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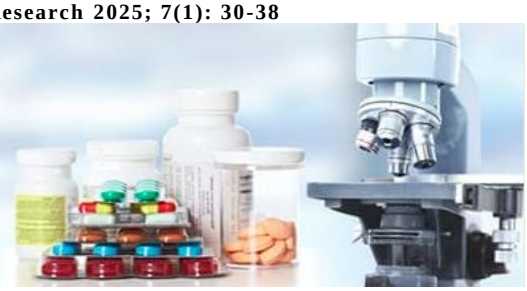

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Emerging trends in photopharmacology: Utilizing light for targeted drug delivery and precision medicine

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Abstract
Photopharmacology provides a novel method that utilizes light to alter the action of medicinal drugs. This study examines the principles governing the utilization of light in medication activation and deactivation, emphasizing molecular photoswitches and photo caging groups. The use of light modulation in medication design facilitates exact spatial and temporal manipulation of pharmacological effects, hence minimizing off-target activity and mitigating undesirable consequences. Recent breakthroughs have led to the discovery of novel chemicals that can be triggered by certain wavelengths, enabling focused therapy of illnesses including as cancer, neurological disorders, and inflammatory ailments. The study assesses advancements in the synthesis and utilization of photoswitchable molecules, the difficulties related to light transport in deep tissues, and the prospects for integrating photopharmacology with other innovative technologies in precision medicine. Additionally, the study examines preclinical and initial clinical studies that highlight the potential of light-controlled therapy. In conclusion, the study emphasizes future possibilities and the potential for photopharmacology to change drug delivery methods and therapeutic procedures, ultimately boosting treatment efficacy and patient safety.

Keywords: Photopharmacology, light-controlled drug delivery, photoswitchable molecules, targeted therapy, precision medicine

Introduction
Photopharmacology is an emerging discipline that utilizes light's unrivaled spatial and temporal precision to influence biological systems, enabling a non-invasive, reversible, and quick technique to alter medication action. Unlike optogenetics which predominantly exploits naturally occurring chromophores such as retinal and flavins to regulate neural activity photopharmacology merges concepts of photochemistry with pharmacology to affect the pharmacokinetic and pharmacodynamic characteristics of manufactured drugs. This study focuses on synthetic photoswitches that offer quick and reversible optical control *in vivo*, spanning both cellular and animal models.

We differentiates between distinct types of light activation. One technique utilizes freely diffusible photochromic ligands (PCLs) that may transition between isomeric forms upon light irradiation, hence modifying their affinity and effectiveness toward their targets. In contrast, covalently tethered ligands are discussed in two categories: photoswitchable tethered ligands (PTLs), which are attached in close proximity to the binding site to primarily modulate local concentration, and photoswitchable orthogonal remotely tethered ligands (PORTLs), which, when tethered via larger bioconjugation tags, mainly influence the ligand's efficacy. Another family of photoswitches contains light-responsive cross-linkers that modify the structure of target proteins by being connected at two locations.

The basic parameters for *in vivo* application, such as good pharmacokinetics, metabolic stability under physiological settings, and minimum photo toxicity. Among numerous scaffolds, azobenzenes are emphasized as the major photo switch due to their high absorbance, acceptable quantum yields, and customizable thermal relaxation rates, but other compounds like diarylethenes and fulgides have also been applied.

Finally, we arranges debate according to biological targets including ion channels, transporters, G-protein-coupled receptors, enzymes, and cytoskeletal components and contrasts photo pharmacological strategies with standard optogenetic approaches.

It finishes by examining the present state of the art and future possibilities for the therapeutic application of photopharmacology in precision medicine.

Complexity of the brain
The brain's distinctive properties its inaccessibility, heterogeneity, fragility, structural complexity, and fast operation make it challenging to create successful neuro-technologies. Invention in this discipline frequently takes a mix of rigorous planning and chance.

Educational and Historical Context
The author, who teaches a course on neuro-engineering at MIT, stresses learning from historical case studies (including triumphs and failures) to better understand the innovation process. Historical examples, like Andrew Hodgkin's work on brain excitability, indicate that scientific development is rarely linear or well planned.

Optogenetics as a Case Study
The tale utilizes the development of optogenetics a method that use genetically encoded molecules to control neuron activity with light as a modern example of neuro-technology advancement. This technique enables researchers to selectively stimulate or mute individual neurons, so correlating neuronal activity to behavior, brain calculations, or disease conditions.

Interdisciplinary Approach
Drawing on his expertise in regulating complex systems (from robotics to quantum computing), the author stresses the necessity of multidisciplinary approach in understanding and designing the brain. By questioning what tools a physical sciences-trained investigator should build, he highlights the necessity for approaches that can alter diverse neuron types within complicated brain circuits [5].

The relevance and progress of medication delivery systems in healthcare, Key points include
Significance and Customization
Drug delivery systems are vital for safely transferring medications into the body to accomplish therapeutic effects. They may be modified for multiple delivery routes such as oral, injectable, ophthalmic, pulmonary, and more, assuring focused therapy and improved patient results.

Historical Evolution
The development of these systems has moved from simple medication administration methods to complex technology.

Key milestones include:
The invention of sustained-release capsules in the 1950s.
- The development of regulated and time-release systems in the 1960s.
  The creation of long-acting injectables and transdermal formulations.

This progress has mirrored improvements in therapeutic agents, solving issues linked to delivering tiny chemicals, proteins, nucleic acids, and live-cell treatments.

Market Growth
The pharmaceutical medication delivery industry has undergone tremendous growth, with a compound annual growth rate (CAGR) of 9.6% from 2017 to 2022. Although growth is predicted to moderate slightly, it is forecast to continue vigorously at 6.4% from 2023 to 2033, with the market size estimated to expand from roughly US$ 1.9 trillion in 2023 to US$ 3.5 trillion by 2033.

Advancements and Emerging Technologies
Recent improvements focus on strengthening therapeutic efficacy, decreasing off-target effects, improving medication solubility, and promoting patient compliance. Innovations like nanotechnology-based medication delivery systems have further enhanced treatment results and minimized adverse effects. These breakthroughs signal the shift to a new age of controlled release technology, answering the demands of contemporary therapeutics [6].

Problem with Current Treatments
Traditional medications interact with molecular targets such as enzymes and receptors throughout the body. Because many targets are expressed in both healthy and sick tissues (e.g., the epidermal growth factor receptor in normal epithelia and cancer), off-target effects sometimes lead to major side effects and restrict the potential of raising therapeutic doses at the targeted location.

Strategies for Selectivity
While measures such as minimizing cross-reactivity with non-human targets, targeting organs or tissues where the target is overexpressed, and local drug delivery have been employed, these approaches are not always sufficient due to the ubiquitous presence of many pharmacological targets.

Concept of Photopharmacology
Photopharmacology tries to address these constraints by utilizing light to control drug action remotely. Drugs are modified with photoswitches chemical groups that change structure when exposed to light thereby enabling precise spatial and temporal modulation of their therapeutic activities. This method enables for the selective activation of medicines at the intended spot, potentially decreasing systemic and environmental adverse effects.

Inspiration and Related Techniques
The method draws influence from proven techniques such as:
- **Photodynamic Therapy (PDT):** Uses light-induced production of singlet oxygen to ablate tissues with remarkable spatial specificity.
- **Optogenetics:** Employs light to alter the activity of genetically modified ion channels.

Other approaches include the utilization of photo activated metal complexes, photo caged compounds, and photo activated molecules like psoralens.

Current Status and Future Directions
Although still in the early phases of development (primarily *in vitro* studies), photopharmacology has showed promise in fields including cancer chemotherapy, neurology, diabetes, and antimicrobial medicines. Future development will depend on *in vivo* testing, extensive toxicity investigations, and the integration of molecular imaging tools to demonstrate localized drug activity. Such developments

might open the path for theranostic applications, where diagnostic and therapeutic procedures are combined [2]

Materials and Methods

The design of photo controlled pharmaceuticals, particularly those employing azobenzene-based photoswitches, needs careful consideration of their pharmacological characteristics to guarantee that biological activity is kept in at least one of the photo isomeric states. Many pharmacological compounds are carefully tuned for potency and efficacy, and adding a photoswitchable moiety may jeopardize their action. Therefore, structural alterations and optimizations, driven by Structure Activity Relationship (SAR) investigations and crystal structure analysis, are important to maintain or increase medication potency while assuring a considerable difference in activity between the two photo isomeric states. Additionally, it is necessary to analyze the possible off-target effects of both isomeric forms, since they might affect medication safety and effectiveness.

Two basic strategies are applied in the creation of photo pharmaceuticals. The first involves directly attaching a photo switch to the pharmacophore, either by partially integrating it into the active structure or by adding it outside. This technique depends on photo isomerization-induced changes in shape and polarity to modify the drug's affinity for its receptor. In certain circumstances, the switched form may demonstrate lower binding affinity due to steric obstruction, polarity alterations, or an inability to fit into the receptor's active site. This technique enables medications to be toggled between states of high and low activity upon exposure to certain wavelengths of light. The second technique applies to multivalent medicines, which consist of two or more pharmacophores joined by a spacer unit. A photoswitchable spacer can be utilized to adjust the stiffness and spacing between pharmacophores, hence affecting pharmacological action. This method has been applied in the creation of photoswitchable inhibitors of mast cell activation and ITAM peptidomimetics, as well as in bivalent opioid receptor agonists. The effectiveness of this technology hinges on the capacity of the photo switch to generate a substantial structural change during photo isomerization.

A critical element in photopharmacology is attaining a good photo isomer ratio at the photo stationary state (PSS), as full conversion between isomers is sometimes not practicable due to thermodynamic restrictions. In the case of azobenzenes, the trans-isomer is generally more stable than the cis-isomer by more than 10 kcal/mol, suggesting that in a thermally equilibrated system, the trans form predominates. However, irradiation with proper wave lengths can shift a fraction of the population to the cis-state. Some sophisticated bidirectional azobenzenes display exceptionally effective switching, where over 95% of the molecules can be changed to the thermodynamically less stable isomer. This bistable switching is particularly significant in situations where the degree of isomerization directly correlates to biological consequences, such as enzyme control or receptor activation. Since photopharmacology largely relies on non-covalent interactions between the drug and its target, altering drug concentration can further improve the pharmacological response, even if only a percentage of the molecules undergo photo isomerization. Another significant design aspect is wavelength tuning, since the type of light utilized for medication activation must balance safety and tissue penetration. UV radiation, although being frequently employed for photo isomerization, carries considerable dangers, including DNA damage, mutagenesis, and apoptosis. Therefore, UV-activated photo pharmaceuticals are inappropriate for therapeutic applications involving direct tissue irradiation. Additionally, the penetrating depth of light into biological tissues is restricted by dispersion and absorption, especially by hemoglobin and water. The optimal therapeutic window for light-based activation falls between 600 and 1200 nm, with red and near-infrared (NIR) light enabling deeper penetration approximately 1 cm for 630 nm and 2 cm for 800 nm allowing for less intrusive therapeutic interventions employing optical fibers.

Photopharmacology provides various intriguing uses in precision medicine. One possible use is in chemotherapy, where localized drug activation inside tumor tissues might limit systemic toxicity and undesirable consequences. Another use includes environmental safety, where antibiotics and hormones might be destroyed by light before excretion, reducing bioactive chemical accumulation in water sources. Additionally, photo pharmacological drugs can be pre-activated by light before delivery to minimize exposure to possibly damaging UV irradiation within the body. Advanced tactics also include medications that may be successively triggered and deactivated at specific places to enhance therapeutic outcomes while reducing off-target effects.

Recent developments in red-light-responsive azobenzenes have considerably boosted the practicality of photopharmacology in live beings. For instance, researchers have successfully employed red-light (635 nm) to produce photo isomerization in biological systems, such as zebra fish embryos, without causing injury. These advances open the path for the practical translation of photo pharmaceuticals, giving a unique and highly controlled method to medication delivery with decreased side effects and enhanced precision [3].

The table presents a vast array of photo-switchable chemicals, categorized by their target receptors or channels, along with their specific switching wavelengths and the model systems in which they have been studied.

For AMPA receptors, the chemical ATA (also known as ATA-3) changes between 440 nm and 480 nm (or remains in the dark) and has been employed in HEK293T cells, mouse cortical neurons, hippocampus neurons, and TKO mouse retina. Another AMPA-targeting drug, ShuBQX-3, acts at 460 nm and 600 nm in HEK293T cells, Xenopus oocytes, and hippocampus neurons.

Several drugs have been produced for kainate receptors. GluAzo switches at 380 nm/500 nm and has been employed in HEK293T cells, rat hippocampus neurons, and Purkinje cells. A group of compounds under the Highlighter banner including L-MAG-0, L-MAG (or L-MAG-1), and L-MAG-2 switch at 380 nm or 820 nm (when using two-photon excitation) to 500 nm and have been used in diverse systems such as HEK293T cells, hippocampal neurons, astrocytes, Chroma fin cells, zebra fish larvae, various rd and TKO mice, and even AAV-transfected wild-type mice (cortex). In a similar vein, L-MAG-0ω (which switches at 460 nm or 840 nm [2P] against dark) has been evaluated in HEK293T cells, hippocampus neurons, rd1 mice, wild-type mice (cortex), and rd1 dogs. Other kainate compounds include tcClMAG (operating at 380 nm or 560-640 nm/440 nm),

MAGπ (425 nm or 900 nm [2P]/dark) used in HEK293T cells and hippocampal neurons, MAGA (also referred to as MAGAπ; 425 nm or 880 nm [2P]/dark) in HEK293T cells, and the compounds TCP-9 and TCP-10 (both switching at 380 nm/500 nm) which have been used in TSA-201 or tsA201 cells, DRG neurons, and rd10 mice.

For NMDA receptors, ATG is photo-switched utilizing 370 nm or 700-740 nm (by two-photon stimulation) to 420 nm and has been used in mouse cortical neurons, hippocampal slices, and Xenopus oocytes. PNRA, with switching wavelengths of 360 nm/420 nm, has been tried in Xenopus oocytes. Additional NMDA receptor drugs include L-MAG-0 and L-MAG-1, which function throughout a range of 360-405 nm/460-560 nm in HEK293T cells, hippocampal neurons, murine hippocampus slices, and zebrafish larvae, as well as PSAA (365 nm/460 nm) employed in HEK293T cells.

A range of chemicals target nicotinic acetylcholine receptors (nAChRs). Several agents-AzoCharCh, Azo-PTA, BisQ, QBr, EW-1, and 2BQ-are triggered by UV light and have been employed in electrophysiological research. AzoCholine, which flips at 360 nm/440 nm, has been exploited in HEK293T cells, rat sensory neurons, mouse hippocampus slices, and even in C. elegans nematodes. For insect nAChRs, AMI-10 functions at 365 nm/430 nm in Musca domestica. Moreover, chemicals MAACh and MAHoCh may be toggled between 380 nm and 500 nm (or remain in the dark) and have been utilized in Xenopus oocytes.

In the arena of GABAA receptors, AP-2 (switching at 360-400 nm/dark) has been exploited in Xenopus oocytes, HEK293T cells, and *Xenopus laevis* tadpoles. MPC-088 and MPC-100, both triggered at 365 nm with white light, have been employed in Xenopus oocytes-with MPC-088 being used in rat retinal ganglion cells and mouse cerebellar Purkinje neurons. Photo-control of GABAA receptors (often termed LiGABAR) is further achieved by MAM-6 and PAG-1C, both of which switch at 380 nm/500 nm; MAM-6 has been tested in HEK293T cells, Xenopus oocytes, and hippocampal rat slices, while PAG-1C has been used in HEK293T cells, cortical and hippocampal slices, and knockin mice.

A number of chemicals target voltage-gated channels. For potassium channels (Kv) and related hyperpolarization activated cyclic nucleotide-gated (HCN) channels, MAQ (also known as Mal-Azo-QA) is applied in both Kv SPARK/HSPARK and TREKI systems, functioning at 380 nm/500 nm in Xenopus oocytes, hippocampal neurons, CHO cells, and HEK293T cells. AAQ, which also switches at 380 nm/500 nm, has been employed in HEK293T cells, hippocampus neurons, rat cerebellar slices, rat retinal ganglion cells, heart neurons from Hirudo medicinalis and rd1 mice. PFAQ operates at the same wavelengths in HEK293T cells, whereas DENAQ and BENAQ-both switching at 460-480 nm or under white light vs dark conditions-have been used in HEK293T cells and rd1 mice, respectively.

For substances influencing various channel types (Nav, Kv, and Cav), QAQ operates at 380 nm/500 nm and has been employed in HEK293T cells, rat hippocampus neurons, mouse DRG neurons, and spinal cord slices. A variation, QAQs with R = OMe, switches at 420 nm/dark in HEK293T and NG108-15 cells, whereas an unaltered form of QAQs works at 380 nm/500 nm in identical cell types. QENAQ, targeting Nav, Kv, and perhaps Cav channels, switches at 480 nm/dark and has been employed in Xenopus oocytes, mouse trigeminal neurons, and DRG neurons. Azo-TAB, which targets Nav, Cav, and Kv channels, works at 365 nm/490 nm in rat cardiomyocytes, while DAD (which affects Kv, HCN, and potentially Nav channels) switches at 460 nm or under white light vs dark circumstances in wild-type mouse cerebral slices and TKO mice.

Specifically for Nav channels, Fotocaine acts at 350 nm/ 450 nm and has been employed in mouse hippocampus neurons. For Hv1 channels, photoGBI-4 flips between 440-480 nm (or remains dark) and has been utilized in Xenopus oocytes, human macrophages, sperm, and epithelial cells.

Regarding TRP channels, two drugs targeting TRPV1-AC-4 and ABCTC-operate at 360 nm/440 nm and 370 nm/470 nm, respectively, in HEK293T cells. In addition, a series of TRPV1 modulators (AzCA-1 to AzCA-8) have been produced with switching wavelengths spanning from 350-365 nm and 450-460 nm; they have been employed in HEK293T cells, DRG neurons, and murine C-fibers. For TRPA1, Optovin switches at 405 nm/dark and has been evaluated in HEK293T cells, DRG neurons, and human cardiomyocytes, zebra fish, and TRPA1-KO mice. In the TRPC family, chemicals PhoDAG-1 to PhoDAG-3 (switching at 365 nm/470 nm) have been employed in HEK293 cells, mouse vomeronasal sensory neurons, and tissue slices from the murine vomeronasal organ, whereas OptoDArG (targeting TRPC3) works at 365 nm/430 nm in HEK293 cells.

Metabolic channel modulators include JB-253 and JB-558 for K(ATP) channels; JB-253 operates between 400-500 nm/dark and has been employed in HEK293T cells, rodent and human beta cells, and CD1 mice, while JB-558 acts between 520-560 nm/dark in HEK293T cells and rodent and human beta cells. The SUR-targeting chemical B3 switches at 365 nm and has been used in larvae of *Mythimna separata* and *Blatella germanica*. For GIRK channels, LOGO-5 (switching at 360 nm/440 nm) has been employed in HEK293T cells, hippocampus neurons, and zebrafish larvae, whereas VLOGO (switching at 500 nm/400 nm or keeping dark) has been applied in HEK293T cells and zebrafish larvae. For epithelial sodium channels (ENaC), PA-1, which functions at 400 nm/500 nm, has been studied in Xenopus oocytes, HEK293T cells, and H441 cell monolayers.

Finally, for purinergic P2X receptors-and in one case even ASIC channels-MEA-TMA and MEA-TEA both switch at 365 nm/525 nm and have been administered in HEK293T cells (with MEA-TMA being employed in hippocampus neurons). Additionally, BMA (targeting both P2X and ASIC channels) works at 360 nm/440 nm in HEK293T cells, PC12 cells, and CHO-K1 cells, while MAM (a P2X chemical) likewise switches at 365 nm/525 nm and has been employed in HEK293T cells and TSA-201 cells.

Photoswitchable chemicals have emerged as potent tools for altering the activity of transporters and pumps with great spatiotemporal accuracy. In this respect, various research have studied the application of photoswitches for neurotransmitter transporters, enabling the modulation of transporter activity by light stimuli.

One such example is the use of compound 6e, a photos witchable ligand targeting GABA transporter 1 (GAT1). This chemical exhibits reversible photo isomerization upon exposure to 375 nm or 450 nm light, or it stays stable in the

dark state. The active version of compound 6e has an azobenzene moiety, which is a frequent structural motif in photoswitchable compounds. Functional investigations of this chemical have been done in *Xenopus laevis* oocytes, indicating its potential to modulate GAT1 activity under light control (Ref. 114).

Another prominent photoswitchable chemical is ATT, which has been created to control the activity of excitatory amino acid transporters (EAAT1-3). ATT displays photo isomerization at 350 nm or 450 nm, allowing bidirectional regulation of EAAT activity. The structural architecture of ATT incorporates an azobenzene core conjugated with pharmacophores that interact with EAAT transporters. Experimental validation of ATT has been undertaken in HEK293 cells and dentate gyrus granule cells, where its capacity to control glutamate transport in response to light was revealed.

Overall, these results emphasize the potential of photoswitchable ligands as helpful tools for researching neurotransmitter transporters and their physiological functions. By utilizing the precise temporal control given by light, such chemicals provide fresh ways for researching transporter dynamics and may offer therapeutic possibilities for neurological illnesses linked with transporter malfunction.

Photoswitches for ion channels

Ion channels serve a critical part in rapid synaptic transmission, secretory processes, and body homeostasis. Due to their well-developed pharmacology and quick kinetics, ion channels have been major targets for photopharmacology-a science that exploits photoswitchable compounds to influence biological activity using light.

Ionotropic Glutamate Receptors (iGluRs)

iGluRs are tetrameric cation channels that open upon activation by glutamate, producing action potentials in postsynaptic neurons. Based on their affinity for agonists and genetic sequence, iGluRs are divided into:

- AMPA receptors (iGluAs)
- Kainate receptors (iGluKs)
- NMDA receptors (iGluNs)

Due to their crucial role in brain processing, iGluRs were among the earliest targets for photopharmacology.

AMPA Receptors

In 2012, Trauner *et al*. created a photoswitchable agonist, ATA, which activated GluA2 receptors in its trans form and was inactivated by blue light (480 nm).

ATA was evaluated in mouse brain slices and HEK293T cells, revealing that it could elicit action potentials in the dark and halt firing with light exposure.

Later, ATA was studied for vision restoration in defective mice retinae, particularly targeting retinal ganglion cells (RGCs) and amacrine cells.

Computational ligand docking demonstrated that trans-ATA binds strongly, but cis-ATA quickly dissociates, inhibiting receptor activation.

More recently, ShuBQX-3, a photoswitchable AMPA antagonist, was created, enabling optical regulation of action potentials in hippocampal CA1 neurons using 460 nm/600 nm light.

Kainate Receptors

GluK receptors were regulated using GluAzo, a photoswitchable tethered ligand (PTL), which permitted signalling through GluK1 and GluK2 receptors using 380 nm/500 nm light.

L-MAG-1, a glutamate photo switch, was covalently linked to GluK2 to generate LiGluR, a light-gated glutamate receptor.

Different varieties of L-MAG were created with longer (L-MAG-2) and shorter (L-MAG-0) linkers, as well as red-shifted versions (L-MAG-0460 and toCl-MAG) to increase performance.

LiGluR was examined in zebra fish larvae, where photo stimulation of Kolmer-Agduhr neurons helped clarify their physiological roles.

Calcium permeability of LiGluR enables optical control of Ca^{2+}-dependent activities, such as exocytosis, neurotransmitter release in chromaffin cells, and glutamate release in astrocytes.

LiGluR was also employed in retinal gene therapy for blindness restoration, where it was expressed in retinal ganglion cells (RGCs) using AAV vectors.

Red-shifted MAG derivatives made *in vivo* applications easier by removing the requirement for UV light exposure.

TCP-9 and TCP-10, photoswitchable glutamate derivatives, were employed to restore light-dependent electrical activity in blind mice retinae by binding to natural kainate receptors.

The HyLighter system was developed by coupling the potassium-selective pore of sGluR0 with a photoswitchable ligand-binding domain (LBD) from GluK2, allowing optical regulation of neuronal activity.

NMDA Receptors

ATG, a photoswitchable agonist, was launched in 2015 targeting NMDA receptors. It is bistable and may be triggered with 370 nm UV light or 740 nm two-photon (2P) pulses.

PNRA, a photoswitchable antagonist, was later created for GluN receptors and was the first to show selectivity for GluN2A and GluN2C over GluN2B and GluN2D.

LiGluNR, a light-controlled NMDA receptor, was developed utilizing L-MAG-0 and L-MAG-1 to enable photoagonism or photo antagonism of GluN2A and GluN2B.

Transgenic zebrafish larvae expressing LiGluNR may be persistently NMDA-antagonized with light flashes, promoting retinal ganglion cell development.

Photoswitchable amino acid (PSAA) technology was also applied to NMDA receptors, enabling both photo activation and photo inactivation of glutamate binding while keeping normal glutamate sensitivity.

Pentameric Ligand-Gated Ion Channels

Nicotinic Acetylcholine Receptors (nAChRs)

The Erlanger group (1969) first applied photopharmacology to nAChRs, generating AzoCharCh and azo-PTA, followed by BisQ and QBr, which were photochromic activators of Electrophorus electro plaques.

BisQ was then re-evaluated and shown to predominantly influence muscle nAChRs, not neuronal nAChRs.

AzoCholine, created by Trauner *et al.*, was a trans-active agonist for α7 nAChRs, allowing optical control of nematode (C. elegans) locomotion.

MAACh and MAHoCh were created as light-gated nicotinic receptor agonists/antagonists, reacting to 380 nm/500 nm light.

GABAA Receptors

In 2012, a light-switchable derivative of propofol (AP-2) was created as an allosteric modulator for GABAA receptors, inactivating with light exposure.

PCL MPC-088 and PTL MPC-100 were also created, providing for light-dependent modulation of Purkinje cell activity.

LiGABAR, a light-controlled GABAA receptor, was created utilizing a cysteine mutation that permitted the attachment of MAM-6, a photoswitchable muscimol antagonist.

Knock-in mice expressing LiGABAR enabled for photo-control of cortical neurons in conscious animals.

Voltage-Gated Ion Channels

SPARK (2004) was the first light and voltage-sensitive potassium channel, created by Trauner, Kramer, and Isacoff.

SPARK was developed from the Shaker Kv channel by introducing a cysteine mutation enabling photo-control of action potential firing in hippocampus neurons.

TREK1, a mechanically gated K^+ channel, was similarly photo-controlled using MAQ.

AAQ, a photoswitchable cationic blocker, was created as a PCL for voltage-gated ion channels, permitting light-dependent suppression and restoration of action potentials in blind retinae.

Description of recently synthesized photoswitchable chemicals and photo caging groups.

Summary of preclinical results on light-triggered medication activation and effectiveness.

Technological Developments

Photoswitches for Transporters, Pumps, and GPCRs

Photoswitches for Transporters and Pumps

Transporters and pumps, unlike ion channels, actively enable cargo transfer across cell membranes. This needs energy, supplied either by ATP hydrolysis (primary active transport) or the discharge of pre-established gradients (secondary active transport).

GABA Transporters (GAT1)

In 2014, Wanner *et al*. introduced photoswitchable inhibitors of GABA transporters.

Assays in HEK293T cells demonstrated that these inhibitors specifically targeted GAT1.

A lead compound (6e) was shown to optically modulate GABAA receptor-mediated currents in dentate gyrus granule cells.

The cis isomer blocked current flow, whereas the trans isomer induced current.

Glutamate Transporter (EAAT2)

A photoswitchable inhibitor of EAAT2 (Excitatory Amino Acid Transporter 2) was created.

Inspired by TFB-TBOA, a strong EAAT inhibitor.

The novel photoswitchable isoster (ATT) displayed selectivity for EAAT2, validated via voltage-clamp recordings in Xenopus oocytes.

The cis isomer was a weaker blocker, but the trans isomer substantially hindered transport. Irradiation with 350 nm light restored EAAT2 transport currents.

Photoswitches for G-Protein Coupled Receptors (GPCRs)

GPCRs are the biggest class of membrane proteins involved in signal transduction. These receptors are particularly ideal for photopharmacology due to their resemblance to opsins, the natural photoreceptors in humans.

Class A, Rhodopsin-like GPCRs

Muscarinic Acetylcholine Receptors (mAChRs)

In the 1980s, BisQ and QBr were identified to interact with mAChRs in frog hearts.

In further investigations, BQCAAI was developed as a photoswitchable ligand for M1 receptors.

BQCAAI behaved as a cis-antagonist and a trans-agonist under 365 nm/455 nm light.

M-Opioid Receptors

A photoswitchable fentanyl derivative (PF-2) was produced.

It functioned as a bistable switch:

- Active in darkness.
- Deactivated by 360 nm light.
- Reactivated using 480 nm light

Patch-clamp electrophysiology demonstrated that PF-2 altered μ-opioid receptor signalling via GIRK channels.

Dopamine Receptors

Photoswitchable dopamine receptor ligands (MAP and AP) were introduced.

These compounds permitted reversible modulation of D1 and D2 receptors using 360 nm/460 nm light.

Depending on the binding location, MAP operated as either a neutral antagonist or an inverse agonist.

Histamine H3 Receptors

VUF-14738 and VUF-14862 were created as photoswitchable agonists.

These chemicals permitted reversible regulation of H3 receptors in Xenopus oocytes under 360 and 434 nm light.

Adenosine A2A Receptor

The agonist APNEA was converted into a photoswitchable homologue, MRS5543.

460 nm light turned MRS5543 into a partial agonist, whereas the cis isomer functioned as an antagonist.

Lipid-responsive GPCRs (e.g., GPR40)

FAAzo-10, a photoswitchable fatty acid, was created.

It regulated Ca^{2+} oscillations in pancreatic β-cells under blue light.

It also lowered KV and KATP potassium currents.

Cannabinoid Receptors (CB1)

Azo-THCs, a class of photoswitchable cannabinoids, were produced.

Azo-THC-3 was active at 360 nm, whereas Azo-THC-4 was active at 440 nm.

Class B, Secretin Receptor Family

Glucagon-like Peptide 1 (GLP-1) Receptor

LirAzo, a photoswitchable liraglutide derivative, was created.

It possessed bistable characteristics alternating between:

- Cis-LirAzo: Stimulated cAMP production.
- Trans-LirAzo: Stimulated Ca^{2+} influx.
- Photo ETP, a small chemical modulator, was generated from BETP and improved GLP-1 signaling.

Class C, Metabotropic Glutamate Receptors (mGluRs)

Metabotropic Glutamate Receptors (mGluRs)

The first photoswitchable mGluR (LimGluR) was produced. Activated with 380 nm light and inactivated with 500 nm light.

Used to

- Hyperpolarize hippocampus neurons.
- Modulate synaptic transmission.
- Control zebra fish escape behavior.
- mGluR5 Photopharmacology
- Alloswitch-1, a photoswitchable allosteric modulator, was invented.
- Activated with violet light (380-390 nm) and inactivated with green light (490-500 nm).
- Used to modulate astrocyte calcium signaling and tadpole movement.

OptoGluNAM4.1

A negative allosteric modulator for mGluR4.

Used to regulate pain perception in animal models.

PORTL Approach (Protein-Tag Based Photoswitching)

SNAP, CLIP, and Halo Tags were utilized to attach photoswitchable ligands to GPCRs.

SNAG-mGluR2, a SNAP-tagged photoswitchable mGluR2, facilitated light-sensitive neuronal signaling.

This method was employed in recovering eyesight in blind mice, allowing them to discern light patterns [1].

Photopharmacology has revolutionized control of transporters, pumps, and GPCRs using light-sensitive molecules. These breakthroughs enable precise spatial and temporal manipulation of neurotransmission, hormone signaling, and pain perception, giving intriguing applications in neuroscience, endocrinology, and vision restoration.

Comparative Analysis

Photopharmacology exploits light-sensitive compounds, such as photocages and photoswitches, to gain precise optical control over biological processes. Each strategy has unique benefits and limits depending on the application. Photo cages (photolabile protecting groups) are very straightforward to construct, as they involve a known active ligand masked by a detachable light-sensitive group. However, their activation is a one-time event, generating by products that may be poisonous or interfere with light absorption. In contrast, photoswitches, such as azobenzenes, offer reversibility, enabling repeated activation and deactivation without producing extra chemical species. This reversibility boosts temporal and spatial control, particularly when tethered versions are employed. Photoswitches also require lower light intensities for activation, generally operating with regular LEDs instead of high-power lasers or mercury lamps used in fluorescence imaging and uncaging.

A significant contrast exists between photopharmacology and optogenetics. Optogenetics depends on naturally existing photoswitches like retinal and flavins, which are already present in cells, whereas synthesized photoswitches in photopharmacology must be externally supplied. Genetically encoded photo pharmacological methods, such as PTLs, PORTLs, and photo BOLTs, act as two-component systems that need exogenous ligands. While this offers practical obstacles, photopharmacology allows for the regulation of native receptors without the requirement for foreign gene expression. Depending on the technique, these receptors can be marginally changed (PTLs) or left totally unmodified while being targeted with auxiliary proteins (PORTLs).

One of the key issues in photopharmacology is the stability and toxicity of synthetic photoswitches, particularly azobenzenes. Historically, azobenzenes like "butter yellow" were discovered as carcinogenic, leading to concern regarding their safety. However, current investigations have proven that some azobenzenes, such as phenazopyridine, remain clinically viable, and several newly developed azobenzenes have high *in vivo* stability with low toxicity, as evidenced in animal models for eyesight restoration. The key to safe application rests in analyzing specific azobenzene derivatives for their metabolic stability, possible mutagenicity, and interactions with biological molecules like glutathione and azoreductases. Additionally, developing heterocyclic azobenzenes helps alleviate toxicity issues by enhancing solubility and lowering hazardous by products. Compared to azobenzenes, other photoswitches have undergone less toxicological examination, necessitating more study to assure their biocompatibility. Ultimately, photopharmacology offers a potent tool for focused biological control, but careful chemical design and toxicity evaluations are necessary for its safe and successful application [1].

Comparison of photopharmacology with standard drug delivery technologies in terms of accuracy and safety.

Results

Challenges and Limitations

Application of Light in Medicine: Opportunities and Challenges

Photopharmacology is an emerging area that employs light to control drug action with great spatial and temporal accuracy. This method enables for targeted activation of medications at specified areas and timings, limiting off-target effects and decreasing systemic toxicity. The ability to accurately regulate the intensity and wavelength of light gives an additional benefit by permitting precise dosage of active medications. However, despite these benefits, a fundamental hurdle in photopharmacology is the efficient delivery of photons to target tissues.

Unlike high-energy radiation (such as X-rays or gamma rays), which can penetrate deep into the body and are commonly used in medical imaging, lower-energy photons from the ultraviolet (UV) and visible light spectrum are significantly limited by tissue scattering and absorption by endogenous biomolecules like hemoglobin and water. Moreover, UV radiation carries extra dangers due to its ability to produce cellular photo damage, thus limiting its usage in deep-tissue applications. Overcoming these constraints is critical for the effective clinical translation of photopharmacology.

To overcome these issues, researchers are drawing inspiration from photodynamic therapy (PDT), a clinically validated treatment that likewise depends on light activation.

PDT has experienced comparable challenges relating to light penetration and has evolved sophisticated solutions throughout the years. Two key methodologies are being studied for photopharmacology based on PDT advancements.

Adaptation of PDT Light-Delivery Systems for Photopharmacology

The area of PDT has resulted to substantial improvements in light-delivery technology, including enhanced lasers, light-emitting diodes (LEDs), fiber-optic devices, endoscopic instruments, and computer-assisted light-control systems. These technologies provide accurate and cost-effective light application with finely regulated dosage and wavelength characteristics. Given their broad clinical use and regulatory approval, such systems might be developed for photo pharmacological applications, allowing for efficient light delivery in therapeutic situations. Researchers are also researching innovative technologies like as structured illumination and multiphoton excitation, which might further increase tissue penetration and selectivity.

Utilization of the Near-Infrared (NIR) Phototherapeutic Window

The "therapeutic window" for light-based therapy resides in the near-infrared (NIR) region (650-900 nm), where light absorption by biological molecules is minimal. Hemoglobin primarily absorbs light below 650 nm, whereas water absorption dominates above 900 nm, making this range suitable for deep tissue penetration. To exploit this window, researchers are creating molecular photoswitches, notably azobenzene-based compounds that can be triggered within this spectrum. These photoswitches enable increased tissue penetration and allow for better control over drug activation at physiological depths. Leading research groups, such as those of Hecht and Woolley, have been essential in generating these innovative photoswitches, and additional improvements are likely to drive the future of photopharmacology.

The combination of cutting-edge light-delivery systems with NIR-compatible photoswitches has the potential to revolutionize photopharmacology, making it a powerful tool for precise, non-invasive treatments. As research continues, these technologies might lead to revolutionary therapies for different diseases, including cancer, neurological disorders, and chronic inflammatory problems, presenting new opportunities for highly focused and regulated medicinal interventions [2].

Tables

The table should be made as simple as possible. Only a few horizontal lines should be used without vertical lines in the table. All tables should be placed after references in the manuscript. Each table should be consecutively numbered in Arabic numerals with a self-descriptive heading and/or legend.

Table 1: It should be designed using table tools of MS Word and exactly same as below

Groups	Change in bodyweight (unit)
Control	
Negative control	
Protective	
Curative	

Any abbreviation or symbol used in the table should be described in the legend. The same data should not be represented in tables and in graphs.

Tables and figures should be cited in the text in numerical order. Should not be first cited before Table 1.

Discussion

The study should be elaborately discussed with the significance of the results with the help of earlier work and reports.

Conclusion

Photopharmacology has swiftly grown into a potential multidisciplinary subject, merging chemistry, medicine, pharmacy, and molecular biology to generate light-activated pharmaceuticals with precise spatial and temporal control. This field has the potential to transform treatment techniques for different diseases, but significant hurdles must be overcome before clinical use becomes widespread. The major focus of future research should be on improving molecular design, ensuring that photoswitchable pharmaceuticals act efficiently within the near-infrared (NIR) therapeutic window (650-900 nm) for deeper tissue penetration.

Additionally, stability and toxicity problems surrounding photoswitches, particularly azobenzene derivatives, require thorough investigation to assure their safety in biological contexts. A key barrier remains the delivery of light into tissues; while external light sources are routinely employed, novel alternatives like as luminous chemicals, internal optical imaging, and PET-based activation might boost accuracy and circumvent tissue penetration restrictions. Furthermore, the dynamic biological activity of photoswitchable medicines, where various isomers may interact with unique targets, needs thorough screening to minimize accidental cross-reactivity. A move toward phenotypic screening and better synthetic approaches will hasten the identification of new photoswitches with improved pharmacological characteristics.

Importantly, photopharmacology stands out as a non-genetic alternative to optogenetics, as synthetic photoswitches may regulate native receptors without requiring gene therapy, facilitating regulatory approval. Potential therapeutic uses vary from microbial infections, diabetes, and cancer to eyesight restoration, which is now in the forefront due to its compatibility with direct light exposure. Advances in light-based medicine, like photodynamic therapy and optogenetics, give vital insights into solving light delivery problems. The introduction of implantable micro-LEDs and biodegradable remote-controlled electronics significantly improves the possibility of photopharmacology in human medicine. With further advancement, this sector has the potential to become a cornerstone of precision medicine, enabling highly focused and regulated therapies for a wide range of disorders.

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