

RESEARCH ARTICLE

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5041Design and synthesis of photoswitchable
desloratadine ligands for histamine H₁ receptor
photopharmacologyLars C. P. Binkhorst,[†] Ivana Josimovic,[†] Daan de Vetten, Tyrone J. Nijman,
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Despite the pharmacological relevance of the histamine H₁ receptor (H₁R), the second most therapeutically targeted G protein-coupled receptor (GPCR), an effective photoswitchable ligand to optically control this receptor remains elusive. In this work, we aimed to identify a suitable photoswitchable H₁R ligand by performing an 'azoscan' on the H₁R antagonist desloratadine. Taking advantage of the synthetic toolbox available for the desloratadine scaffold, aniline groups were regioselectively installed on the aromatic positions of this scaffold to enable the synthesis of azobenzene analogs targeting the orthosteric binding pocket of H₁R. Additionally, we functionalized the piperidine ring of desloratadine with azobenzene moieties. These two strategies resulted in a total of nine photoswitchable compounds, displaying efficient *trans* to *cis* isomerization (PSS_{cis} > 87%) and a broad range of thermal relaxation half-lives. Pharmacological evaluation revealed the 2-position (**10a**) to be most suitable for accommodation of a photoswitchable group, as it exhibits the most balanced profile in absolute affinity (*K_i* *trans* = 2 nM) and a 3.2-fold light-induced affinity shift. Computational docking studies provide a rationale, with the binding pose of the *trans* and *cis* isomer in the H₁R binding pocket potentially being inverted. While the development of effective photoswitchable ligands for H₁R remains challenging, this study provides promising opportunities for future optimization to achieve optical control of this GPCR.

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Introduction

Photopharmacology enables precise spatiotemporal control of protein function using light, offering powerful tools to investigate dynamic signaling processes.¹ Photopharmacology uses photoresponsive ligands,² employing one of two main strategies: (i) photocaging, which uses ligands with photocleavable protecting groups³ or (ii) photoswitching, which uses small-molecule ligands that undergo light-induced isomerization.^{1,4,5} Successful design of photoswitchable ligands requires incorporation of a photoswitchable moiety (often an azobenzene) in such a way that the two isomers have different pharmacological properties. This can be achieved by (i) azologization, where a bioisoster (azosteres) in the core of the template ligand is replaced by an azobenzene or (ii) azoextension, where the template ligand is expanded with a photoswitchable unit.^{5,6}

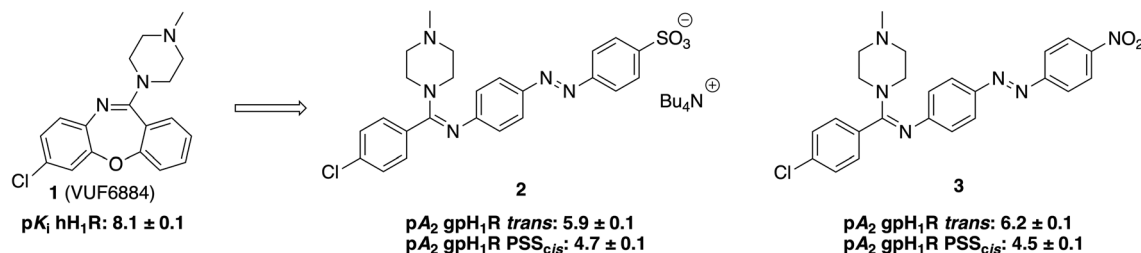
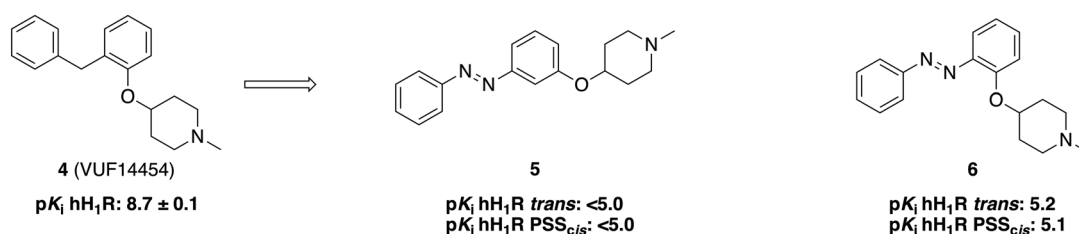
Photoswitchable ligands have been developed for a broad range of biological targets, including ion channels, enzymes and G protein-coupled receptors (GPCRs).^{6,7} GPCRs represent one of the most pharmacologically relevant protein families, with approximately 36% of the approved drugs targeting GPCRs.⁸ After the dopamine D₂ receptor, the histamine H₁ receptor (H₁R) is the second most frequent GPCR targeted by approved drugs, with 59 drugs targeting this receptor.⁸ H₁R is widely distributed throughout the body, in, for example, smooth muscle cells, endothelial cells and the central nervous system. H₁R antagonists, also known as antihistamines, are a class of drugs used to treat allergic diseases like allergic rhinitis, allergic conjunctivitis, and urticaria.⁹ These drugs alleviate symptoms such as itching, swelling, and redness by blocking the action of histamine on the H₁R. Despite significant progress in the GPCR photopharmacology field,^{10–13} and the high number of drugs targeting H₁R,⁸ it has proven remarkably difficult to develop a photoswitchable ligand that effectively modulates this receptor. Rustler *et al.* previously published photoswitchable ligands targeting guinea pig H₁R (gpH₁R)¹⁴ based on a clozapine derivative (**1**, Fig. 1A).¹⁵ However, the resulting photoswitchable compounds **2** and **3** exhibit low affinity for gpH₁R and no data on human H₁R

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A

Work by Rustler *et al.*¹⁴Previous in-house work¹²

B

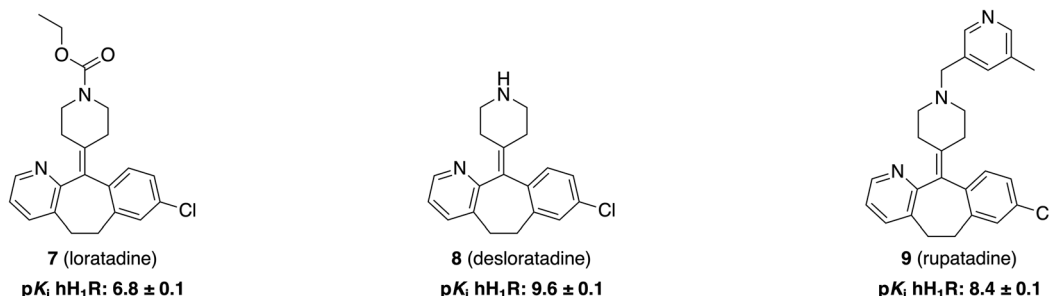


Fig. 1 Structures and pharmacological data of key compounds. Except for **2** and **3**, in-house affinity data and associated references are provided. (A) Previously reported photoswitchable ligands targeting gpH₁R¹⁴ based on **1** (VUF6884)¹⁵ or targeting hH₁R¹² based on **4** (VUF14454)¹⁶ (B) structures of loratadine,²³ desloratadine (value from Table 2) and rupatadine.²⁴

(hH₁R) were disclosed. Previous in-house efforts with photoswitchable molecules **5** and **6** based on VUF14454 (**4**)¹⁶ were also unsuccessful with the ligands having low H₁R affinity and no appreciable affinity shift between isomers.¹² Likewise, the desmethyl analog¹⁶ of these compounds or substitution of the nitrogen atom with an acidic moiety connected through a linker,¹⁷ were ineffective (unpublished data). Thus, an effective photoswitchable hH₁R ligand remains elusive to date. We reasoned that the 11-(piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridine core, as in antihistamines loratadine (**7**, Fig. 1B) and desloratadine (**8**), provides a promising scaffold. Both are well-characterized compounds that are frequently used in exemplification for late-stage aromatic functionalization.^{18–22} In the current work, we capitalized on this synthetic accessibility by performing an ‘azoscan’ on desloratidine, a unique approach in which the azobenzene moieties are systematically installed on different positions of the template scaffold to identify a suitable posi-

tion for placement of a photoswitchable moiety. These include aromatic vectors, but also *N*-substitution on the piperidine ring, generating analogs of rupatadine (**9**).

Results and discussion

Design

The design of new photoswitchable ligands targeting hH₁R (Fig. 2) is based on the second-generation antihistamine desloratadine (**8**) as the template. It exhibits an approximately 600-fold higher affinity for hH₁R than loratadine (**7**, Fig. 1B).^{23,24} The cryo-EM structure of desloratadine bound to hH₁R, published by Wang *et al.*,²⁵ has revealed that it engages in key hydrogen bond interactions with D107^{3,32} and Y431^{6,52} within the orthosteric hH₁R pocket. The structure suggests that there is space for growth on desloratadine, particularly on the side of the pyridine ring (Fig. S1). Notably, Wang *et al.* also found that the ligand-binding pocket of H₁R



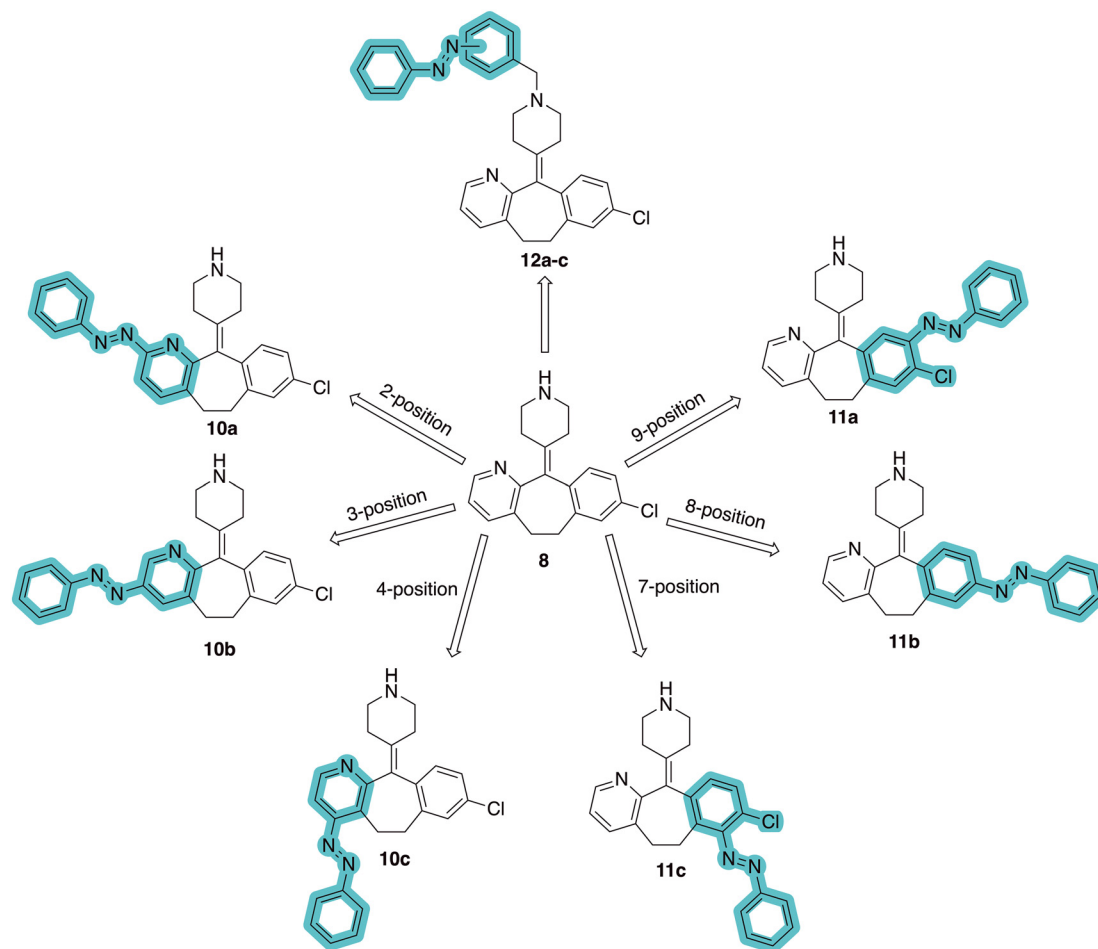


Fig. 2 Design strategy towards a photoswitchable hH₁R ligand by performing an 'azoscan' on desloratadine (8).

shows significant conformational flexibility based on the ligand bound, offering additional opportunities to potentially accommodate a photoswitchable ligand in the orthosteric pocket.²⁵

The 11-(piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-*b*]pyridine core of desloratadine has proven compatible with several late-stage synthetic functionalization approaches.^{18–22} We hypothesized that the use of such literature approaches would enable the installation of aniline moieties on the pyridine and phenyl rings, thereby providing synthetic vectors for the subsequent formation of an azo bond. Leveraging this synthetic accessibility, we conducted a systematic 'azoscan'. By introducing azobenzene moieties at various positions of desloratadine, we sought to identify a photoswitchable ligand where one isomer has a favorable conformation within the binding site, while the other isomer induces steric clashes and/or unfavorable interactions to induce an affinity shift. In total, three series were explored (Fig. 2). The first two series involve introduction of an azobenzene on the pyridine ring on the 2-, 3-, and 4-positions (10a–c) and at the phenyl ring on the 7-, 8-, and 9-positions (11a–c) to target the orthosteric binding pocket. Substitution of the 8-position required removal of the chlorine of desloratadine. Importantly, Lall *et al.* have shown that replacement of the chlo-

rine atom of loratadine with a hydrogen atom results in an equipotent compound.²⁶ Furthermore, we did not pursue the 10-position, located on the phenyl ring, due to the significant synthetic challenges expected with this sterically hindered position. The third series we explored is substitution at the piperidine ring (12a–c), *i.e.*, based on rupatadine as a template.

Synthesis

The synthesis routes for the first two series of photoswitchable desloratadine analogs (10a–c, 11a–c) were designed to regioselectively install aniline groups on the aromatic rings (Scheme 1), enabling subsequent azobenzene formation. For the preparation of the 2-isomer (10a), desloratadine (8) was first protected to give Boc-protected intermediate 13, which was oxidized with *m*-CPBA to *N*-oxide 14. *ortho*-Amination, following the method of Verbeet *et al.*,²⁷ yielded aminopyridine 15. Subsequent formation of the azobenzene using PhNO under acidic Mills conditions afforded azobenzene 16, which was deprotected with HCl to yield 10a. Intermediate 14 was also used for the preparation of the 4-isomer (10c). Substitution of the hydrogen atom through a triflate-intermediate, based on a procedure by Choi *et al.*,²⁸ gave intermediate 17. Due to poor





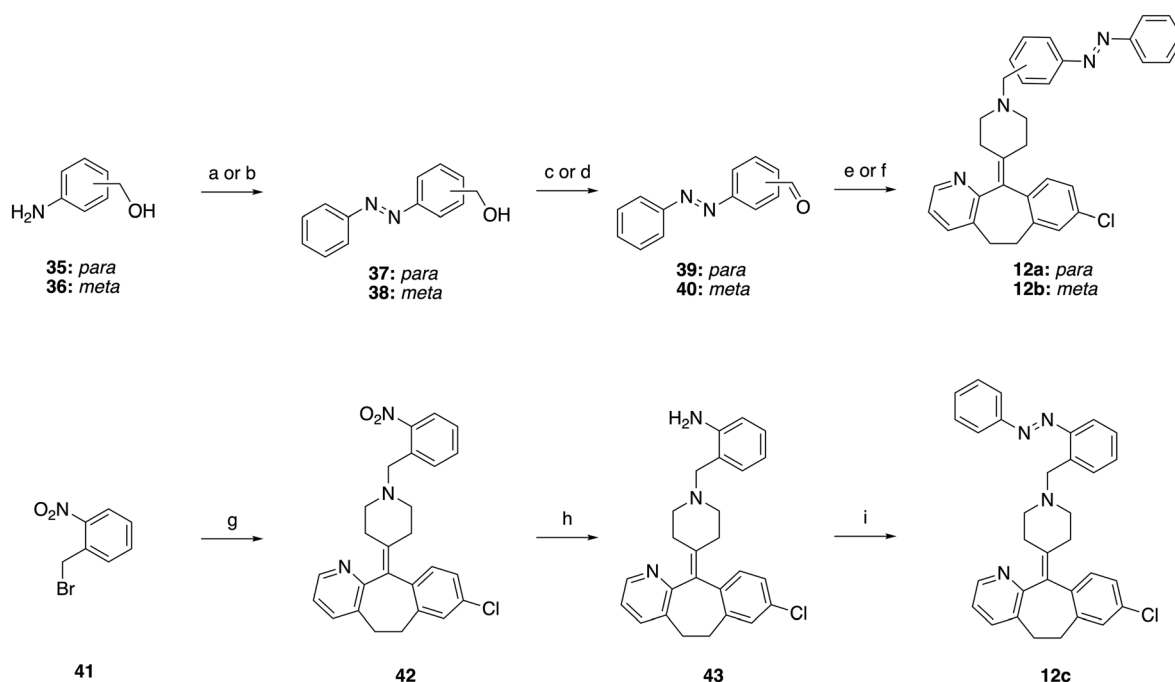
reactivity of this intermediate in the Mills reaction under acidic conditions, the aniline was rendered more nucleophilic by deprotonation successfully providing **18**. Deprotection of the Boc group in **18** with HCl afforded **10c**. The 3-isomer was synthesized *via* regioselective nitration of loratadine (**7**).^{29,30} Reduction of the resulting nitro-compound **19** *via* a Béchamp reduction provided aniline **20**, which was subjected to acidic Mills conditions (affording **21**) and carbamate deprotection with KOH to yield **10b**.

For installation of the azobenzene at the 8-position (**11b**), a Buchwald–Hartwig amination of loratadine (**7**) with *tert*-butylcarbamate yielded **22**. Boc-deprotection to **23** followed by the Mills reaction under acidic conditions afforded intermediate **24**, which was deprotected using KOH to give **11b**. The 7- and 9-analogs were accessed using a method for the nitration²⁹ of loratadine that produces the two regioisomers **25** (major) and **28** (minor). For the synthesis of **11c** from **28**, the ethylcarbamate protecting group was replaced with a Boc protecting group (through intermediacy of **29**) to avoid the formation of side products observed in deprotection attempts of the ethylcarbamate in the last step (data not shown). Reduction of the nitro group of resulting intermediate **30** gave aniline **31**, which was converted to **32** *via in situ* diazotization and reaction with PhMgBr, based on a procedure of Barbero *et al.*³¹ This alternative strategy was chosen because both acidic and basic Mills conditions on **31** were ineffective. Similarly, to obtain **11a**, compound **25** was converted to Boc-protected intermediate **27** *via* **26**. After reduction of the nitro group to **33** and a Mills reaction to **34**, Boc group deprotection afforded **11a**.

Rupatadine analogs (**12a–c**) were synthesized using two different routes (Scheme 2). For analogs **12a** (*para*) and **12b** (*meta*), the corresponding anilines **35** and **36** were coupled to PhNO *via* the Mills reaction under acidic conditions to afford azobenzenes **37** and **38**. These compounds were then oxidized to give aldehydes **39** and **40** using DMP or MnO₂, respectively. Reductive amination with desloratadine (**8**) yielded rupertadine analogs **12a** and **12b**. In contrast, synthesis of **12c** (*ortho*) required an alternative approach, as aldehyde formation from the corresponding azobenzene was unsuccessful. Instead, alkylation of desloratadine (**8**) with alkylbromide **41** gave nitro-compound **42**, which was reduced to aniline **43** and subjected to acidic Mills conditions to afford **12c**.

Photochemistry

The photochemical properties of the photoswitchable ligands (Table 1, Fig. S2–S10) were first characterized by UV-vis absorption spectroscopy. Spectra were recorded at a concentration of 25 μ M in HBSS buffer containing 50% DMSO (Fig. S2–S10). Most compounds exhibit absorption patterns characteristic for azobenzenes and azopyridines.^{32–34} The absorption maxima (λ_{max}) of the *trans* isomers are observed around 310–340 nm (π – π^* absorption band). Of note is the π – π^* transition band of **11c**, which is observed as a shoulder around 310 nm. Next to a potential effect of the *ortho*-Cl atom,³⁵ the absence of a comparable blue-shift in π – π^* band for the related compound **11a** could highlight a steric effect on the absorption profile in **11c**. The λ_{max} values of the *cis* isomers are observed at 419–435 nm (n – π^*



Scheme 2 Synthesis of **12a–c**. Reagents and conditions: (a) for **37**: PhNO, AcOH, rt, 66 h, 12%; (b) for **38**: PhNO, DCM, AcOH, rt, 18 h, 70%; (c) for **39**: DMP, DCM, rt, 1.5 h, 89%; (d) for **40**: MnO₂, DCM, rt, 2 h, 75%; (e) for **12a**: **8**, NaBH(OAc)₃, AcOH, DCE, rt, 16 h, 26%; (f) for **12b**: **8**, NaBH(OAc)₃, AcOH, DCM, rt, 2 h, 62%; (g) **8**, MeCN, K₂CO₃, reflux, 3 h, 91%; (h) Fe, NH₄Cl, 1,4-dioxane, EtOH, H₂O, 80 °C, 3 h, quantitative; (i) PhNO, PhMe, AcOH, 75 °C, 16 h, 12%.



Table 1 Photochemical parameters of 10a–c, 11a–c and 12a–c

Compound	Structure	A			B		C		
		R ¹	R ²	R ³	$\lambda_{\max}^{trans^a}$ (nm)	$\lambda_{\max}^{cis^a}$ (nm)	PSS _{cis} (area% cis) ^b	PSS _{trans} (area% trans) ^b	Approximate $t_{1/2}^c$
10a	A		H	H	332	429	91	85	38 d
10b	A	H		H	335	430	87	79	31 d
10c	A	H	H		319	419	n.d. ^d	n.d. ^d	15 min
11a	B		Cl	H	340	429	97	79	78 d
11b	B	H		H	338	435	91	80	5 d
11c	B	H	Cl		~310 ^e	419	67	82	211 d
12a	C		H	H	327	432	93	83	19 d
12b	C	H		H	325	423	91	81	198 d
12c	C	H	H		329	—	n.d. ^d	n.d. ^d	45 s

^a Determined at 25 μ M in HBSS buffer containing 50% DMSO. ^b Photostationary state area percentages either after illumination of *trans* isomer with 360 ± 20 nm at 10 mM in DMSO as determined by acidic LC-MS analysis at the isosbestic point, or after illumination of PSS_{cis} states with 434 ± 9 nm at 10 mM in DMSO as determined by acidic LC-MS analysis at the isosbestic point. ^c Thermal relaxation ($t_{1/2}$) of PSS_{cis} states in HBSS buffer containing 50% DMSO, as estimated by the method of Ahmed *et al.*³⁶ by extrapolating to 20 °C. Arrhenius plots are available in SI. ^d Photostationary state area percentages could not be determined by LC-MS analysis due to the small $t_{1/2}$ value. ^e Approximate value due to overlapping bands.

absorption band). Due to the short thermal half-life of **10c** and **12c** (*vide infra*), determination of the $\lambda_{\max}$ value of their *cis* isomer and quantification of their photostationary states (PSS) was not feasible. The *trans* to *cis* isomerization for all other compounds could be quantified upon illumination with 360 nm, resulting in PSS_{cis} values ranging from 87–97%. The exception was compound **11c**, which only reaches a moderate PSS_{cis} value of 67% (*vide supra*, Fig. S7C). Indeed, UV analysis (Fig. S7B) clearly shows that 360 nm is near an isosbestic point of **11c**. All compounds show expected PSS_{trans} values between 79–85% upon illumination with

434 nm. The approximated dark stabilities of these compounds in buffer vary substantially, with thermal half-lives ranging from seconds (**12c**) and minutes (**10c**) to days (**11b**, **12a**) and even months (**10a**, **10b**, **11a**, **11c**, **12b**).

Pharmacology

The affinities (pK_i values) of **10a–c**, **11a–c** and **12a–c** for the hH₁R were evaluated in competition radioligand-binding experiments with the labelled H₁R antagonist [³H]mepyramine



(Table 2, Fig. S11–S13). For **10c** and **12c**, continuous illumination at 365 nm was used to counteract the short half-lives of their PSS_{cis} states, while for the other compounds PSS_{cis} states were obtained by pre-illumination with 360 nm. In the first series, featuring substitutions on the pyridine ring (**10a–c**), substitution on the 2-position (**10a**) provides a compound with high affinity for the *trans* isomer ($pK_i = 8.3$, template **8**: $pK_i = 9.6$) and a lower affinity in the PSS_{cis} state ($pK_i = 7.8$), resulting in a significant light-induced affinity shift of -0.5 log unit (*i.e.*, a 3.2-fold shift in affinity). Incorporation of an azobenzene at the 3-position (**10b**) is also well tolerated (pK_i *trans* = 8.7). However, a reduced light-induced affinity shift

was observed between *trans*-**10b** and **10b**-PSS_{cis} (-0.3 log unit). Placement of the azobenzene on the 4-position (**10c**) reduces affinity for the *trans* isomer compared to **10a** and **10b**, providing high-nM affinities (pK_i **10c** = 6.8). However, **10c** shows no affinity shift upon photoisomerization, indicating that this position is not optimal for azobenzene placement. In the second series (**11a–c**), which involves substitution on the phenyl ring, *trans*-**11a** and *trans*-**11b** have comparable affinity to *trans*-**10c** ($pK_i = 6.8$). Noteworthy, **11b** shows a significant affinity shift (-0.6 log unit) between *trans* and PSS_{cis}. In contrast, substitution at the 7-position (**11c**) results in a loss of affinity for hH₁R for either state ($pK_i < 6.0$), indicating that

Table 2 Human histamine H₁R binding affinity (pK_i) values and affinity shifts of **10a–c**, **11a–c** and **12a–c**

	A	B	C				
	10a-c	11a-c	12a-c				
Compound number	Structure	R ¹	R ²	R ³	p <i>K</i> _i <i>trans</i> ^a	p <i>K</i> _i PSS _{cis} ^a	p <i>K</i> _i shift ^b
8	A	H	H	H	9.6 ± 0.1	—	—
10a	A		H	H	8.3 ± 0.2	7.8 ± 0.2	−0.5
10b	A	H		H	8.7 ± 0.1	8.4 ± 0.1	−0.3
10c	A	H	H		6.8 ± 0.0	6.8 ± 0.0 ^c	0.0
11a	B		Cl	H	6.8 ± 0.2	6.6 ± 0.1	−0.2
11b	B	H		H	6.9 ± 0.0	6.3 ± 0.1	−0.6
11c	B	H	Cl		<6.0	<6.0	—
12a	C		H	H	8.6 ± 0.5	8.5 ± 0.2	−0.1
12b	C	H		H	8.3 ± 0.1	8.2 ± 0.1	−0.1
12c	C	H	H		8.4 ± 0.2	8.3 ± 0.2 ^c	−0.1

^a Affinity (pK_i) values as obtained from radioligand competition experiments with [³H]mepyramine. Values are mean $\pm$ SEM of $n = 3$ experiments, performed in triplicate. Competition binding curves are available in the SI. ^b Affinity shifts between PSS_{cis} and *trans* states are defined as pK_i PSS_{cis}– pK_i *trans*. ^c Continuous illumination at 365 nm was used during 4 h incubation at 25 °C.



this position is not suitable for azologization. The third series (12a–c), involving rupatadine analogs, provides high affinities for the *trans* isomers ($pK_i = 8.3$ – 8.6 , template 9: $pK_i = 8.4$, Fig. 1). This is in line with other reports showing that the piperidine of 8 can be substituted without eroding H_1R affinities.^{24,37,38} However, none of the ligands 12a–c shows an affinity shift upon photoisomerization, indicating that the *N*-substitution of 8 is not a viable strategy to achieve photochemical modulation of hH_1R . In all, the 10 and 12 series are generally more amenable to appending *trans*-azobenzene moieties while maintaining affinities, with only the 10 series also showing some appreciable affinity shifts upon photoisomerization. The 11 series notably suffers from reduction in H_1R affinity upon appending a *trans* azobenzene, although some members in this series show affinity shifts upon photoisomerization. In all, 10a and 11b demonstrate the most pronounced light-induced affinity shifts among the three series (-0.5 and -0.6 , respectively). Notably, 10a displays an approximately 25-fold higher H_1R affinity (pK_i *trans* = 8.3) compared to 11b and therefore emerges as the most suitable photopharmacological H_1R ligand in this study.

Proposed binding mode of 10a

Molecular modelling using the recently disclosed cryo-EM structure of H_1R with 8 (PDB ID: 8X64)²⁵ was performed to gain insight in the observed affinities of *trans*- and *cis*-10a. We investigated whether both isomers could bind to H_1R in a similar fashion as desloratadine. Indeed, *trans*-10a adopts a conformation similar to that of desloratadine (Fig. 3A). In this docking pose, the key interactions of the protonated amine with D107^{3.32} and of the pyridine nitrogen atom with Y431^{6.52} are maintained. The azobenzene moiety is directed towards the solvent-exposed region. In contrast, no comparable docking poses could be identified for *cis*-10a. Instead, for *cis*-10a a binding mode was identified in which the desloratadine core was flipped 180 degrees in the binding

pocket. In this binding mode *cis*-10a maintains the key interaction with D107^{3.32} via its protonated amine but lacks the hydrogen bond interaction with Y431^{6.52}. The azobenzene moiety is buried deep in the pocket where it forms a π -stacking interaction with W428^{6.48}, while the chloro-substituted ring of the desloratadine core forms an arene-H interaction with Y108^{3.33}. These binding modes explain the reduced affinity of *cis*-10a compared to that of *trans*-10a, while also providing a rationale for the still appreciable affinity of *cis*-10a owing to the maintained key ionic interaction with D107^{3.32} and the two newly formed interactions with Y108^{3.33} and W428^{6.48}. Based on these findings, computer-aided approaches could help the design of the next generation of desloratadine-based photoswitchable ligands, for example by focusing on increasing the bulk on the peripheral phenyl ring of 10a. These modifications may allow the *trans* isomer to maintain a similar binding mode to *trans*-10a as its azobenzene moiety is directed towards the solvent-exposed region, while the *cis* isomer in its inverted binding mode would experience steric clashes with the protein. This in turn would lower the affinity of the *cis* isomer and therefore improve the affinity shift.

Conclusion

Finding effective photoswitchable ligands for optical control of the hH_1R remains challenging, which may be attributed to the intrinsic flexibility of the orthosteric binding pocket of hH_1R . Here, a total of nine potential photoswitchable ligands for hH_1R was explored by performing an 'azoscan' on the antihistamine desloratadine (8). Late-stage regioselective installation of aniline groups on the aromatic rings of the desloratadine scaffold enabled azobenzene formation and overall an aromatic azoscan. This was supplemented by a concise series of *N*-functionalized derivatives. Most ligands show efficient *trans* to *cis* isomerization ($PSS_{cis} > 87\%$) by using an illumination wavelength of 360 nm, except for 11c

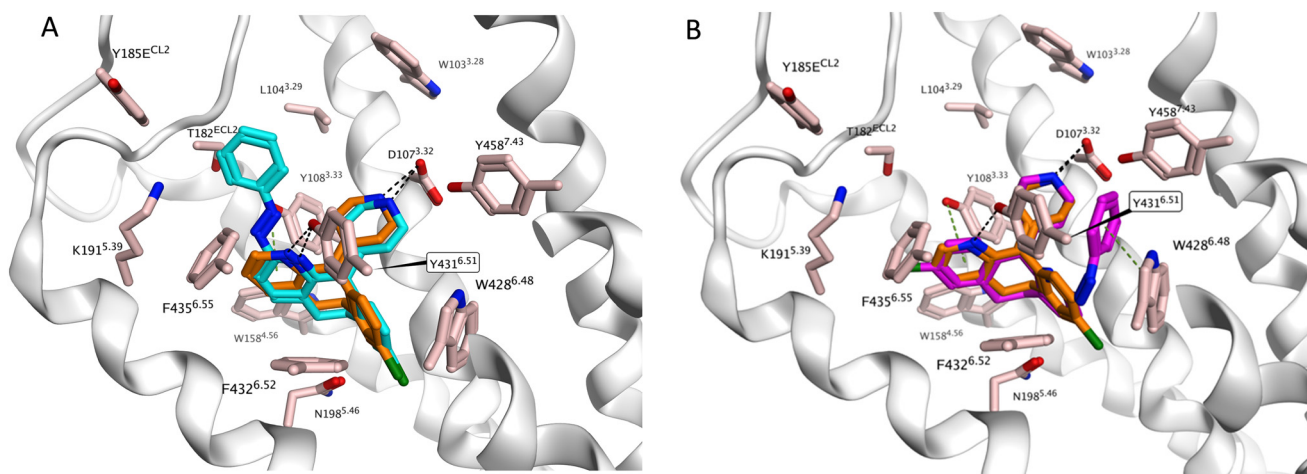


Fig. 3 Proposed binding mode of desloratadine (orange) in the H_1R binding pocket as determined by cryo-EM (PDB ID: 8X64)²⁵ in overlay with the docking pose of (A) *trans*-10a (cyan) and (B) *cis*-10a (purple).



(PSS_{cis} = 67%). Additionally, a wide range of half-lives was observed ranging from seconds to months. Pharmacological evaluation revealed marked differences in effect upon probing azobenzenes in the three regions of **8**, and only a few compounds show an appreciable light-induced H₁R affinity shift upon installation of an azobenzene. Two suitable positions, *i.e.* the 2-position (**10a**) and the 8-position (**11b**), were identified with similar H₁R affinity shifts between the *trans* and PSS_{cis} states. Of these, **10a** shows the most balanced profile (pK_i *trans* = 8.3, pK_i PSS_{cis} = 7.8). Molecular modeling studies indicate that the docking pose of *trans*-**10a** in H₁R shows good overlap with the binding mode of desloratadine, but that, in contrast, *cis*-**10a** adopts a flipped binding mode. Building on these findings, a light-induced H₁R affinity shift could potentially be improved by decorating the peripheral phenyl ring of the azobenzene of **10a**. Thus, photoswitchable ligand **10a** may provide a promising starting point for future development of improved hH₁R photoswitchable ligands.

Methods

Molecular modeling, synthetic chemistry, photochemistry, pharmacology and chemical analyses can be found in the SI.

Author contributions

LCPB: conceptualization, investigation, methodology, formal analysis, visualization, writing – original draft; IJ: conceptualization, investigation, methodology, formal analysis, writing – review & editing; DdV: investigation, formal analysis; TJN: investigation, formal analysis; NJH: conceptualization, investigation, formal analysis, writing – review & editing; SA: investigation, formal analysis; OPJL: visualization, supervision, writing – review & editing; IJPdE: supervision, writing – review & editing; HFV: supervision, funding acquisition, writing – review & editing; MW: supervision, funding acquisition, writing – original draft; RL: supervision, funding acquisition, writing – review & editing.

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

Supplementary Information available: Detailed photochemical characterization, synthesis, chemical analyses, molecular modeling and pharmacological characterization. See DOI: <https://doi.org/10.1039/D5MD00589B>.

The data supporting this article have been included as part of the SI.

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