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Session 1: Photoswitches and beyond

Photoisomerization of Azobenzene-Extended Charybdotoxin for the Optical Control of Kv1.2 Potassium Channel Activity

Yanis Achouba [1], Basile Pérès [2], Steven Ascoet [1], Hervé Meudal [3], Cecile Caumes [4], Claude Zoukimian [5], Hugo Millet [1], Maureen Choteau-Bodor [1], Cathy Carvalhosa [6], Mikaël Croyal [1], Fella Bouchama [7], Heike Wulff [8], Stéphane Téletchéa [9], Rémy Béroud [4], Eléna Ishow [10], Celine Landon [3], Ahcène Boumendjel [11], Jérôme Montnach *† [1], Michel De Waard * ‡ [1]

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Natural peptides from animal venoms are powerful and highly selective modulators of ion channels, making them attractive templates for precision pharmacology. While photoswitchable compounds have been extensively developed to control ion channel activity, these approaches have largely focused on small molecules. Extending photoswitch technology to natural peptides remains challenging due to their large pharmacophores, complex folding, and dense disulfide-bridge networks. Here, we present a proof-of-concept study demonstrating that photoswitchable control can be successfully implemented in a structurally complex natural peptide.
We investigated charybdotoxin (ChTx), a potassium channel blocker containing three disulfide bridges, as a model system. Click-compatible azobenzene photoswitches with varying length and amide orientation were synthesized and grafted onto ChTx using site-specific incorpora-

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tion of L-azidohomoalanine at selected positions. Post-folding click chemistry was employed to preserve native disulfide connectivity and peptide bioactivity. Structure-activity relationship analyses revealed that monomeric Az-ChTx analogues were superior to dimers, with azobenzene attachment at position 14 producing the most robust photo-modulation.

Illumination induced reversible, light-dependent changes in potassium channel block at nanomolar concentrations. In the *cis*configuration, Az1 disrupted the ChTx pharmacophore and reduced channel inhibition, whereas substitution with Az2, differing only in linker length and amide orientation, unexpectedly enhanced blocking potency. NMR analysis confirmed that azobenzene isomerization alters the chemical environment of key pharmacophore residues, highlighting how subtle chemical differences in the photoswitch can drive gain- or loss-of-function effects.
This study represents the first demonstration of photoswitchable control in a natural peptide with complex disulfide architecture. It establishes design principles for integrating photoswitches into large peptide scaffolds and underscores the versatility of photopharmacology for controlling ion channel activity. Given the vast diversity of venom peptides, this strategy opens new opportunities for light-controlled peptide therapeutics and research tools.

Keywords: Photopharmacology, Azobenzene, Photoswitch, Natural peptide, Ion channel

Light-controlled inhibition of COX-2 using photoswitchable derivatives

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Inflammation is a biological response to infection or injury, regulated by molecular mediators such as prostaglandins, lipid compounds derived from arachidonic acid through the action of cyclooxygenase enzymes (COX-1 and COX-2).(1) Among these, COX-2 plays a central role in acute inflammatory response and is therefore a major therapeutic target. Both traditional nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, such as celecoxib, effectively reduce inflammation. However, their systemic distribution can lead to adverse gastrointestinal and cardiovascular effects, highlighting the need for more precise therapeutic strategies.(2)
Recent advances in photopharmacology provide a promising solution by enabling spatial and temporal control over drug activity through light. This approach relies on photosensitive compounds that remain pharmacologically inactive until exposed to specific wavelengths, allowed targeted at the desired site while reducing systemic side effects.(3)

Based on this concept, our research group has developed a photoswitchable derivative of celecoxib, termed photocoxib, using computational modeling studies. This compound retains the essential functional groups of celecoxib responsible for COX-2 selectivity, particularly the sulfonamide and trifluoromethyl (CF3) moieties, while incorporating a photoresponsive core that enables light-triggered activation.

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Keywords: Synthesis, photoswitches, COX2inhibition, photopharmacology

Structure–Activity Relationship Study of 8-Bromo-7-Hydroxyquinoline based photoremovable protecting groups for Enhanced Blue-Light Photorelease

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Photoremovable protecting groups (PPGs) play a central role in photopharmacology by allowing the controlled release of bioactive compounds with high spatial and temporal resolution. Quinoline-based PPGs are particularly effective for caging tertiary aliphatic amines. Notably, 8-bromo-7-hydroxyquinoline (BHQ) has been shown to release ivabradine from its corresponding caged compound enabling the *in vivo* blue-light photoactivation of the drug in zebrafish models. (1)
Building on this in vivo success, we aimed to further optimize the photochemical and optical properties of the BHQ scaffold through a systematic structure–activity relationship (SAR) study. Specifically, we introduced various substituents at the 3-position, that is directly conjugated with the 7-hydroxy group and located near the drug–PPG linkage. This strategy was chosen to directly influence both the electronic properties of the chromophore and the photorelease efficiency.
A series of BHQ derivatives was synthesized and photochemically characterized. Among the compounds investigated, those 3-substituted with electron-withdrawing groups showed the most significant improvements across all evaluated parameters, including absorption properties, photorelease efficiency, and overall optical performance. These findings provide valuable design principles for the development of next-generation quinoline-based PPGs optimized for visible-light-driven photopharmacology.

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Keywords: Photoremovable protecting groups, photoactivation, photorelease

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Fully Reversible Optical Regulation of 8-17 DNAzyme Catalysis by Nucleoside-Based Diarylethenes

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Diarylethenes (DAEs) and azobenzenes are among the prevalently used photochromic compounds in biological research. In 2021, our group reported high-performance photoswitchable nucleoside-based DAEs and demonstrated their biological applicability by incorporating them into the T7 polymerase promoter via solid-phase synthesis, thereby enabling indirect optical control of T7 polymerase activity. Building on this approach, the present study aims to achieve direct light-dependent control over enzymatic function. As a model system, we selected the well-characterized RNA-cleaving 8-17 DNAzyme. The nucleoside-based DAE was incorporated into the catalytic core, and systematic screening identified position 2.1 as the optimal modification site. Detailed kinetic analyses revealed full photochemical control over the DNAzyme's catalytic activity. Comparison of the initial velocities showed that the open form (OF) retained approximately 50% of the unmodified DNAzyme's activity, whereas the UV-induced photostationary state (PSSUV, 87% closed form (CF)) exhibited only 9% of the OF's activity. This residual activity could be attributed to the 13% OF fraction remaining in the PSSUV. Upon isolating the CF, the catalytic rate decreased further to 0.5% of the OF's initial velocity, corresponding to a 200-fold reduction in activity. Moreover, the isolated CF was found to be stable for several months when stored at -21 ∘C under light exclusion conditions. As a final experiment, the sample was subjected to repeated irradiation cycles to verify reversible, light-controlled regulation of the DNAzyme. Starting from the OF, the sample was alternately irradiated to generate the PSSUV and subsequently reverted to the OF. This alternating irradiation resulted in a staircase-like pattern when the initial reaction velocity (y-axis) was plotted as a function of time (x-axis). The OF consistently exhibited substantial cleavage activity, whereas the PSSUV was nearly inactive, thereby confirming effective optical control of the DNAzyme's catalytic function.

Keywords: Photoswitch, DAE, 8, 17 DNAzyme, Optical Regulation, Nucleosie, Based Diarylethenes, Fully Reversible

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In vitro pharmacological evaluation of a photoswitchable modulator in dopaminergic receptors

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Dopamine is a key neurotransmitter involved in essential physiological and neurological processes including motor control, learning, motivation, and cognition. Dysregulation of dopaminergic signaling may arise due to neuronal degeneration, receptor malfunction, or diseases. Current treatment for these disorders relies on pharmacological dopamine agonists to modulate dopaminergic receptors and transmission. However, these conventional agonist often produce significant side effects due to their limited receptor and saptiotemporal specificity. To overcome these limtiations, BRJ-1 was developed as a reversible photopharmacological agonist designed to obtain a spatiotemporal modulation of dopaminergic receptors. To characterize its photopharmacological properties, we performed real-time calcium imaging assays in transiently transfected HEK-tsA201 cells under different illumination conditions. Cells were transfected with D1and D2 receptors, a calcium sensor, and specific chimeric/promiscuous proteins needed for intracellular calcium release. We demonstrated that BRJ-1 activates D1 receptors in its *trans* configuration and this effect can be abolished upon illumation at 380 nm, which switches the molecule into the *cis* form. Thus, BRJ-1 enables a reversible photocontrol of D1R. These results highlight a potential of BRJ1 as a tool for therapeutic approaches requiring selective spatiotemporal modulation of this receptor subtype or for future research studies to establish how dopaminergic neurotransmission governs neuronal circuits and its influence on physiological processes.

Keywords: Photopharmacology, Dopamine receptors, Calcium imaging, Spatiotemporal control, Dopamine agonists

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NIR Switching: Single photon, singlet manifold azobenzene photoswitching at up to 1000 nm

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This study introduces a high-performance method for near-infrared (NIR) photoswitching of azobenzenes via single-photon, singlet manifold photoredox processes, enabling efficient Z→E isomerization using light > 630 nm with $> 97\%$ completion. By employing covalently attached auxiliary chromophores, this approach overcomes the limitations of UV-based systems and triplet photochemistry, achieving photon-efficient, biocompatible, and photostable switching. The method is broadly applicable without requiring re-engineering of azobenzene substituents, preserving intrinsic chemical properties. Demonstrated in live cells and intact brain tissue, this technology enables reversible photocontrol of biological activity, including G protein-coupled and glutamate receptors, under physiological conditions. This innovation establishes a versatile and robust platform for deep-tissue optogenetics, biophysics, and materials science applications.

Keywords: Azobenzene

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Deuteration as a General Strategy to Enhance Azobenzene-Based Photopharmacology

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Photopharmacology has emerged as a powerful approach for precise spatiotemporal optical control of biological processes. Central to this field are photoswitchable molecules, among which azobenzenes are the most widely used and have been extensively explored for wavelength tunability, photostationary states and switching kinetics.

Due to the uniquely large kinetic isotope effect, deuteration is a well-established strategy to improve metabolic stability and pharmacokinetics of drugs. More recently, it has been applied to fluorophores, resulting in enhanced fluorescence quantum yields, reduced photobleaching, and improved cellular imaging performance. In our laboratory, this strategy was extended to azobenzenes, where deuteration led to markedly accelerated photoswitching and increased photoisomerization quantum yields. These advances enabled the development of deuterated azobenzene-based probes for optical control of ion channels and G protein-coupled receptors, demonstrating the general potential of this approach in photopharmacological applications.

To date, deuteration-enhanced azobenzenes have been limited to ultraviolet-light-responsive systems. Herein, through rational molecular design, we expand this strategy to azobenzene derivatives that operate in the blue–green spectral region. The resulting compounds exhibit similarly enhanced photoisomerization kinetics, indicating that the deuteration effect is broadly applicable across azobenzene scaffolds. Notably, we identify a new class of azobenzene that undergo efficient trans–cis photoisomerization under 550 nm irradiation, significantly broaden the photopharmacological toolbox.
Collectively, our results highlight deuteration as a general and effective molecular design strategy with wide adaptability in photopharmacology.

Keywords: Photoswitch, Azobenzene, Deuteration, Photoisomerization

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Targeting Pseudomonas aeruginosa LecB with Photoswitchable Glycomimetic Ligands

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Antimicrobial resistance (AMR) represents an escalating global health challenge, particularly in relation to nosocomial infections. A key factor driving the persistence and dissemination of AMR is the formation of biofilms, which establish a protective microenvironment that promotes microbial survival and facilitates horizontal gene transfer (1). Bacterial adhesion proteins play a fundamental role in biofilm initiation and maturation by mediating interactions between microbial cells and biotic or abiotic surfaces, ultimately enabling the development of highly resistant microbial communities. Due to their central involvement in biofilm formation, these adhesion factors have emerged as promising molecular targets for the development of alternative anti-AMR therapeutic strategies (2).

Among these targets, the outer membrane virulence factor lectin LecB from Pseudomonas aeruginosa has attracted considerable interest. LecB contributes to bacterial virulence and persistence in clinical environments and exhibits strong carbohydrate-binding properties, interacting with both components of the bacterial outer membrane and exopolysaccharides within the biofilm matrix. The present work focuses on the identification and development of novel photoswitchable ligands capable of binding to and modulating LecB activity. By exploiting light-responsive control mechanisms, these compounds aim to provide a non-invasive therapeutic approach with precise spatiotemporal regulation, potentially addressing limitations associated with conventional antimicrobial treatments. Following the identification of an initial photoswitchable hit compound that established proof of concept for targeting bacterial adhesion proteins, a computationally guided *hit*-expansion strategy was initiated (3).

This approach was designed to identify new photoswitchable LecB binders exhibiting enhanced affinity in the *cis*-enriched state, thereby enabling the evaluation of light-dependent antibiofilm activity. The computational studies led to the identification of several photoswitchable glycomimetics, showing higher affinity compared to the reference *hit*compound, underlining the power of Computer Aided Drug Discovery (CADD) in the photopharmacology field.

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Keywords: resistance, biofilm, glycomimetics, Pseudomonas, antimicrobials

An optonanobody for reversible photoactivation of recombinant and native α7 nicotinic receptors

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α7 nicotinic receptors are calcium permeable ligand-gated ion channels that modulate synaptic neurotransmission and neuronal excitability, and are critical targets for cognitive enhancement. Despite their therapeutic relevance, the development of α7-selective pharmacological agents has been hindered by off-target effects and limited spatiotemporal control. The rapid desensitization of α7 receptors imposes a requirement for precise temporal control that is not met by existing pharmacological approaches. Here, we report a nanobody-based photopharmacology strategy to achieve optical control of α7 activity with high specificity. By covalently coupling the photoswitchable agonist azocholine to the α7-selective nanobody C4, we engineered MalAzoCh-C4, an optonanobody that targets α7 nAChRs without requiring genetic modification. In *Xenopus* oocytes, MalAzoCh-C4 enables light-dependent activation and desensitization of recombinant α7 receptors, with higher efficacy in the *trans*configuration. In hippocampal brain slices, MalAzoCh-C4 allows rapid and reversible photoactivation of native α7 nAChRs in GABAergic interneurons, offering unprecedented optical control of endogenous receptor function and action potential firing. This approach provides a versatile platform for dissecting α7 receptor physiology in native circuits with high spatiotemporal and pharmacological precision.

Keywords: nicotinic receptor/nanobody/electrophysiology

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Engineering Quinoline-Based Photoremovable Protecting Groups for Blue-Light Activation of Tertiary Aliphatic Amines

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Photoremovable protecting groups (PPGs) are powerful tools in photopharmacology, enabling the light-controlled release of bioactive molecules with high spatial and temporal precision. Quinoline-based systems are among the most effective PPGs for caging and releasing tertiary aliphatic amines. In particular, the 8-cyano-7-hydroxyquinoline (CyHQ) scaffold has been shown to efficiently release tertiary aliphatic amines upon irradiation with UVA light via one-photon excitation (1PE) and near-infrared (NIR) light via two-photon excitation (2PE).(1) However, the use of UVA light is poorly suited to in vivo applications due to limited tissue penetration and phototoxicity. To overcome these limitations, we explored structural modifications of the quinoline scaffold by introducing various electron-withdrawing substituents at the 8-position, including halogens, sulfur-containing moieties, trifluoromethyl and carboxylic groups, with the aim of red-shifting the absorption profile.

All derivatives were successfully synthesized and thoroughly photochemically characterized. Our results demonstrate that substitution at the 8-position with halogens represents the most promising strategy, enabling efficient photorelease under blue-light irradiation. Compared to the parent CyHQ system, these halogenated analogues show improved suitability for biological systems and considerable prospect for in vivo photopharmacological applications.
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Keywords: PPG, quinoline, based PPGs, CyHQ, BHQ

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A series of photoswitchable antagonists for a precise spatiotemporal control of adenosine A2A receptors with light

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Caffeine is the most extensively consumed psychoactive drug in the world, and its effects are associated to Adenosine Receptors (ARs), in particular A2ARr. To obtain selectivity, medicinal chemistry extended the xanthine moiety with a styrene to give a family of heterostilbenes that includes MS-DMPX, MSX-2/3 or istradefylline, which is currently approved for treatment of Parkinson's Disease (PD). However, the widespread distribution of A2AR in the body makes challenging to develop drugs that target A2A in a specific location.
Photopharmacology may be a solution for this lack of selectivity. Of note, the heterostilbene moiety of istradefylline is photochromic and may be used to control of A2A receptors with light. However, Istradefylline photoisomerization reaction competes with a (2+2) cycloaddidtion that leads to four inactive dimers. In the present work, we aimed to develop a photopharmacological toolbox of A2A antagonists that overcome the limitations of heterostilbene family. Thus, we employed an azologization strategy to obtain a family of fully reversible photochromic phenylazoxanthines, which show robust *trans*-to *cis* photoisomerization upon blue light illumination and almost complete back isomerization under green illumination. As xanthine derivatives commonly show low aqueous solubility, we synthesized four aqueous-soluble azo-istradefylline analogues that included a carbon chain with a charged amine.

The pharmacological characterization as A2A antagonists in *trans*-configurations showed nanomolar potencies for most compounds, and four molecules, among the 14 molecules developed, possess a 7-12-fold activity shift upon blue-light illumination. Moreover, the two hit compounds showed a good selectivity among the rest of adenosine receptors and show light-dependent activity in murine in vivo assays.
Ultimately, these photopharmacological tools provide the possibility to target A2AR with an unprecedented spatiotemporal precision, constituting a potential technology to explore the specific

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contribution of A2AR in different pathologies, including neurodegenerative and cardiovascular diseases and cancer.

Keywords: Adenosine receptors, xanthines, A2A, Istradefylline, Parkinson Disease

Traceless Photopolymerization with Non-Pulsed Red Light for Cell-Laden Bioscaffold Fabrication

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Photocrosslinking of hydrogels with non-pulsed red light offers improved biocompatibility and deep tissue penetration in contrast to traditional UV-initiated methods. However, current red-light photopolymerisation systems for hydrogel fabrication usually suffer from several critical limitations, such as cytotoxic photoinitiators and/or co-initiators. Moreover, hydrogels fabricated upon red-light excitation are always colored by a photoinitiator, limiting their use in applications requiring high optical transparency, such as (bio)sensors, ophthalmological applications, or wound dressings. Herein, a photoinitiating system leveraging the FDA-approved methylene blue drug/photosensitizer is introduced. With this approach, gelatine methacrylate hydrogel is successfully polymerized under ambient conditions. The hydrogel is permanently colorless with well-controlled stiffness due to the light-dependent nature of the polymerization process. The system is successfully applied in extrusion-based 3D-bioprinting with NIH-3T3 fibroblasts, followed by photocuring to produce cell-laden 3D structures. The red-light excitation enables polymerization through at least 5 mm of biological tissue, projecting, inter alia, its use for transdermal photopolymerization in minimally invasive implantation.

Keywords: hydrogels, red light, 3D (bio)printing, cell encapsulation

*Speaker

Coarse-grained Molecular Dynamics Simulations of Photoswitches in Photopharmacological Systems

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Molecular photoswitches are typically organic molecules with extended aromatic systems that undergo light-induced double-bond isomerization, a feature that renders them inherently lipophilic. As a result, their water solubility remains limited, and their interactions with biological membranes are insufficiently explored. Coarse-grained molecular dynamics simulations are a valuable tool for studying molecular interactions and dynamics at near-atomistic resolution while allowing simulations on biologically relevant spatiotemporal scales.

Here, we present the parameterization of seven molecular photoswitches and a library of a wide range of substituted azobenzenes for the Martini 3 coarse-grained force field. The models are derived from semi-empirical quantum-mechanical reference data and capture the structural differences between the two isomeric states even at coarse-grained resolution. These models enable simulations under equilibrium conditions. While the photoswitching process itself is not explicitly modeled, it can be emulated by changing from the cis to the trans model.

In combination with experimental partitioning data, we investigate the solubility and membrane permeability of substituted azobenzenes. Finally, we demonstrate the applicability of these models to photopharmacological systems, including membrane modulation, light-controlled peptide structure, and ion-channel regulation, at system sizes and timescales inaccessible to atomistic simulations. Overall, we show that coarse-grained molecular dynamics simulations are a valuable tool for studying photoactive compounds in biomolecular ensembles.

Keywords: Azobenzene, Molecular Dynamics, solubility

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Photo-modulated cell-penetrating peptides for light-triggered release and delivery of RNA

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In this project, we want to develop a light-activated intracellular delivery system for oligonucleotides by combining molecular photoswitches with cell-penetrating peptides. Oligonucleotides are prospective therapeutics in rare diseases, viral infections, and cancers. Yet, their targeted delivery to tissues of interest remains the main clinical bottleneck. Oligoarginine-based dynamic covalent RNA delivery vectors are a viable alternative to standard formulations, such as lipid nanoparticles. Yet, the selectivity of these methods could be improved to further reduce systemic side effects during therapies. We will redesign the known cell-penetrating dynamic covalent polymers (DCPs) in order to make the RNA complexation and delivery photocontrollable.(1-3) We will use red-light switchable azobenzenes and arginine trimers that self-assemble to covalent, pH sensitive, cationic polymers, that complex oligonucleotides.(4) We hypothesize that a substantial and reversible geometry and polarity difference upon isomerization of a photochromic building block will reversibly influence the complexation propensity of the DCPs, which in turn will provide a unique way to light-inducible release of the RNA with control in both space and time – thus increasing the precision and efficiency of the whole delivery process. Our preliminary in vitro results demonstrate significant photomodulation of DCPs' physical properties such as aggregation propensity. (1) Bouillon C, Bessin Y, Poncet F, Gary-Bobo M, Dumy P, Barboiu M, et al. Biomolecular dynamic covalent polymers for DNA complexation and siRNA delivery. J Mater Chem B. 2018;6(44):7239-46.
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(4) Leistner AL, Kirchner S, Karcher J, Bantle T, Schulte ML, Godtel P, et al. Fluorinated Azobenzenes Switchable with Red Light. Chemistry. 2021;27(31):8094-9.

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Keywords: Molecular Photoswitches, Dynamic Covalent Polymers

Manipulating Physicochemistry with Light

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Photoswitches have been widely used to enable light-based control of biological systems, typically through their change in geometry. One underexplored aspect is the change in physicochemical properties that accompanies isomerisation. This poster investigates how photoswitch design impacts these physicochemical changes, using a synthesised library of systematic azobispyrazoles to compare against "benchmark" azo-photoswitches. Experimental changes in logP upon $E \rightarrow Z$ isomerisation were quantified by an octanol-based HPLC method. Variation in light-switchable logP was found across the azobispyrazoles series, in both absolute logP values of E and Z isomers and relative E-Z differences, with notable differences found when comparing to the "benchmark" photoswitches, showing photoswitch design can be used to tune these effects. To investigate the consequences of these light-induced lipophilicity changes, passive membrane permeability was measured by PAMPA (Parallel Artificial Membrane Permeation Assay). Importantly, the isomeric differences in logP lead to significant differences in permeability. This highlights a key aspect for consideration in the design of drugs for photopharmacology. Additionally, computational parameters are explored for comparison to experimental logP and permeability values, with the aim of providing greater understanding and identifying a predictive method for identifying changes in logP and permeability in novel photoswitches.

Keywords: Photoswitches, logP, Permeability

*Speaker

Membrane-Targeted Azobenzene Photoswitches for Optical Control of Bacteria

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The development of intelligent light-responsive materials has transformed biomedical research by enabling precise, non-invasive control of biological processes. Photoactive systems provide spatiotemporal regulation of cellular functions and are powerful tools in photopharmacology. Azobenzenes, in particular, undergo reversible light-induced trans–cis isomerization that alters their shape and physicochemical properties. This transformation modulates interactions with lipid membranes, enabling reversible control of cellular functions, including membrane potential, without genetic modification. Although validated in eukaryotic systems, their application in bacteria remains largely unexplored.

Here, we investigate membrane-targeted azobenzene photoswitches to optically control bacterial membrane potential, a key regulator of different biological functions(1). We designed amphiphilic azobenzenes, with absorption in the visible range, to promote spontaneous partitioning into bacterial membranes. Spectroscopic characterization was followed by biological assays evaluating membrane association, toxicity, and functional effects in *Bacillus subtilis*.

Results demonstrate efficient membrane incorporation and light-dependent modulation of bacterial bioelectric states. A designed push–pull azobenzene (MTP2) hyperpolarizes resting membrane potential in dark and undergoes reversible depolarization upon illumination, enabling optical control without genetic manipulation (2). In parallel, a structure–function analysis of aminoazobenzenes with varying cationic substitution shows that charge density and symmetry influence membrane affinity, photoisomerization behavior, and downstream physiological responses (3).

Together, these findings establish azobenzene photoswitches as reversible chemical optostimulators in bacteria and define molecular design principles for controlling microbial electrophysiology. This work extends photopharmacology to microbial systems and introduces new strategies to probe bacterial bioelectric signaling and modulate antibiotic responses with light.

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*Speaker

(2) Bertolotti, P., *et al Dipolar photoswitch modulates bacterial membrane potential and reveals ion-channel buffering networks.* (Under revision)
(3) Keller, H.R.,*et al Structure-function study of a family of membrane-targeted azobenzene phototransducers with Bacillus Subtilis.* (Under revision)

Keywords: Photoswitches, Azobenzene, Bacteria, Membrane Potential

Light-activated MDM2 inhibitors: Toward spatiotemporal control in cancer therapy

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Tumoral cases among the population have been steadily increasing, and the treatment of cancer remains a major challenge. Due to the large number of chemotherapeutic agents employed and the frequent occurrence of relapses, patient life expectancy is often severely compromised. (1)
Targeting protein–protein interactions (PPIs) with high spatiotemporal precision remains a central challenge in drug discovery and chemical biology. The oncoprotein MDM2, a key negative regulator of the tumor suppressor p53, represents a particularly compelling target due to its pivotal role in cancer progression and its structurally well-defined binding pocket. Although conventional MDM2 inhibitors designed to restore p53 activity have shown considerable promise, their clinical translation is limited by systemic toxicity arising from p53 activation in healthy tissues.

To address this limitation, we investigate light-activated pharmacological strategies-such as the incorporation of photoswitchable groups to achieve precise spatiotemporal control over the MDM2–p53 interaction. In this approach, the inhibitors remain biologically inactive in the dark and are converted into their active anticancer form only upon irradiation with visible light. To enhance clinical applicability, we have designed and synthesized a series of novel compounds that are responsive to green light, allowing for deeper tissue penetration and reduced phototoxicity. We will present our most recent findings on the visible-light-controlled inhibition of the MDM2–p53 interaction by small molecules, including results from comprehensive biological evaluations demonstrating their activity in relevant cellular models.

Keywords: Photoactivatable, anticancer, photoswitchable, protein, protein interaction inhibitor

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Fully reversible control over DNA-intercalation with visible light

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DNA-binding agents are widely used chemotherapeutics in cancer therapy. Many established drugs, such as Cisplatinum, share one intrinsic obstacle, the treatment comes with severe side-effects due to low specificity. This prevalent problem in cancer therapy can be mitigated by employing the emerging concept of Photopharmacology, where the activity of a drug can be spatiotemporally controlled by the use of non-harmful visible light.
We introduce Diazocine photoswitches (cyclic Azobenzenes) as a promising scaffold for reversible DNA-intercalation in photopharmacological cancer therapy. Diazocines are stable in *cis*-configuration and can be isomerized to *trans*-configuration by the use of blue light (400 nm). The metastable *trans*-Isomer can revert to the *cis*-state thermally or by irradiation with green light (535 nm). The difference in DNA binding behaviour can be explained by the change in geometry upon switching. While the flat *trans*-Isomer can intercalate between the base pairs, the sterically demanding, angled *cis*-Isomer is expelled from the DNA-Diazocine complex.

In our study, we synthesized a library of potential Diazocine based DNA-intercalators based on the results of Molecular Dynamics screening. All molecules were photochemically characterized under physiological conditions and the binding to genomic DNA was assessed with Circular-Dichroism Spectroscopy. Our compounds show full reversibility of DNA-Binding upon irradiation, and could do so without fatigue for at least 5 cycles.
The large change in affinity combined with the near-quantitative photoconversion of the Diazocines isomers lead to highly selective binding and unbinding over a wide concentration range, promising better targeting for chemotherapeutics.

Keywords: DNA, binding, photoswitches, visible light

*Speaker

Design and Synthesis of Photoswitchable Ligands for Light-Controlled Modulation of Melatonin Receptors

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Melatonin is a neurohormone that synchronizes circadian rhythms and regulates the sleep–wake cycle in response to light. In vertebrates, it is mainly synthesized from tryptophan in the pineal gland, generating the nocturnal rise in circulating melatonin responsible for its role as a systemic circadian signal. Melatonin acts primarily through two G protein-coupled receptors (GPCRs), MT and MT, which are prototypical Gi/o-coupled receptors and represent excellent drug targets. (1) While several melatonin receptor agonists are clinically available, most lack subtype selectivity, which often limits therapeutic precision and leads to off-target effects. Dissecting the distinct and often compartmentalized functions of these receptors requires molecular tools with high spatiotemporal resolution. (2) Photopharmacology offers such precision through photoswitchable ligands that reversibly modulate activity upon light exposure.

Our work focuses on the design and synthesis of photoswitchable MT-selective melatonin ligands by integrating azobenzene motifs into melatonin analogues. (3) We report here the synthesis and preliminary photochemical characterization of a novel series of azobenzene-based MT ligands. Following the photochemical study, we performed binding affinity assays in cells to evaluate their selectivity and potency compared to the non-specific action of natural melatonin. Furthermore,

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we evaluated the compounds in vivo using a zebrafish (*Danio rerio*) model. The zebrafish is a particularly compelling model for melatonin research, as it is a diurnal organism with a robust and highly marked circadian rhythm, (4) making it ideal for monitoring light-dependent behavioral changes. Such compounds illustrate how photopharmacology can provide innovative chemical tools to interrogate and manipulate receptor function across time and subcellular compartments, and may pave the way for light-regulated therapeutic strategies targeting circadian rhythm–related disorders.

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(2) Jockers et al. *Br. J. Pharmacol.* **2016**
(3) Ricart-Ortega et al. *Mol. Cell. Endocrinol.* **2019**
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Keywords: melatonin, circadian rythms, sleep, wake cycle, G protein, coupled receptors, photoswitches, photopharmacology, zebrafish

Photoxenase engineering: establishing and optimizing reversible photocontrol in enzymes

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The use of light sensitive unnatural amino acids has emerged as a versatile tool for the spatio-temoral control of protein and enzyme function. The resulting proteins (without enzyme activity) or enzymes have been dubbed photoxenoproteins and photoxenases, respectively. In particular, the reversible control using photoswitchable unnatural amino acids (psUAAs) has gained considerable attention, in which our group specializes in order to engineer switchable photoxenases for diverse applications. To be able to engineer switchable photoxenases in a targeted manner, it is necessary to build a large base of knowledge and tools to improve the methodology. To this end, we approach the topic from five directions: 1) Photoswitch customization: We have been extending the repertoire of available psUAAs with different interaction potentials, thermal stabilities and absorbance properties. We also discovered a novel state of Azobenzenes formed under dichromatic irradiation leading to altered photocontrol properties. 2) Adjustment of the (de)activation strength: We have set up a screening process and have shown that via directed evolution, light regulation of at least 100-fold is possible. 3) Mechanism of photocontrol: By use of extensive biochemical and in silico analyses we have been analyzing how light regulation influences conformational equilibria in photoxenases and how this affects the chemical mechanism of the catalyzed reaction. 4) Requirements on the enzyme target: In our model system type II asparaginase from *E. coli* that is used in chemotherapy, we have identified conformational heterogeneity as a determining factor for susceptibility for photocontrol. 5) Requirements on the position of incorporation: By systematically testing various positions for psUAA incorporation, we have been narrowing in on properties that reliably enable photocontrol. Our work shows that, given the right information, reversible photocontrol of enzymes can be achieved, customized and improved with a high rate of success.

Keywords: unnatural amino acids, enzymes, azobenzene, reversible photocontrol, photoswitches

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Natural Product-Inspired Diketopiperazine Core Engineering for Tunable Hemipiperazine-Based Photoswitches

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Natural products such as neihumicin and nocazines, which feature hemipiperazine-like (HPI) motifs embedded in diketopiperazine (DKP)-derived frameworks, exhibit pronounced cytotoxic and antibacterial activities. These biologically privileged architectures render hemipiperazine scaffolds highly attractive for the development of photopharmacological agents. In our previous work, we extensively investigated side-chain modifications of DKP-based systems, including Plinabulin and its derivatives as antitumor agents as well as indolo- and pyrrolo-DKP scaffolds as photoswitchable fluorescence probes. Building on these studies, we now shift our focus from peripheral substitution patterns toward systematic core modifications of the DKP framework itself, inspired by the structural features of neihumicin and related natural products.
In this work, we synthesize a focused library derivatives and systematically investigate how structural modifications within the DKP core influence their photophysical and photochromic properties. Particular emphasis is placed on electronic and steric modulation of the amide backbone. We performed targeted acetylation, methylation, deacetylation, and thionylation of the DKP core to systematically probe structure–property relationships. These modifications led to distinct bathochromic and hypsochromic shifts in λ_abs,max, altered acidochromic behavior, and changes in switching kinetics and thermal stability. In particular, thionylation induced pronounced redshifts and modified electronic distribution. The experimental observations were supported by DFT calculations, which rationalize the substituent-dependent modulation of conjugation, orbital energies, and isomer stability.
Overall, this work expands the chemical space of photoswitchable scaffolds derived from diketopiperazine motifs. By bridging natural product-inspired design with contemporary photopharmacology, we advance hemipiperazine-based photoswitches as promising platforms for therapeutics

Keywords: Hemipiperazine, Diketopiperazine, Core modification, Thionylation, Acetylation, Methy-

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lation, Structure–property relationship, DFT calculations, Natural product, inspired design, Photochromism, Wavelength tuning, Sulfur modification

Elucidating Photochemical Structure-Activity Relationships in Photopharmacology via Multiscale Simulations

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Molecular photoswitches enabling precise photocontrol of protein function. Their performance in photopharmacology depends critically on how substituents and protein environments modulate excited-state dynamics, quantum yields, and the light-responsive difference in binding affinity between their isomeric forms. Yet, the photochemical structure-activity relationships underlying these effects remain poorly understood. In this talk, I will discuss our recent multiscale simulations aimed at addressing this challenge. Using an integrated computational framework that combines docking, classical and QM/MM molecular dynamics, excited-state enhanced sampling, first-principles non-adiabatic dynamics, and alchemical free-energy calculations, we investigated a diverse series of photostatin (PST) derivatives bound to tubulin. Our results reveal how protein electrostatics and steric confinement reshape excited-state free-energy landscapes, influencing non-radiative decay rates, excited-state lifetimes, and photoisomerization quantum yields. We identify the directional alignment of torsional motion with non-adiabatic coupling vectors and backward ground-state isomerization as key factors affecting the isomerization quantum yield. These findings align well with and explain the trends observed in ultrafast time-resolved crystallography, absorption spectra, and isomer-dependent bioactivity. I will also present a systematic benchmark of free-energy methods for predicting the light-responsive differences in binding affinity of photoswitchable antagonists targeting β-adrenergic GPCRs. Thermodynamic Integration consistently yields the best agreement with experiments, accurately capturing the effects of substituents and stereochemistry, whereas endpoint and enhanced-sampling approaches show notable limitations. Together, these studies establish a predictive multiscale platform for quantifying photochemical structure-activity relationships of molecular photoswitches in complex biomolecular environments, guiding the rational design of next-generation light-regulated drugs in photopharmacology.

Keywords: Photochemical Structure Activity Relationships, Quantum Dynamics, Free Energy simulations

*Speaker

Design and Synthesis of Styryl-Substituted Cyclic Enone Photoswitches for Photolipid-Mediated Membrane Modulation

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Photoswitchable lipids - photolipids - are emerging as powerful tools for the precise, light-controlled manipulation and investigation of lipid function. These systems enable the modulation of membrane biophysical properties such as permeability and fluidity, as well as receptor activation. In this project, we investigated the synthesis of a new family of photolipids featuring a phosphatidylcholine polar headgroup and a photoswitchable unit incorporated into the lipid tail for membrane-targeting applications.(1,2)
Initially, we developed and characterized a new class of photoswitchable styryl-substituted cyclic enones. We evaluated the influence of different cyclic enone cores and subsequently explored the effects of various aryl substituents introduced on a chromone scaffold. Rational selection of both the cyclic enone framework and the substitution pattern on the aryl ring led to optimized conversion efficiency, *i.e.* molar extinction coefficients and switching quantum yields. To further extend their applicability, two-photon activation was also investigated.(3,4)

Four candidate photoswitches were ultimately selected for lipid incorporation. We evaluated the photoswitching behavior of the four photolipids in liposomes and Giant Unilamellar Vesicles (GUVs), which served as model membrane systems to assess their effects on membrane organization and properties under light irradiation.

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(2) S. Pritzl, J. Morstein, N. Pritzl, J. Lipfert, T. Lohmüller, D. Trauner, *Commun Mater* **2025**, 6, 59.

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(4) J. Pecourneau, R. Losantos, A. Delova, Y. Bernhard, S. Parant, M. Mourer, A. Monari, A. Pasc, *Langmuir* **2022**, *38*, 15642.

Keywords: Photoswitches, Photolipids, Photoisomerization, Two Photon Absorption.

A photoswitchable positive allosteric modulator to control the activation of the metabotropic glutamate receptor 5 by light

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The metabotropic glutamate receptor 5 (mGlu5) is widely expressed in the brain, where it plays an important role in synaptic plasticity, learning and memory, making it a therapeutic target of interest in various neurological disorders. In this study, we developed a photoswitchable positive allosteric modulator (PAM) of the mGlu5, as a novel tool for this clinically relevant drug target. To that aim, we used an azologisation strategy of the mGlu5 PAM agonist VU0424465 leading to the molecule azoglurax. We observed a reversible photoisomerization of azoglurax in solution with optimal wavelengths of 365 nm and 435 nm for trans to cis and cis to trans isomerization, respectively. In cell-based assays, azoglurax potentiates the agonist-induced activity of mGlu5 with a sub-micromolar potency in the dark. This potency is reduced under UV illumination. Similar to its parent molecule, azoglurax acts as an allosteric agonist of mGlu5, activating the receptor in the absence of glutamate, as demonstrated on a glutamate-insensitive mutant receptor. Docking and site-directed mutagenesis experiments also suggest that azoglurax and VU0424465 bind the same pocket. In addition, molecular dynamics on cis-azoglurax-bound mGlu5 suggests that its azoglurax cis isomer does not bind stably in the receptor, in contrast to the trans-isomer, explaining the difference of activity between the two isomers. In conclusion, azoglurax is the first mGlu5 photoswitchable PAM agonist reported to date, retaining the properties and the binding mode of its parent compound in the dark, while the insertion of an azobenzene confers light-regulated activity.

Keywords: GPCR, Glutamate, Photochromic ligand, Photopharmacology, Photoswitch, mGlu(5).

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Light-Modulable AChE Inhibition Through Aurone-Based Molecular Photoswitches

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Photopharmacology represents a powerful strategy to achieve spatiotemporal control over drug activity, potentially reducing systemic side effects in the treatment of neurodegenerative disorders such as Alzheimer's Disease (AD). In this study, we report the rational design and synthesis of a new series of aurone-based molecular switches developed as photomodulable acetylcholinesterase (AChE) inhibitors. By employing an isosteric substitution strategy on the 2-benzylideneindan-1-one scaffold, previously proposed by our research group(1), we successfully optimized the electronic properties to induce a 30 nm bathochromic shift of the isosbestic point, enabling effective Z→E isomerization in a safer biological window (368 nm). In vitro biological assays demonstrated that these derivatives exhibit potent activity in the sub-micromolar range of inhibitory concentration, alongside significant isoform selectivity. Notably, meta-substituted compounds showed the most promising light-modulated behavior, with photo-irradiated mixtures exhibiting a marked decrease in inhibitory power compared to the pure *Z*-isomers. These findings validate the aurone scaffold as a versatile platform for the development of high-precision phototherapeutics for neurodegenerative disorders, offering a robust starting point for light-controlled treatment of AD.

Reference: (1) Paolino, M. et al., RSC Med. Chem. 2022, 13, 873–886.

Keywords: Aurones, Acetylcholinesterase, Molecular Photoswitches, Photomodulable activity, Photopharmacology

*Speaker

Optical control of the Gastrin-releasing peptide receptor, GRPR, using photoswitchable peptides

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Gastrin-releasing peptide receptor (GRPR/BB2) is frequently overexpressed in aggressive malignancies, where it orchestrates oncogenic Gq-coupled signaling (PI3K, PLC, DAG), promoting angiogenesis, cellular proliferation, invasion, and metastasis. However, its therapeutic relevance and precise spatiotemporal modulation remain unattainable with conventional ligands, which limits mechanistic interrogation and targeted intervention in oncogenic GPCR pathways. Herein, we report a modular photopharmacological approach to open the possibility to reversible control BB2 signaling. Our design is based on Bombesin peptide analogues that incorporate an arylazopyrazole-phenylalanine (AAPF) photoswitch within the peptide scaffold, allowing light-driven conformation while maintaining receptor engagement and binding affinity.
Photophysical characterization by UV-visible spectroscopy in various polar solvents demonstrated favorable absorption profiles and efficient photoisomerization behavior upon Irradiation at 528 nm resulted in highly efficient E-isomer formation, achieving $> 95\%$ E-enrichment. However, Z-isomer enrichment upon irradiation at 365 nm remained suboptimal under the current conditions, highlighting the need for further optimization of the methodology. Functional activity was evaluated using a FRET-based inositol monophosphate (IP) accumulation assay, enabling direct quantification of BB2-mediated Gq signaling in CHO cells, correlating photochemical switching with biological response. All peptide analogues bearing a photoswitch retained basal agonistic activity in the dark, confirming their pharmacological competence. Nevertheless, five derivatives (Bomb2, Bomb4, Bomb7, Bomb10, Bomb11) exhibited pronounced light-dependent potency enhancement, classifying them as "*cis*-on, photoactivatable" agonists. Among these, Bomb4 emerged as a lead compound, displaying pEC values of 9,55 $\pm$ 0,16 in the dark and 10.23 $\pm$ 0.13 upon 365 nm irradiation, both higher than the reference ligand Bombesin (8.97 $\pm$ 0.19 and 9.13 $\pm$ 0.19, respectively), proving an irradiation boost in activity, directly correlating Z-isomer enrichment with functional amplification.
To sum up, this work represents the first systematic application of arylazopyrazole-based photoswitchable Bombesin ligands targeting BB2. This strategy expands the GPCR photopharmacology toolkit, implementing a foundation for precision manipulation of complex signaling networks.

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Keywords: Bombesin receptor, photoswitchable peptide, photochemistry, and photopharmacology.

Molecular Photoswitches as Next Generation Contrast Agents for Photoacoustic Medical Imaging

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Photoacoustic (PA) medical imaging is a noninvasive technique that combines optical excitation with acoustic detection. Because acoustic waves scatter less in tissue than photons, PA imaging enables high-resolution visualization at greater depths. Endogenous chromophores, such as hemoglobin, generate PA signals and support imaging of anatomical structures. However, visualizing specific cell populations requires exogenous agents, whose effectiveness is often limited by interference from endogenous absorbers, reducing contrast specificity. Overcoming this limitation is essential for high-resolution, real-time imaging of individual cells and their dynamics.[1]
Shifting PA contrast formation from the spectral to the time domain offers a promising strategy. By modulating the signal of a contrast agent, background can be suppressed and contrast enhanced. Photoswitchable molecules enable such modulation: if one isomer absorbs strongly in the target spectral region while its metastable counterpart absorbs weakly, switching between them toggles the PA signal ON and OFF. The signal can be restored through thermal or photochemical reversion to the stable isomer.[2] While this concept has been validated using photoswitchable proteins expressed in cells,[3] clinical applications require small-molecule, drug-like agents.

This work presents the synthesis and evaluation of azobenzene derivatives as potential PA contrast agents. These molecules can be switched with red light (525–650 nm) and revert rapidly to their stable isomer on the millisecond timescale. A concise three-step synthesis enables late-stage introduction of diverse *para*-substituents, supporting a compound library to study how substitution influences photochemical behavior and suitability for time-modulated PA imaging.

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Keywords: Photoswitches, azonium ions, photoacoustic imaging, contrast agents

Red-Light–Responsive Stapled Peptide for Optical Control of the MDM2/MDMX–p53 Interaction

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In various cancers, the p53 function is silenced by the overexpression of its negative regulators, MDM2 and MDMX, which bind p53 and target it for degradation. Reactivating the p53 pathway by disrupting its complexation with MDM2 and MDMX is therefore a validated and potent therapeutic strategy in oncology. To this end, several compounds including Idasanutlin, Siremadlin, and Alrizomadlin are already under clinical investigation. Although interrupting this protein-protein interaction is a proven strategy, continuously blocking these protein–protein interactions (PPIs) is often difficult because it can cause side effects, such as p53 induced apoptosis of healthy tissues, at doses close to the effective level. Therefore, achieving spatiotemporal control is essential to mitigate systemic toxicity and expand the manageable dose range.
The use of light to switch on and off inhibitors offers a sophisticated solution to gate biological activity. Implementing this strategy with stapled peptides, which have gained high attention in the past because of their enhanced conformational stability and high binding affinity, creates attractive scaffolds for externally controlled modulation. Additionally, the well-defined α-helical structure, causes particular susceptibility to structural perturbations induced by photoswitch isomerization.
Here, we report the design of a red-light–responsive, photoswitchable stapled peptide targeting the MDM2–p53 interaction derived from a known MDM2/MDMX inhibitor, which restores p53 signaling by competitively blocking its binding to MDM2 and MDMX. By enabling reversible cis–trans isomerization, we aim to modulate the peptide's secondary structure and thereby dynamically regulate its biological activity. We describe the synthetic pathway of the photoswitchable peptide, its photochemical characterization, and preliminary biological evaluation. This work establishes a platform for reversible control of peptide–protein interactions and expands the toolkit of photopharmacology for targeted cancer therapy.

Keywords: Photoswitch, Stapled Peptide, MDM2, p53

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Unified Determination of Photoisomerization and Fluorescence Quantum Yields for Accurate Photochemical Profiling of Styryl-Substituted Cyclic Enones

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Light-activated molecular systems capable of exerting precise and non-invasive control over biological structures are at the forefront of chemical and biomedical research. Amphiphilic photoswitches and photosensitive lipids (photolipids) offer reversible regulation of membrane organization and function with high spatial and temporal resolution.(1) The implementation of such approaches requires chromophores that combine efficient photoisomerization with optical responsiveness in spectral regions compatible with deep-tissue applications. Here, we investigate styryl-substituted cyclic enones inspired by cyclocurcumin, which undergo reversible E/Z photoisomerization under UV irradiation (250–400 nm).(2–3) Molecular dynamics simulations further indicate that these chromophores are amenable to excitation within the biological NIR-I window (650–900 nm) via two-photon absorption (2PA), supporting deeper light penetration while reducing photodamage.(4)

A central aspect of this work is the implementation of a single, integrated spectrophotometric setup that simultaneously records absorption and emission during photoinduced processes. This unified approach enables direct and reliable determination of both photoisomerization quantum yields and fluorescence quantum yields for each isomer under identical experimental conditions. Using this platform, we demonstrate efficient two-photon-driven isomerization of the styryl-substituted cyclic enones and evaluate switching fatigue under both one- and two-photon excitation. By combining structural analysis with simultaneous photophysical and photochemical quantification, this study establishes a robust methodology for characterizing photoswitchable systems and guiding the optimization of next-generation photolipids for deep-tissue optical control with minimized phototoxicity.

(1) *ChemBioChem*, **2021**, 22, 73-78

(2) *J. Org. Chem*, **2021**, 86, 8112-8126

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(3) *Langmuir*, **2022**, 38, 15642-15655
(4) *J. Photochem. Photobiol. Chem.* **2023**, 439,11458

Keywords: Photoswitches, Isomerization, Fluorescence, Quantum Yields

Design of photochromic blocker for complete optical control of calcium-permeable AMPA receptor

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AMPA receptors are glutamate-gated ion channels responsible for fast excitatory signaling in the vertebrate central nervous system. They exist in calcium-impermeable and calcium-permeable subtypes, the latter being crucial in brain development, synaptic plasticity, and neurological disorders. Due to the structure of their ion pore, calcium-permeable AMPA receptors are sensitive to organic cation channel blockers, enabling their selective pharmacological targeting. However, the action of blockers of calcium-permeable AMPA receptors is slow and often purely reversible in experiments on native tissue. A promising alternative is photochromic blockers, which can instantly change their structure and function under light exposure. Existing photochromic blockers do not provide effective optical control of calcium-permeable AMPA receptors, as they demonstrate modest photoswitchable effects and selectivity. We synthesized azobenzene derivatives of spermine and studied their biological activity in electrophysiological experiments on native and recombinant ionotropic glutamate receptors, as well as on synaptic transmission in rat brain slices. The lead compound, azobenzene-spermine-6 (ABSP-6), showed selective, nanomolar block of calcium-permeable AMPA receptors under ambient light, with an IC50 under blue light illumination three orders of magnitude higher. Furthermore, our experiments on slices clearly demonstrated the selective photoswitchable effect of ABSP-6 on excitatory postsynaptic currents (EPSCs) in interneurons, which mainly express calcium-permeable AMPA receptors, while EPSCs in cortical pyramidal neurons were unaffected. Computer modeling suggests that, formation of an intramolecular hydrogen bond in the *cis* – form reduces the effective length of the polyamine chain, resulting in marked loss of activity. Thus, our work provides the first photochromic blocker of calcium-permeable AMPA receptors, which demonstrates excellent characteristics of selectivity and sensitivity to illumination. ABSP-6 is well suited to neurophysiological studies, thus offering an important tool to investigate the contribution of these receptors to various neuronal activities.

Keywords: photoswitch, AMPA receptor, ion channel block, glutamate

*Speaker

Motor-based DNA-binder with photocontrolled affinity

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DNA is a polynucleotide with a double-stranded helical structure, which contains the genetic information of all living organisms and plays a crucial role in life. Controlling the structure of nucleic acids allows the study and modulation of in situ genetic processes (DNA repair, replication, and transcription) and associated cellular functions. For this purpose, numerous external stimuli could be employed, such as light.
Particularly, molecular photoswitches provide a non-invasive, reversible, spatially and temporally controlled approach to modulate biological activity through structural isomerization. In DNA modulation, photoswitches have been widely employed as covalent nucleoside surrogates. Photoswitchable noncovalent DNA-binders are synthetically more attractive, as they do not require oligonucleotide modification and can be applied in vivo. Their efficiency, however, depends on the binding mode, which is difficult to predict.
Nevertheless, the first visible light-driven switchable DNA-intercalators were developed to control DNA and nucleosome binding. Additionally, our group synthesized the first molecular motor-based DNA-hairpin to control DNA hybridization under physiological conditions. This approach offers greater precision and photocontrol due to the multistate character, unidirectional rotation, and helicity inversion during rotation. In our study, we describe the synthesis of a molecular motor-based DNA-binder, explore its motor properties, and investigate its noncovalent interactions with DNA.

Keywords: Photopharmacology, Molecular Motors, DNA

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Development of photoswitchable monoamine oxidase B inhibitors targeting inflammation in osteoarthritis

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Osteoarthritis is an inflammatory disease for which there is currently no curative treatment. Its progression is strongly associated with oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) and antioxidant defense systems. Monoamine Oxidase B (MAO-B), a mitochondrial membrane-bound enzyme, contributes to this process through the production of hydrogen peroxide, a key ROS. Although MAO-B inhibitors are clinically available (e.g., selegiline, used in the treatment of Parkinson's disease), their systemic activity is associated with significant side effects. To overcome these limitations, we propose a photopharmacological approach based on the development of photoswitchable MAO-B inhibitors enabling precise spatiotemporal control of enzymatic activity. This work focuses on hemithioindigo (HTI) and hemiindigo (HI) photoswitches, which undergo reversible isomerization under visible light and exhibit favorable bistability. These compounds show promising inhibitory activity against MAO, with high selectivity for the MAO-B isoform. Building on our previous results, the objective of this project is to modulate the structure of these chromophores to optimize their photophysical properties. To enable biological applications, we specifically aimed to red-shift absorption into the visible region, thereby avoiding the cytotoxicity and limited tissue penetration associated with UV irradiation. Theoretical calculations predicted that the introduction of an electron-donating group at the C5 position of the indigoid core would induce such a shift. To date, only a single example of 5-amino-substituted HTI has been reported, exhibiting promising photophysical properties. Accordingly, our strategy relies on a late-stage Buchwald-Hartwig coupling reaction with a variety of amines, enabling access to a new series of 5-amino-substituted aurones, HTIs, and HIs. Spectroscopic analyses confirmed the predicted bathochromic shift, validating C5-substitution as an effective strategy to tune absorption toward the visible range. This work presents a comparative study of these three series, evaluating the influence of substitution on key parameters including absorption maxima, photoswitching efficiency, and thermal half-lives.

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Keywords: Photopharmacology, Monoamine Oxidase B, Hemithioindigo, Hemiindigo, Photoswitchable inhibitors

Introducing Visible-Light Addressability into Nucleoside-Based Diarylethenes

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Nucleoside-based diarylethenes are highly attractive photoswitches for the light-mediated control of biological function due to their outstanding photophysical performance, including high photostationary state compositions, thermal stability, and fatigue resistance. In the past our group has developed a series of nucleoside-derived diarylethenes and incorporated them into oligonucleotides via solid-phase synthesis. Incorporation into a single-stranded oligonucleotide representing the promoter sequence of T7 ribonucleic acid polymerase allowed light-dependent modulation in an *in vitro* transcription assay, and selected switches were successfully applied to control translation efficiency. Despite these promising results, two central limitations remain. First, most diarylethenes require ultraviolet light for switching, which is undesirable in biological contexts due to phototoxicity and limited penetration depth. To address this challenge, we introduced intramolecular proton transfer motifs based on Schiff base architectures into nucleoside-derived switches. This strategy resulted in a pronounced bathochromic shift, enabling switching with visible light at 400 nm and photostationary state compositions of up to 90%. However, these modifications also led to compromised photophysical performance in some cases, and uracil-based systems in particular exhibited substantial spectral overlap between the open and closed forms. Second, the geometrical perturbation induced by diarylethene photoisomerization within nucleic acids is comparatively small, limiting their ability to modulate structure and function. To overcome this constraint, we designed a photoswitchable hydrogen-bonding motif based on a synthetic C-nucleoside. A model compound was synthesized and displayed promising switching behavior. Upon photoisomerization, a significant decrease in aromaticity of the artificial nucleobase analogue is expected to alter its hydrogen-bonding pattern, enabling light-dependent modulation of base pairing interactions. Such systems may provide new opportunities for controlling ribonucleic acid function, for example in riboswitch-based regulatory architectures. Overall, these approaches expand nucleoside-based diarylethene photoswitches toward visible-light responsiveness and enhanced functional impact in biological systems.

Keywords: Photoswitches, Diarylethenes, Visible, light, Hydrogen, Bonding, DNA, RNA

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Modeling photoswitchable β-Blockers to uncover their Binding Mode

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The azologization of classical β-blockers led to the development of photoazolols, photoswitchable ligands designed to preserve the pharmacophoric fingerprint of carazolol while enabling optical control of β-adrenergic receptors. Time-resolved serial femtosecond crystallography (TR-SFX) studies of photoazolol-1 provided structural insight into receptor-ligand dynamics within the β-adrenoceptor (βAR). The room-temperature structure of the trans bounded complex represents the initial state, while nanosecond to second resolved snapshots captured after illumination revealed that the cis isomer does not dissociate from the orthosteric pocket. Instead, it adopts an alternative binding pose that induces adaptive rearrangements within the transmembrane helical bundle, illustrating receptor plasticity and an induced-fit mechanism.
Importantly, prior to these studies, no crystallographic structures were available for either trans or cis photoazolol-1 bound to β-adrenergic receptors. The TR-SFX snapshots therefore constitute valuable structural references and may serve in the future as starting points for molecular dynamics simulations or docking studies aimed at understanding ligand-specific conformational effects.

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Building on this structural framework, we performed computational docking studies to explore the binding modes of other photoswitchable β-blockers named parazolols. Multiple βAR conformations retrieved from GPCRmd were employed as receptor templates, and selected frames from trajectories were incorporated to account for conformational variability. Rigid docking protocols were applied alongside approaches allowing limited rotational flexibility of selected side chains to probe alternative accommodation scenarios within the orthosteric site.

Rather than providing definitive solutions, these modeling efforts generate plausible binding geometries that help rationalize how substitution patterns may influence ligand orientation and interactions within the pocket. Together, experimental time-resolved structures and computational exploration contribute to a more comprehensive structural understanding of photoswitchable β-blockers and their receptor engagement.

Keywords: β, blockers, photoswitchable ligands, Time, resolved crystallography, βAR, induced, fit mechanism, docking

DEVELOPMENT OF TETRA-ORTHO-METHOXYLATED AZOBENZENE AMINO ACIDS TO ACCESS PHOTOSWITCHABLE ANTIMICROBIAL PEPTIDES

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Antimicrobial resistance (AMR) is a crucial threat to global health. The accumulation of antibiotics in the environment, as a result of extensive or inappropriate use in healthcare and agriculture, increases the evolutionary pressure on microorganisms, leading to accelerated rise in resistance.
Novel strategies are being researched in order to develop new paradigms of action, one of these being photopharmacology. Employing light to switch between two different forms with a difference in activity, effectively switching drugs on and off, can mitigate side-effects or the emergence of resistance.

For this strategy, antimicrobial peptides have emerged as a key target, due to their structure-relying activity as perturbations to their 3D scaffold usually causes a decrease, or complete, loss of function. As such, the introduction of photoswitches, to either the backbone structure or side-chain crosslinkers, can allow control over these structural changes with light.

Several visible-light photoswitchable derivatives have been employed to design peptides, but to our knowledge this would be the first tetra-*ortho*-methoxylated azobenzene amino acids.

Two different tetra-*ortho*-methoxylated azobenzene amino acid derivatives have been synthesized based on the methodology reported by our group. The photoswitchable amino acids have been introduced into the backbone sequence of an antimicrobial peptide, synthesizing different analogues.
These analogues have been photocharacterized on their isomerization, as well as circular dichroism to study their secondary structure change. And are now being tested for their antimicrobial activity.

Keywords: Antimicrobial resistance, Photopharmacology, visible, light photoswitch, tetra, ortho, methoxylated azobenzene, peptide synthesis.

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Fluorescence: How dark quencher azobenzenes actually make fluorophores better.

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Photobleaching and phototoxicity of fluorophores are major limiting factors in high-resolution fluorescence imaging, often restricting the duration and quality of live-cell and single-molecule imaging. We present azobenzenes as a versatile new class of photostabilizing agents that significantly enhance fluorophore performance by quenching reactive triplet states. We are currently developing a comprehensive library of fluorophore-azobenzene-attachment conjugates to identify optimal pairings for various biological imaging contexts. Our results position azobenzenes as powerful, easily tuned tools for creating the next generation of photostable imaging probes. By maximizing the photon output and longevity of standard fluorophores, this method could enable more robust and longer-term imaging in complex biological environments.

Keywords: Fluorescence Imaging, Azobenzenes, Fluorophores, Triplet State Quenchers, Photostabilisation

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DEVELOPMENT OF PHOTOSWITCHABLE ANTIPSYCHOTIC DRUGS

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Schizophrenia remains one of the primary diseases under investigation in the field of neuroscience. This and other severe dopamine-dependent neurological diseases are treated with antipsychotic drugs that inhibit dopamine type 2 receptors (D2R). First-generation antipsychotic drugs, such as haloperidol and aripiprazole, are proposed to act through a mechanism involving heterodimerization of D2R with the adenosine A2A receptor, which is associated with extrapyramidal symptoms (EPS) as side effects. In contrast, second-generation antipsychotics like clozapine inhibit D2R without favoring heterodimerization, thereby avoiding EPS but increasing cardiovascular risks. Despite their clinical use, both generations of drugs therefore present significant side effects. To address this issue, photopharmacology offers a promising strategy by enabling light-controlled modulation of drug activity with spatial and temporal precision. To pioneer the development of light-controlled antipsychotic drugs, we are herein focusing on the synthesis of photoswitchable D2R ligands based on azobenzene and stilbene photochromes that can toggle between two pharmacological states: they emulate clozapine in their cis state and aripiprazole in their trans isomer, acting as light-sensitive probes to elucidate the mechanism of action of current antipsychotics. In the near future, photoresponsive D2R inhibitors with minimal side effects will be designed that switch between inactive and active states upon irradiation.

Keywords: Dopamine receptor, photoswitch, heteromerization

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Engineering Opto-Chemical Tools – Towards Complex Function in Biological Environment

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Organic chromophores are the foundation for developing light-responsive compounds that enable control over bioactive functions and site-specific labeling reactions in opto-chemical biology and photopharmacology. These light-responsive molecules include photoswitches, photocages, and click reagents, and are often appended onto a bioactive molecule or structurally merged with it to couple the light-mediated structural change to a change in bioactive function or site-specific labeling reactions.
To achieve optimal performance in biological systems, the chromophore structure and properties need to match the requirements for photopharmacology, such as fast and clean conversions with pronounced structural changes. This can be achieved through substituent design and optimization of the chromophore core structure, and is constrained by considerations of the intended application.

We will present approaches for designing and optimizing different types of chromophores for opto-chemical biology and photopharmacology. We will showcase both small molecule modulation and biomolecule conjugates, for example, using azobenzene-based photoswitches for controlling protein function, and the development of photocages for site-specific labeling of biomolecules.
Our work aims to provide a deeper understanding of the design principles for light-responsive chromophores and their potential applications in opto-chemical biology and photopharmacology as well as challenges and opportunities of the field.

Keywords: chromophore engeneering, opto, chemical tools, physical, organic chemistry, photochemistry

*Speaker

Reaching subunit stoichiometry selectivity with optogenetic pharmacology: selective control of GluN1/GluN2A/GluN2B NMDA receptors with light

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NMDARs are calcium-permeable heterotetrameric receptors that belong to the ionotropic glutamate receptor family. They play not only a key role in excitatory neurotransmission in the brain, but also participate in brain development, synaptic plasticity, and cognitive function. Impairment of these receptors can lead to neuropsychiatric disorders, such as schizophrenia and epilepsy.
NMDARs exist as multiple subtypes according to the GluN2 subunits (GluN2A to GluN2D) they incorporate. They are di-heteromeric, composed of two GluN1 subunits and two identical GluN2 subunits (e.g., GluN1/GluN2A/GluN2A or GluN1/GluN2B/GluN2B), or tri-heteromeric, composed of two GluN1 subunits and two different GluN2 subunits (e.g., GluN1/GluN2A/GluN2B). Each subtype has specific biophysical and pharmacological properties and studies have shown that GluN1/GluN2A/GluN2B tri-heteromers form the major NMDAR population in the adult brain (Zhang et al., 2025). Yet, there is currently no tool to selectively target them.

Current pharmacological tools cannot indeed discriminate between receptors containing one of several copies of a given subunit. On the other hand, thanks to its exquisite molecular selectivity, we have previously shown that optogenetic pharmacology allows reaching subunit stoichiometry resolution (Sicard et al., 2025). Thus, our project aims at selectively targeting GluN1/GluN2A/GluN2B tri-heteromeric NMDARs using optogenetic pharmacology.
This approach combines thiol–maleimide conjugation for covalent drug attachment with an azobenzene-based, photoswitchable drug to achieve light-controlled receptor modulation. In the present study, two types of photoswitchable compounds were tested: (i) one based on a photoswitchable, GluN2B-selective positive allosteric modulator (spermine) (Sicard et al., 2025), and (ii) another based on a bifunctional maleimide linked by an azobenzene moiety (Peverini et al., 2022). We managed to obtain selective photomodulation of GluN1/GluN2A/GluN2B triheteromers relative to their diheteromeric counterparts (GluN2A and GluN2B diheteromers) but with a photomodulation ratio that remains poor (max. 15%). Further developments will require improvement of the photoswitchable molecule properties to increase the photomodulation ratio of GluN1/GluN2A/GluN2B tri-heteromers.

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Keywords: NMDARs, photoswitch, electrophysiology, Glutamate receptors, optogenetic pharmacology

In vivo photoreversible neuromodulation with infrared light

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Photoswitchable ligands enable reversible control of receptor function by photoisomerization between two conformations having different biological activity. Shifting the operating wavelengths of photoswitchable ligands towards the red and infrared (IR) spectrum, while maintaining thermodynamically stable isomers, has been pursued to reduce phototoxicity and to increase photosensitivity. However, no photoswitchable ligands have been reported that support bidirectional switching with IR light under physiological conditions, which would further allow deep tissue penetration *in vivo*.
We have developed a set of photoswitchable compounds targeting muscarinic receptors, named neuroswitches, that optimally respond to IR light. These compounds can be operated by conventional one-photon as well as by two-photon excitation (2PE) to remotely activate receptor signaling. Importantly, bidirectional 2PE was achieved with IR wavelengths between 730 nm and 910 nm, allowing the activation and deactivation of receptor signaling *in vitro* and enabling effective and reversible neuromodulation of the brain cortex of wild-type mice.

Neuroswitches therefore offer the opportunity to study and manipulate intact receptor activity *in vivo* with unprecedented pharmacological and spatiotemporal selectivity, while minimizing phototoxicity. They support the development of novel non-invasive phototherapies based on muscarinic neuromodulation, offering the promise of a single-component drug that is intrinsically devoid of adverse effects in the dark and could be photoactivated on demand in selected

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cortical regions to improve treatment efficacy, safety, and versatility.

Keywords: photopharmacology, two, photon pharmacology, photoswitch, azobenzene, neuromodulation

Diketopiperazines: Biocompatible Photoswitches for Cell Culture Matrices and Medical Applications

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Molecular photoswitches undergo reversible structural changes upon light stimulation, making them attractive for designing smart materials whose properties can be modulated with high spatiotemporal resolution. In this context, we identified a novel photochromic scaffold, arylidene-2,5-diketopiperazine (Hemipiperazine, HPI), within the anticancer drug candidate Plinabulin. The arylidene unit undergoes reversible E/Z photoisomerization and exhibits a long thermal half-life.(1)
Building on these findings, monosubstituted DKP derivatives with electron-donating heteroarylidene groups were investigated to exploit the biocompatible nature of these cyclic dipeptide-derived switches while inducing a red-shifted absorption spectrum. This shift enhances their therapeutic relevance, potentially enabling their application as photopharmaceuticals with tunable bioactivity. This strategy was based on reports of bathochromic shifts observed in other photochromic scaffolds (azobenzenes, indigoids) upon substitution with heteroarenes. In contrast to carbocyclic HPIs, the heterocyclic HPIs exhibited more efficient photoconversion, with less spectral overlap. Moreover, the heteroaromatic-substituted HPIs displayed several additional favorable properties, such as good thermal stability, good isomerization efficiency in water, and resistance to reducing agents.(2)

Other studies on photoswitchable photopharmacology materials conducted in our group led to the development of hydrogelators bearing a 2,5-diketopiperazine (DKP) core, functionalized with both a lysine residue and an azobenzene group. Substitution of the azobenzene with electron-withdrawing halogens yields a bathochromic shift of the absorption spectrum into the visible range.(3) Concurrently, electrostatic interactions between the lysine residue and co-gelators support reversible hydrogel assembly upon photo switching of the azobenzene group.(4) We are further developing this system for drug delivery applications with minimally invasive release triggers and dynamically tunable cell culture matrices.

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Keywords: Hemipiperazine, 2, 5, Diketopiperazine, Biocompatible photoswitches, Visible, light activation, Reversible hydrogel assembly

SELF-ASSEMBLING PHOTOACIDIC SYSTEMS FEATURING MEROCYANINE/SPIROPYRAN AMPHIPHILES

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Meta-stable-state photoacids (PAHs) hold significant interest due to their peculiar photoswitching mechanism and reversibility. Examples of these compounds include protonated merocyanines, which can undergo light-driven E/Z isomerization, leading to ring closure and formation of a spiropyran structure1. The process also results in proton release and is fully reversible: by removing the light source, the ring reopens, and the resultant merocyanine restores the proton gradient by reclaiming the proton. A method to tune pH changes in response to external stimuli would be highly useful across a wide array of applications, from drug delivery to smart engineering. Other works described the use of these molecules in organic media, such as vesicles and hydrogels, to modulate membrane permeability through proton gradients and facilitate drug release2. A key weakness that prevents the wide applicability of merocyanine/spiropyran systems is their low solubility. This project aims to synthesize water-soluble photoacids by modifying the basic "Liao's photoacid" structure. The addition of polar groups to the EA moiety and a hydrophobic chain to the NuH one would allow the creation of amphiphilic compounds with increased water solubility and, potentially, self-assembly characteristics. These molecules will then be studied to determine how the photochemical properties and the merocyanine/spiropyran equilibrium are influenced by both the structural modifications and supramolecular assembly. The current focus is on the synthesis of trimethylammonium-substituted merocyanines bearing an alkyl chain, the length of which could be changed for better self-assembly and membrane affinity.

Keywords: Photoacid, Merocyanine

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SYNTHESIS AND EVALUATION OF PHOTOSWITCHABLE PEPTIDES TO MODULATE CELL PENETRATION WITH VISIBLE LIGHT

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Light has emerged as a powerful external trigger providing activation with high spatiotemporal resolution. This has enabled the development of light-responsive molecules that address the lack of selectivity of active drugs. However, beyond the regulation of the molecular activity itself, another limitation is the lack of control over the uptake of therapeutic agents into cells. Thus, using light to modulate cell penetration represents a big interest for drug delivery and imaging, for example. In this context, cell-penetrating peptides (CPPs), have emerged as efficient vectors due to their remarkable ability to cross cellular membranes. However, although they have been shown to be effective in transporting cargo across the cell membrane, CPPs can be degraded *in vivo* and are non-cell-type specific. To overcome these limitations, researchers have focused on a new class of vectors based on CPPs that can be selectively activated by light irradiation, enabling a precise spatiotemporal control.
In this work, our approach is to design photoactivatable conjugates that combine a cationic CPP with a complementary anionic sequence, together linked via a diazocine photoswitch which adopts a bent geometry in its ground state. In the thermodynamically stable *cis* form, the CPP should be inactive and protected from proteases through intramolecular electrostatic interactions. Upon photoisomerization with visible light, the diazocine switches to its elongated *trans* form, disrupting the intramolecular interactions and activating the CPP for cellular uptake. (Prestel, Chem.Commun, 2015)
Towards this goal, we have developed a strategy, based on solid-phase synthesis, that allowed obtaining several CPP-diazocine conjugates (M.S.Maier, J.Am.Chem.Soc, 2019; J.Berry, Chem.–Eur.J. ,2022; A.Bruneau, Chem.–Eur.J ,2015). Using spectroscopy and scattering methods, we have been investigating how the nature of the peptide sequence influences the photochemical and conformational switching properties. Finally, we plan to incorporate a fluorescent tag to switching-effective structures in order to assess the cellular uptake capability.

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Keywords: cell, penetrating peptides, diazocine, peptide synthesis, photoswitches, cellular uptake

Unlocking Tetrazine Reactivity with Light

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Tetrazines are among the most powerful bioorthogonal handles due to their exceptionally fast inverse-electron-demand Diels-Alder (IEDDA) reactivity. However, precise spatiotemporal control over their activation remains a central challenge in chemical biology. Herein, we introduce a light-responsive macrocyclization strategy to reversibly suppress and restore tetrazine reactivity. In the caged state, the tetrazine core is incorporated into a macrocyclic framework that constrains its electronic and conformational properties, resulting in significantly attenuated reactivity toward dienophiles. This macrocyclization effectively "locks" the tetrazine in an inactive form. Upon irradiation, photochemical cleavage of the macrocycle induces ring opening and releases the structurally unconstrained tetrazine, thereby restoring its intrinsic IEDDA reactivity. This light-triggered transformation functions as a molecular reactivity switch, enabling external control over bioorthogonal ligation processes without permanent modification of the tetrazine scaffold. Our results demonstrate that macrocyclization can serve as a general photocaging principle for tetrazines, providing a new strategy for the spatiotemporal regulation of fast bioorthogonal reactions.

Keywords: tetrazine, bioorthogonal chemistry, inverse, electron, demand Diels, Alder reaction, photocaging, light activation

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Mechanisms of Ziapin2-Mediated Cardiac Action Potential Generation: A Computational Study

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Optical stimulation offers a precise and non-invasive alternative for controlling cellular processes, particularly in cardiac electrophysiology. Recently, Ziapin2, a light-sensitive azobenzene compound, was introduced as a photomechano-transducer capable of modulating excitation-contraction coupling in cardiomyocytes. Experimental data suggested that light-driven action potential (AP) generation mediated by Ziapin2 involves the contribution of stretch-activated channels (SACs), but the precise biophysical mechanism remains unclear.
This study presents an advanced computational model of the murine AP to elucidate the role of SACs and the photostimulation mechanism mediated by Ziapin2. The model incorporates two key effects arising from photoisomerization: 1) variations in membrane capacitance (Cm) associated with trans-cis isomerization, and 2) activation of SACs driven by membrane tension changes.

The numerical model accurately reproduces experimental observations in adult mouse ventricular myocytes (AMVMs), showing a characteristic modulation of membrane potential: an initial hyperpolarization coincident with the Cm change, followed by a delayed depolarization culminating in AP generation once the light is interrupted.

By selectively blocking SACs in the model, we demonstrate that only Ca^2-selective SACs contribute significantly to AP generation, in agreement with experimental evidence. Consistently, reducing extracellular Ca^2 prevents AP generation, underscoring the pivotal role of Ca^2 influx.

These findings enhance our understanding of the biophysical interplay between mechanical perturbations (membrane thickness/stretch) and electrical responses in cardiac cells mediated by Ziapin2. Our validated model provides a tool for predicting cellular behaviour and paves the way for the development of novel light-based strategies for precise cardiac control.
Additionally, ongoing work is extending the proposed framework to a human induced pluripotent stem cell-derived cardiomyocyte (iPSC) model. Preliminary results indicate that the iPSC-

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based model remains consistent with the murine findings, preserving the key dynamical features. Moreover, the model shows numerical stability and robustness upon integration of experimentally derived parameters, demonstrating its ability to accommodate and reproduce experimental data.

Keywords: Optical stimulation, Cardiac electrophysiology, Ziapin2, Stretch, activated channels, Action potential modeling, Murine cardiac model, iPSC, derived cardiomyocytes

Toward Predictive Photopharmacology: AI-Accelerated Excited-State Simulations for High-Throughput Photoswitch Screening

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Photopharmacology seeks to redefine drug action by replacing systemic exposure with light-controlled precision, activating therapeutics only where and when they are needed. Yet designing viable photoswitchable drugs is an inherently multi-objective challenge: absorption must be tuned to clinically relevant wavelengths, excited-state dynamics must yield efficient switching and controlled lifetimes, and thermal relaxation must set the duration of biological activity, all within biological constraints. Systematically exploring these coupled requirements across chemical space demands computational screening, but conventional ab initio methods are too expensive to enable high-throughput discovery.

Here we introduce an AI-driven computational pipeline for predictive photoswitch design. We develop transferable excited-state machine learning interatomic potentials, trained on quantum chemistry data spanning diverse azobenzene-derived scaffolds, that accelerate non-adiabatic molecular dynamics by orders of magnitude. This enables scalable prediction of quantum yields, relaxation pathways, and excited-state lifetimes across large chemical libraries. In parallel, an automated thermal isomerization workflow provides rapid, mechanistically grounded estimates of cis half-lives. Together, these advances enable simultaneous optimization of photochemical and thermal properties at screening scale, enabling systematic discovery of novel photoswitches for next-generation light-activated therapeutics.

Keywords: Photopharmacology, photoswitches, nonadiabatic molecular dynamics, machine learning interatomic potentials, virtual screening, AI for drug discovery

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SYNTHESIS OF PHOTOSWITCHABLE FGFR3 INHIBITORS FOR IMPROVING CHEMOTHERAPY AGAINST BLADDER CANCER

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Bladder cancer is a commonly diagnosed malignancy, characterized by high recurrence rates and poor outcomes, especially in more advanced stages of the disease. Even with the recent advances in treatment, efficacy is limited, and side effects are a common problem. In the search for a new therapeutic target, the oncogenic role of fibroblast growth factor receptors (FGFRs) was uncovered, especially the FGFR3 isoform. FGFRs are a family (FGFR1-4) of highly conserved tyrosine kinase receptors that control many normal physiological functions like cell proliferation, survival, migration, and angiogenesis. Because of the highly conserved tyrosine kinase ATP-binding position between FGFR isoforms, and tyrosine kinases in general, while kinase inhibitors present a good potential therapeutic option, they often lead to side effects due to lack of selectivity. We hope that the use of photopharmacology could enable spatiotemporal control of the drug activity that would, by achieving localized effect in tumor, reduce the side effects and improve patient outcomes. To this end, we are currently modifying known FGFR inhibitors through azologization strategies, which involve preparing azobenzenes at the 3-position of a pyrazole heterocycle. Here, we will present our efforts towards the synthesis of these compounds, some encountered synthetic difficulties of this scaffold, and photochemical characterization of synthesized molecules, with focus on changing the photochemical properties of the molecules by varying the substituents.

Keywords: Oncology, Bladder Cancer, FGFR3, Azoheteroarenes

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Thermo-Bistable Red and Sensitized Near-Infrared Photoswitches

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Molecular photoswitching in the red and near-infrared (NIR) region is highly sought after for applications in biological systems, optoelectronic devices, and functional materials, where low-energy light minimizes photodamage and enables deep-tissue penetration. However, developing photoswitches that simultaneously achieve long-wavelength responsiveness with robust thermal bistability and high quantum efficiency remains a formidable challenge. Here, we report an intrinsic thermo-bistable, red-light-responsive (605 nm/730 nm) photochromic motif based on a perylene bisimide (PBI) scaffold, which further enables an unprecedented sensitized NIR (808 nm/730 nm) photoisomerization through triplet pathway. Rational side-chain engineering with aryl substituents of distinct aromaticity and electronic character finely tunes the transition-state energy barrier ($\Delta G‡ = 45.07$ kcal mol^{1}), leading to exceptional thermal stability and a long-lived closed isomer. Further molecular engineering of PBI-based photoswitches also delivers high photoisomerization quantum yield, bright fluorescence, and near-quantitative photo-conversion efficiency. This work provides a new photochromic motif that boosts the overall photochemical/thermal performances of molecular photoswitching at the red-light end, thereby enriching the structural and functional landscape of high-performance photoswitching system. Demonstrations in dynamic cell-membrane imaging further highlight the potential of these PBI-based photoswitches as a powerful photochemical platform for advanced biomedical and optoelectronic applications.

Keywords: photoswitching, perylene bisimide, triplet

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Light-regulated molecules to improve the pharmacology of cancer drugs

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Metabotropic glutamate receptor 3 (mGlu3) is a G protein-coupled receptor belonging to the group II. It plays a significant role in neurotransmission modulation and is mainly expressed in the nervous system but also in other tissues such as liver, kidney and bladder. Additionally, mGlu3 plays an important role in cell proliferation and growth, including tumoral cells.
Photopharmacology allows the manipulation of the desired target protein's activity with a high spatiotemporal precision using light. For this purpose, light-sensitive drugs are developed and used, including a photochromic unit that respond to light radiation.
Here, we present the design and synthesis of different photoswitchable ligands, that will be used as molecular tools for studying the activity of mGlu3. These are based on the azologisation of mGlu3 reported inhibitors (decoglurant, VU0469941 and VU0650786), thus maintaining the core structure with some minor changes to introduce the photoswitchable moiety.

Keywords: Photopharmacology, photoswitches, mGlu3, Inhibitors, NAMs

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Session 2: Optical engineering and novel applications

Soft self-written waveguides enable photorelease of a photocaged adenosine A1 receptor agonist for local suppression of neuronal excitability in the brain

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Temporal lobe epilepsy is the most common form of medication-resistant focal epilepsy. The hippocampus plays a crucial role in the generation of seizures and therefore is a target for focal neuromodulation strategies.

Adenosine is an endogenous anticonvulsant substance, effective in inhibiting epileptic seizures by activating the adenosine A1 receptor (A1AR), a G protein-coupled receptor. Due to the ubiquitous presence of inhibitory A1R in the body, systemic treatment with A1R agonists is associated with multiple side effects. Recently, a 7-(diethylamino)-4-(hydroxymethyl) coumarin (DEACM) caged derivative of the A1R agonist N6-cyclopentyl-adenosine (pcCPA) enabled local and irreversible release of CPA with 405 nm light in vitro and in vivo. Typically, stiff optical probes (e.g., silica fibers) are used for intracerebral light delivery, which causes profound neuroinflammatory responses due to the mechanical mismatch between the stiff probe material and the soft brain tissue.

In this work, we report the use of soft hybrid polymer-based probes, consisting of light-induced self-written waveguides (SWWs), which are advantageously self-assembled and self-aligned at the tip of a silica optical fiber. Low insertion losses with total transmission over 90% (for 405 nm and 440-840 nm wavelengths) measured at the tip of 2.974 ± 0.394 mm (n = 5) long SWWs were demonstrated. Furthermore, in an acute experiment, SWWs (diameter of 119.08 ± 12.83 μm) were implanted in mice above the hippocampal dentate gyrus (DG), where perforant path evoked potentials (EPs) were recorded every 10 seconds. After intracerebroventricular administration of pcCPA (25 μg in 1.25 μl DMSO), the amplitude of the EPs decreased during

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illumination with pulses of 405 nm light (8mW, 100 ms pulse duration, 0.1 Hz pulse frequency). This proof-of-concept study highlights the potential of using soft SWWs to uncage CPA from pcCPA for local inhibition of neuronal excitability.

Keywords: light delivery, photouncaging, in vivo photouncaging, self written waveguides (SWWs), adenosine, soft probes, epilepsy, temporal lobe epilepsy (TLE)

Non-invasive Cardiac Modulation via Triplet-Sensitized Photocontrol of Muscarinic Agonist

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Red, far red, or near-infrared photoswitchable drugs offer immense photo-pharmacological advantages due to the higher light penetration through the skin. Such photoactivation is achieved using processes such as two- and three-photon absorption, excited-state absorption, and triplet-triplet annihilation upconversion, which require higher photon fluences than the resilience constraints of skin (200mWcm–2). We developed a generalized approach of *cis*-to-*trans* photoisomerization of azobenzenes via triplet sensitization with NIR-I illumination (850nm) of a new Zn-octa-substituted phthalocyanine photosensitizer, in aqueous medium at 2.62mWcm–2. The approach is applied to control the heart rate of a frog tadpole via *cis*-to-*trans* photoisomerization of an azobenzene-functionalized muscarinic acetylcholine receptor M2 agonist in the phototherapeutic window (730nm excitation: 42mWcm–2). This advance highlights a powerful photo-pharmacological strategy for modulation of in vivo activity at 2-4 orders of magnitude lower photon fluences of NIR light compared to established methods. (Nat. Commun. 2025)

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Keywords: Triplet, sensitized photoswitching, photopharmacology, Controlling the cardiac rate

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Optical modulation of ion channels using Automated Patch-Clamp

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Introduction

The discovery of light-activated ion channels has paved the way for many exciting developments in the field of optogenetics. These ion channels change their conformation following optical stimulation allowing ions to pass through their pore. Since their discovery, many genetically engineered versions have been generated, exhibiting a broad spectrum of biophysical properties.

Light can further be used to indirectly modulate ion channels through the use of caged or photoswitchable compounds, or by optically activating secondary messenger pathways.

Optical modulation of ion channels is traditionally studied using a manual patch clamp system combined with a light source. This approach, however, is limited by a very low throughput. Here, we present data recorded using both a semi-automated 8-well patch clamp system and a full automated 384-well based patch clamp system equipped light sources.

Methods and results

HEK293 cells stably expressing Channelrhodopsin 2 (ChR2) were electrophysiologically characterized using blue light pulses. Light activation curve of the rhodopsin was recorded by application of various light intensities. It was further shown that ion selectivity and activation kinetics are in agreement with literature values.

Rubi-GABA is a caged version of GABA that is released following exposure to blue light. Using this compound in combination with the microfluidic flow channel of the QPlate and QChip consumables allows reduced ligand exposure of

Finally, HEK293 cells co-expressing HCN2 and photoactivated adenylyl cyclase (bPAC) were characterized on Qube Opto. Optical stimulation resulted in a right shift of the HCN2 activation curve.

Conclusion

We provide compelling evidence that it is possible to study ion channels modulated by light on a high throughput patch clamp platform. This new capability opens the door for many novel applications in the field of ion channel research.

*Speaker

Keywords: Automated Patch Clamp, Ion Channels, ChR2, RuBi GABA

Photocleavable Ruthenium polypyridyl-based mass-tags for targeted mass spectrometry imaging in cancer tissues

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While MSI has seen widespread application in metabolomics and lipidomics, its direct deployment to proteins remains limited due to several factors, including their size, poor desorption, and low sensitivity. This led to the introduction of the mass tag (MT) concept, in which targets that are otherwise hard to detect are detected via proxy molecules (reporter group), usually a small molecular entity. Most of these mass tags use antibodies to achieve specificity in binding to their target protein.
In this lecture, I present the innovative concept of photocleavable ruthenium-based mass-tags for MSI. In detail, we deployed a Ru(II) polypyridine complex as a reporter unit, offering the advantages of aive charge to in permanent positcrease ionizability, a distinct isotopic pattern to facilitate identification, and multiplexing capabilities through ligand modification. The Ru(II) moiety was tethered to either a cyclic peptide (TATE) targeting SSTR2 receptors in cancer cells or to a small-molecule PARP-1 inhibitor (Olaparib). We demonstrated that Ru(II)-MTs enables multimodal visualisation of SSTR2 and PARP-1 in cancer tissues using matrix-assisted laser desorption/ionisation (MALDI) or desorption electrospray ionisation (DESI) MSI.

Our approach provides greater flexibility in MT design tailored to specific targets of interest. In addition, Ru(II) MTs are synthesized via well-established procedures, enabling cost-effective, straightforward manufacturing, and can be stored as solids, reducing time-dependent degradation and increasing shelf life.

Keywords: mass spectrometry imaging, photo cleavable mass tags, ruthenium polypyridyl complexes

*Speaker

Engineering a genetically encoded fluorescent biosensor for relaxin-3

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First reported in 2001, relaxin-3 is an insulin-like neuropeptide found in the brain that primarily binds a class A G protein-coupled receptor (GPCR), RXFP3 (formerly known as GPCR135). Relaxin-3 has been implicated in the modulation of arousal, the stress response, feeding and metabolism, and memory; however, the molecular mechanisms underpinning this modulation remain largely unknown. Currently, efforts to study the function and mechanisms of relaxin-3 rely on pharmacological manipulations and genetic knockdowns. On the other hand, genetically encoded fluorescent biosensors, which modulate their fluorescence upon ligand binding are an attractive alternative because they allow for the direct visualization of their target and their high spatiotemporal resolution. Indeed, within the last decade, GPCR-based biosensors have exploded in popularity within the fields of neuroscience and cellular biology due to their high specificity and spatiotemporal resolution. Moreover, their potential application as a platform for drug discovery as an alternative to bioluminescent sensors is also of increasing interest. To date, however, there is no such biosensor for relaxin-3, impeding our efforts to study its dynamics. To address this gap in science, we present our efforts on engineering the first genetically encoded relaxin-3 biosensor using its endogenous receptor and a circularly permuted green fluorescent protein. We expect that this new peptide biosensor, especially in conjunction with existing strategies, will help to understand the role of relaxin-3 and its mechanisms by facilitating its real-time detection.

Keywords: fluorescent protein, biosensor, GPCR, optogenetics, neuroscience, fluorescence

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Localized photopharmacology using a wireless cardiac implant to modulate cardiac electrical function via photoactivatable peptides

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Despite major advances in cardiac electrophysiology, current antiarrhythmic therapies remain limited by systemic drug exposure, off-target effects, and the lack of spatial and temporal control over ion channel modulation. Poor selectivity often results in narrow therapeutic windows and adverse effects. Natural animal venom peptides represent a promising alternative due to their high potency and ion-channel selectivity. To overcome limitations associated with systemic delivery, we developed photoactivatable peptides enabling light-controlled, spatiotemporally precise modulation of ion channel activity. We previously demonstrated that photoactivatable natural peptides can modulate cardiac electrophysiology *in vitro*, *ex vivo*, and *in vivo*. In this study, we developed a photoactivatable analogue of the sodium channel-modulating venom peptide AaH-II and evaluated its efficacy across complementary experimental models. We further investigated whether a fully wireless, battery-free cardiac implant could locally activate this peptide in vivo to modulate cardiac electrical activity.

Photoactivation of caged AaH-II was validated using high-throughput patch-clamp recordings in HEK293 cells, multi-electrode array recordings in isolated perfused rat hearts, and optical stimulation in open-chest anesthetized Wistar-Han rats. A miniaturized wireless optical device was surgically implanted on the right ventricular free wall. Device tolerance was assessed over one month using ECG, echocardiography, circulating cardiac injury biomarkers, and histological analyses. The photoactivatable peptide was administered intravenously and locally activated using 405 nm illumination.

Light activation of caged AaH-II reproducibly altered cardiac electrophysiology *in vitro* and *in vivo*, consistent with slowed sodium channel inactivation. The implanted device showed excellent biocompatibility, with no evidence of inflammation, arrhythmias, or cardiac dysfunction. Local optical activation induced a significant increase in ECG T-wave area, indicating effective modulation of ventricular repolarization. Animals rapidly recovered, enabling repeated photoac-

*Speaker

tivation without mortality.
Together, these results demonstrate that implantable optical devices enable safe, local modulation of cardiac electrophysiology via photopharmacological peptide activation, establishing a foundation for precision cardiac photopharmacology.

Keywords: Cardiac Photopharmacology, Implantable Device

DESIGN AND CHARACTERIZATION OF A LIGHT-CONTROLLED ION TRANSPORTER MODULATOR: IN VITRO AND IN VIVO PROTECTIVE ROLE IN MYOCARDIAL ISCHEMIA/REPERFUSION INJURY MODELS

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Acute Myocardial Infarction (AMI) is still one of the main causes of death worldwide. This is partly due to myocardial ischemia/reperfusion injury (MIRI) during angioplasty, which is characterized by a fast calcium overload that occurs for a short period of time at the beginning of reperfusion, causing cardiomyocyte hypercontraction and cell death. Therefore, a pharmacological intervention during this initial phase of reperfusion has been proposed for MIRI attenuation, but continued ion transport dysregulation beyond this phase could impair physiological calcium extrusion and would be detrimental. The need for a time- and location-selective methodology has prevented successful implementation of this approach.

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Here, we describe a new photopharmacological strategy using a photoswitchable ion transporter modulator. In a heterologous cell model, induced calcium entry is reduced only after illuminating the compound at 365nm. In mouse primary cardiomyocytes, only the light-activated form of the compound is able to prevent both calcium entry and the associated cell morphology changes. In these cells, electrophysiology experiments show a time-dependent activation of the inhibitor and its partial inactivation with a second wavelength (550nm). Furthermore, in a perfused rat heart model subjected to ischemia/reperfusion, only brief incubations with the 365nm-illuminated compound conferred protection (less LDH release, reduced infarct size).

Finally, in a sustained coronary artery occlusion pig model we assessed the protective effect of our compound against reperfusion injury. Intra-coronary administration of the active form of the compound was combined with its *in situ* inactivation with a 520nm light by means of a light delivery catheter, a prototype system specifically developed for this project. Under these conditions, we observed a reduction in infarct size only when both active compound and inactivating light were used.
In conclusion, a photopharmacological approach to reduce MIRI after heart angioplasty has been developed, combining novel compounds and light delivery systems.

Keywords: Photopharmacology, Photoswitch, Cardiomyocyte, Myocardial Reperfusion Injury, Light Devices

Characterizing Channelrhodopsin2 using a 384-well automated patch-clamp setup - SOL for SyncroPatch 384

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We studied channelrhodopsin-2 (ChR2) expressed together with the voltage-gated sodium channel Nav1.5 in HEK293 cells, using the SyncroPatch 384 automated patch clamp platform with integrated optical stimulation. Photocurrents were recorded across a range of irradiances, from near-threshold activation to saturating intensities. Under voltage-clamp conditions with sodium channels blocked by tetracaine, we quantified peak and steady-state photocurrents, activation and deactivation kinetics, and desensitization during illumination. To examine temperature effects, kinetics were compared at 20∘C and 30∘C (analysis pending). Ion selectivity was further assessed by systematically varying external (bath) and internal (pipette) ionic compositions (analysis pending).
In current-clamp recordings, increasing light intensities produced graded membrane depolarizations, and strong illumination reliably activated Nav1.5, resulting in rapid additional depolarization. These experiments demonstrate how ChR2-mediated conductances influence voltage-gated sodium channel activity and how environmental factors such as temperature and ionic composition influence functional properties.
This study provides a comprehensive analysis of ChR2 in a heterologous system, combining optical stimulation and automated patch-clamp to evaluate kinetics, desensitization, ion selectivity, and channel interplay under defined experimental conditions.

Keywords: automated patch clamp, optical stimulation, Channelrhodopsin, ChR2, Nav1.5

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Three-colour Photopharmacology: Chromatically Orthogonal Photocages for Precision Optical Control of G-protein Coupled Receptors

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Photocaged compounds are rendered biologically inert until their activity is restored upon light illumination, enabling precise spatiotemporal control of biological processes. G protein–coupled receptors (GPCRs) represent major drug targets, with approximately 36% of FDA-approved medicines acting on this receptor family. Among them, α1-adrenoceptors (β-ARs) regulate cardiovascular, genitourinary, and central nervous system functions. Since adrenoceptors are widely distributed throughout the body, therapeutic and experimental strategies would benefit from light-based control to minimize off-target effects and to interrogate tissue-specific GPCR signaling.
Photopharmacological multiplexing-the orthogonal control of distinct biological processes within a single living cell-is particularly attractive for studying complex phenomena such as sequential signaling events, synergistic drug combinations, or selective activation of multiple receptor subtypes. However, most photocleavable protecting groups (PPGs) exhibit overlapping absorption spectra, limiting their utility for multiplexed uncaging. The key feature for such optically independent photolysis of multiple caged compounds is the lack of selective excitation of a red-shifted chromophore.

We recently reported a set of water-soluble xanthenium-based photocages capable of efficiently releasing payloads upon irradiation up to 650 nm.1 Here, we demonstrate the use of three distinct PPGs that can be selectively cleaved using violet (405 nm), blue (488 nm), and red (650 nm) light to release α1-AR agonist (phenylephrine) and antagonists (tamsulosin, desipramine). The photocaged ligands displayed high chemical stability and minimal background activity in the absence of light, ensuring low off-target effects. Upon illumination, rapid and efficient ligand release was observed. Chromatic orthogonality was validated in vitro by LC–MS analysis and in cellulo using real-time confocal imaging of intracellular calcium signaling in HEK293T cells.

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Keywords: photocage, multicolour, adrenoceptor, G, protein coupled receptor, calcium imaging

How to time GltTk transporter: towards kinetic probing with photo-triggered substrate release

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GltTk is a sodium-dependent neurotransmitter transporter responsible for the uptake of aspartate, which plays a key role in synaptic transmission and implicated in neurodegenerative disorders such as Parkinson's disease. The transport cycle of GltTk involves complex conformational changes, transitioning between outward-facing and inward-facing states to alternately expose substrate-binding sites to either side of the membrane. Understanding the fast kinetics and conformational dynamics of GltTk requires precise spatial and temporal control of substrate availability. To achieve this, we developed a caged aspartate analog using an improved photoremovable protecting group, a second generation coumarin that allows the controlled release of aspartate (Asp) upon light irradiation. Synthesis of coumarin-Asp was performed and optimized using substrates protected at different functional groups. Photorelease of aspartate was studied by NMR and UV-Vis spectroscopies, and its bioactivity will be validated using electrophysiology assays with reconstituted GltTk systems. Fast uncaging of coumarin photochemical probes will enable precise stimulation of GltTk, allowing us to track aspartate and sodium ion fluxes and transporter conformational changes within a short timescale. This approach provides a powerful tool to study real-time transport cycle of GltTk and offers insights into how its dysregulation contributes to neurodegeneration.

Keywords: photocage, structural study, fast kinetics

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Photoresponsive prodrug-based loaded nanoparticles for enhanced anti-retinoblastoma therapy

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Drug delivery to posterior segment of eyes for treatment of fundus diseases remains a challenging task. Traditional chemotherapy and super-selective intra-arterial chemotherapy by chemotherapeutics for treatment of retinoblastoma still face many drawbacks that lead to various systemic and local adverse events, although the rate of vison preservation has been improved. The total inhibition rate of severe and advanced retinoblastoma is also not satisfying. Therefore, it is of great necessity to explore a new strategy to improve anti-tumor efficacy while reducing the risk of adverse events. Herein, we developed a light triggered drug release nanosystem for targeted and controlled release of chlorambucil for treatment of retinoblastoma. The chlorambucil drug molecule was conjugated with BODIPY to make BC prodrug and co-assembled with RGD peptide-modified PLA-PEG copolymer and platinum (II) tetraphenyltetraben zoporphyrin (PtTPBP) to make nanoparticles. The triplet-triplet energy transfer (TTET) process within the particle further enabled drug release by red light instead of green light. The nanoparticle itself presented the ability to overcome blood-retinal-barrier (BRB), and the cRGDfk modification further enhanced its penetration ability. The therapeutic efficacy and biocompatibility of our nanoparticles were confirmed both in vitro and in an orthotopic mouse models of retinoblastoma. This study provides a promising approach to treat retinoblastoma and a proof-of-concept strategy to achieve light-controlled delivery to posterior segments of eyes for various ocular diseases.

Keywords: Retinoblastoma, photoresponsive drug delivery, photocleavable prodrugs, chemotherapy, triplet, triplet energy transfer

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Photocontrolled hERG Channel Blockade by Diazirine Integrated into BeKm-1 Pharmacophore

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Peptide therapeutics offer exceptional potency and target specificity, making them attractive candidates for precision medicine. However, their broader clinical deployment remains limited by rapid clearance, non-oral administration, and off-target effects arising from incomplete receptor selectivity. Current strategies to extend peptide efficacy typically rely on chemical stabilization or formulation approaches that lack spatial and temporal control. Photopharmacology provides an alternative paradigm by enabling light-dependent modulation of drug activity with high precision.

Here, we introduce a light-controlled strategy to dynamically regulate peptide pharmacology using photosensitive amino acids. By incorporating diazirine-containing residues (photoleucine and photomethionine) into BeKm-1, a high-affinity yet reversible blocker of the hERG potassium channel, we demonstrate that optical stimulation can reorganize the peptide pharmacophore in real time. Upon illumination, specific BeKm-1 analogues exhibit tunable changes in channel-blocking potency, and in one configuration, form a covalent crosslink with the ion channel under physiological conditions. This photo-induced crosslinking results in a dramatic prolongation of

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peptide activity, effectively transforming a transient blocker into a long-lasting, locally acting modulator.

Light-mediated targeted prolongation of action provides a powerful framework for achieving tissue-restricted, on-demand peptide therapeutics at low concentrations. Importantly, this approach circumvents key limitations of systemic peptide delivery while preserving molecular specificity. Although demonstrated here using a hERG channel ligand, the strategy is broadly applicable to other peptide-target systems. More generally, light-controlled peptide pharmacology opens new avenues for spatially-confined and temporally-precise therapeutic interventions in cardiology, neuromodulation, and beyond.

Keywords: Photocoupling, peptides, diazirine, hERG, BeKm, 1

Multiplexing: Caging the central step in chemigenetic ligation for multipurpose imaging and photocontrol

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HaloTag proteins spontaneously ligate onto any chemical reagent featuring a chloroalkane motif (CA). We introduce the conditional CHalo motif, which ligates to HaloTag only after uncaging by light or enzymes.
(1) Photo-triggered CHalo fluorogenic reagents allow spatiotemporally-specific labeling.

(2) photo-triggered CHalo heterodimerisers can photocontrol protein recruitment.
(3) enzyme-triggered CHalo reagents can durably record diverse enzyme activities, and multiplexing them should allow quantitative ratiometric recording of multiple activities in parallel. CHalo thus permits manifold extensions to the HaloTag technology.

Keywords: HaloTag, Conditional Ligation, photo & enzyme triggered, spatiotemporal control

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TOWARDS IN VIVO BRAIN BIOLUMINOLYSIS OF A G PROTEIN-COUPLED RECEPTOR PHOTODRUG

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Photopharmacology has emerged as a promising approach to modulate receptor activity with defined spatial and temporal resolution. This discipline relies on the use of light-modulable compounds (photodrugs), enabling precise control over drug activity while reducing off-target engagement compared to conventional pharmacological strategies. It was previously reported that the selective A2AR antagonist SCH442416 can be released *in vivo* from its photocaged derivative MRS7145 following striatal irradiation through implanted optical fibers in mice (1). Subsequently, in this follow-up study, we explore the use of bioluminescence resonance energy transfer (BRET) generated by the reaction between nanoluciferase (NL) enzyme with its substrate to effectively photouncage MRS7145, a process known as bioluminolysis (2). First, we demonstrated the photorelease of SCH442416 from MRS7145 in HEK-293 cells expressing A2AR tagged with NL at the N-terminus (A2AR-NL). Bioluminolysis-mediated A2AR blockade was monitored by cAMP accumulation determinations upon activation of the receptor using the selective agonist CGS21680. To transition to in vivo studies, we utilized an adeno-associated virus encoding a functional A2AR conjugated with an NL enzyme (AAV-A2AR-NL). The expression and functional activity of A2AR-NL in the mouse striatum were demonstrated by immunohistochemical analysis, immunoblotting, and luminescence assays. The chemiluminescent properties and pharmacokinetics of selected NL substrates were investigated by in vivo bioluminescence imaging (Spectral Instruments, Lago X). Finally, the bioluminolysis-dependent activation of MRS7145 in living animals was evaluated through locomotor and anticataleptic behavioral paradigms. Thus, this method will offer the potential to improve animal behaviour studies by eliminating the requirement of restraining cables or optical fiber implantation and to support the development of new photopharmacology strategies.

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Keywords: Bioluminolysis, In vivo photouncage, Adenosine A2A receptor, Nanoluciferase

Switching Pain On and Off with Light: Photopharmacology and Drug-Free Analgesia through Two-Pore-Domain K+ Channels

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Pain research needs tools that control nociceptive signaling with high temporal precision and reversibility, while avoiding systemic drug effects and invasive genetic manipulations. Here we present two complementary, non-invasive optical strategies that exploit peripheral K2P potassium channels as bidirectional switches to tune pain in intact wild-type animals.
Using LAKI (Light Activated K+ channel Inhibitor), a photoswitchable small molecule targeting the K2P channels TREK and TRESK, we achieve wavelength-dependent and reversible modulation of channel function through the skin. LAKI is functionally silent in the dark/ambient light, but alternating illumination at 365 nm and 480 nm toggles inhibition and relief of inhibition of TREK/TRESK currents. Because TREK/TRESK normally constrain excitability at sensory endings, their light-driven inhibition provides a rapid, repeatable "pain ON" command that enables optical facilitation of nociception in freely moving animals.

Conversely, Light-Induced Analgesia (LIA) enables drug-free pain suppression by directly activating the endogenous K2P channel TRAAK with brief 365 nm illumination. Activation is mediated by oxidation of a native regulatory methionine, which increases K+ conductance, reduces nociceptor excitability, and produces robust analgesia without compound administration. In this setting, light functions as an "analgesia ON" command.
Together, LAKI and LIA form a bidirectional optical toolkit for switching pain states: LAKI promotes nociception by inhibiting inhibitory K2P channels, whereas LIA suppresses nociception by activating TRAAK. This approach enables mechanistic dissection of peripheral pain pathways and provides a practical route to improve experimental control, reproducibility, and animal welfare in preclinical pain research.

Keywords: photochromic ligand, photoswitchable tethered ligands, pain, migraine, Light, inducded analgesia

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Targeted covalent photoswitch for two-photon control of endogenous receptors

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The study of intact cells and their signaling circuits with light requires a stimulation strategy that is focused, deeply penetrating, and that does not damage them. Implanted optic fibers, light emitting diodes, and luminescent materials operated externally with tissue-penetrating infrared (IR) light are invasive or limited by light attenuation around the illumination point. To overcome these barriers, two-photon pharmacology takes advantage of femtosecond-pulsed IR laser light to produce deep and spatiotemporally precise cellular stimulation using specially designed photoswitchable drugs. Compounds that can be covalently tethered to the target neuroreceptor perform particularly well. However, the tethered photoswitches reported to date require mutagenesis of the target protein, which prevents using photopharmacology to stimulate the nervous system in wildtype animals. Here, we report the first two-photon optimized targeted covalent photoswitch (TCP2P) that combines the efficient two-photon isomerization of *ortho* fluoro substituted azobenzene with the ability to conjugate to nucleophilic residues of endogenous proteins (AMPA and kainate ionotropic glutamate receptors in neurons). TCP2P is readily obtained by click coupling of two precursor compounds prior to use and after simple incubation it enables controlling neuronal activity at one and two-photon excitation up to 800 nm without genetic modifications.

Keywords: multiphoton, azobenzene, inductive push, pull, covalent drug, click chemistry, nucleophilic bioconjugation, electrophilic reagent, photopharmacology, optopharmacology, chemical optogenetics, caged ligand, glutamate receptor, covalent warhead.

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Rhodamine-based photocages in chemical biology and drug delivery

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Photocages are chemical protecting groups capable of releasing specific molecules in a biological context upon light irradiation. Visible to NIR light activatable photocages often feature chromophores from various fluorescent dyes, such as coumarins, BODIPYs or cyanines (1). In 2023, we reported a set of unique, xanthenium-based photocages that were based on rhodamine or related fluorophores (2). They offer high photolysis efficiencies across the visible spectrum up to the near infrared range, high absorption, water solubility and easy derivatization. The latest findings on this intriguing class of photocages will be presented including their opitimized synthesis, detailed photochemical analysis and advanced applications in photoactivated chemotherapy. The challenges and limitations as well as the future research directions based on these novel chemical tools will be discussed in detail.

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(2): *J. Am. Chem. Soc.* **2023**, *145*, 4026.

Keywords: photocages, photoactivated chemotherapy, rhodamines, xanthenium photocages, photopharmacology

*Speaker

Limiting the phototoxicity of meso-Methyl BODIPY photocages using Contact-Ion Pair stabilization strategies.

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Boron dipyrromethene (BODIPY) has been established as a key scaffold in biomedical research. Its excellent absorptivity and wavelength-tunable absorption, as well as its potential biological safety, make BODIPY an exceptional chromophore for photopharmacology. It has received a lot of attention for their ability to be turned into photocages (photocleavable protecting groups), compounds able to release upon light-irradiation a desired biological payload. However, key challenges still hinder *in vivo* application of BODIPYs as photocages, mainly related to its inherent phototoxicity. Several studies highlight the photosensitizing nature of BODIPYs cages, which leads to reactive oxygen species (ROS) formation upon photorelease, limiting the amount of payload being released and potentially harming the surrounding local environment. Additionally, the core of the BODIPYs cage tends to photobleach after uncaging, which creates multiple unknown, potentially (photo)toxic, products. In this work, we introduce a carbocation-stabilizing modification at the *meso* position of the BODIPY core that promotes a clean and controlled uncaging process. This modification results in the formation of a well-defined, non-competing, safer *meso*-unsaturated BODIPY. Comparative photophysical studies reveal that these stabilized photocages produce up to seven times less singlet oxygen than their unmodified counterparts, significantly reducing the risk of ROS-mediated toxicity. The uncaging mechanism was elucidated through a combination of femtosecond and nanosecond spectroscopy, complemented by density functional theory (DFT) analyses. Furthermore, injection of the modified and unmodified compound in zebrafish embryos have been carried out to assess and compare their (photo)toxicity *in vivo*. These findings represent a key step in the improvement in BODIPY photocages development, both in the fundamental understanding of the uncaging mechanism, as well as the limitation of the inherent photo-toxicity of the scaffold.

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Keywords: Photocages, BODIPY, CIP, Toxicity, Phototoxicity

Photocaging Enables Optical Control of S-acyltransferase Activity in Mammalian Cells

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Protein lipidation is a post-translational modification (PTM) which plays a pivotal role in protein function, localisation, and protein-protein interactions. Despite > 150 potential cancer drug targets being lipidated, the full spectrum of lipid PTMs and opportunities to target their dysregulation in various diseases remains unexplored. Protein *S*-acylation is a PTM where long-chain fatty acids are reversibly transferred onto cysteine residues through a thioester linkage, a process mediated by 23 S-acyltransferases of the ZDHHC enzyme family and reversed by acyl-protein thioesterases (APTs). Over 3000 cysteine residues across 12% of the human proteome are lipidated by ZDHHCs. Therefore, it comes as no surprise that the ZDHHC enzyme family is implicated in numerous neurological, immune diseases, and cancer.

The ZDHHC catalytic domain is conserved across the family and the mechanism starts with auto-acylation of the active site Cys (**Fig.A**). This "loading" step is followed by *S*-acyl transfer to a proximal Cys in the substrate protein. *S*-acylation remains notoriously difficult to study due to the absence of a well-defined substrate recognition sequence, lack of inhibitors and due to the dynamic reversible nature wherein the lipid is sometimes rapidly installed and removed on minute timescales.

To better understand the dynamics of protein *S*-acylation by ZDHHCs we combined genetic modification and light-responsive molecules to introduce spatio-temporal control over the activity of a single ZDHHC *S*-acyltransferase within the context of a mammalian cell (**Fig.B**). The modified cellular machinery is utilized to site-specifically incorporate unnatural photocaged amino acids onto the active site cysteine of ZDHHC20. The caged ZDHHC remains inactive, whereas upon irradiation with light the active site is uncaged thus initiating *S*-acylation and lipidation of its substrates (**Fig.C**). This elegant approach offers a unique opportunity to match *S*-acylation of known and potentially new substrates to intrinsic dynamics of cellular activity in a spatio-temporal manner.

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Keywords: Post, translational modifications, Photocage, Genetic code expansion, Protein lipidation

Photocontrolled Delivery of a STING Agonist Using Photoresponsive Lipid Nanoparticles

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Near-infrared (NIR) light is attractive for in vivo photoactivation, yet translating NIR irradiation into precise, localized therapeutic action depends on efficient photosensitizer-based transduction and well-controlled delivery. In parallel, cytosolic delivery of STING agonists is potent but hard to spatially confine, motivating photocontrolled strategies that restrict activation to illuminated regions. Here, we leverage lipid-verteporfin (LipVER) lipid nanoparticles (LNPs) as a photoresponsive carrier to enable photocontrolled delivery of an immunostimulatory payload (cGAMP) while coupling photodynamic effects with innate immune activation.
Rather than introducing a new nanoparticle chemistry, we focus on integrating cGAMP loading and light-regulated function within a LipVER-LNP framework. We characterize the resulting formulation for size, stability, and payload association, and evaluate its performance in vitro through cellular uptake, light-triggered ROS generation, and downstream immune-relevant readouts. We further examine photocontrol in tumor models by assessing delivery, activation, and therapeutic response under practical irradiation constraints.
Overall, this study highlights a strategy for turning a photoresponsive LNP platform into a programmable carrier for immune agonist delivery, providing a modular route toward more spatially confined and controllable immuno-phototherapy in optically challenging tissues.

Keywords: Photosensitive nanoparticles, Photosensitizers, Photoresponsive drug delivery, Immuno, phototherapy, STING agonist

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Metronomic photodynamic immunotherapy via wireless LED-triggered drug release for postsurgical care of breast cancer

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Implanted wireless LEDs are widely used as light sources to trigger metronomic photodynamic therapy (PDT) and photothermal therapy (PTT). However, achieving controllable drug release and enhanced therapeutic effects with wireless LEDs remains challenging. To address this, we developed a photoresponsive nanoparticle, termed NBTNP. Its design incorporates photocleavable building blocks with intrinsic photodynamic activity, immunomodulators, and photocleavable trigonal molecules. Using an implanted wireless LED as a metronomic light source in mice, we demonstrated that under its long-term irradiation, NBTNPs exhibited significant ROS generation and potent phototoxicity in vitro. Furthermore, they also displayed significant inhibition on primary tumor recurrence and distant tumor progression by inducing systemic immune activation in vivo. Ultimately, this work utilizes an implanted wireless LED to achieve long-term metronomic PDT and immune activation with NBTNPs, presenting a promising strategy for the postsurgical care of breast tumors.

Keywords: Metronomic photodynamic therapy, photocleavage, photoresponsive drug release, wireless LEDs

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Session 3: Emerging targets and therapeutic potential

NIR-responsive Ru-COUBPY complexes as potent next-generation phototherapeutic agents

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Photodynamic therapy (PDT) is a non-invasive anticancer modality that enables precise spatiotemporal control of therapeutic activity using light. However, most clinically approved photosensitizers (PSs) absorb weakly in the deep-red and near-infrared (NIR) region, limiting their efficacy against large or hypoxic tumors due to their oxygen dependent mechanisms and shallow light penetration. In contrast, photoactivated chemotherapy (PACT) provides a complementary, oxygen-independent strategy, with metal-based agents offering diverse and synergistic light-triggered pathways.
To address the limitations of conventional PDT, we have developed a family of Ru(II) polypyridyl complexes incorporating coumarin-derived COUBPY ligands that display excellent *in vitro* and *in vivo* PDT performance upon irradiation within the phototherapeutic window. Here, we introduce π-extended Ru-COUBPY complexes obtained through a vinylogation strategy and post-coordination assembly. These structural modifications enhance molar absorptivity and red-shift absorption into the NIR region without compromising photostability. The resulting complexes show potent *in vitro* phototoxicity against cancer cells under deep-red and NIR irradiation, even under hypoxic conditions, representing a significant improvement over the parent complexes. Notably, the lead compound Ru6 achieved strong *in vivo* tumor growth inhibition in mice bearing subcutaneous colorectal tumors upon irradiation with one-photon NIR light at 780 nm. This constitutes one of the first examples of Ru(II) polypyridyl complexes with potent antitumor activity under true NIR one-photon activation.

In parallel, we report a new generation of Ru(II) polypyridyl complexes carrying COUBPY photocages of FDA-approved anticancer drugs, designed to act as dual PDT/PACT agents and to broaden the therapeutic potential of the platform within the phototherapeutic window.
Overall, the broad activation window, strong NIR photoresponsiveness, and high phototoxicity of the Ru-COUBPY platform highlight its potential for treating deep-seated, oxygen-deficient tumors.

*Speaker

Keywords: photosensitizer, PDT, PACT, coumarin, ruthenium, anticancer

Arylazopyrazoles enable high affinity photoswitchable inhibitors of N-myristoyltransferase

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N-myristoyltransferase (NMT) catalyses the co- and post-translational attachment of myristate to a wide range of substrate proteins; a lipid modification with diverse functional roles in both healthy physiology and disease.(1) NMT is therefore an attractive therapeutic target, with demonstrated relevance in antiparasitic, antiviral, and anticancer contexts.(2)
IMP-1088, a NMT ligand, inhibits both human isoforms with sub-nanomolar potency.(3) Here, we "azologised" this inhibitor scaffold by replacing the aryl indazole core with an arylazopyrazole (AAP) photoswitch, leveraging the favourable photopharmacological properties of azoheteroarenes. This strategy delivered the first photoswitchable NMT inhibitors that combine high affinity with light-dependent activity. Our lead compounds show single-digit nanomolar binding, functional inhibition in biochemical assays, and cellular target engagement, with a clear activity difference between the (E) and (Z) isomers. The strong binding interactions within NMT enable us to observe photoinduced ejection of the protein-bound, active (E) isomer from the binding pocket, accompanied by a conformation rearrangement of surrounding residues into the vacant site.

Together, these results establish NMT as an enzymatic target for photopharmacology and underscore APP as a powerful platform for generating high-affinity, light-controllable inhibitors, while providing insight into target-bound switching.
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Keywords: Photopharmacology, Azologisation, Azoheteroarenes

PhotoCORMs Rhenium(I) complexes: impact of isomerism on 1O2/CO production

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Nowadays, antimicrobial resistance is rising due to the overuse of antibiotics, creating an urgent need for alternative therapies. Among the strategies being explored, therapies based on transition metal complexes are particularly promising. Photoactive rhenium(I) carbonyl complexes have the remarkable property of enabling a bimodal antimicrobial therapy through the combination of carbon monoxide (CO) photorelease and singlet oxygen (1O2) sensitization (Figure 1). In this work, four isomeric photochemically CO-releasing molecules (PhotoCORMs) sharing a Re(CO)3(PPh3) core have been studied. Variations were made in a pyridyltriazole (Pyta) bidentate ligand, in which a second nitrogen atom is inserted at various positions (the absence of this second nitrogen atom corresponds to the reference **Re-Pyta-TPP** complex (1)). In this **Re-Ln-TPP** series, we have examined how the position of the extra nitrogen atom influences the photophysical properties (absorption, phosphorescence quantum yield, excited state lifetime, 1O2 sensitization quantum yield) as well as the photochemical properties (CO photorelease quantum yield and kinetics). These experimental studies have been complemented with a thorough computational study. DFT calculations have shown that ligand isomerism significantly alters the potential energy profile of the lowest triplet state involved in CO photorelease, and consequently impacts singlet oxygen photosensitization. These results provide insight into structure-property relationships in rhenium(I) PhotoCORMs and suggest trails for optimizing their dual antimicrobial activity (2).

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Keywords: PhotoCORMs, rhenium, carbon monoxide, singlet oxygen, antibacterial agent

Recent progress in the photopharmacology of select potassium and calcium channels

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As the field of photopharmacology matures, there remains ample interesting molecular targets. This poster will focus on the design, synthesis, and characterization of two sets of photoswitchable ligands that inhibit calcium (calcium release activated calcium, CRAC) and potassium (two pore potassium, K2P) ion channels, as well as a new set photoswitchable activators for another family of potassium channels (KV7, KCNQ).

Keywords: azobenzene, diazocine, CRAC channel, K2P, KCNQ

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LIGHT-INDUCED PHOTOTHERMAL TRANSPORT OF ION AND WATER CHANNELS MEDIATED BY A TWO-PHOTON–RESPONSIVE MOLECULAR TRANSDUCER

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Natural aqueous and ionic channels are transmembrane proteins that are crucial for proper cellular function. They enable the highly selective transport of molecules such as water, ions (e.g., Na, K, Cl), and certain small solutes across cell membranes. Among these proteins, some channels are responsive to specific stimuli, including thermosensitive ion channels such as TREK and TRPV proteins in neurons. Insights into the structure and function of these natural systems have facilitated the development of artificial channels designed to replicate the properties of their biological counterparts. These synthetic channels offer considerable promise across diverse scientific and technological domains, from water desalination to biomedical applications. In particular, light-gated artificial channels incorporating a photosensitive component have attracted significant interest. This project aims to engineer photothermally activatable artificial water channels by embedding photothermal transducers directly into the channel structure. To accomplish this, we designed molecular building blocks that integrate urea groups to promote

*Speaker

self-assembly into supramolecular channels, transport units that allow selective conduction of water or ions and a chromophore unit for photothermal conversion and activation of the channel. As the chromophore component, push–pull distilbene derivatives were selected for their efficient light-to-heat conversion and strong two-photon absorption properties, enabling potential two-photon activation of the channels in future studies. Several of these molecular building blocks have been successfully synthesized, and their self-assembly and transport capabilities have been preliminarily assessed using membrane model systems (giant unilamellar vesicles, GUVs) as well as stop-flow and HPTS assays.

Keywords: artificial channels, ion and water transport, push, pull dyes, photothermal effect, two, photo absorption

Optimized xanthenium photocages with fused ring systems for photoactivated chemotherapy and GPCR photopharmacology

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Photocages are light-responsive chemical protecting groups that enable the spatiotemporally controlled release of bioactive molecules. As biological systems studied by chemical biology and medicine become increasingly complex, the development of new photocage scaffolds with improved photochemical and biological performance is essential. Here, we show how the structural and electronic properties of xanthenium-based photocages modulate their ground-state stability. Guided by rational molecular design, we introduce a next-generation xanthenium photocage platform incorporating a julolidine auxochrome, yielding highly efficient green-to-red light activatable photocages, X590 and X600H. X590 was successfully applied to the light-controlled release of the potent tubulin inhibitor monomethyl auristatin E (MMAE) and the topoisomerase inhibitor SN38 using low light doses at wavelengths above 600 nm. The resulting photoactivatable prodrugs exhibit excellent photoindices in both two-dimensional cell cultures and three-dimensional tumor spheroids and demonstrate pronounced antitumor activity in the chorioallantoic membrane assay in live chicken embryos. The versatility of the scaffold was further demonstrated by the development of a caged agonist enabling optical activation of the serotonin 2C G protein–coupled receptor. Overall, these photocages represent a broadly applicable platform for photopharmacology, and the detailed studies presented herein contribute to the clinical translation of photoactivated chemotherapy.

Keywords: photocages, photoactivatable chemoterapy, chicken chorioallantoic membrane assay, G protein, coupled receptor

*Speaker

Restoration of edge detection and visually guided behavior in ambient white light with photoswitchable small molecules

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Blinding diseases due to degeneration of photoreceptors (PhRs) like geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD) and retinitis pigmentosa (RP) leave the rest of the retinal circuitry largely intact, albeit unable to respond to light. Gene therapy has been able to revert PhR degeneration, but it can only be applied to a rare mutation affecting a small subset of RP patients. Alternatively, implanted electronic retinal prostheses aim at a larger population by electrically stimulating the surviving neurons. However, the treatment is invasive, costly, and provides limited resolution. Photopharmacology can develop

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photoswitchable small molecules to restore vision impairment by conferring light sensitivity to ion channels that are widely expressed in the remaining inner retinal neurons, and a first-in-human clinical trial is ongoing. Here, we have developed novel photoswitchable small molecule ligands of metabotropic glutamate 6 (mGlu6) receptors, which are located exclusively at the dendrites of ON bipolar cells (postsynaptic to PhRs) and can leverage a privileged position to mimic physiological signals in the remnant retinal circuit. These photoswitchable ligands (prosthe6) thus act as 'molecular prostheses' that can restore the light input to the retina *via* upstream-targeted control of the circuit after PhRs degeneration. Prosthe6 compounds are allosteric, drug-like, water soluble, and display outstanding *in vitro* properties including full efficacy, nanomolar potency, fast deactivation in ambient white light, and fast reactivation in the dark. *In vivo* experiments show that they readily recover the edge detection ability of blinded zebrafish larvae and restore the innate light avoidance behavior in mouse models of blindness (GA and RP). These effects are mediated by mGlu6 receptors *in vivo*. In addition, at least two compounds (prosthe6-**12** and -**15**) can restore sight by topical administration and display promising safety properties to become potential drug candidates for sight restoration in patients of degenerative blinding diseases.

Keywords: photopharmacology, photoswitch, allosteric modulator, metabotropic glutamate receptor, mGlu6, blindness, visual acuity, optokinetic reflex

Azoheteroarene-stapled peptides for the photoregulation of protein-protein interactions

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Protein-protein interactions (PPIs) play a crucial role in regulating nearly all cellular processes and are characterised by extensive contact surfaces between proteins. Unlike ligand-receptor complexes, these contact surfaces are often challenging to target using small molecules. However, stapled α-helical peptides have emerged as valuable tools to disrupt these interactions. To achieve this, an intramolecular cross-linker (staple) is inserted between strategically spaced residues on the water-exposed surface of the helix, thereby stabilising the peptide helical conformation and generally improving its binding affinity, cellular uptake, and proteolytic stability. Integrating a photoswitchable molecule in the staple further complements the high pharmacological selectivity of these agents with precise light-induced spatiotemporal resolution. Upon photoisomerisation, the photoswitch undergoes a drastic change in shape, which propagates to the peptide backbone, either stabilising the bioactive helical conformation (ON state) or inducing partial unfolding that reduces the peptide binding affinity for the target protein (OFF state). This strategy can be employed to reduce the side effects of clinically relevant PPI inhibitors, as well as to generate powerful tools capable of interrogating complex biological systems in a highly dynamic way. Azobenzene (AzB) has been successfully employed to develop photoswitchable stapled peptides; however, its non-quantitative *E*-*Z* isomerisation ($Z \leq 85\%$) and short thermal half-life (minutes at 25 ∘C) limit the use of AzB-based staples. Consequently, our group has devoted considerable efforts to the development of novel azoheteroarene photoswitches, which are characterised by improved photochemical properties, i.e. quantitative bidirectional photoisomerisation and longer thermal half-lives (days or years at 25 ∘C). Here, we present the development of a series of azoheteroarene-based cross-linkers and their use to generate light-responsive stapled PPI inhibitors addressing the Bak-Bcl-xL interaction, a well-validated target in oncology

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Keywords: protein protein interactions, stapled peptides, azoheteroarene

A novel non-invasive photoswitchable molecule restores light sensitivity and visual acuity in blind animal models

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Some blinding disorders, such as retinitis pigmentosa (RP), cause a complete degeneration of photoreceptors, resulting in loss of visual function while preserving the inner retinal circuitry. Approaches including implanted electrodes or gene therapy have demonstrated certain benefits, but they rely on invasive and costly procedures. In contrast, photopharmacology has achieved the development of small photoswitchable compounds capable of restoring visual responses by providing light sensitivity to ion channels in the remaining retinal cells. The aim of this study is to introduce a novel photoswitchable molecule that successfully restores light sensitivity and visual acuity in blind animal models. Prosthe6 pharmacokinetics were evaluated in vitro. Optokinetic responses were assessed in blinded zebrafish larvae. Light avoidance assays and the Optomotor Test (OptoDrum) were performed to evaluate the recovery of light-driven behavior and visual acuity in a mouse model of RP, after topical administration of the compound. In vitro analyses revealed that prosthe6 compounds were water-soluble and acted allosterically, exhibiting nanomolar potency, rapid deactivation and reactivation under ambient white light and darkness, respectively, and adequate solubility for topical delivery. In vivo studies demonstrated recovery of edge-detection capacity in blinded zebrafish. Light avoidance test showed that in the retinitis pigmentosa mouse model, prosthe6 restored light-driven behavior, and now animals were able to identify the illuminated compartment. With the OptoDrum setup, we were able to see

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that treated animals perceived optomotor characteristic stimuli (black and white gratings with different spatial frequencies and contrast), indicating a substantial improvement in visual acuity. This innovative photoswitchable compound achieved restoration of edge detection, light responsiveness, and visual acuity in blind animal models following topical administration. Prosthe6 represents a promising therapeutic strategy for vision restoration in retinal neurodegenerative diseases.

Keywords: allosteric modulator, retina, retinitis pigmentosa, light sensitivity, visual acuity

Novel 3D-Printed Biophotonic Scaffold Displaying Luminescence under Near-Infrared Light for Photopharmacological Activation

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The development of platforms for precise spatiotemporal control over drug activity remains a central goal in photopharmacology. While photoswitchable compounds offer powerful opportunities for light-mediated modulation of biological systems, their application in deep tissues is limited by poor penetration of activating wavelengths in the UV–visible range. Upconversion-based strategies provide a promising solution by converting tissue-penetrant near-infrared (NIR) light into higher-energy photons capable of triggering photochemical processes locally.
Here, we report the design and characterization of 3D-printed, bioresorbable biophotonic scaffolds embedded with upconversion (UC) crystals, enabling localized NIR-to-visible light conversion for on-demand activation of photoswitchable molecules. These scaffolds act as implantable

*Speaker

optical transducers, combining structural functionality with remote optical control.

We demonstrate that the scaffolds exhibit stable upconversion emission under NIR excitation and maintain chemical integrity in simulated physiological conditions. Importantly, their emission is sufficient to drive biologically relevant photoreactions, including the controlled release of nitric oxide (NO) and the photoisomerization of the muscarinic photoswitchable ligand Phthalimide-Azo-Iperoxo (PAI), enabling receptor-level modulation under NIR illumination.
This work establishes bioresorbable upconversion scaffolds as a versatile strategy for deep-tissue photopharmacology, enabling minimally invasive, spatially confined, and temporally precise control of drug activity using NIR light.

Keywords: Photopharmacology, Upconversion materials, Near, infrared activation, Photoswitchable ligands, Biophotonic scaffolds

When Light Meets Protein Kinase Inhibition: The Promise and Obstacles of pi-Extended Coumarin as Photolabile Protecting Groups

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This work presents the development of photocleavable tyrosine kinase inhibitors as a potential targeted cancer therapy. Focusing on the TAM family-Tyro3, Axl, and Mer-overexpressed in several cancers (bladder, lung, and pancreas), we used the clinically relevant inhibitor **UNC2025** to enable optical control. We report the use of π-extended coumarins as photoremovable protecting groups to generate visible-light-responsive photocleavable versions of **UNC2025**. Our study reports on the synthesis, photophysical characterization, and enzymatic and cellular assays performed with and without irradiation. This study also highlights the effects of electron-withdrawing and donating groups in the π-extended coumarins on both the photophysical properties of the resulting photocleavable inhibitors and their biological activity.

Keywords: uncaging, photoremovable protecting groups, photocaged compounds, cancer, protein kinases

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Photocontrol of zebrafish behavior with a photoswitchable antagonist of α7 nicotinic acetylcholine receptors

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The α7 nicotinic acetylcholine receptor (α7 nAChR) is a key modulator of cognitive function, inflammation, and neuronal signaling, making it an attractive therapeutic target for neurodegenerative and neuropsychiatric disorders. However, traditional pharmacological interventions lack precise spatial and temporal control, often leading to off-target effects. Photopharmacology offers a novel approach to modulate α7 nAChRs with high precision. Here, we present the functional characterization of a novel photoswitchable α7 ligand, CPZ-2. Behavioral assays in zebrafish larvae revealed the ability of CPZ-2 to modulate nicotine-induced locomotion in a light-dependent manner. Our findings establish CPZ-2 as a promising tool for optically controlled α7 nAChR modulation, with potential applications in neuroscience, inflammation, and pain research. Further studies will explore its utility in circuit dissection and therapeutic interventions.

Keywords: Photopharmacology, α7 Nicotinic Acetylcholine Receptor, Zebrafish Behavioral Assay

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Spatiotemporal Control of Inflammation via Light-Responsive Anti-Inflammatory Agents

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Inflammation is a fundamental defence mechanism of the human body, helping to fight infections and repair tissue damage. However, when the inflammatory response is not properly resolved, it can turn harmful, leading to chronic inflammation. This destructive ending phase can be the responsible for many degenerative diseases, autoimmune disorders, and even cancer. A key player in this process is the enzyme cyclooxygenase-2 (COX-2). It regulates the production of pro-inflammatory lipid mediators such as prostaglandins (e.g. PGE2), which can contribute to tumour progression by helping on the development of the tumour microenvironment (TME). While COX-2 selective inhibitors (known as coxibs) have proven effectiveness in reducing inflammation and preventing disease progression, their widespread use is limited due to significant gastrointestinal and cardiovascular side effects.

In this work, we present a new approach to anti-inflammatory therapy using light-induced derivatives of celecoxib (a known coxib). By combining computational modelling (*in silico*), laboratory experiments (*in vitro*), and animal studies (*in vivo*), we demonstrate that these photoactivatable compounds allow precise control over the timing and location of drug activity. Our results highlight the potential use of these compounds as next-generation therapeutics to control inflammation. These new photoswitches are offering safer and more targeted treatment options for patients with cancer and other inflammation-related diseases.

This study highlights the potential of photopharmacology to transform anti-inflammatory therapies. Our results provide a proof of concept that light-controlled modulation of inflammation is feasible and effective, opening the door to safer and more precise clinical treatments.

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Keywords: inflammation, NSAIDs, coxibs, cyclooxygenase 2, cancer, azobenzene, photoswitches

Light-controlled modulation of neuronal activity with photoswitchable sodium channel blockers

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Sodium channel blockers constitute an important class of drugs used to treat epilepsy, neuropathic pain, and cardiac arrhythmias. However, their systemic administration prevents localized and on-demand control of sodium channel inhibition and leads to adverse effects. To address this limitation, we designed and developed a family of photoswitchable derivatives of sodium channel blockers. One of the compounds exhibited robust photoswitchable activity. At 30 μM in cultured hippocampal neurons, the trans isomer suppressed action potential firing, consistent with Nav channel inhibition. Illumination at 365 nm induced isomerization to the cis configuration, restoring neuronal firing, while subsequent irradiation at 420 nm returned the compound to its pharmacologically active trans isomer. This bidirectional switching demonstrates reversible optical control over sodium channel–mediated excitability. *In vivo* evaluation in zebrafish larvae further confirmed isomer-dependent activity. The trans-enriched compound (50 μM) significantly increased locomotor activity compared to vehicle controls, whereas the cis-enriched compound produced no significant effect. Thus, consistent with the electrophysiological findings, the trans isomer constitutes the pharmacologically active isomer *in vivo*. In contrast, the other analogs in the library did not exhibit significant photoinduced activity under the same experimental conditions, indicating that the ligand pocket displays demanding binding constraints. Together, these findings introduce a novel light-responsive modulator of voltage-gated sodium channel–mediated excitability and establish reversible optical control over a clinically validated antiepileptic drug. This work advances the development of photopharmacological strategies for precise, on-demand regulation of neuronal excitability.

Keywords: Photopharmacology, Voltage, gated sodium channels, Antiepileptic agents.

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Light-Regulated Agonists Spatiotemporally Activating the Vitamin D Receptor Mitigate Psoriasis-like Inflammation in Mice without Inducing Hypercalcemia

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Activation of the vitamin D receptor (VDR) has shown therapeutic benefit in psoriasis; however, its central role in calcium homeostasis severely limits systemic administration due to the risk of hypercalcemia. To overcome this long-standing limitation, a series of light-controllable VDR agonists incorporating a photoswitchable azobenzene moiety within the ligand scaffold were designed and synthesized.

The optimized compound, PhotoVDRM, remains inactive in the dark and can be selectively activated using specific wavelengths of light, including non-phototoxic visible blue light and clinically relevant UVB. A modified hydrogen/deuterium exchange method was employed to identify the binding site and study VDR dynamics upon ligand binding.

Importantly, in a psoriasis mouse model, PhotoVDRM enabled precise spatiotemporal activation of VDR in localized diseased tissue. This targeted activation results in a robust therapeutic effect without systemic hypercalcemia, a major historical barrier to VDR agonist therapies.

This work highlights the potential of photopharmacology to precisely modulate VDR activity,

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enabling the discovery of innovative targeted medicines that can be applied to the development of future therapies targeting VDR.

Keywords: Photopharmacology, Azobenzene, Photoswitch, VDR, Psoriasis, Hypercalcemia

X-ray activated Photopharmacology

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Photopharmacology aims to revolutionize medicine through the local activation of drugs only at the required site, using light irradiation. In this manner, side effects would be largely circumvented since the drug remains inactive in the rest of the body. However, a main challenge in photopharmacology remains the limited penetration depth of light, which requires alternative light-delivery strategies. In contrast, X-rays are extensively used in medical imaging and external beam radiotherapy, specifically because of their high penetration depth. The use of X-rays to control drug activity would break the penetration depth barrier in photopharmacology. One of the main strategies in photopharmacology relies on photocleavable protecting groups. These compounds -once attached covalently to a payload of interest- silence the bioactivity of this payload. Subsequently, upon light irradiation, the payload is released and its native activity restored. In recent research, the analogous radiocages have been developed, that are able to release a payload of interest upon irradiation of the sample with high energy photons, such as x-rays. However, these molecules are thus far inefficient and require high and damaging irradiation doses, making them practically unusable. Here, we aim to achieve a deeper understanding of the two-stepped payload-release mechanism of these compounds and thereby improve their function. We will describe the strategies we developed to increase the efficiency of these steps, resulting in superior radiocages. Furthermore, we will present the synthesis of radiosensitive molecules bearing a clinically relevant anticancer payload and their response to radiation.

Keywords: Photocleavable protecting groups, PPGs, Photolabile protecting groups, Photocages, X, ray, radiation, prodrugs

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Obtaining Optical Control of the Glucocorticoid Receptor

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Glucocorticoids (GCs) are a vital component of the hypothalamic-pituitary-adrenal (HPA) axis which plays a central role in regulating inflammation and the body's stress response. Synthetic GCs, such as prednisone and dexamethasone, are among the most prescribed drugs, commonly used to treat inflammatory conditions, autoimmune diseases and select cancers. However, their therapeutic benefits are often marred by severe and broad side effects. Consequently, there is a need for targeted GCs, both as pharmacological tools and clinical therapeutics. Functionalization with photoswitchable molecules allows for the spatial and temporal resolution based on delivery of tunable wavelengths of light as an external stimulus. Herein, we introduce a library of optically activated glucocorticoids and evaluate their light responsive agonism of the glucocorticoid receptor. We report AzoCort1, a photoswitchable prednisolone derivative with an irradiated EC50 = 11pM, which is 36x more potent than in its dark state (dark EC50 = 400 pM). As such, we establish photoswitchable glucocorticoids as a platform for advanced modes of glucocorticoid administration.

Keywords: glucocorticoids, photoswitch, targeted

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Validation of mGlu6 as novel photoswitchable drug target to restore vision

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In retinal degenerative diseases such as retinitis pigmentosa and age-related macular degeneration, the progressive loss of photoreceptor cells leads to irreversible blindness. However, most inner retinal neurons remain viable, enabling vision restoration by diverse approaches. Here, we present a drug-based strategy to restore sight that targets the metabotropic glutamate receptor 6 (mGlu6), which is specifically expressed in retinal ON bipolar neurons. We identify azobenzene-based compounds that act as mGlu6 photoswitchable agonists and positive allosteric modulators (ago-PAMs). One of them reversibly activates the receptor with light in the absence of glutamate, mimicking native phototransduction. In degenerated retinas from

*Speaker

rd10 mice, it restores light-dependent firing patterns in retinal ganglion cells, including distinct ON and OFF responses, which indicate reactivation of the upstream retinal circuit and improved vision restoration signatures ex vivo. Intravitreal injection of the compound reinstates visually guided behavior (light avoidance) in chemically blinded mice. In acutely blinded zebrafish larvae, drug application rapidly and completely restores visual acuity measured by the optokinetic reflex. These findings validate mGlu6 as a novel drug target for vision restoration and identify the compound as the first one-component, receptor-targeted photoswitch capable of reactivating physiological retinal signaling. This work establishes a foundation to develop safe, reversible, and non-invasive pharmacological therapies to restore sight in blindness caused by photoreceptor degeneration.

Keywords: azobenzene, phenylazopyridine, metabotropic glutamate receptor, allosteric modulator, visual acuity, light avoidance, transition cage, visually guided behavior, on bipolar cell, visual encoding, zebrafish, mice, retinitis pigmentosa, macular degeneration

Silencing alanyl-tRNA synthetase AARS1 Gene Based on Photosensitive Lipid Nanoparticles for Esophageal Cancer Immunotherapy

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Esophageal cancer (EC) is a highly aggressive cancer with limited response to current treatments like surgery, chemo, radiotherapy, and immunotherapy, especially in advanced stages. Novel strategies are urgently needed to boost antitumor immunity. AARS1, an essential aminoacyl-tRNA synthetase, also functions as a lactyltransferase that senses tumor lactate, promoting oncogenic signaling via lysine lactylation. Targeting AARS1 may offer a new therapeutic approach by linking cancer metabolism to proliferation and therapy resistance, providing potential for improved EC treatment. In this study, we encapsulated AARS1-siRNA into photosensitive lipid nanoparticles, which could be delivered to p53-mutant esophageal cancer cells KYSE450. Light irradiation triggered strong gene silencing , resulting in a significant inhibition of cancer cell viability. This outcome provides a reference for the application of therapeutic siRNA in esophageal cancer therapy.

Keywords: Esophageal cancer, siRNA delivery, photosensitive nanoparticles, lipid nanoparticles

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Computational Design of Photoswitchable Aspirin Analogues for Targeted Inflammation and Metastasis Control

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Aspirin (acetylsalicylic acid) is one of the most used nonsteroidal anti-inflammatory drugs (NSAIDs) over the years. Its biochemical action is produced when covalently acetylates the serine residue (Ser530) of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), leading to irreversible enzymatic inhibition. Cyclooxigenases are homodimeric bifunctional hemoproteins responsible for the oxygenation of polyunsaturated fatty acids such as arachidonic acid, into prostaglandin H (PGH).
Although their molecular structures are similar and have near-identical catalytic sites, their biological activity is very different. COX-1 is present in a variety of areas of the body and is involved in homeostatic functions such as gastric lining protection and blood fluidity regulation by promoting platelet aggregation via thromboxane A (TXA) production. In contrast, COX-2 is an inducible enzyme that is expressed during an inflammation, infection or cancer, which produces prostaglandins that mediate pain, fever, and inflammation.

Beyond its anti-inflammatory activity, aspirin has additional therapeutic potential. A recent study reveals that low-dose aspirin can inhibit COX-1 in platelets helping to prevent cancer metastasis mediating by inhibiting platelet-derived thromboxane A (TXA), a lipid compound that suppresses T-cell immunity. Since some tumours or inflammatory responses are usually located in a specific part of the body, the need to find selective drugs that can be active only at the affected site becomes crucial to avoid side effects and enhance the drug efficacy. In this context, photopharmacology addresses this need by designing drugs with photoswitchable moieties that can be activated with visible light, enabling localized, non-invasive, and more effective treatment.
This computational study aims to design aspirin-based photoswitchable drugs activated by visible light to combat local cancer effects, specifically inflammation and metastasis. Photochemical properties are evaluated using TD-DFT calculations, while mechanistic studies related to the biological and medical activity are investigated through combined molecular dynamics simulations and QM/MM calculations.

Keywords: photopharmacology, drug design, Photoswitchable Aspirin Analogues, COX, 2

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A Novel Photoresponsive Curcumin-PAMAM Conjugate for Co-Delivery of VEGF siRNA and Chemotherapeutics in Uveal Melanoma

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Uveal melanoma is the most common primary intraocular malignancy in the adult population, characterized by aggressive metastatic potential and the risk of vision loss if left untreated. Current treatment strategies primarily involve surgical excision and radiotherapy. However, recent advances in genetic therapy offer promising new avenues for management. Preclinical studies have demonstrated that VEGF-targeted siRNA therapy can inhibit angiogenesis and tumor growth across various cancer models, including melanoma. Nonetheless, the stability of siRNA is highly dependent on the delivery method, and targeting VEGF alone does not intrinsically induce cytotoxicity. Curcumin, a traditional herbal extract derived from turmeric, has exhibited potent anticancer properties by modulating cellular pathways and generating reactive oxygen species upon light irradiation. In this study, we developed a novel photoresponsive curcumin-polyamidoamine (pAM-Cur) conjugate that forms dendriplexes with VEGF siRNA, enabling the co-delivery of chemotherapeutic and gene therapy agents. This work provides insights into the development of a photosensitive drug delivery platform for gene therapy in melanoma.

Keywords: PAMAM, curcumin, gene therapy, photodynamic therapy, photoresponsive drug delivery

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Multifunctional BODIPY Photocages for Photoactivatable Combination Therapy

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Photocages, also denoted as photocleavable protecting groups, are compounds whose chemical bonds can be cleaved by light irradiation. Based on such photoactivatable characteristics, photocages have been widely applied in synthesizing photoresponsive prodrugs that enable spatiotemporally controllable drug release at lesions. However, most of the photocages cannot be activated by near-infrared (NIR) light due to the low photon energy, and the sole therapeutic effect from the released drug usually leads to resistance, which limits the clinical application of photoresponsive prodrugs. Here, we investigated the structure-activity relationships of BODIPY photocages and developed NIR light-responsive BODIPY photocages (NBOs: NBOF2-OH, NBOMe2-OH) by rational molecular engineering. By introducing the iodination strategy, multifunctional BODIPY photocages (NIBOs: NI1BOMe2-OH, NI2BOMe2-OH) were endowed with PDT activity that can be further regulated by delicate modifications. Consequently, the resulting multifunctional photocages enable photoactivatable prodrugs to generate both reactive oxygen species (ROS) and therapeutic agents upon NIR light. The prodrug (NIBO-RG) of the DNA methyltransferase inhibitor RG108, developed using NIBO, enabled efficient photoactivatable PDT-epigenetic combination therapy, potentially advancing phototherapy applications in clinical settings.

Keywords: BODIPY, photocages, prodrugs, photodynamic therapy, photoresponsive drug delivery

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Development of Photoswitchable Cholesterol Derivatives through Side Chain Replacement

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Cholesterol is ubiquitous in biology, shaping membrane properties and serving as a biosynthetic precursor for essential signaling molecules and hormones and, in some contexts, acting as a signaling molecule itself. Here, we describe the development of photoswitchable versions of cholesterol that retain the lipophilic profile of the parent compound. These analogs were designed through computationally guided replacement of the native *iso*-octyl side chain with azobenzene-based photoswitches. Our compounds, termed photocholesterols (PChols), were assembled through a modular and readily diversifiable semisynthetic route involving transition metal-catalyzed cross-couplings followed by stereo- and chemoselective hydrogenations. They can be used to optically control binding to the sterol transport proteins ORP1/2 and OSBP, which play key roles in distributing cholesterol within intracellular compartments. Our work establishes a template for photoresponsive sterols that closely mimic cholesterol and may be applied broadly to investigate cholesterol's roles in membrane behavior, signaling, and transport.

Keywords: cholesterol, azobenzene, photoswitch, sterol transport

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Session 4: Brain, diseases and photopharmacology

In Silico to in Cerebro - Development of the Orexin Receptor Antagonist 'Photorexant' for Photomodulation in Vitro and in Mouse Brains

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In this study, we report the first photoswitchable small molecule dual ligands for the orexin receptor subtypes 1 (OX1R) and 2 (OX2R) as molecular tools for optical control of orexin signaling. The orexin system is critical for several physiological processes and has been increasingly implicated in the pathogenesis of various psychiatric disorders. We implemented a prospective structure-based design approach, generating azobenzene-containing derivatives of the FDA-approved dual orexin receptor antagonist suvorexant with a computational workflow that featured a novel fragmentation and azobenzene-fusion strategy. The derivatives were subsequently evaluated by molecular docking to ensure preservation of the characteristic binding mode of suvorexant. Top candidates were synthesized and characterized by photophysical and pharmacological methods, namely our recently developed β-arrestin 2 and miniGαq recruitment assays for both receptor subtypes. Optimization of the photoswitchable moiety yielded the highly potent antagonist 'photorexant', exhibiting an up to 11-fold activity difference between photoisomers. A newly optimized assay protocol for the characterization of photoswitchable GPCR antagonists demonstrated dynamic, reversible photomodulation of orexin receptors by photorexant *in vitro*. Electrophysiological studies in hypothalamic and locus coeruleus neurons in mice demonstrated photomodulation of its antagonistic properties *in vivo*, positioning photorexant as an excellent tool for further investigation of orexin signaling.

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Keywords: Orexin, Docking, Neuromodulation, Computational Chemistry

Optochemical modulation of cold-activated TRPM8 channels

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TRPM8 is a TRP ion channel activated by cold and cooling compounds, and the principal sensor of environmental cold. TRPM8 channels are downmodulated by Gq-coupled GPCRs in sensory neurons and heterologous expression systems. However, the mechanisms underlying this modulation are disputed. Some studies propose direct inhibition of the channel by Gαq while others propose activation of PLC and reduced membrane PI(4,5)P2 availability as the primary mechanism.
In HEK293 cells overexpressing TRPM8 and the muscarinic M1 receptor to monitor whole-cell currents activated by cold or menthol. In both cases, application of 10 μM carbachol (Cch) produced a drastic reduction of currents. These effects were replicated by brief application of blue light (460 nm) in cells overexpression melanopsin, a light-sensitive GPCR.

In cells expressing *Danio rerio* Dr-VSP, a voltage-sensitive lipid 5-phosphatase which dephosphorylates PI(4,5)P2, application of brief depolarizing voltage pulses produced a strong and immediate suppression of menthol-activated currents. In cells co-expressing Dr-VSP, melanopsin and TRPM8, the inhibition produced by a +100 mV voltage pulse was not potentiated by melanopsin activation. This result suggests that activation of a GqPCR does not increase inhibition evoked by exclusive PI(4,5)P2 depletion.

In cells co-expressing M1R and the PI(4,5)P2 optical sensor PH-GFP, stimulation of PLC by M1R activation caused the rapid translocation of fluorescence from the membrane to the cytosol, reflecting the cleavage of PI(4,5)P2. The kinetics of TRPM8 current decay mirrored the time course of PI(4,5)P2 depletion, suggesting a strong coupling between both processes. A short incubation with 10 μM edelfosine, a PLC inhibitor, prevented the translocation of the PH-GFP probe by Cch, and the inhibition of TRPM8 currents was drastically reduced.

Collectively, our results indicate that PI(4,5)P2 depletion is crucial for TRPM8 inhibition after Gq-coupled GPCR activation.
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Keywords: TRPM8 cold melanopsin GPCRs

Light-controlled uncaging of a mGlu4 positive allosteric modulator restores social behavior in a mouse model of autism

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Light-based technologies have revolutionized the study of neural circuits and behavior, among other applications. Photopharmacology is an emerging field based on the use of synthetic light-regulated molecules to allow spatiotemporal control of target receptors in native tissues without the need for genetic modification. These ligands have the potential to provide a controllable action that can be used as a precise research tool for the study of the targeted receptors. Here, we present MCS1419, as an inactive, photocaged derivative of the potent and brain-penetrant positive allosteric modulator (PAM) ADX88178, which selectively targets the metabotropic glutamate type 4 receptor (mGlu4). Upon exposure to violet light, MCS1419 undergoes a photochemical reaction that facilitates the release of the active drug, thereby effectively modulating mGlu4 receptor activity.

Facilitating mGlu4 activity was shown to alleviate autistic-like behavior in several mouse models of autism spectrum disorder (ASD). This effect may result from the ability of mGlu4 activation to put a brake on the activity of D2 dopamine receptor expressing striatal projection neurons (D2-SPNs). Indeed, when these neurons become excessively active in the nucleus accumbens (NAc), mice display autistic-like social behavior deficits and stereotypies. To assess whether excessive activity of NAc D2-SPNs would contribute to social deficit in the *Shank3Dex13-16* knockout mouse model of autism, we injected MCS1419 in the projection site of these neurons, the ventral pallidum (VP). Remarkably, light-controlled uncaging of ADX88178 in the VP of *Shank3Dex13-16* knockout mice fully restored direct social interaction.

This study highlights the interest of light-controlled uncaging to enable spatial and temporal

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control of endogenous mGlu4 activity. Photopharmacology opens new perspectives for the development of drugs with improved efficacy and lower side effects, with applications for ASD treatment and beyond.

Keywords: Autism, GPCR, In vivo, Ventral pallidum

Targeting epilepsy with photoactivatable drugs in post-surgical human brain tissue

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Photopharmacology is a rapidly emerging research field utilizing photoactivatable drugs (PDs) as potential precision therapeutics in various biomedical fields. PDs have been studied across the biomedical spectrum, for the treatment of cancer, cardiac arrhythmia, pain disorders or vision loss, but they have remained understudied in epilepsy research. A third of epilepsies remain refractory to anti-seizure medications (ASM) and $> 50\%$ of patients with ASM experience multi-organ side effects. Redesigning ASM as PDs with precise temporal and spatial activation would allow adoption of powerfully antiepileptic drugs that cannot be used in an outpatient setting (e.g. general anesthetics), and minimize systemic side-effects. Here, we tested the effect of photoswitchable ion-channel blockers QAQ and CQAQ and a newly developed caged Propofol (CaP) on neuronal activity under physiological and epileptiform conditions, in acute murine brain slices and postsurgical brain tissue from patients with epilepsy or brain tumors. While QAQ inhibited neuronal firing in its activated configuration in patch clamp experiments in both mouse and human brain slices, photoactivated CQAQ inhibited neuronal firing in mouse brain slices but unexpectedly increased neuronal firing in human brain slices. Upon electrical Schaffer collateral stimulation, light activated CaP increased inhibitory postsynaptic current decay time and leak current in patched CA1 neurons in mice. Furthermore, activated CaP inhibited epileptiform activity (interictal epileptiform activity and seizure like episodes) in local field potential recordings across species. Our results showcase the promising potential of PDs as precision

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therapeutics for the treatment of hard-to-treat epilepsies, and underscore that evaluation of potential therapeutic approaches should be tested in the human model systems early on.

Keywords: Human epilepsy, Photopharmacology

Photoactuation of mGlu5–Homer Interactions to Control Synaptic Plasticity

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G protein-coupled receptors (GPCRs) operate within dynamic signaling complexes that tightly regulate synaptic function. Among them, the metabotropic glutamate receptor mGlu5 plays a central role in synaptic transmission and neuronal plasticity, processes critically involved in social and cognitive behaviors and altered in autism spectrum disorders (ASD). mGlu5 assembles with scaffolding proteins of the Homer family to form highly regulated receptor-associated signaling platforms, termed "receptosomes". In particular, interaction between mGlu5 and the constitutive isoform Homer1c is required for plasticity induction, whereas neuronal activity induces expression of the short isoform Homer1a, which competitively disrupts mGlu5–Homer1c complexes and remodels synaptic signaling.
We hypothesize that dynamic mGlu5–Homer interactions gate synapse availability for plasticity induction. To establish causal links, we developed molecular actuators enabling precise spatiotemporal control of these interactions. First, we implemented a chemically inducible FKBP–FRB heterodimerization system to recruit Homer1a to mGlu5 in cultured hippocampal neurons. By addition of rapalog, it allowed rapid modulation of the interaction, monitored in real time using BRET imaging.

Second, we engineered LOV2-based photoactuators to achieve light-dependent control of mGlu5–Homer dynamics. Our strategy is that, upon blue-light illumination, LOV2-Homer1a will disrupt mGlu5–Homer1c interaction, enabling spatiotemporal interrogation of receptosome function.

These tools will be deployed *in vivo* to modulate mGlu5-associated signaling pathways critical for plasticity, including ERK and mTOR activities, monitored with BRET biosensors during learning paradigms. By selectively photoactuating receptor-scaffold interactions rather than globally targeting receptor activity, this approach will offer a refined strategy to dissect and potentially restore synaptic function in ASD models.
Our work highlights photopharmacology as a powerful framework to manipulate dynamic GPCR-associated complexes with high precision and therapeutic potential.

Keywords: mGlu5, Homer, interaction, synaptic plasticity, photoactuation, LOV2, Rapalog, recep-

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tosome

Control of Wildtype Zebrafish Optomotor Response with a Photoswitchable Drug

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For animals to interact effectively with their environment, the brain must integrate sensory information and generate appropriate motor responses. Multiple neuronal circuits contribute to this process, and identifying their roles remains a central focus in neuroscience.
The recently developed photoswitchable compound Carbadiazocine (Camerin et al., 2024) controls neuronal firing, modulates zebrafish larvae locomotion, and alleviates neuropathic pain in rodents in a reversible, light-induced manner. Given its effects in both motor and somatosensory circuits, we first investigated the impact of Carbadiazocine on sensorimotor behaviors. In particular, we focused on the optomotor response in zebrafish larvae and assessed its potential as a tool for circuit perturbation and behavioral analysis.
We then performed experiments in head-fixed and free-swimming larvae to assess their capacity to detect and follow the direction of visual stimuli, as well as to characterize swimming speed patterns and individual tail bout properties following administration of Carbadiazocine photoisomers. In both paradigms, treatment with the pre-illuminated compound led to a marked decrease in accuracy in responding to visual stimuli (correctness dropping from 95 % to 70 % and 68 % to 20 % respectively). Speed analysis revealed an increased number and duration of fast movements while decreasing count and length of slow movements, even during periods without visual stimulation. Tail bout analysis further showed an increase in 15-30 Hz bout frequencies, corresponding to incomplete, erratic tail movements. All these effects were absent when the dark-relaxed compound was administered. Together, these findings deepen our understanding of sensorimotor transformations and highlight Carbadiazocine as a spatiotemporally controllable tool for probing native neuronal circuits underlying behavior without requiring genetic modifications.

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Keywords: Optomotor response (OMR), Circuit perturbation, Sensorimotor behavior, Photopharmacology, Neuromodulation

Photocontrol of muscarinic receptor activity in the mouse somatosensory cortex monitored by two-photon calcium imaging

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Muscarinic acetylcholine receptors (mAChRs) contribute to both the facilitation and inhibition of cortical activity, with a role in attention, wakefulness and sleep states regulation. Acetylcholine is sensed by extrasynaptic mAChRs, which are present in all cortical layers where they modulate the excitability of pyramidal cells. Current pharmacological tools that regulate neural activity lack tissue selectivity and affect the entire nervous system and thus cannot be used to activate or inhibit selective regions on demand. On the other hand, photostimulation with optogenetics requires gene manipulation, which poses hurdles for clinical translation. Photopharmacology, the development of molecules with photoswitchable moieties that can be activated and deactivated with illumination, allows focalized switching, reduce adverse effects and enhances efficacy. Here we characterise a photoswitchable muscarinic activator derivative that is inactive in the dark and activates mAChRs when they are illuminated with tissue-penetrating amber light (590 nm). We combined the use of this light-responsive effector with two-photon calcium imaging to optically control neuron activity of the somatosensory cortex layer II/III. We demonstrate that a photoswitchable molecule and the application of patterns of light can be used to control drug activity on demand. Muscarinic activation with 590 nm light produced a clear difference in activity, whereas no changes in calcium activity were observed in the control group for the same illumination cycles. All mice recovered without behaviour impairments, which demonstrates that this compound does not produce acute toxicity. This photoswitchable

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drug is thus a unique tool to optically control muscarinic endogenous receptors in brain tissue *in vivo* and without genetic manipulation.

Keywords: Muscarinic, two photon, calcium imaging, in vivo, brain, mouse

Functional mapping of the extrasynaptic dopaminergic neurotransmission and dopaminergic circuits of C. elegans

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Dopamine is a neuromodulator involved in many key functions of the nervous system, including learning, motivation, reward, and movement. Furthermore, disruption of dopaminergic systems is central to numerous disorders/diseases, including addiction, depression, Parkinson's Disease and Schizophrenia. While dopamine receptor (DAR) agonists have proven to be valuable therapeutic agents for alleviating disease symptoms, their broad expression across the nervous system results in significant off-target side effects. Thus, there is a strong therapeutic need for tools that allow manipulation of dopaminergic circuits with high temporal and spatial precision. Furthermore, although the differential expression of DAR subtypes (e.g., D1- and D2-like receptors) contributes to specificity in endogenous dopaminergic modulation of neural circuits, a precise understanding of how dopamine acts extrasynaptically to influence such a broad range of circuits and behaviours remains lacking. In this project we set out to 1) develop and validate photoswitchable compounds that can selectively activate specific DAR subtypes, 2) test these compounds in *Caenorhabditis elegans*, allowing both in-vivo validation of the compounds and research on the mechanisms by which extrasynaptic dopamine modulates neural circuits. *C. elegans* is an ideal model for this purpose, given its high genetic amenability, optical accessibility, and well-characterised nervous system and behavioural repertoire. Currently we have validated photoswitchable dopamine receptor agonists in *C. elegans* using behavioural tests and generated *C. elegans* strains that will allow simultaneous recording of neuronal activation and identification of D1-receptor positive neurons.

Keywords: neuronal circuits, dopamine receptors, C. elegans

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A photoswitchable cannabinoid enables precise, low-side-effect seizure control in a mouse model of drug-resistant epilepsy

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Temporal lobe epilepsy with drug-refractory seizures is a neurological disease with a high unmet need for precision treatments that target the affected brain region to suppress seizures while avoiding effects on other parts of the body to minimise side effects. Photopharmacology is such a novel approach that could allow precise spatiotemporal symptom control by combining systemic administration of a photoswitchable drug with implantation of an optic fibre to induce the light-dependent conversion of the administered compound to a configuration that allows pharmacodynamic interaction with its target receptors specifically in the seizure focus. Cannabinoids, including the psychoactive 9-tetrahydrocannabinol (9-THC), have gained substantial attention as therapies for refractory epilepsies. While 9-THC has potent seizure suppressing effects, its therapeutic use is limited by its extensive side effects. In this study, we used a photoswitchable variant of 9-THC, azo-THC-3, which transitions from an inactive trans configuration to an active cis configuration upon irradiation with ultraviolet (UV) light of 365 nm. We assessed the anticonvulsant potential of azo-THC-3 by examining its effects on hippocampal hyperexcitability in a slice electrophysiology setup, then demonstrating its ability to light-dependently suppress difficult-to-treat seizures in a mouse model of temporal lobe epilepsy following intrahippocampal and, most importantly, also following intraperitoneal (i.p.) administration. As such, we provide the first demonstration of systemic administration and local light-dependent activation in the seizure focus of a photoswitchable compound for seizure suppression. Furthermore, our findings illustrate how the photoswitchable approach effectively mitigates hypothermia and hypolocomotion which are side effects commonly associated with 9-THC use.

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Keywords: epilepsy, seizures, cannabinoids, THC, azoTHC, photoswitch

Photoswitching endogenous glutamate receptors in neural ensembles and single synapses in vivo

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To interrogate animal physiology *in vivo*, there is a lack of non-genetic methods to control the activity of endogenous proteins with pharmacological and spatiotemporal precision. To address this need, we recently developed targeted covalent photoswitchable (TCP) compounds that enable the remote control of endogenous glutamate receptors (GluRs) using light.
We combine the photopharmacological effector TCP9 with neuronal activity sensors to demonstrate all-optical reversible control of endogenous GluRs across multiple spatiotemporal scales

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in rat brain tissue *ex vivo* and in *Xenopus* tadpole brains *in vivo*.

TCP9 allows photoactivation of neuronal ensembles, individual neurons, and single synapses in *ex vivo* tissue and in intact brain *in vivo*, which is challenging using optogenetics and neurotransmitter uncaging. TCP9 covalently targets AMPA and kainate receptors, maintaining their functionality and photoswitchability for extended periods ($>$ 8 h) after a single compound application. This allows tracking endogenous receptor physiology during synaptic plasticity events such as the reduction of functional AMPA receptors during long-term depression in hippocampal neurons.
TCP9 is a unique non-invasive tool for durable labeling, reversible photoswitching, and functional tracking of native receptors in brain tissue without genetic manipulation.

Keywords: Covalent drug, Azobenzene, Photoswitch, AMPAR, Kainate, Dendritic spines, Plasticity, Long, term depression, Pulse, chase, Hippocampus, Calcium imaging, Xenopus, Rat

Light-Activated Agonist-Potentiator of GABAA Receptors for Reversible Neuroinhibition in Wildtype Mice

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Gamma-aminobutyric acid type A receptors (GABAARs) play a key role in the mammalian central nervous system as drivers of neuroinhibitory circuits and are commonly targeted for therapeutic purposes with potentiator drugs. However, due to their widespread expression and strong inhibitory action, systemic pharmacological potentiation of GABAARs inevitably causes adverse effects, regardless of drug selectivity. Photopharmacology offers a promising solution to this problem. However, a suitable light-activated potentiator of GABAARs for use in wild-type mammals has remained elusive.
We address this need by developing azocarnil, a diffusible GABAergic agonist–potentiator based on the anxiolytic drug abecarnil, which is inactive in the dark and activated by visible violet light. Azocarnil can be rapidly deactivated with green light or by thermal relaxation in the dark. We demonstrate that it selectively inhibits neuronal currents in hippocampal neurons in vitro and in the dorsal horns of the spinal cord in mice, decreasing mechanical sensitivity as a function of illumination without producing systemic adverse effects.

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Azocarnil expands the in vivo photopharmacological toolkit with a novel chemical scaffold and represents a milestone toward future phototherapeutic applications for the safe treatment of muscle spasms, pain, anxiety, sleep disorders, and epilepsy.

Keywords: GABA receptors, potentiator, mechanical sensitivity

Circuit-Specific Control of mGlu5 Receptors by Photopharmacology in Neuropathic Pain and Stroke Recovery

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Photopharmacology provides a powerful approach to resolve neuronal spatial complexity, enabling identification of the neural substrates responsible for therapeutic and adverse drug effects. Understanding circuit-mechanisms that regulate synaptic plasticity is essential for developing targeted therapeutic strategies for neurological disorders such as chronic pain and ischemic brain injury. Metabotropic glutamate receptor 5 (mGlu5), a postsynaptic receptor coupled to G q/11 proteins, plays a central role in intracellular signaling pathways that regulate Ca^2 dynamics and protein kinase C activation, ultimately modulating long-term synaptic plasticity processes including long-term potentiation (LTP) and long-term depression (LTD). While these mechanisms are critical for physiological plasticity, their dysregulation may contribute to maladaptive circuit remodeling and functional deficits observed in neuropathic pain and after stroke. Here, we employed photopharmacology, a strategy that combines systemically administered light- sensitive ligands with spatially restricted optical stimulation, to dissect the brain region–specific functions of mGlu5 receptors in vivo. Optical activation of the caged NAM JF-NP-26 revealed that mGlu5 receptor blockade in the medial prefrontal cortex and thalamus is sufficient to suppress neuropathic pain hypersensitivity. Conversely, optical inactivation of the photoswitchable NAM alloswitch-1 in these regions reversed systemic analgesia, demonstrating that mGlu5 receptor inhibition in these circuits is necessary for the analgesic effects of mGlu5 antagonists. Interestingly, opposite effects were observed in the basolateral amygdala, where mGlu5 receptor blockade reduced pain thresholds and limited overall analgesia. Similarly, in rodent models of ischemic stroke, systemic administration of mGlu5 receptor NAMs enhanced recovery of sensorimotor function. Photopharmacological manipulation demonstrated that the beneficial effects

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of mGlu5 receptor inhibition are preferentially mediated by receptors located in the contralesional hemisphere, suggesting that endogenous activation of mGlu5 receptors after stroke may suppress functional recovery by promoting maladaptive plasticity and network disconnection between peri-infarct and remote brain regions.These findings open new directions for applying photopharmacology to treat neurological disorders.

Keywords: pain, stoke, metabotropic glutamate receptor 5, NAM mGlu5 receptor

Photomodulation of Plinabulin – a Tubulin Polymerization Inhibitor with low-nanomolar Toxicity

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Photopharmacology has attracted growing interest in recent years. In this research area, molecular photoswitches are attached to bioactive agents to precisely control their activity both temporally and spatially. For example, the severe side effects of chemotherapy may be significantly reduced by local activation of a photomodulable drug in tumor tissue. However, modulation of the structure of a bioactive agent with a photoswitch often suffers from drastic reduction in its activity or biostability.
Plinabulin is a tubulin polymerization inhibitor with low-nanomolar activity which is currently in phase III clinical trials against non-small cell lung cancer (NSCLC) and chemotherapy-induced neutropenia (CIN). We found that plinabulin itself is capable of photomodulation without further modification as it contains a previously unexplored photoswitch motif in its structure, which we refer to as hemipiperazine (HPI). In contrast to other photopharmacological agents, plinabulin does not suffer from loss of activity due to structural changes and furthermore exhibits pronounced thermal stability and compatibility with aqueous media. In addition, the difference in toxicity between the two isomers is significant, being 85-fold (unidirectional) and 11-fold (bidirectional), respectively.1 Recently, we were able to use the in vivo photomodulation of plinabulin to reversibly influence the early development of zebrafish embryos.2

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Keywords: photopharmacology, microtubules, zebrafish

Photopharmacological Targeting of the Adenosine A1 Receptor: From Concept to Photochemical Pitfalls

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Photopharmacology holds a great promise to treat neurological diseases such as epilepsy. Approximately 50 million people worldwide are affected by epilepsy and nearly 30% of them suffer from a drug-resistant form of the disease. Activation of the adenosine A1 receptor (A1R) is known to suppress neuronal excitability and seizure activity. However, systemic administration of A1R agonists, including N6-cyclopentyladenosine (CPA), has failed clinically due to unacceptable peripheral side effects. To overcome these limitations, we designed a photocaged derivative of CPA using 7-diethylamino-4-hydroxymethylcoumarin (7-DEACM) as a photolabile protecting group. This approach enables light-triggered release of the active agonist, allowing localized activation of A1R in seizure-relevant brain regions such as the hippocampus on demand, i.e. when a seizure arises. Such release of CPA in a closed-loop controlled manner has recently been studied both in vitro and in vivo. In the latter study, the caged CPA (cCPA) was administered via intracerebroventricular injection. Despite the promising results, an important limitation of the 7-DEACM cage is that its photorelease requires near-UV light (405 nm), which limits tissue penetration and may increase the risk of cytotoxicity. To improve translational applicability, a thiocoumarin was introduced as cage to enable activation at wavelengths that coincide with reduced light absorption and scattering and improved penetration. However, the strategy did not yield the anticipated outcome. Upon irradiation, the caged CPA was depleted without detectable formation of the desired CPA. Mechanistic investigations suggested the involvement of photoinduced degradation pathways. Notably, the rate of compound depletion was slowed in the presence of sodium azide, consistent with quenching of singlet oxygen. These findings indicate that the thiocoumarin cCPA moiety may act as a photosensitizer, thereby competing with, or even overriding, the intended uncaging reaction.

Keywords: Photocaging, DEACM, Adenosine A1 receptor, Epilepsy, Drug resistant epilepsy

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Investigating the role of peripheral metabotropic glutamate receptors mGlu5 in inflammatory pain using photopharmacology

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Glutamate is the principal excitatory neurotransmitter involved in pain transmission. Receptors activated by glutamate include ionotropic receptors, which are ion channels responsible for rapid synaptic responses, and metabotropic receptors (mGluRs), which are coupled to G proteins (GPCRs) involved in the modulation of pain signaling. Among these, metabotropic glutamate receptor 5 (mGlu5) is widely expressed throughout the peripheral and central nervous system, where it plays a key role in synaptic plasticity. Several studies suggest that mGlu5 predominantly plays a pronociceptive role, and that its inhibition can attenuate nociception, making it an attractive therapeutic target. However, the specific role of mGlu5 in the peripheral nervous system, where nociceptive stimuli are detected and transduced, remains poorly characterized. Photopharmacology is an emerging strategy based on the use of small, diffusible ligands whose interaction with their target is controlled by light and therefore does not require genetic manipulation, unlike optogenetics. In recent years, several photoswitchable negative allosteric modulators of mGlu5 have been developed as innovative tools to achieve precise spatiotemporal control of mGlu5 activity. Using a combination of biochemical approaches (RNAscope, immunofluorescence) and behavioral assays with photopharmacological mGlu5 ligands, I am conducting an in-depth investigation of the role of peripheral mGlu5 receptors in a murine model of inflammatory pain.

Keywords: Inflammatory pain, Metabotropic glutamate receptor 5, Periphery

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Towards Therapeutic Innovation in Temporal Lobe Epilepsy: Spatially Selective and Closed-loop Adenosinergic Modulation of Dentate Gyrus Excitability through Photopharmacology

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Reducing hyperexcitability of the dentate gyrus (DG) by focally activating the adenosine A1 receptor (A1R) is a potential therapeutic strategy in mesial temporal lobe epilepsy (MTLE). This can be achieved using a recently synthesized photocaged A1R agonist. This study investigated the feasibility of suppressing DG excitability in a spatially selective way and to a predefined level using a closed-loop protocol both ex vivo and in vivo through a photopharmacological approach.
Evoked field postsynaptic potentials (fPSPs) were recorded in the DG and CA1 in acute hippocampal slices from intrahippocampal kainic acid (IHKA)-injected mice incubated with 3 μM coumarin-caged N5-cyclopentyladenosine (cCPA). Subregion-selective inhibition of fPSPs was evaluated through application of spatially restricted illumination to DG or CA1. The ability to reset DG activation to a predefined level was tested using closed-loop illumination with PS amplitude as the control variable. Finally, this closed-loop protocol was applied in vivo, using intracerebroventricular injection of 33 mM cCPA and closed-loop illumination to maintain DG evoked fPSP amplitude at a target level in a healthy anesthetized mouse.

Using cCPA, the fPSP slope decreased selectively upon localized illumination of the DG to 64.8±9.93% in the DG and to 95.2±2.85% in the CA1 in slices from IHKA mice (n=6, $p< 0.001$). Using a closed-loop system, the PS amplitude in hippocampal slices from IHKA mice could be maintained at 50% of baseline (n=5, $p< 0.001$) and *in vivo*, the fPSP amplitude could be maintained at 75% of baseline in the DG of a healthy anesthetized mouse in a first proof-of-concept (n=1).
These results indicate that the use of cCPA enables spatially targeted modulation of DG excitability and regulation to a predefined target level via a closed-loop system, both ex vivo and

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in vivo. These findings support the potential of photopharmacology as a targeted therapeutic approach for MTLE.

Keywords: Adenosine A1 receptor, epilepsy, intrahippocampal kainic acid mouse model, closed, loop control, field postsynaptic potential

Bioorthogonal Chemistry of Water-Soluble Blue Fluorescent Coumarin-Substituted Azole Derivatives for Bioimaging and Bioconjugation Applications

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Given the extensive reliance on the DAPI-blue fluorescent dye for molecular imaging under in vitro conditions, we believed that a dye with comparable photophysical characteristics, but with additional functionalities, including higher water solubility and bioorthogonal functionality, would be more efficacious. With this intention, a set of azolium salts decorated with various coumarin derivatives and a click-functional group was synthesised and investigated. These organic salts displayed enhanced solubility in aqueous buffers, and the most soluble compounds exhibited a quantum yield of approximately 0.40 in biologically relevant buffer systems. In bioimaging studies, one of the synthesized compounds showed selective localization within the cell nucleus. Furthermore, the most water-soluble fluorescent azolium salt demonstrated robust bioorthogonality under stringent conditions.

Keywords: Bio, imaging, Water solubility, Azolium salts

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Chromocontrol: Ideal Efficacy Photoswitching for Photopharmacology in vivo

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Precisely probing the endogenous roles of target proteins is crucial for biological research. Photochemical tools can be photoactuated with high spatiotemporal resolution but often they are unreliable in vivo because spatiotemporal variations of reagent concentration result in inhomogeneous bioactivity. We now describe ideal efficacy photoswitching, a paradigm that internally compensates for reagent concentration by self-competitive binding, allowing purely wavelength-dependent chromocontrol over bioactivity that is consistent from cell culture to deep tissues. We demonstrate this with photoswitches for endogenous transient receptor potential (TRP) C4 and C5 ion channels, reproducibly delivering strong agonism under 360 nm illumination, weak agonism under 385 nm illumination and strong antagonism under 440 nm illumination. These ligands unlock a range of high-precision investigations in TRP biology, from neuronal activity to exocytosis, reproductive signaling and smooth muscle contractility. The ideal efficacy photoswitching paradigm should also unlock high-performance chromocontrol over a wide range of sensory or signaling channels and receptors even in vivo.

Keywords: Photoswitches, Photopharmacology, Efficacy photoswitching, Affinity photoswitching, TRP channels

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Construction of Drug-Active Acylhydrazone Photoswitches for Photopharmacology

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Photoresponsive drugs enable high spatiotemporal regulation of drug activity, enhancing selectivity and demonstrating considerable promise for precision disease treatment. However, photoresponsive drugs based on traditional photoswitch molecules face significant limitations, such as the difficulty of coordinating photoregulation with drug activity, high toxicity in physiological environments, and poor stability, hindering their applicability in vivo(1). Acylhydrazones are widely represented in drug-screening databases for ligand screening with biological targets. Nevertheless, the potential E/Z isomerization of the C=N bond in these molecules has rarely been considered during bioactivity assessments. In this study, we examined hydroxyl-substituted acylhydrazone compounds identified via virtual screening. We observed that these compounds, particularly in their ionized forms, readily undergo E/Z isomerization under light exposure. Notably, different isomers exhibited significantly different bioactivities toward N-methyl-D-aspartate (NMDA) receptors, with up to a nearly 70-fold activity difference between isomers. Furthermore, glutathione present within cells catalyzed the dynamic EZ isomerization of these acylhydrazones. Interestingly, the intracellular ratio of acylhydrazone isomers was determined solely by the relative stability of the isomers, independent of the initial isomer ratio administered. The detailed structure-activity relationship study allowed for further optimized coordination between photoregulation and bioactivity. This work represents the first example of applying acylhydrazone molecules within photopharmacology, providing a new strategy for the design of photoresponsive drugs and offering novel insights for photopharmacological applications(2).

Keywords: photoswitch, acylhydrazone, photopharmacology, ion channel

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