Synthesis of *Iso*-Dimethyltryptamines and Biological Analysis in a Model of Light-Induced Retinal Degeneration

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KEYWORDS Serotonin receptor agonists, 5-HTR, ergot alkaloids, iso-dimethyltryptamines, LIRD, ophthalmology, retinal diseases.

ABSTRACT: IsoDMT analogs with heterocyclic substitutions at the indole C(3) were prepared in a hydrogen-autotransfer (HA) alkylation and tested in combination with natural and unnatural clavine alkaloids in a model of light-induced retinal degeneration for protection against retinal degeneration. As assessed with OCT and ERG, three compounds showed better efficacy than positive-control bromocriptine at equivalent systemically administered doses. These studies provide further insight into the role that 5-HT receptors play in ocular diseases.

The discovery of serotonin (5-hydroxytryptamine, 5-HT) receptors (5-HTRs) in retinal cells in the 1960's was followed by seminal studies that demonstrated that 5-HTR binding is involved in retinal pathology and photoreceptor survival.[1] The *de novo* synthesis of 5-HT from tryptophan, activation of cAMP signaling pathways by binding to 5-HTRs, reuptake by 5-HT transporters, as well as 5-HT degradation by monoamine oxidases (MAO) are active processes in retina cells (Fig. 1). A subset of retinal interneurons (amacrine cells) both synthesize and release 5-HT and therefore act as serotonergic neurons. 5-HTRs in retinal bipolar and ganglion cells are responsible for neuromodulation.[1,2,3] Importantly, while many pharmacological studies have focused on the expression of 5-HTRs in animals, they are also expressed and play a neuroprotective role in human retina cells.[2,3] However, the specific signaling pathways differ between cells and are influenced by off-target effects of the chemical probes utilized in earlier studies (Table 1).

Among the constitutively expressed 5-HT receptors, 5-HT_{1A}, 5-$HT_{2A,B,C}$, 5-HT_{3A}, 5-$HT_{5A,B}$, and 5-HT_7 have been detected in the retina of various species, including humans.[1] Activation of ocular 5-HT receptors was shown to rapidly initiate a CNS survival pathway and protect against injuries such as severe photooxidative damage induced by exposure to blue light.[4] 5-HT_{1A}R agonists, such as buspirone, xaliproden, and 8-hydroxy-2-(di-*n*-propylamino)-tetralin (8-OH-DPAT), protect ARPE-19 human retinal pigment epithelium (RPE) cells against oxidative damage, as well as mouse RPE cells *in vivo* in geographic atrophy models,[5] but currently there is only anecdotal evidence that links 5-HT_{1A}R agonists to protection against light-induced retinal degeneration (LIRD).[6] In contrast, this effect has been more thoroughly investigated in glaucoma. Activation of 5-HT_{1A}R in the retina facilitates presynaptic GABA release by suppressing cAMP-PKA signaling and decreasing PKA phosphorylation (Fig. 2),[7] which can explain the reduction of excitotoxicity in retinal ganglion cells (RGCs) during experimental glaucoma.[8] Excessive cAMP signaling is also linked to inherited retinal degenerative diseases,[9] and drugs that suppress cAMP show a remarkable therapeutic potential.[10]

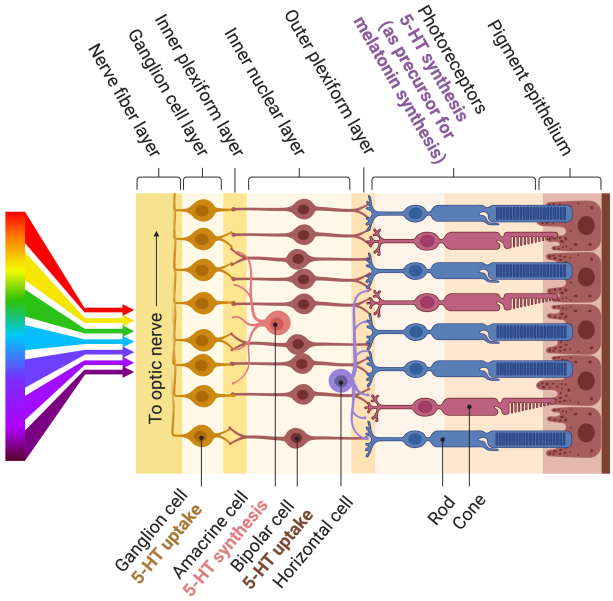


Figure. 1. Serotonin (5-HT) synthesis and uptake in retina cells (created with BioRender).[1]

Due to the insufficient subtype selectivity of the current generation of small molecule 5-HT modulators,[11] it is not yet clear which 5-HTR among 5-HT_{1A}, $_{2A,2B}$ and 5-HT_{2C} receptors is mainly responsible for the protective effects of agonists, or if pan-activation is useful for therapeutic purposes. Furthermore, only limited information is currently available about the interplay of 5-HT_{3A}, 5-$HT_{5A,B}$, and 5-HT_7 receptors in the retina. Literature data suggest that serotonergic 5-HT_{1A}R activation in the retina is neuroprotective, whereas pan-5-HT_2R activation might have a detrimental effect on retinal survival.[1,2,3] In conrast, 5-HT_2R agonists were found to be effective in reducing intraocular pressure (IOP) in a primate model of glaucoma,[12] and 5-HT_{2C} regulates neurite growth and retinal processing of visual information.[13] Sarpogrelate, a 5-HT_{2A}/5-HT_{2B} antagonist, also proved protective in light-induced retinopathy.[14] Significantly, 5-HTR agonists or antagonists have not yet been used in vision

therapies, despite the large need for new treatment options in ocular diseases. Accordingly, we envisioned that specific 5-HTR probes will be useful to clarify receptor properties and identify new therapeutic opportunities in ocular diseases.

Table 1. 5-HTR expression in retina, signaling pathways, and relevant chemical probes.[1]

Tissue or cell	5-HTR	Activated signaling pathway	Agonist/ antagonist used
Rabbit & goldfish retina	5-HT$_{1A}$	Increased cAMP	Buspirone/ spiroxatrine
Culture human retinal pigment epithelium (RPE)	5-HT$_{1A}$	Decreased cAMP	Buspirone/ spiroxatrine
Cultured rat RPE & retinal ganglion cells (RGC)	5-HT$_{2A,C}$	Increased inositol and Ca^{2+}	5-HT/ methysergide/ spiperone/ WAY-161503

Retinal degeneration is a common symptom of several blinding diseases such as retinitis pigmentosa (RP)[15] and age-related macular degeneration (AMD).[16] Interestingly, RP is a leading cause of vision loss for people under the age of 55, while AMD is the leading cause of vision loss in the elderly.[17] Both diseases are prevalent worldwide, and AMD is projected to be diagnosed in 288 million patients by 2040.[18] Advanced AMD can be categorized as either "wet" or "dry" AMD with their differentiating characteristic being the abnormal formation and leakage of blood vessels.[17] While dry AMD is much more common, available treatments remain limited. In fact, the FDA approved the first two drugs for treatment of dry AMD as recently as 2023.[19,20] Treatments for RP have historically focused on attenuating symptoms, but new research efforts have leveraged gene therapy, resulting in the first gene therapy to gain FDA approval for the eye.[21]

Constant and intense exposure to light is associated with photoreceptor cell death and ultimately retinal degeneration.[22,23] This can lead to the acceleration of RP[24,25,26] and is a risk factor for the development of AMD.[16,27,28] Mechanistically, prolonged light exposure can disrupt the retinoid cycle by hindering the clearance of intermediates such as all-*trans*-retinal, which results in its accumulation and eventual retinopathy.[29,30,31,32] Build-up of all-*trans*-retinal may also lead to the formation of toxic byproducts that can cause additional damage to the retina.[33,34,35,36,37] Furthermore, extended light exposure can result in the excessive production of reactive oxygen species (ROS) in the retina. Elevated ROS levels increase oxidative stress and activate apoptotic and pro-inflammatory pathways, both of which are contributing to retinal degeneration.[14,38,39,40,41] There is also growing evidence that ROS play a significant role in the development and progression of glaucoma.[42]

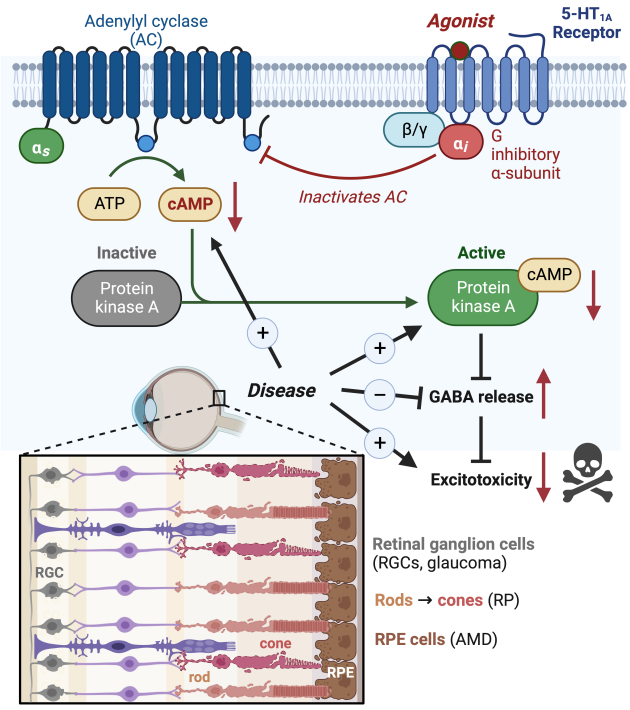


Figure. 2. Mechanistic hypothesis for the neuroprotective effects of 5-HT$_{1A}$R agonists. Cyclic adenosine monophosphate (cAMP) levels are elevated during retinal disease and are driving further degeneration.[9] For instance, cAMP-activated PKA-mediated protein phosphorylation reduces GABA release causing hyperexcitability associated with glaucomatous damage. Agonists at 5-HT$_{1A}$ inhibit this cascade by exchanging GDP for GTP on the α-subunit of Gi/o (Giα/Goα), inhibiting adenylyl cyclase (AC), and resulting in decreased cAMP (created with BioRender).

Iso-Dimethyltryptamines (isoDMTs) are potent 5-HTR agonists and have garnered considerable interest in recent years due to their potential as treatments for anxiety and depression with reduced hallucinogenic side-effects (Fig. 3).[43,44,45] For example, AAZ-A-154 is a non-hallucinogen that has anti-depressant properties similar to the drug ketamine.[45] Structure-activity relationship (SAR) studies of the tryptamine scaffold typically include three major zones: the benzene ring of indole, the indole side chain, and the degree of alkylation at the terminal, basic nitrogen.[4351] We have recently developed a high yielding, robust indole C(3)-alkylation reaction that allows the installation of a pyridyl substituent at this position and offers opportunities to expand the SAR of isoDMTs.[52]

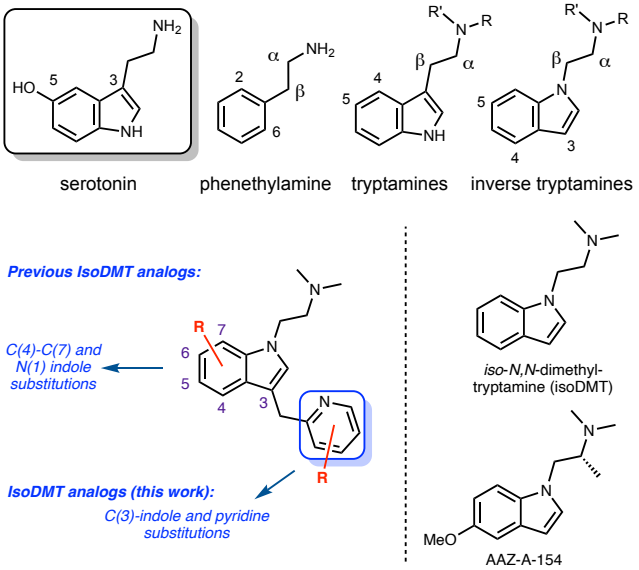
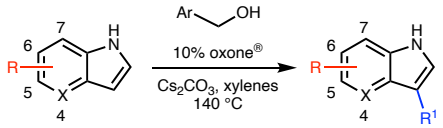


Figure 3. Examples of tryptamines, isoDMTs and novel 3-methylpyridyl isoDMT analogs.

Specifically, pyridyl-substituted isoDMT analogs were synthesized following a two-step sequence (Scheme 1).[52,53] Treatment of halo-, methoxy-, or aza-indoles **1**-**7** with 2- or 4-pyridinemethanol in the presence of oxone® and Cs_2CO_3 in xylenes at reflux afforded the corresponding 3-substituted indoles **8**-**11**, **13**, and **16**, and 2-aza-indole **12** in good to excellent yields. Hydrogen autotransfer (HA)-type alkylation of fluorinated indoles was also performed with 2-pyrimidinemethanol and 6-methyl-2-pyridinemethanol and provided the substituted indoles **14** and **15** in good yields. Furthermore, 5-fluoroindole successfully reacted with 1-(2-pyridyl)ethanol to give **17** in 60% yield, which suggests that carbon chain branching at the benzylic position is possible with readily available starting materials. Subsequent treatment of **8**-**17** with 2-dimethylaminoethyl chloride hydrochloride, potassium hydroxide, and potassium iodide in DMSO at room temperature gave the *N*-alkylated isoDMT analogs **18** to **27** in 24% to 71% yield. With some substrates, oxidized side products were also isolated, decreasing the yields of the desired products. Although these side products were formed in relatively low amounts, they were difficult to remove chromatographically from the desired products. We explored changing solvent and base conditions to minimize side product formation, but these modifications resulted in sluggish reaction rates.

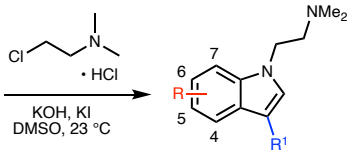
In order to obtain an assessment of the potential for the isoDMT derivatives to serve as lead structures for retinal degeneration therapeutics, we selected the halogenated analogs **18**-**20** for evaluation in a well-established model of light-induced retinal degeneration (LIRD).[54] In addition to the isoDMTs, we also tested the protective effects in this model of recently synthesized natural and unnatural clavine alkaloids that were demonstrated to have considerable 5-HTR subtype selectivity (Fig. 4).[55,56,57] For example, (+)-cycloclavine was shown to possess ≥10-fold greater potency at 5-HT_{2C} versus 5-$HT_{1A/2A/2B}$.[58] In contrast, the bridged diethylamide **28** did not show any notable activity at 5-$HT_{1A,2A,2B,2C}$.[59]

Scheme 1. Synthesis of isoDMT analogs by a hydrogen autotransfer (HA) process followed by *N*-alkylation.[52]



1 (X=CH, R=4-Br)
2 (X=CH, R=5-F)
3 (X=CH, R=6-F)
4 (X=CH, R=5-OMe)
5 (X=N, R=H)
6 (X=CH, R=5,6-F_2)
7 (X=CH, R=7-F)

8 (X=CH, R=4-Br, R^1=pyridin-2-ylmethyl); 67%
9 (X=CH, R=5-F, R^1=pyridin-2-ylmethyl); 78%
10 (X=CH, R=6-F, R^1=pyridin-2-ylmethyl); 63%
11 (X=CH, R=5-OMe, R^1=pyridin-2-ylmethyl); 81%
12 (X=N, R=H, R^1=pyridin-2-ylmethyl); 88%
13 (X=CH, R=5-F, R^1=pyridin-4-ylmethyl); 78%
14 (X=CH, R=5-F, R^1=pyrimidin-2-ylmethyl); 85%
15 (X=CH, R=5-F, R^1=1-(pyridin-2-yl)ethyl); 57%
16 (X=CH, R=5,6-F_2, R^1=pyridin-4-ylmethyl); 80%
17 (X=CH, R=7-F, R^1=(6-methylpyridin-2-yl)methyl); 60%



18 (X=CH, R=4-Br, R^1=pyridin-2-ylmethyl); 59%
19 (X=CH, R=5-F, R^1=pyridin-2-ylmethyl); 66%
20 (X=CH, R=6-F, R^1=pyridin-2-ylmethyl); 24%
21 (X=CH, R=5-OMe, R^1=pyridin-2-ylmethyl); 45%
22 (X=N, R=H, R^1=pyridin-2-ylmethyl); 64%
23 (X=CH, R=5-F, R^1=pyridin-4-ylmethyl); 59%
24 (X=CH, R=5-F, R^1=pyrimidin-2-ylmethyl); 71%
25 (X=CH, R=5-F, R^1=1-(pyridin-2-yl)ethyl); 69%
26 (X=CH, R=5,6-F_2, R^1=pyridin-4-ylmethyl); 59%
27 (X=CH, R=7-F, R^1=(6-methylpyridin-2-yl)methyl); 30%

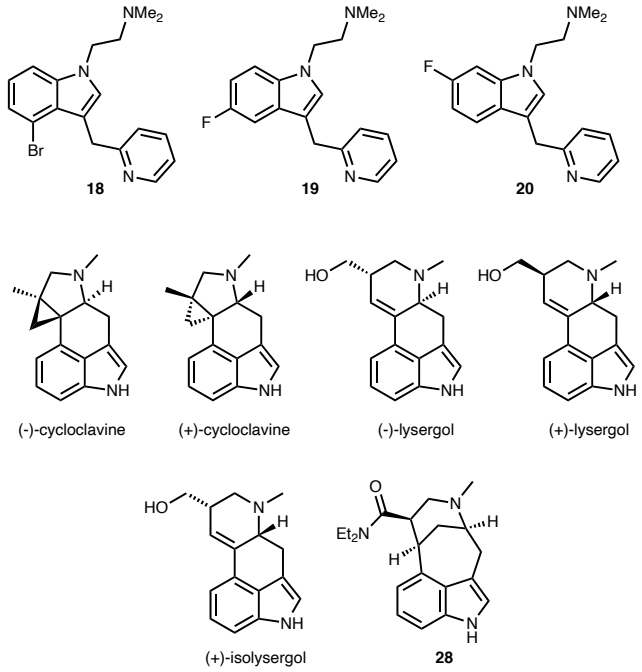


Figure 4. IsoDMT and clavine alkaloids selected for LIRD analysis.

BALB/c albino mice aged 5-8 weeks were used in the LIRD experiments. Mice were housed in a temperature-controlled animal facility with a 12-hour light/dark cycle and fed a standard rodent diet *ad libitum*. All procedures were conducted in accordance with the Directive 86/609/EEC for animal experiments, FELASA Guidelines and

Recommendations, and ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Experiments were approved by the Finnish Project Authorization Board, with protocol number ESAVI/26320/2021.

The isoDMTs and clavine alkaloids (Fig. 4), or bromocriptine, were first individually dissolved in DMSO to make 10 mg/mL stock solutions. On the day of LIRD induction, stock solutions were mixed with saline at a 1:4 ratio. The mice were dark-adapted overnight and all handling prior to LIRD induction was performed under dim red light. Drugs (10 mg/kg, b.w.) or vehicle (25 % DMSO, 75 % saline; volume adjusted to 100 uL) were intraperitoneally (i.p.) injected 30 min prior to the bright light exposure, and the mouse pupils were dilated using duplicate corneal administrations of metaoxedrin (20 mg/mL) and tropicamide (4 mg/mL) solution; first at 30 min prior and second at 15 min prior to light exposure. LIRD was induced with a 30 min exposure to 15 kLux white light in freely moving mice (see schematic presentation of method in Supplementary Figure 1) and then transferred back to the vivarium. One week later, the optical coherence tomography (OCT) imaging[60] and electroretinography (ERG) recording[61] were performed to assess retinal structure and function, respectively.

The method's validity was confirmed since the retinas of all vehicle-treated mice showed severe LIRD (Fig. 5; Supplementary Figure 2). As measured from the OCT images, the outer nuclear layer (ONL) thickness, a readout of mouse rod photoreceptor population, was reduced from baseline mean at 55.6 µm to 0 µm as a result of LIRD. ERG a- and b-wave amplitudes, representing primarily rod photoreceptor and ONL bipolar cell population activation,[62] respectively, were significantly attenuated across a large range of light intensities used for stimulation (Supplementary Figures 3 and 4). We used bromocriptine, an FDA-/EMA-approved semisynthetic ergot alkaloid drug, as a reference compound and positive control.[63] Bromocriptine has been shown to possess therapeutic properties in multiple neuropathological contexts, including amytrophic lateral sclerosis (ALS) and Alzheimer´s disease.[64,65] In our experiments, systemically administered bromocriptine (10 mg/kg) protected from ONL thinning by 70% (Fig. 5) and ERG a- and b-wave amplitude (at 10 cd·s/m^2 stimulus) deterioration also by 70% each (Fig. 6). At equal dose, (+)-lysergol, (+)-isolysergol, and isoDMT **18** protected against LIRD on average better than bromocriptine did (Figs. 5 and 6). In contrast, (–)-isolysergol was devoid of therapeutic efficacy, and (–)-lysergol showed only a minute ERG amplitude improvement (Fig. 6). Both (–)- and (+)-cycloclavines were approximately equally effective against LIRD as bromocriptine was, whereas **19** and **20** showed lower efficacy on average (Figs. 5 and 6). Notably, the OCT data obtained from treatments with cycloclavines and compounds **19** and **20** showed high variance of responses to treatments: some mice displayed LIRD damage equal to vehicle-treated mice whereas some mice were practically fully protected. The higher variance of responses with partially effective compounds, however, may be a characteristic of the LIRD model rather than arising from the compounds´ properties *per se*.

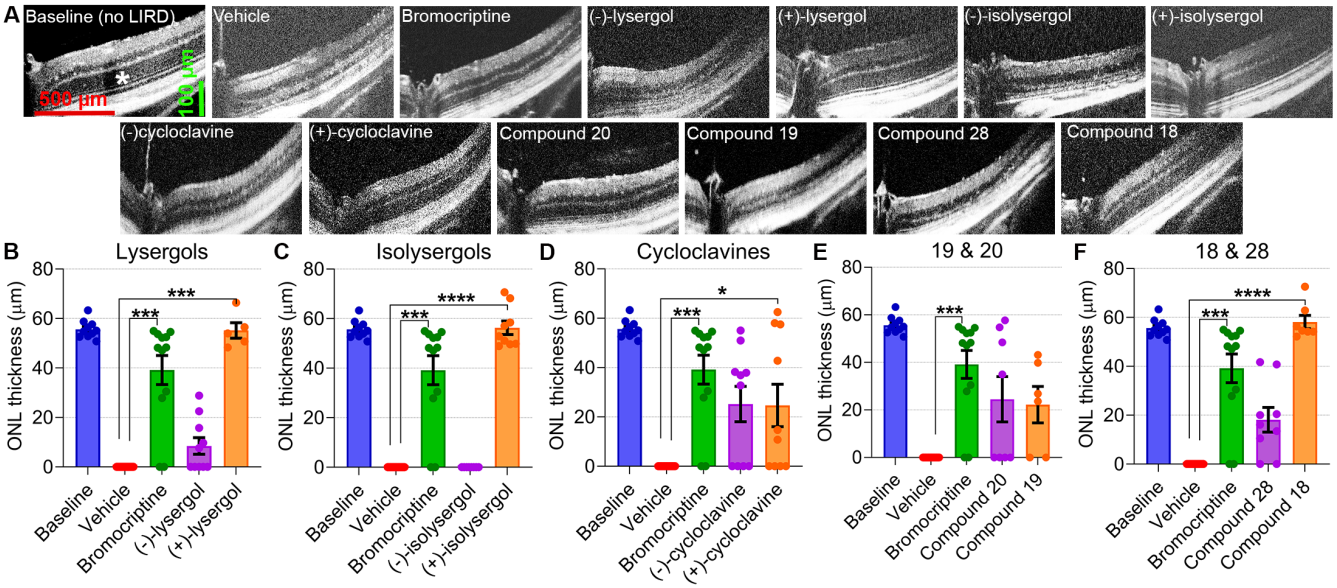


Figure 5. Systemically administered (+)-lysergol, (+)-isolysergol and **18** display strong protection against LIRD-associated photoreceptor death. A: Representative OCT images from each study group. Imaging was centered at the optic nerve head (ONH). ONL thickness was measured at 500 µm distance from the ONH border. Panels B-F display ONL thickness measurements (data averaged from superior, inferior, nasal, and temporal retinal quadrants) from experiments with lysergols (B), isolysergols (C), cycloclavines (D), **19** and **20** (E), and **18** and **28** (F), all contrasted with the data obtained from vehicle- and positive control(bromocriptine)-treatments, or baseline condition (*i.e.* BALB/c mouse retinas without LIRD). The statistical analysis was performed using the nonparametric K-W test followed by Dunn´s tests for multiple comparisons. The asterisks signify results from the Dunn´s tests: $^{*}P < 0.05$, $^{***}P < 0.001$, $^{***}P < 0.0001$. Data is presented as mean ± SEM.

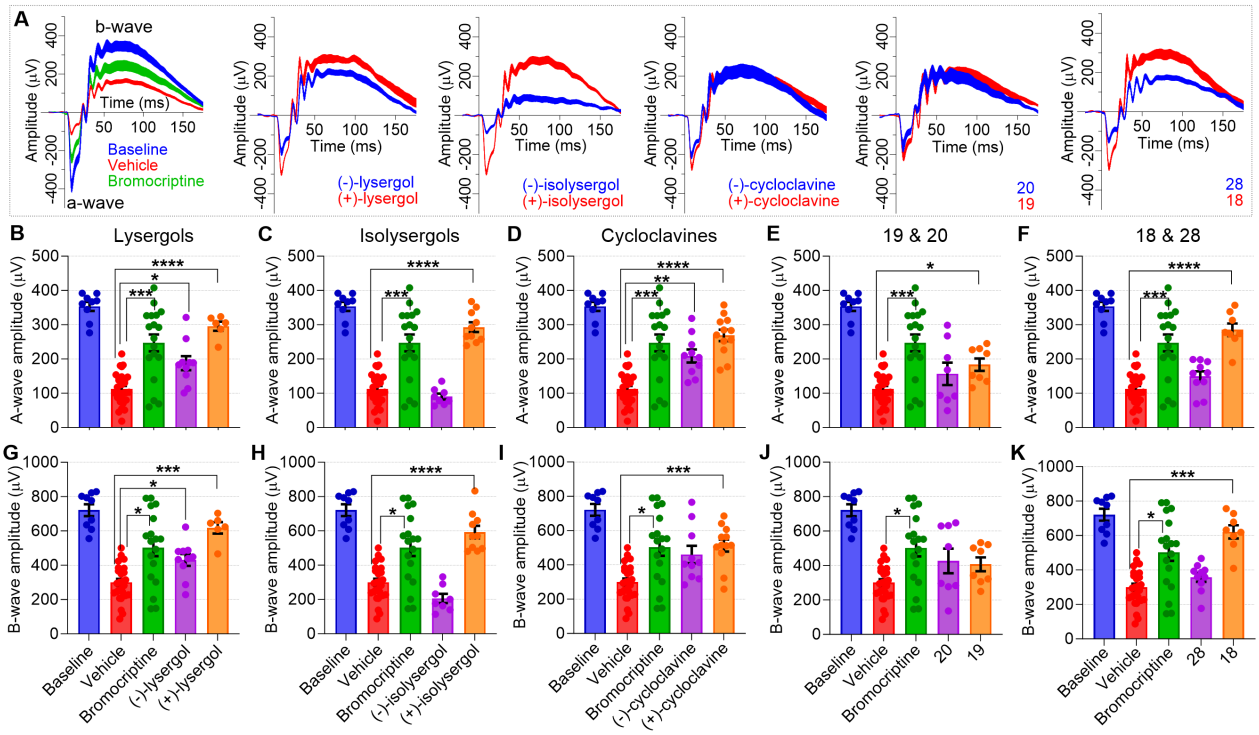


Figure 6. Retinal protection by (+)-lysergol, (+)-isolysergol and **18** leads to near normal ERG responses seven days after LIRD induction. For clarity, this figure presents ERG data from only 1 of 12 stimulation intensities used (10 cd·s/m^2); full stimulus intensity-amplitude graphs are presented in supplementary figure 4. Panel A shows group-averaged ERG waveforms from all study groups. Panels B-F and G-K display ERG a- (B-F) and b-wave (G-K) amplitudes, respectively, from experiments with lysergols (B, G), isolysergols (C, H), cycloclavines (D, I), **19** and **20** (E, J), and **18** and **28** (F, K). The data of study compounds is contrasted with the data obtained from the treatments with vehicle- and positive control (bromocriptine), or at baseline condition (no LIRD). The statistical analysis was performed by using the Welch´s ANOVA test followed by Dunnett´s T3 post hoc tests. The asterisks signify results from the post hoc tests: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. Data is presented as mean ± SEM.

In summary, we have synthesized several new isoDMT analogs with heterocyclic substitutions at the indole C(3) and tested representative analogs in a LIRD model for protection against retinal degeneration. The clavine alkaloids (+)-lysergol and (+)-isolysergol share strong agonistic activities at 5-HT$_{1A}$R and 5-HT$_{2C}$R[66] and demonstrate a similar high level of protection in the LIRD model, whereas (–)-lysergol and (–)-isolysergol are both inactive in the LIRD model and at 5-HT$_{2C}$R. However, (–)-isolysergol is quite potent as an agonist at 5-HT$_{1A}$R.[66] (+)-Lysergol is very potent at 5-HT$_{2A}$R, but (+)-isolysergol, (–)- and (+)-cycloclavines lack potency at this receptor as well as at 5-HT$_{2B}$R and have moderate to high potency at 5-HT$_{2C}$R.[66] The bridged scaffold **28** did not bind to 5-HT$_{1A,2A,2B,2C}$ receptors and was also inactive in the LIRD assay. Accordingly, the data suggest that activity at 5-HT$_{2C}$R likely drives the observed efficacy in the LIRD model. Interestingly, the structurally much simpler isoDMT **18** also demonstrates significant LIRD protective properties and therefore validates this scaffold for future investigations of its potential for therapeutic applications in retinal degeneration. Combined, these studies provide valuable insights into the role that serotonin receptors and their agonists play in ocular diseases and provide suitable lead compounds for further preclinical development.

ASSOCIATED CONTENT

Supporting Information

Experimental details and biological assay information.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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ABBREVIATIONS

5-HT, serotonin (5-hydroxytryptamine)
5-HTR, 5-hydroxytryptamine receptor
8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)-tetralin
ALS, amytrophic lateral sclerosis
AMD, age-related macular degeneration
ARPE-19, spontaneously arising retinal pigment epithelia cell line
cAMP, cyclic adenosine monophosphate
ARVO, Association for Research in Vision and Ophthalmology
BALB/c, Bagg albino c
DMT, dimethyltryptamine
ERG, electroretinography
FELASA, Federation of European Laboratory Animal Science Associations
GABA, γ-aminobutyric acid
GDP, guanosine diphosphate
GTP, guanosine triphosphate
HA, hydrogen autotransfer
IOP, intraocular pressure
isoDMT, *iso*-dimethyltryptamine
LIRD, light-induced retinal degeneration
MAO, monoamine oxidase
OCT, optical coherence tomography
ONL, outer nuclear layer
PKA, protein kinase A
RGC, retinal ganglion cell
ROS, reactive oxygen species
RP, retinitis pigmentosa
RPE, retinal pigment epithelium
SAR, structure-activity relationship

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