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Reversible Antagonism of Dopamine D1 Receptor Using a Photoswitchable Remotely Tethered Ligand

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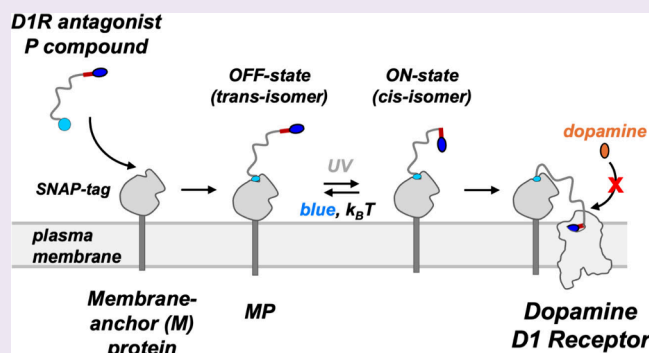


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ABSTRACT: Dopamine D1 receptor (D1R) plays key roles in health and disease. D1R is broadly expressed throughout the brain and body and is dynamically activated in response to endogenous dopamine, making it difficult to target this receptor with sufficient precision. We previously developed a robust light-activatable, tetherable agonist for D1R, wherein a temporally precise photoswitch (the P compound) binds to a genetically encoded membrane anchoring protein (the M protein) in specific brain locations and cell types. Here we extended our approach by developing a complementary antagonist P compound that could be used to block specific populations of D1R in the brain with precise timing. Together, we have generated a robust toolkit for interrogating D1R function in the brain with unprecedented precision.



INTRODUCTION

The neuromodulator dopamine plays key roles in health (movement, reward, motivation, aversion, vasodilation) and disease (Parkinson's disease, schizophrenia, addiction, hypertension) via its actions on five G protein-coupled dopamine receptors.^{1–7} Dopamine receptors are divided into two subfamilies, the $G_{s/o/f}$ -coupled D1-like receptors (D1R, D5R) and the $G_{i/o/z}$ -coupled D2-like receptors (D2R, D3R, D4R). Considerable effort has gone toward developing small molecule dopamine receptor ligands for the treatment of disease. For example, D1-like receptors are putative targets for treatment of central nervous system (CNS) disorders such as Parkinson's Disease, and they have been targeted peripherally for hypertension.^{8–12} However, D1-like receptors are broadly expressed throughout the body, including outside the nervous system, and are activated with complex temporal dynamics, making it difficult to identify precisely which receptor populations must be targeted to maximize therapeutic efficacy and avoided to minimize adverse side effects.

Existing methods for interrogating the function of D1-like receptors lack precision. Most conventional small molecule drugs cannot differentiate between D1R and D5R due to the high degree of homology in the orthosteric dopamine binding site.¹³ In addition, these agents are freely diffusible so they cannot be used to target specific cell types and tissues. Genetic approaches (knockin, knockout, overexpression) are molecularly and spatially specific but are long lasting, which limits our understanding of the temporal dynamics of receptor activation

and are prone to compensatory changes in gene expression. Chemogenetic (DREADDs) and optogenetic (opto-XRs) techniques can be used to engage signaling with cellular and spatiotemporal specificity, but these tools are ectopically overexpressed unnatural proteins that lack biochemical selectivity for dopamine and potentially overdrive the system.^{14,15}

We have had a long-standing interest in developing chemical tools to interrogate complex receptor systems and deconvolve the contribution of individual receptor subtypes in specific cells to neural circuit function.^{16,17} In an approach called photopharmacology, a photochromic ligand can be rendered biologically active or inactive under the action of light.¹⁸ In its simplest conception, a photoreactive protecting group can be removed under irradiation with light to reveal the biologically active ligand that remains active until it is removed by diffusion. For example, photocaged dopamine can enable timed dopamine release by light.^{19–21} Alternatively, a ligand can also be equipped with a permanent photochromic unit that is incorporated into its scaffold. For example, azobenzene-based photoswitches can be reversibly toggled between a *cis*-

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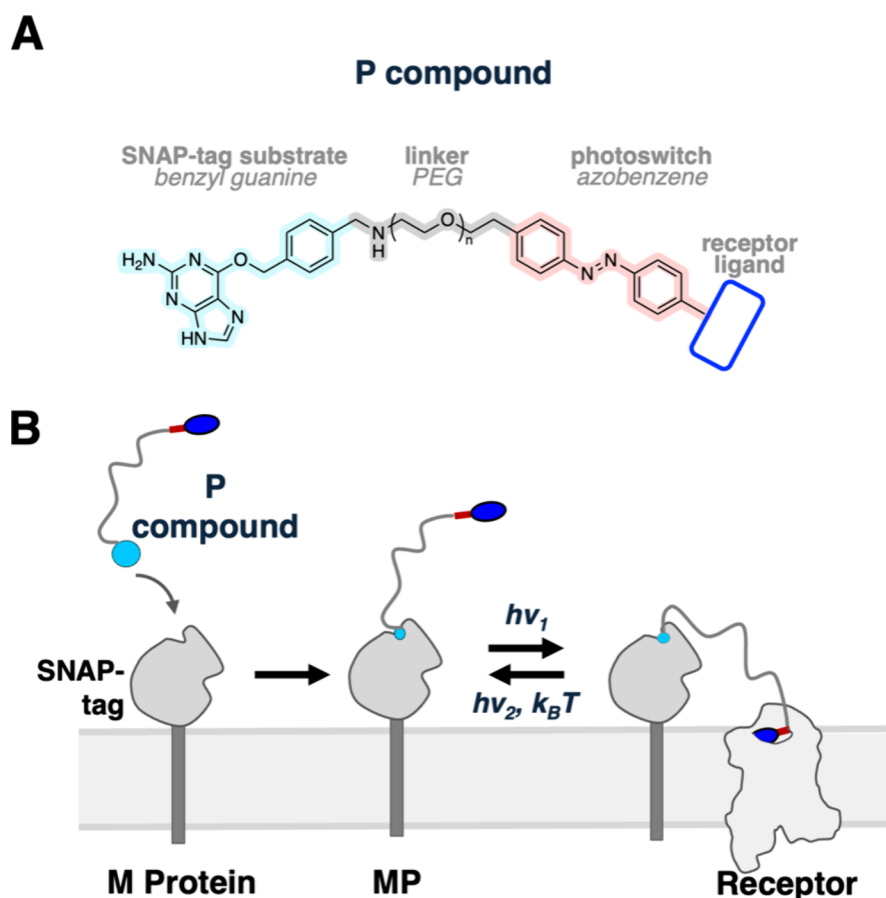


Figure 1. Design of a photopharmacological system to control a GPCR such as D1R in a cell type-specific and spatiotemporal manner. (A) The chemical component (the P compound) is comprised of a SNAP-tag reactive benzylguanine linked via a flexible polyethylene (PEG)-linker to a photoswitchable ligand. (B) Specific cells are genetically modified to express the membrane anchored protein (M), a SNAP-tag anchored to the cell membrane via a single-pass transmembrane segment anchor. After application of the P compound to M protein-expressing cells, the covalent MP complex is formed. The P reaches from the M to the receptor and reversibly binds in response to a specific wavelength of light.

and *trans*-configuration, with one form ideally being biologically inactive and the other being active.¹⁸ However, these compounds diffuse out of the illuminated target area, undermining spatial precision. Moreover, while light can provide spatial focus to tissues and tissue areas of interest for switching the ligand to an active or available state, dopamine receptors are expressed in different cell types within the same brain area.

We recently solved the problems of diffusion and cell-specificity using an approach called membrane-anchored photoswitchable orthogonal remotely tethered ligand (MP), which has two components (Figure 1).^{22–24} The first component is a photoswitchable ligand (the P compound) that is linked to a reactive substrate (e.g., benzylguanine) via a flexible linker (Figure 1A). The second component is a genetically encoded membrane-anchoring protein (the M protein) that contains a self-labeling protein-tag (e.g., SNAP-tag) that is compatible with the reactive substrate, which is selectively expressed in the cell type of interest (Figure 1B). After the P compound attaches to the M protein in a chemically specific covalent labeling event, the MP complex redistributes in the cell membrane, where it encounters the target receptor, thereby placing the P within reach of the receptor ligand binding site so that the ligand is able to bind in a light-gated manner (Figure 1B).

We recently developed D2-like receptor selective agonist and antagonist MPs that are tethered via chloroalkane to a HaloTag M protein (MP-D2_{ago} and MP-D2_{block}, respectively).²⁴ We also developed a D1-like receptor agonist MP that can be tethered via benzylguanine to a SNAP-tagged M protein.^{16,23} This compound, MP-D1_{ago}, is based on the ligand PPHT and operates as a bistable photoswitch that is active in the *trans*-configuration under blue light and inactive in the *cis*-configuration under near-UV light. Using this *trans*-active MP-D1_{ago} system, we found that the acute activation of D1R in the dorsal striatum of mice promotes movement initiation and reinforces antecedent patterns of cortical brain activity.^{16,25}

In this study, we set out to develop a light-mediated D1-like receptor antagonist MP to complement our existing dopamine receptor MP toolkit. We designed compounds that conjugate to SNAP-tag, enabling future multiplexed experiments wherein SNAP-M for D1-like receptors and Halo-M for D2-like receptors can be controlled independently. Here, we report the development of a thermally bistable D1R receptor-specific tethered antagonist (MP-D1_{block}) that completes a set of tethered ligands to activate or inactivate dopamine receptors.^{16,23,24} This new MP will provide the chemical basis to study cell-specific D1R action *in vivo*.

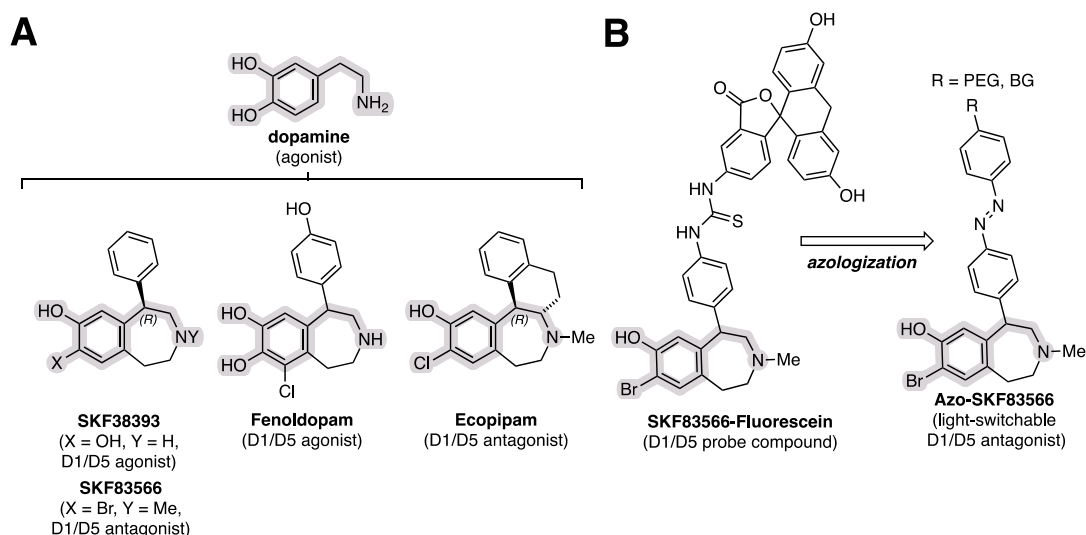
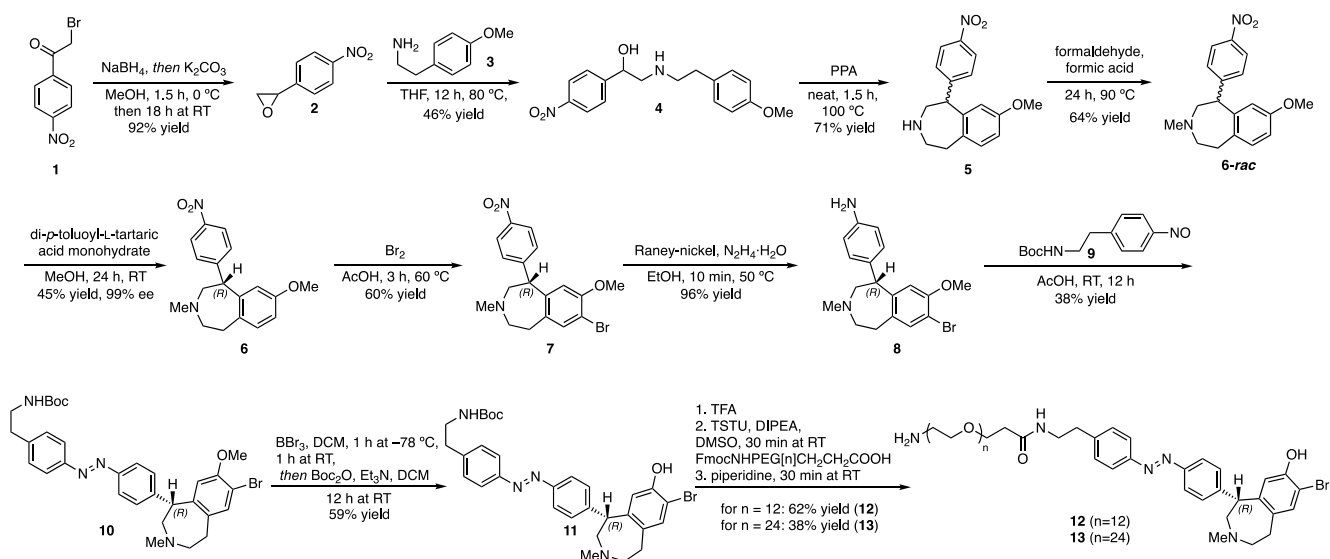


Figure 2. Design of a D1R MP blocker. (A) Dopamine and conformationally restricted D1R partial agonists and antagonists sharing a common tetrahydro-1H-3-benzazepine scaffold. (B) Tool compounds based on D1R antagonist SKF83566 (such as SKF83566-Fluorescein) indicate that the elongation of the phenyl ring in the *para*-position is tolerated without compromising potency. This site is suitable for the incorporation of azobenzene connected to a PEG linker and benzylguanidine (BG) at that position for the design of a D1R tool for proximity photopharmacology.

A Synthesis of PEG-ylated, photo-switchable D1R antagonist intermediates



B Synthesis of tethered D1R antagonists P-D1_{block12} and P-D1_{block24}

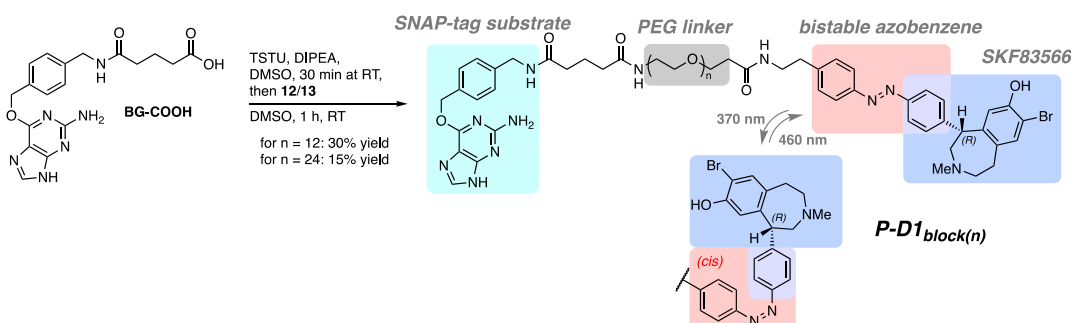


Figure 3. Multistep chemical synthesis of P-D1_{block12} and P-D1_{block24}. (A) Synthesis of PEGylated D1R antagonist intermediates 12 and 13 harboring a photoswitchable azobenzene moiety. (B) Assembly of the tool compounds P-D1_{block12} and P-D1_{block24} by connecting intermediates 12 and 13 and to benzyl guanidine carboxylic acid (BG-COOH).

RESULTS AND DISCUSSION

D1R can be blocked by synthetic small molecule inhibitors based on a tetrahydro-1H-3-benzazepine scaffold (Figure 2). One of the first reported D1-like selective partial agonists was the catechol benzazepine SKF38393 (Figure 2A).^{26–28} With this scaffold, the biologically active conformation of dopamine is mimicked by constraining the amine into a seven-membered ring.²⁹ The substitution pattern on the aryl moiety was subsequently optimized, leading to the discovery of the D1R full agonist drug **fenoldopam** (Figure 2A), which has an additional chlorine substituent and a phenol instead of a phenyl group.³⁰ Within these benzazepine derivatives, the benzylic stereocenter is important, with the *S*-enantiomer being virtually inactive.^{31–33} The exchange of one catechol hydroxy group to a halogen and *N*-Methylation led to the development of D1-like receptor selective antagonists such as aryl-bromide variant SKF83566.³⁴ Further modifications on the benzazepine scaffold include the rigidification of the pendant phenyl with an ethane bridge onto the azepine moiety, yielding D1R antagonist **ecopipam** (Figure 2A), which is currently under clinical investigations for several CNS disorders.¹²

A series of tetrahydro-1H-3-benzazepine based-D1R tool compounds were previously developed to visualize and study dopamine receptors in cells. Here, the appendant phenyl group on the tetrahydro-benzazepine was elongated with a short linker to connect to large residues, such as fluorescein and BODIPY (Figure 2B) without compromising their ability to bind D1R.^{35–37} We identified the phenyl group as ideal azologization motif for the development of D1R antagonist P compound, as the phenyl can be extended with an azobenzene and linked to the PEG linker to the benzylguanine, the substrate for the SNAP-tag in the M protein.³⁸ Recent cryo-EM structures of a D1R-G_s complex bound to benzazepine agonists confirm that the phenyl lies at the solvent accessible top region of the orthosteric site in the seven transmembrane domain of the D1R, further supporting this proposed design of a D1R antagonist P compound.³⁹

Synthesis of P-D1_{block12} and P-D1_{block24}. To set the stage for the installment of the azobenzene unit, we first prepared the known aniline **8** following literature reported methods (Figure 3A).³⁵ To this end, commercial bromoketone **1** was converted to epoxide **2** in excellent yield by reduction with NaBH₄, followed by treatment with base. Epoxide opening of **2** with 4-methoxyphenylethylamine installed racemic phenyl-ethanolamine derivative **4** that was cyclized to tetrahydro-1H-3-benzazepine **5** using polyphosphoric acid at 100 °C. In an Eschweiler–Clarke reaction, methylation of the secondary amine **5** was achieved in good yield. Resolution of **6-rac** using a chiral tartaric acid derivative yielded the biologically active *R*-enantiomer **6** in >99% *ee*, as determined by chiral HPLC. The sign of the optical rotation matched literature reported values, and absolute configuration was assumed based on literature precedence.⁴⁰

Bromination followed by Raney-Nickel reduction furnished the desired aniline **8** in overall good yields that underwent Baeyer–Mills reaction with freshly prepared nitroso-phenyl-ethyl Boc-amine **9** in acceptable yields. Boron tribromide effected methoxy deprotection of **10**, but also resulted in Boc-deprotection. For purification purposes, we protected the primary amine with Boc₂O to yield **11** that was stable and could be purified on SiO₂. Boc-deprotection of **11** with TFA

provided a primary amine as the connecting point for introduction of the long flexible linker.

For our tethered photopharmacological approach, PEG-linkers have proven to be suitable as they are soluble, monodisperse, commercially available in different lengths, and biocompatible. Reaction of the crude primary amine in a TSTU-mediated peptide coupling with FmocNHPEG[n]-CH₂CH₂COOH yielded photoswitchable D1R antagonists with the desired flexible linker. We chose to use PEG[12] and PEG[24], lengths that have previously successfully spanned the distance between orthosteric GPCR binding site and proximal M protein-bearing reactive tag.^{17,24} Piperidine effected Fmoc-deprotection to unveil primary amines **12** (PEG[12]) and **13** (PEG[24]) that were then coupled to the SNAP-tag substrate benzyl guanine (BG-COOH) by TSTU-mediated peptide coupling (Figure 3B).⁴¹ Finally, the desired remotely tethered D1R antagonists (*R*)-P-D1_{block12} and (*R*)-P-D1_{block24} were obtained. The procedure starting from **6** was performed using pure (*R*)-intermediate. Additionally, an (*S*)-configured sample of **6** with 56% *ee* was used to generate (*S*)-P-D1_{block(12)}.

Photophysical Characterization of P-D1_{block(n)}. We then characterized the photophysical properties of P-D1_{block24} by UV–vis and NMR spectroscopy to confirm classic azobenzene behavior in response to light (Figure 4). P-

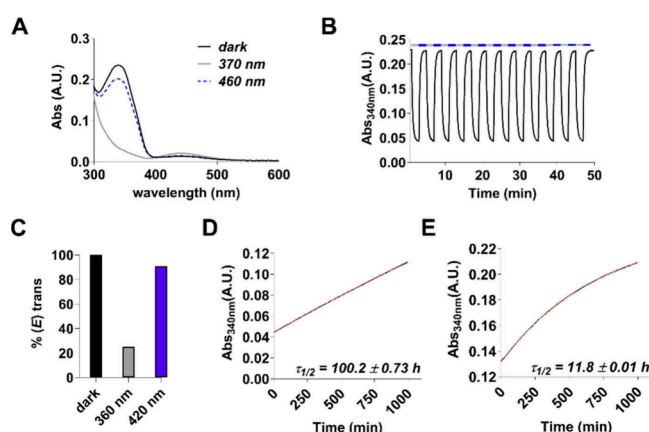


Figure 4. Photophysical characterization of P-D1_{block24}. (A) UV–vis absorption spectra of dark-adapted (100% *trans*) P-D1_{block24} in DMSO (20 μM), and after preirradiation with 370/460 nm for 10 min. (B) Reversible switching of P-D1_{block24} without fatigue in DMSO (20 μM) under 370/460 nm irradiation. (C) Photostationary state (PSS) of P-D1_{block24} in DMSO (20 μM, 24 °C), after preirradiation with 360/420 nm for 10 min. Determination of the photostationary state was achieved by LCMS by separation of isomers and integration of the Abs at the isosbestic point of *cis*- and *trans*-isomers at the respective elution solvent mixtures. (D, E) P-D1_{block24} was determined to be thermally stable in 10% DMSO (*t*_{1/2} = 100 h) and 100% DMSO in PBS (*t*_{1/2} = 11.8 h) at 37 °C, detection of the Abs was performed at 340 nm after preirradiation of the samples for 10 min at 360 nm.

D1_{block12} was assumed to perform on par to P-D1_{block24}, as no change in the chromophore unit has occurred. Full thermally relaxed *trans*-P-D1_{block24} has an absorption maximum of 338 nm in DMSO (Figure 4A). After irradiation with 370 nm light for 10 min, *cis*-enriched P-D1_{block24} absorbs visible light maximally at 436 nm and can be switched back into its *trans*-enriched form under irradiation with 460 nm light (10 min). P-D1_{block24} can be switched reversibly without fatigue using alternating 370 nm/460 nm light irradiation (Figure 4B). We

determined the photostationary state by preirradiating a 20 μM solution of **P-D1_{block12}** in DMSO at ambient temperature for 10 min and physically separating the sample into its *cis*- and *trans*-**P-D1_{block24}** isomers by LCMS to measure their ratio by peak integration. Under 360 nm, 25% *trans*-isomer remains, at 420 nm, 9% *cis*-isomer remains (Figure 4C). The thermal relaxation half-life of the *cis*-isomer was determined in DMSO and 10% DMSO in PBS to confirm the bistable nature of the tool compound with a τ of 100.2 and 11.8 h, respectively (Figure 4D).

Functional Analysis of MP-D1_{block}. Next, we measured the effect on D1R of the **P-D1_{block(n)}** compounds when tethered to the M protein (MP-D1_{block}). To determine D1R function, we used a whole-cell patch clamp electrophysiology assay in HEK293T cells that employs the G protein-activated inwardly rectifying K⁺ (GIRK) channel as an effector (Supplementary Figure 1). Cells were coexpressed with D1R, GIRK, a modified G protein G α_{i13} that allows D1R to couple to GIRK, and the M protein (Supplementary Figure 1). Following labeling with a **P-D1_{block(n)}** compound, cells were exposed to alternating 460 nm light and 370 nm light in the absence and presence of dopamine, which activates D1R and promotes an inward current via GIRK.

We first tested the effect of (*S*)-**P-D1_{block12}** tethered to the M protein on D1R. Dopamine-induced current decreased slightly in response to 370 nm light, an effect that was reversed in response to 460 nm light (Figure 5A,D). In contrast, when tethered to the M protein, its enantiomer (*R*)-**P-D1_{block12}** robustly inhibited dopamine-induced current (Figure 5B,D). Together, these results indicate that (*R*)-**P-D1_{block12}** tethered to the M protein is a robust photoantagonist of D1R in its *cis*-configuration and is inactive in its *trans*-configuration. The

ability of (*S*)-**P-D1_{block12}** to weakly inhibit D1R is likely due to the presence of (*R*)-**P-D1_{block12}** in the sample (56% *ee*). Overall, this is consistent with earlier evidence that (*R*)-tetrahydro-1H-3-benzazepines being better binders of D1R than their (*S*)-enantiomers.^{31,32} Next, we tested the effect of extending the PEG linker from 12 to 24 PEGs. We observed (*R*)-**P-D1_{block24}** to have enhanced photoblock (Figure 5C,D), with the potency of dopamine reduced by ~ 216 -fold in the *cis*-configuration (Figure 5E).

According to Schild analysis, this level of inhibition aligns with that expected from a ~ 430 nM concentration of the parent compound SKF83566 ($K_i = 2$ nM).^{36,42} Consistent with the thermal stability of (*R*)-**P-D1_{block24}**, only a short pulse of light was required to inhibit (370 nm) or disinhibit (460 nm) dopamine-induced receptor activation (Figure 5F).

CONCLUSION

Together with our previous work, we have successfully completed a robust chemical toolbox of photoswitchable agonist and antagonist P compounds that can rapidly activate or prevent the activation of endogenous D1R and D2R.^{16,24} By engineering a photochromic azobenzene unit into a dopamine receptor ligand, a specific wavelength of light toggles the P compound into a bioactive configuration that binds to the receptor orthosteric site and a different wavelength of light that reverses the compound back to its binding-incompatible inactive configuration. The P compound is restricted to a desired cell type and location via covalent attachment to a genetically encoded membrane-anchored self-labeling protein tag (the M protein). On the membrane of that cell, the MP complex interacts with the target receptor via random collision on the cell surface. Here, we report the development of a novel light-controllable, reversible, and cell type-specific D1R antagonist (MP-D1_{block}) based on a tetrahydro-1H-3-benzazepine scaffold.

We have previously developed a robust D1R MP agonist (MP-D1_{ago}) and demonstrated that its photoactivation in striatal direct-pathway medium spiny neurons (dMSNs) increases movement initiation and reinforces antecedent cortical patterns.^{16,25} This agonist tool enables selective and precisely timed activation of D1R in living animals and is therefore able to reveal whether a receptor in a particular cell is sufficient for a specific behavior. In parallel, the herein reported tool MP-D1_{block} could provide complementary results if used to block endogenous dopamine from activating D1R and to, thereby, reveal whether the receptor is necessary for the behavior. Together, the insights from studies using either MP-D1_{ago} or MP-D1_{block} could provide a comprehensive view of the functional role of D1R in the brain.

The MP-D1 toolkit will enable studies of individual receptor contributions within the dopaminergic signaling system. The current experimental setup requires two light sources to reversibly switch the system between the active and inactive *cis*- and *trans*-states. Future iterations could leverage azobenzene variants that are single-wavelength activated and fully self-relax back to the inactive *trans*-state as shown in previously reported MP-D2 tools.²⁴ By requiring only one light source, the experimental setup is streamlined and the experimental applicability is broadened. In addition, MP-D1 and MP-D2 currently both require blue light and thus cannot be controlled independently in the same sample, limiting our understanding of the synergistic effects of D1-like and D2-like receptors in the brain.^{16,24,43} To address this, far-red

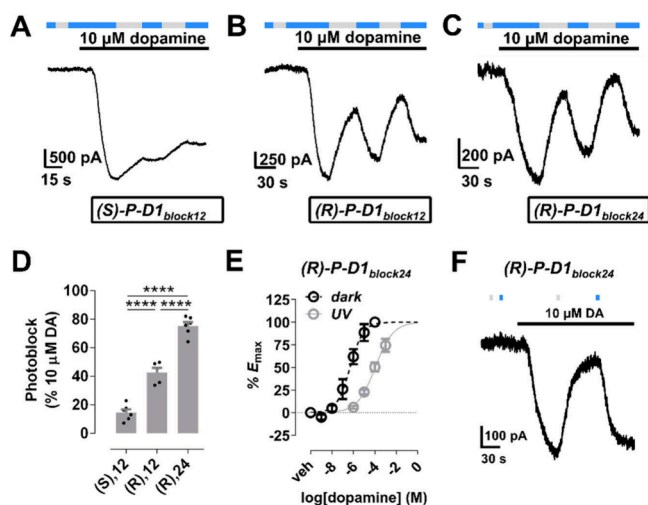


Figure 5. MP-D1_{block} photoblocks D1R. (A) When tethered to the M protein, (*S*)-**P-D1_{block12}** weakly blocks D1R in its *cis*-configuration, which is likely due to the presence of the (*R*)-configured enantiomer in the sample (56% *ee*; 22% (*R*)-content). (B–D) (*R*)-**P-D1_{block24}** tethered to the M protein more effectively inhibits D1R than (*S*)-**P-D1_{block12}** or (*R*)-**P-D1_{block12}** tethered to the M protein in response to 370 nm light. (E) (*R*)-**P-D1_{block24}** tethered to the M protein decreases the potency of dopamine at D1R, consistent with competitive antagonism. (F) Consistent with its bistability, (*R*)-**P-D1_{block24}** tethered to the M protein elicits sustained inhibition of D1R in the dark following a short pulse of 370 nm light (gray bar), a process that is reversed with a short pulse of 460 nm light (blue bar).

azobenzene variants could be incorporated into either MP-D1 or MP-D2.⁴⁴ Finally, the MP system relies on a genetically encoded protein to achieve cell type- and spatial specificity, which may limit its versatility in certain models. Incorporating immunochemical strategies into future designs could enhance use across to a wider range of biological systems without genetic modification.

When released, dopamine coactivates multiple dopamine receptors at once. Based on conventional behavioral pharmacology studies in rodents, dopamine receptor coactivation has been suggested to synergistically control downstream behaviors such as movement.^{43,45} However, because conventional D1R agonists and antagonists bind this receptor throughout the body, it is unclear which dopamine receptor populations in which cell types drive these effects. By employing orthogonal SNAP-tag labeling for our D1R MPs and HaloTag labeling for our D2R MPs, we can now selectively and simultaneously target multiple dopamine receptors, offering unique insight into dopamine action in the brain.

D1R is an attractive but historically intractable target for treating Parkinson's Disease and other CNS disorders. This is in part because existing drug scaffolds have poor physiochemical properties, but also because these drugs broadly affect D1Rs across the brain and body. In addition, existing methods lack cellular and spatiotemporal precision, hindering identification of the D1R populations that need to be targeted to treat disease. Our D1R MPs offer a unique opportunity to systematically target specific D1Rs in the brain and periphery and uncover their clinical potential. Furthermore, MP and related technologies could potentially be used in the clinic to treat disease with unprecedented precision, maximizing therapeutic efficacy and minimizing off-target effects.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acschembio.5c00441>.

Additional experimental details; materials and methods; synthetic procedures, and characterizations for all compounds (¹H NMR, ¹³C NMR, LCMS, HRMS, and IR spectra) (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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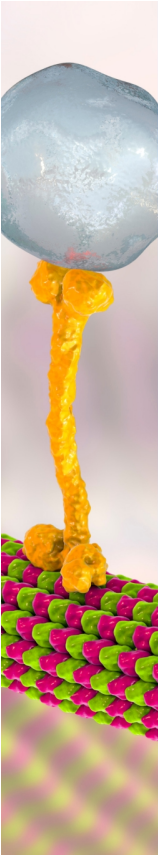
■ REFERENCES

- (1) Beaulieu, J.-M.; Gainetdinov, R. R. The Physiology, Signaling, and Pharmacology of Dopamine Receptors. *Pharmacol. Rev.* **2011**, *63* (1), 182–217.
- (2) Beaulieu, J.-M.; Espinoza, S.; Gainetdinov, R. R. Dopamine Receptors – IUPHAR Review 13. *Br. J. Pharmacol.* **2015**, *172* (1), 1–23.
- (3) Klein, M. O.; Battagello, D. S.; Cardoso, A. R.; Hauser, D. N.; Bittencourt, J. C.; Correa, R. G. Dopamine: Functions, Signaling, and Association with Neurological Diseases. *Cell Mol. Neurobiol.* **2019**, *39* (1), 31–59.
- (4) Martel, J. C.; Gatti McArthur, S. Dopamine Receptor Subtypes, Physiology and Pharmacology: New Ligands and Concepts in Schizophrenia. *Front. Pharmacol.* **2020**, *11*. DOI: [10.3389/fphar.2020.01003](https://doi.org/10.3389/fphar.2020.01003).
- (5) Latif, S.; Jahangeer, M.; Maknoon Razia, D.; Ashiq, M.; Ghaffar, A.; Akram, M.; El Allam, A.; Bouyahya, A.; Garipova, L.; Ali Shariati, M.; Thiruvengadam, M.; Azam Ansari, M. Dopamine in Parkinson's Disease. *Clin. Chim. Acta* **2021**, *522*, 114–126.
- (6) Seeman, P.; Niznik, H. B. Dopamine Receptors and Transporters in Parkinson's Disease and Schizophrenia. *FASEB J.* **1990**, *4* (10), 2737–2744.
- (7) Foll, B. L.; Gallo, A.; Strat, Y. L.; Lu, L.; Gorwood, P. Genetics of Dopamine Receptors and Drug Addiction: A Comprehensive Review. *Behavioural Pharmacology* **2009**, *20* (1), 1.
- (8) Jones-Tabah, J.; Mohammad, H.; Paulus, E. G.; Clarke, P. B. S.; Hébert, T. E. The Signaling and Pharmacology of the Dopamine D1 Receptor. *Front. Cell Neurosci.* **2022**, *15*, No. 806618.
- (9) Szymanski, M. W.; Richards, J. R. Fenoldopam. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2025.

- (10) Biglan, K.; Munsie, L.; Svensson, K. A.; Ardayfio, P.; Pugh, M.; Sims, J.; Brys, M. Safety and Efficacy of Mevidalen in Lewy Body Dementia: A Phase 2, Randomized, Placebo-Controlled Trial. *Movement Disorders* **2022**, *37* (3), 513–524.
- (11) Bezard, E.; Gray, D.; Kozak, R.; Leoni, M.; Combs, C.; Duvvuri, S. Rationale and Development of Tavapadon, a D1/D5-Selective Partial Dopamine Agonist for the Treatment of Parkinson's Disease. *CNS Neurol Disord Drug Targets* **2024**, *23* (4), 476–487.
- (12) Gilbert, D. L.; Murphy, T. K.; Jankovic, J.; Budman, C. L.; Black, K. J.; Kurlan, R. M.; Coffman, K. A.; McCracken, J. T.; Juncos, J.; Grant, J. E.; Chipkin, R. E. Ecopipam, a D1 Receptor Antagonist, for Treatment of Tourette Syndrome in Children: A Randomized, Placebo-Controlled Crossover Study. *Mov Disord* **2018**, *33* (8), 1272–1280.
- (13) Missale, C.; Nash, S. R.; Robinson, S. W.; Jaber, M.; Caron, M. G. Dopamine Receptors: From Structure to Function. *Physiol. Rev.* **1998**, *78* (1), 189–225.
- (14) Tichy, A.-M.; Gerrard, E. J.; Sexton, P. M.; Janovjak, H. Light-Activated Chimeric GPCRs: Limitations and Opportunities. *Curr. Opin. Struct. Biol.* **2019**, *57*, 196–203.
- (15) Whissell, P. D.; Tohyama, S.; Martin, L. J. The Use of DREADDs to Deconstruct Behavior. *Front. Genet.* **2016**, *7*. DOI: 10.3389/fgene.2016.00070.
- (16) Donthamsetti, P.; Winter, N.; Hoagland, A.; Stanley, C.; Visel, M.; Lammel, S.; Trauner, D.; Isacoff, E. Cell Specific Photoswitchable Agonist for Reversible Control of Endogenous Dopamine Receptors. *Nat. Commun.* **2021**, *12* (1), 4775.
- (17) Levitz, J.; Broichhagen, J.; Leippe, P.; Konrad, D.; Trauner, D.; Isacoff, E. Y. Dual Optical Control and Mechanistic Insights into Photoswitchable Group II and III Metabotropic Glutamate Receptors. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114* (17), E3546–E3554.
- (18) Broichhagen, J.; Frank, J. A.; Trauner, D. A Roadmap to Success in Photopharmacology. *Acc. Chem. Res.* **2015**, *48* (7), 1947–1960.
- (19) Hagen, V.; Kilic, F.; Schaal, J.; Dekowski, B.; Schmidt, R.; Kotzur, N. [8-[Bis(Carboxymethyl)Aminomethyl]-6-Bromo-7-Hydroxycoumarin-4-Yl]Methyl Moieties as Photoremovable Protecting Groups for Compounds with COOH, NH₂, OH, and C=O Functions. *J. Org. Chem.* **2010**, *75* (9), 2790–2797.
- (20) Lee, T. H.; Gee, K. R.; Ellinwood, E. H.; Seidler, F. J. Combining 'Caged-Dopamine' Photolysis with Fast-Scan Cyclic Voltammetry to Assess Dopamine Clearance and Release Auto-inhibition in Vitro. *J. Neurosci. Methods* **1996**, *67* (2), 221–231.
- (21) Araya, R.; Andino-Pavlovsky, V.; Yuste, R.; Etchenique, R. Two-Photon Optical Interrogation of Individual Dendritic Spines with Caged Dopamine. *ACS Chem. Neurosci.* **2013**, *4* (8), 1163–1167.
- (22) Donthamsetti, P. C.; Broichhagen, J.; Vyklicky, V.; Stanley, C.; Fu, Z.; Visel, M.; Levitz, J. L.; Javitch, J. A.; Trauner, D.; Isacoff, E. Y. Genetically Targeted Optical Control of an Endogenous G Protein-Coupled Receptor. *J. Am. Chem. Soc.* **2019**, *141* (29), 11522–11530.
- (23) Donthamsetti, P. C.; Winter, N.; Schönberger, M.; Levitz, J.; Stanley, C.; Javitch, J. A.; Isacoff, E. Y.; Trauner, D. Optical Control of Dopamine Receptors Using a Photoswitchable Tethered Inverse Agonist. *J. Am. Chem. Soc.* **2017**, *139* (51), 18522–18535.
- (24) Hetzler, B. E.; Donthamsetti, P.; Peitsinis, Z.; Stanley, C.; Trauner, D.; Isacoff, E. Y. Optical Control of Dopamine D2-like Receptors with Cell-Specific Fast-Relaxing Photoswitches. *J. Am. Chem. Soc.* **2023**, *145* (34), 18778–18788.
- (25) Vendrell-Llopis, N.; Read, J.; Boggiano, S.; Hetzler, B.; Peitsinis, Z.; Stanley, C.; Visel, M.; Trauner, D.; Donthamsetti, P.; Carmena, J.; Lammel, S.; Isacoff, E. Y. Dopamine D1 Receptor Activation in the Striatum Is Sufficient to Drive Reinforcement of Antecedent Cortical Patterns. *Neuron* **2025**, *113* (5), 785–794.
- (26) Pendleton, R. G.; Samler, L.; Kaiser, C.; Ridley, P. T. Studies on Renal Dopamine Receptors with a New Agonist. *Eur. J. Pharmacol.* **1978**, *51* (1), 19–28.
- (27) Setler, P. E.; Sarau, H. M.; Zirkle, C. L.; Saunders, H. L. The Central Effects of a Novel Dopamine Agonist. *Eur. J. Pharmacol.* **1978**, *50* (4), 419–430.
- (28) Iorio, L. C.; Barnett, A.; Leitz, F. H.; Houser, V. P.; Korduba, C. A. SCH 23390, a Potential Benzazepine Antipsychotic with Unique Interactions on Dopaminergic Systems. *J. Pharmacol. Exp. Ther.* **1983**, *226* (2), 462–468.
- (29) Pettersson, I.; Liljefors, T.; Boegesoe, K. Conformational Analysis and Structure-Activity Relationships of Selective Dopamine D-1 Receptor Agonists and Antagonists of the Benzazepine Series. *J. Med. Chem.* **1990**, *33* (8), 2197–2204.
- (30) Brogden, R. N.; Markham, A. Fenoldopam: A Review of Its Pharmacodynamic and Pharmacokinetic Properties and Intravenous Clinical Potential in the Management of Hypertensive Urgencies and Emergencies. *Drugs* **1997**, *54* (4), 634–650.
- (31) Kinter, L. B.; Horner, E.; Mann, W. A.; Weinstock, J.; Ruffolo, R. R. Characterization of the Hemodynamic Activities of Fenoldopam and Its Enantiomers in the Dog. *Chirality* **1990**, *2* (4), 219–225.
- (32) Neumeyer, J. L.; Kula, N. S.; Baldessarini, R. J.; Baidur, N. Stereoisomeric Probes for the D1 Dopamine Receptor: Synthesis and Characterization of R-(+) and S-(−) Enantiomers of 3-Allyl-7,8-Dihydroxy-1-Phenyl-2,3,4,5-Tetrahydro-1H-3-Benzazepine and Its 6-Bromo Analog. *J. Med. Chem.* **1992**, *35* (8), 1466–1471.
- (33) Kaiser, C.; Dandridge, P. A.; Garvey, E.; Hahn, R. A.; Sarau, H. M.; Setler, P. E.; Bass, L. S.; Clardy, J. Absolute Stereochemistry and Dopaminergic Activity of Enantiomers of 2,3,4,5-Tetrahydro-7,8-Dihydroxy-1-Phenyl-1H-3-Benzazepine. *J. Med. Chem.* **1982**, *25* (6), 697–703.
- (34) Ohlstein, E. H.; Berkowitz, B. A. SCH 23390 and SK&F 83566 Are Antagonists at Vascular Dopamine and Serotonin Receptors. *Eur. J. Pharmacol.* **1985**, *108* (2), 205–208.
- (35) Bakthavachalam, V.; Baidur, N.; Madras, B. K.; Neumeyer, J. L. Fluorescent Probes for Dopamine Receptors: Synthesis and Characterization of Fluorescein and 7-Nitrobenz-2-Oxa-1,3-Diazol-4-Yl Conjugates of D-1 and D-2 Receptor Ligands. *J. Med. Chem.* **1991**, *34* (11), 3235–3241.
- (36) Neumeyer, J. L.; Baidur, N.; Bakthavachalam, V.; Yuan, J.; Gao, Y.; Kula, N. S.; Campbell, A.; Baldessarini, R. J. Stereoisomeric, Photoaffinity, Affinity and Fluorescent Probes for Characterization of Dopamine D1 and D2 Receptors. In *Pharmacochimistry Library*; Angeli, P.; Gulini, U.; Quaglia, W., Eds.; Trends in Receptor Research; Elsevier, 1992; Vol. 18, pp 175–184. DOI: 10.1016/B978-0-444-88931-7.50016-5.
- (37) Monsma, F. J., Jr.; Barton, A. C.; Chol Kang, H.; Brassard, D. L.; Haugland, R. P.; Sibley, D. R. Characterization of Novel Fluorescent Ligands with High Affinity for D1 and D2 Dopaminergic Receptors. *Journal of Neurochemistry* **1989**, *52* (5), 1641–1644.
- (38) Morstein, J.; Awale, M.; Reymond, J.-L.; Trauner, D. Mapping the Azolog Space Enables the Optical Control of New Biological Targets. *ACS Cent. Sci.* **2019**, *5* (4), 607–618.
- (39) Zhuang, Y.; Xu, P.; Mao, C.; Wang, L.; Krumm, B.; Zhou, X. E.; Huang, S.; Liu, H.; Cheng, X.; Huang, X.-P.; Shen, D.-D.; Xu, T.; Liu, Y.-F.; Wang, Y.; Guo, J.; Jiang, Y.; Jiang, H.; Melcher, K.; Roth, B. L.; Zhang, Y.; Zhang, C.; Xu, H. E. Structural Insights into the Human D1 and D2 Dopamine Receptor Signaling Complexes. *Cell* **2021**, *184* (4), 931–942.
- (40) Neumeyer, J. L.; Baidur, N.; Yuan, J.; Booth, G.; Seeman, P.; Niznik, H. B. Development of a High Affinity and Stereoselective Photoaffinity Label for the D-1 Dopamine Receptor: Synthesis and Resolution of 7-[125I]Iodo-8-Hydroxy-3-Methyl-1-(4'-Azidophenyl)-2,3,4,5-Tetrahydro-1H-3-Benzazepine. *J. Med. Chem.* **1990**, *33* (2), 521–526.
- (41) Gautier, A.; Juillerat, A.; Heinis, C.; Corrêa, I. R.; Kindermann, M.; Beaufils, F.; Johnsson, K. An Engineered Protein Tag for Multiprotein Labeling in Living Cells. *Chem. Biol.* **2008**, *15* (2), 128–136.
- (42) Arunlakshana, O.; Schild, H. O. Some Quantitative Uses of Drug Antagonists. *Br J. Pharmacol. Chemother* **1959**, *14* (1), 48–58.
- (43) Keefe, K. A.; Gerfen, C. R. D1–D2 Dopamine Receptor Synergy in Striatum: Effects of Intrastriatal Infusions of Dopamine Agonists and Antagonists on Immediate Early Gene Expression. *Neuroscience* **1995**, *66* (4), 903–913.

(44) Konrad, D. B.; Savasci, G.; Allmendinger, L.; Trauner, D.; Ochsenfeld, C.; Ali, A. M. Computational Design and Synthesis of a Deeply Red-Shifted and Bistable Azobenzene. *J. Am. Chem. Soc.* **2020**, *142* (14), 6538–6547.

(45) Robertson, G. S.; Robertson, H. A. Synergistic Effects of D1 and D2 Dopamine Agonists on Turning Behaviour in Rats. *Brain Res.* **1986**, *384* (2), 387–390.



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