Supplemental material

Systems Pharmacology Approach to Prevent Retinal Degeneration in Stargardt Disease

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Supplemental Table 1. Expression of GPCRs in the eye and retina of C57BL/6J mice and the retina of a human donor eye (normalized FPKM values)[A].

Genes	B6 mouse eye	B6 mouse retina	Human retina
Rho	6162.04	11630.18	6896.09
Rgr	355.74	97.66	123.98
Opn1sw	125.13	198.54	31.69
Drd4	93.84	241.78	139.49
Opn1mw	62.97	95.77	172.56
Gprc5b	29.82	12.95	22.85
Gpr162	29.37	73.32	46.29
Gpr37	28.47	41.28	66.65
Ednrb	22.27	1.94	5.77
Rorb	21.69	23.52	24.31
Gpr153	20.42	37.18	15.31
Gabbr1	19.78	40.24	35.38
Rrh	19.29	9.23	40.34

Gpr152	18.55	40.46	3.05
Adora1	16.20	18.26	13.55
Lphn1	15.98	29.73	31.85
Tm2d1	15.56	10.31	17.63
Cxcr7	14.30	3.58	2.37
Ppard	13.68	19.37	21.61
Agtrap	13.64	17.21	8.18
Cd97	12.93	1.77	1.55
Gpr19	12.21	8.45	1.11
Fzd1	11.99	3.29	7.35
Fzd6	11.34	1.85	2.76
Gpr87	11.34	0.04	0.00
Lgr4	11.09	9.50	18.07
Drd2	10.82	23.10	26.33
Smo	10.75	6.35	5.91
S1pr1	10.66	11.21	11.78
Bai1	10.08	27.10	10.82

Glp2r	9.94	34.85	0.31
Ptger1	9.59	14.88	0.94
Gpr124	9.56	8.94	19.82
F2r	9.31	5.32	0.15
Adra2c	8.96	7.17	2.38
Gpr146	8.91	7.49	6.17
Vipr2	8.79	14.33	10.69
Fzd5	8.69	10.01	7.73
Gpr110	8.59	0.08	0.02
Adrb1	8.43	20.18	3.84
S1pr3	8.42	6.95	3.56
Gabbr2	7.80	17.03	10.57
Lphn2	7.66	9.02	8.79
Lpar1	7.47	0.91	0.45
P2ry2	7.20	0.62	2.29
Adrb2	7.13	1.03	0.98
Hrh3	7.11	19.12	3.75

Bai2	6.81	15.34	14.64
Gpr143	6.80	1.25	0.80
Celsr2	6.53	7.26	10.80
Fzd7	6.34	1.88	2.51
Drd1a	6.15	9.49	8.45
Adora2b	6.09	2.53	3.83
Celsr3	5.82	20.00	9.87
Fzd4	5.39	4.28	0.43
Gprc5c	5.26	2.13	3.13
Gpr56	5.12	4.31	2.92
Npr3	5.10	0.72	0.44
Tacr3	4.95	4.63	2.36
Grm8	4.77	6.43	2.04
Ramp1	4.68	1.39	5.25
Adra2a	4.60	9.91	0.25
Gpr85	4.56	5.72	2.70
Lphn3	4.22	6.49	2.90

Htr3a	4.14	2.54	0.00
Bai3	3.92	6.01	1.91
Fzd2	3.89	0.79	3.24
Fzd10	3.86	6.31	0.36
Gpr98	3.79	7.30	3.64
Tacr1	3.72	2.06	0.95
Gpr158	3.72	5.07	3.58
Fzd8	3.56	3.26	15.06
Opn4	3.35	2.94	1.11
Tshr	3.24	1.55	0.00
S1pr2	3.20	1.13	0.63
Mrgprf	3.18	0.64	0.80
Oprl1	3.15	4.42	0.81
F2rl1	3.13	0.24	2.58
S1pr5	3.12	0.48	0.01
Gpr135	3.07	8.35	1.99
Crhr1	3.02	6.49	12.76

Eltd1	3.00	1.65	0.51
Mrgpre	2.96	2.80	1.74
Gpr27	2.92	3.88	8.45
Ednra	2.87	0.52	0.16
Grm4	2.86	4.93	3.10
Emr1	2.60	0.22	0.03
Opn3	2.55	1.38	2.62
Cnr1	2.41	2.97	0.48
Grm7	2.39	3.95	1.16
Gpr37l1	2.39	0.96	7.73
Grm1	2.27	3.52	4.97
Crhr2	2.24	1.12	4.34
P2ry14	2.23	0.59	0.00
Gpr176	2.21	3.43	4.23
Celsr1	2.18	0.24	0.57
Gpr22	2.17	1.74	0.61
Lgr5	2.10	4.08	0.33

Gpr26	2.06	3.96	0.32
Agtr2	2.02	0.07	0.01
Gpr68	2.02	1.33	0.47
Calcrl	2.02	0.31	0.10
Cckbr	2.00	3.94	0.21
Gpr75	1.92	2.74	10.70
P2ry1	1.91	1.06	4.43
Chrm2	1.89	1.98	0.55
Fzd3	1.86	2.98	6.25
Grm5	1.83	2.19	1.57
Adcyap1r1	1.81	1.50	2.86
Htr1b	1.80	3.99	0.80
Cx3cr1	1.79	0.90	2.05
Gpr4	1.74	1.15	0.30
P2ry6	1.73	0.25	0.79
Adra1d	1.72	3.83	0.08
Tbxa2r	1.72	0.44	0.20

Gpr61	1.66	3.41	3.81
Sstr2	1.66	3.01	3.56
Chrm3	1.64	2.46	0.96
Sstr4	1.64	0.55	0.04
Adra1b	1.60	1.62	1.12
Cmklr1	1.60	0.27	0.24
Chrm1	1.53	1.54	0.34
Htr1d	1.49	2.58	0.00
Cxcr4	1.42	0.71	2.65
Kiss1r	1.37	2.59	0.87
C5ar1	1.35	0.12	3.01
Mc1r	1.32	2.05	5.65
Ptgfr	1.32	0.06	0.12
Fzd9	1.30	1.86	1.39
Ptgir	1.20	0.38	0.17
Hcrtr1	1.19	2.00	0.18
Ccrl2	1.16	0.27	0.07

P2ry12	1.16	0.54	0.34
Gpr12	1.15	1.94	6.01
Gpr173	1.13	1.77	5.26
Gpr88	1.11	1.78	0.91
Chrm4	1.10	0.78	7.70
Galr2	1.08	0.59	0.00
Cysltr1	1.07	0.02	0.12
Lepr	1.06	0.03	0.56
Gpr161	1.05	0.99	1.54
Oxtr	1.02	0.72	1.60
Gpr64	1.01	0.17	0.26
Gpr157	0.95	1.05	0.61
Drd5	0.90	1.66	2.26
Gpr182	0.87	1.28	0.11
Rxfp3	0.76	1.09	0.00
Nmbr	0.72	1.16	0.61
Grik3	0.70	1.24	4.18

Ccr10	0.68	1.47	5.60
Gpr156	0.67	1.16	0.43
Tas1r3	0.64	1.15	0.95
Gpr3	0.60	1.33	1.91
Tas1r1	0.59	1.76	0.27
Gpr84	0.43	1.59	1.89

[A]Analyses were done as described in Materials and Methods. Transcriptome data were used to determine reads per kilobase of gene product per million reads (RPKM) for normalization and differential expression analyses. Higher expression values in the retina relative to the eye indicate their enrichment in retina. Such high values highlight those GPCRs that may be critical in the eye and retina for drug discovery and therapeutic approaches. Both processed and raw fastq files for transcriptome analyses were deposited in GEO (accession numbers GSE29752 and GSE38359).

Supplemental Table 2. Summary of pharmacologic agents targeting multiple GPCRs examined in the *Abca4*$^{-/-}$ *Rdh8*$^{-/-}$ mouse bright light-induced retinopathy model[A].

Name	**Major action**	**Efficacy**	**Dose per kg BW**	**Brand name/ Application**
Agomelatine	melatonergic receptor agonist; 5-HT_{2C}R antagonist	50%	25 mg	
Nefazodone	5-$HT_{2A, 2C}$R antagonist	100%	30 mg	Serzone/ antidepressant
Eltoprazine	5-$HT_{1A/1B}$R agonist; 5-HT_{2C}R agonist	20%	10 mg	
Cyproheptadine	5-HT_2R antagonist, inverse agonist	0%	20 mg	
Pizotifen	5-HT_2R antagonist	75%	10 mg	Sandomigran/ migraine therapy
RS 23579-190	5-HT_4R	100%	20 mg	

	antagonist			
GR 125487	5-HT_4R antagonist	0%	10 mg	
RS 39604	5-HT_4R antagonist	0%	5 mg	
SB 203186	5-HT_4R antagonist	0%	5 mg	
RO 04-6790	5-HT_6R antagonist	100%	30 mg	Has nootropic effects, reduces amnesia
SB 399885	5-HT_6R antagonist	>25%	30 mg	
SGS 518 oxalate	5-HT_6R antagonist	>75%	30 mg	Useful for treating cognitive impairment associated with AD and schizophrenia
SB 269970	5-HT_7R, α2-AR antagonist	>75%	30 mg	Potentially useful for treating anxiety and depression; nootropic effect

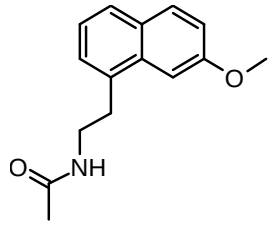
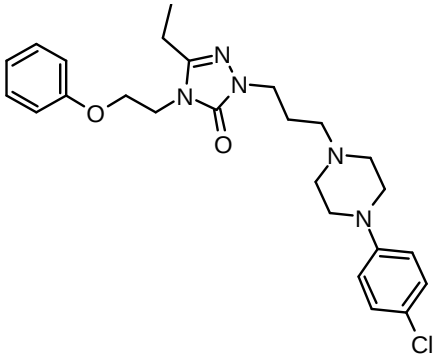
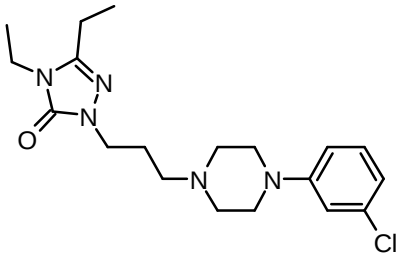
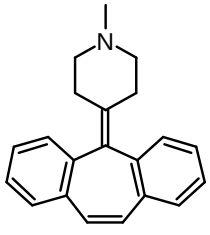
LY 215840	5-$HT_{7,2}$R antagonist	100%	10 mg	
Doxazosin	α1-AR antagonist	100%	10 mg	Cardura/ treatment of benign prostatic hyperplasia
Prazosin	α1-AR antagonist	75%	2 mg	Minipress/ hypertension treatment
Tamsulosin	α1-AR antagonist	75%	2 mg	Flomax/ treatment of benign prostatic hyperplasia
Phenoxybenzamine	α1,2-AR antagonist	0%	25 mg	
Phentolamine	α1,2-AR antagonist	0%	5 mg	
Guanabenz	α2-AR agonist	100%	2 mg	Wytensin/ hypertension treatment
Guanfacine	α2-AR agonist	100%	2 mg	Intuniv, Tenex/hypertension

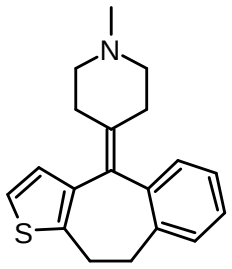
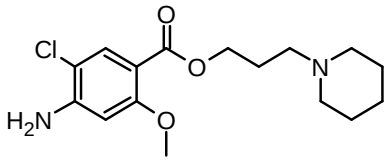
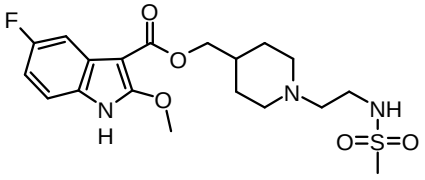
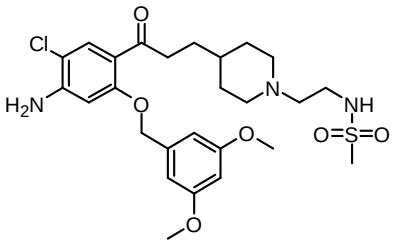
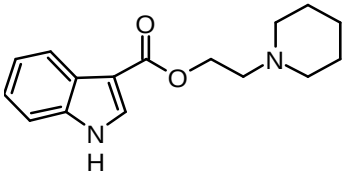
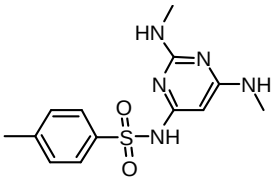
				treatment
Lofexidine	α2-AR agonist	100%	2 mg	Britlofex/Short-acting anti-hypertensive used to alleviate heroin and opiate withdrawal
Fexofenadine	H1 histamine receptor antagonist	50%	2 mg	
Tolterodine	muscarinic receptor antagonist	50%	20 mg	
ABT-724	dopamine D4 receptor agonist	0%	2 mg	
PD-168,077	dopamine D4 receptor agonist	60%	10 mg	
Yohimbine	antagonist at multiple receptors	toxic	25 mg	

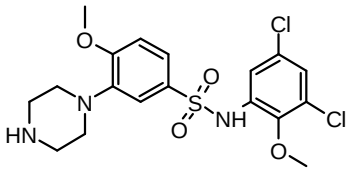
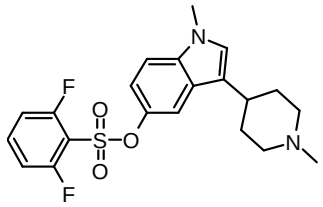
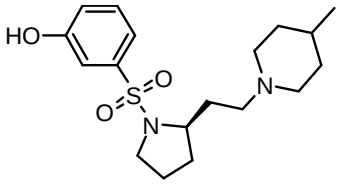
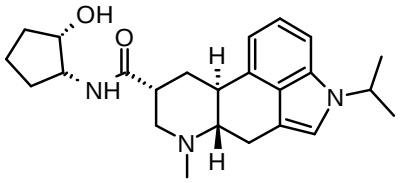
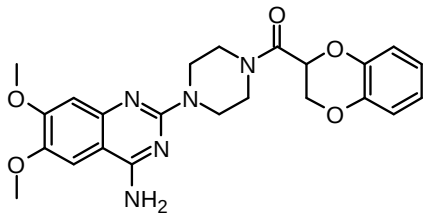
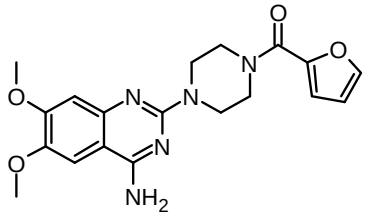
SQ 22536	AC inhibitor	100%	0.5 mg	

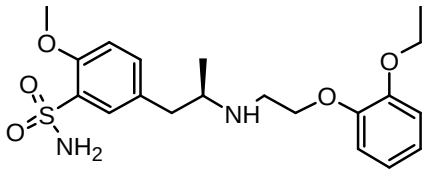
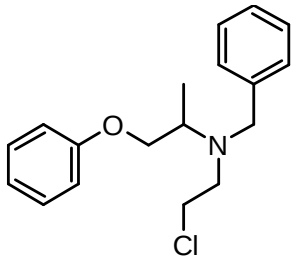
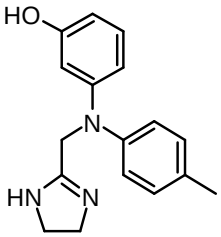
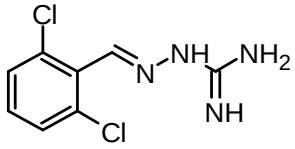
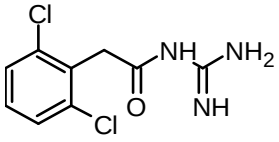
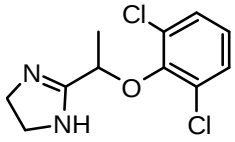
[A]Various pharmacologic agents targeting multiple classes of GPCRs were examined for their effects on bright light-induced retinopathy in 4 to 5-week-old *Abca4*$^{-/-}$*Rdh8*$^{-/-}$ mice. The name, major mechanism of action, efficacy (% of mice manifesting well-preserved retinal structure revealed by OCT imaging), dose and current clinical applications are indicated.

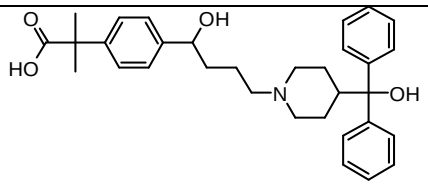
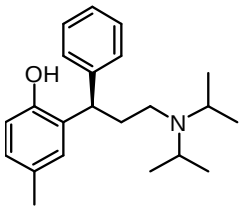
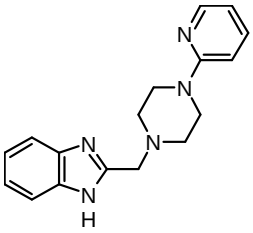
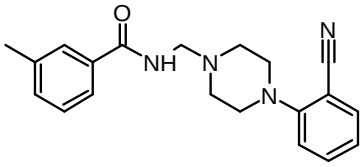
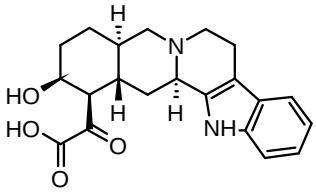
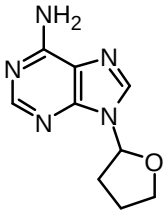
Supplemental Table 3. Chemical structure of the pharmacologic agents coupling with multiple GPCRs examined in the *Abca4*$^{-/-}$*Rdh8*$^{-/-}$ mouse bright light-induced retinopathy model.

Name	**GPCR coupling**	**Chemical structure**
Agomelatine (1, 2)	melatonin receptor 1; melatonin receptor 2; 5-HT_{2C}R	
Nefazodone (3-5)	5-$HT_{2A,C}$R (primary); 5-HT_{1A}R (moderate); α1-AR (moderate);	
Eltoprazine (6, 7)	5-$HT_{1A/1B}$R; 5-HT_{2C}R	
Cyproheptadine (8-10)	H1 histamine receptor; 5HT_2R; dopamine D3 receptor	

Pizotifen (11-13)	5-$HT_{2A, 2C}$R	
RS 23579-190 (14)	5-HT_4R	
GR 125487 (15, 16)	5-HT_4R	
RS 39604 (17)	5-HT_4R	
SB 203186 (18)	5-HT_4R	
RO 04-6790 (19-21)	5-HT_6R	

SB 399885 (22)	5-HT_6R	
SGS 518 oxalate (23, 24)	5-HT_6R	
SB 269970 (25, 26)	5-HT_7R, α2-AR	
LY 215840 (27, 28)	$5HT_{2/7}$R	
Doxazosin (29)	α1-AR	
Prazosin (30, 31)	α1-AR, α2B-AR; melatonin MT_3 receptor	

Tamsulosin (32, 33)	α1-AR	
Phenoxybenzamine (34)	AR	
Phentolamine (35)	AR	
Guanabenz (36, 37)	α2-AR	
Guanfacine (38)	α2-AR	
Lofexidine (39, 40)	α2-AR	
Fexofenadine (41, 42)	H1 histamine receptor	

		
Tolterodine (43)	muscarinic receptor 1-5	
ABT-724 (44)	dopamine D4 receptor	
PD-168,077 (45)	dopamine D4 receptor	
Yohimbine (46)	α2, α1-AR	
SQ 22536 (47, 48)		

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