
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## ANALOGUES OF INCADRONATE - PROBING OF HYDROPHOBIC FRAGMENT OF THE MOLECULE

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28 analogues of a promising antiosteoporotic 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-aminomethylenebisphosphonic acids were selected for medication of sheep with induced osteoporosis. They appeared to exert mild antiosteoporotic 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.