MOL #68106

Molecular Pharmacology

SUPPLEMENTAL DATA

Histidine 6.55 is a major determinant of ligand biased signaling in dopamine D_{2L} receptor

Nuska Tschammer, Stefan Bollinger, Terry Kenakin, Peter Gmeiner

Supplemental Scheme 1: Reaction conditions: (i) 3-bromopropionitrile, K_2CO_3, NaI, MeCN, reflux 20 h (49%); (ii) Et_2O, $LiAlH_4$, 0^oC to rt, 1 h (64%), (iii) pyrazol[1,5-a]pyridine-3-carboxylic acid, CH_2Cl_2, DIPEA, TBTU, 0^oC to rt, 2 h (77%). **Synthesis: 3-[4-(2,3-Dihydro-benzofuran-7-yl)-piperazin-1-yl]-propionitrile (2)** To a solution of 4-(2,3-dihydro-benzofuran-7-yl)-piperazine (Kerrigan et al., 1998) (**1**, 482.0 mg, 2.36 mol) and 3-bromo-propionitrile (0.23 mL, 2.75 mmol) in acetonitrile (13.5 mL) potassium carbonate (663.1 mg, 4.80 mmol) and sodium iodide (58.7 mg, 0.39 mmol) were added and the mixture was heated to reflux. After 20 h, the solvent was removed in vacuo, then H_2O and methylene chloride were added. After dissolution of the residue, the organic layer was separated, dried with $MgSO_4$ and the solvent was removed *in vacuo*. The residue was dissolved in hexane under reflux conditions; subsequently the brown residue was removed by filtration. Cooling to room temperature and collection of the precipitate afforded **2** (296.0 mg, 49%) as a light grey solid. The material was used for the following reaction without further purification. ^1H

NMR (600 MHz) δ 2.56 (t, J = 7.1 Hz, 2H), 2.68-2.73 (m, 4H), 2.78 (t, J = 7.1 Hz, 2H), 3.15-3.20 (m, 4H), 3.22 (t, J = 8.7 Hz, 2H), 4.61 (t, J = 8.7 Hz, 2H), 6.71 (dd, J = 7.7 Hz, 1H), 6.82 (dd, J = 7.7, 7.4 Hz, 1H), 6.88 (dd, J = 7.4, 0.8 Hz, 1H). **3-[4-(2,3-Dihydro-benzofuran-7-yl)-piperazin-1-yl]-propylamine (3)** A solution of **2** (240 mg, 0.93 mol) in diethyl ether (10 mL) was cooled in an ice bath and then a $LiAlH_4$ solution in diethyl ether (2 mL, 2 mmol) was added. The solution was allowed to warm to rt and after 1 h, the solution was again cooled down in an ice bath and a saturated aqueous solution of sodium hydrogen carbonate (0.8 mL) was added. The solution was filtered through a layer consisting of celite/$MgSO_4$/celite and the solvent was removed in vacuo to afford **3** (155.6 mg, 64%) as a brownish solid. The material was used for the following reaction without further purification. ^{1}H NMR (600 MHz) δ 1.67-1.82 (m, 2H), 2.46-2.57 (m, 2H), 2.62-2.72 (m, 4H), 2.81-2.92 (m, 4H), 3.12-3.30 (m, 6H), 4.62 (t, J = 8.6 Hz, 2H), 6.70-6.76 (m, 2H), 6.79-6.85 (m, 2H), 6.86-6.91 (m, 2H). **{3-[4-(2,3-dihydro-benzofuran-7-yl)-piperazin-1-yl]-propyl}-pyrazol[1,5-a]pyridine-3-carboxamide (FAUC350)** To a solution of pyrazol[1,5-a]pyridine-3-carboxylic acid (89.2 mg, 0.550 mol) in methylene chloride (18 mL) *N,N*-diisopropyl-*N*-ethylamine (0.53 ml, 3.096 mmol) was added and the mixture was cooled to 0 °C. A solution of TBTU (173.4 mg, 0.540 mmol) in DMF (1.6 mL) was added and the mixture was allowed to warm to rt. Subsequently, a solution of **3** (145.0 mg, 0.550 mmol) in methylene chloride (1.5 mL) was added and the reaction mixture was stirred for 2 h. Thereafter, the solution was washed with a saturated $NaHCO_3$ solution and the aqueous layer was reextracted with methylene chloride. The combined organic layers were washed with a sat. NaCl solution, dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by flash column chromatography (methylene chloride / MeOH 95:5) afforded **FAUC350** (171.7 mg, 77%) as a white brown solid; IR (film, NaCl) 3316, 2942, 1637, 1621 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.77 (tt, J = 6.0, 6.0 Hz, 2H), 2.55 (t, J = 6.0 Hz, 2H), 2.59-2.67 (m, 4H), 3.09-3.17 (m, 4H), 3.13 (t, J = 8.7 Hz, 2H), 3.54 (dt, J = 6.0, 6.0 Hz, 2H), 4.52 (t, J = 8.7 Hz, 2H), 6.63 (dd, J = 7.5,

1.2 Hz, 1H), 6.74 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.80 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.82 (ddd, *J* = 7.0, 7.0, 1.1 Hz, 1H), 7.25 (ddd, *J* = 8.9, 7.0, 1.1 Hz, 1H), 7.47 (t, *J* = 6.0 Hz, 1H), 8.12 (s, 1H), 8.26 (ddd, *J* = 8.9, 1.1, 1.1 Hz, 1H), 8.39 (ddd, *J* = 7.0, 1.1, 1.1 Hz, 1H); EIMS 405 [M^+]; HR-EIMS calcd for $C_{23}H_{27}N_5O_2$ [M^+] 405.2165; found: 405.2164; purity: S1: >99% (t_r: 15.3 min); S2: >99% (t_r: 15.1 min).

Reference:

Kerrigan F, Martin, C. and Thomas G H (1998) Synthesis of arylpiperazines *via p*alladium-catalysed aromatic amination reactions of bromoarenes with *N-tert-butoxycarbonylpiperazine*. *Tetrahedron Lett.* **39**, 2219-2222.

Supplemental Table 1. pK_i values for the dopamine receptor antagonists and agonists on D_{2L} wild type and D_{2L} His393$^{6.55}$Lys receptor. The affinities of investigated substances were determined on membrane preparations of stably transfected CHO cells expressing either D_{2L} wild type, D_{2L} His393$^{6.55}$Ala or D_{2L} His393$^{6.55}$Phe receptor using [^{3}H]spiperone displacement study. Data are derived from normalized curves of 3-6 experiments done in triplicate. Data were analyzed by non-regression and were best fit to one-site (monophasic) or two-site (biphasic) competition curves. p*Ki* values were calculated according to Cheng and Prusoff (1973). [b] SEM. [c] Hill slope. [d] Fraction of high-affinity sites.

Supplemental Table 2: The *p*EC_{50} values and the efficacies for the inhibition of cAMP accumulation mediated by D_{2L} wild type, D_{2L} His393$^{6.55}$Ala and D_{2L} His393$^{6.55}$Phe. The cells were incubated with 20 µM forskolin and the D_{2L} wild type, D_{2L} His393$^{6.55}$Ala and D_{2L} His393$^{6.55}$Phe receptor mediated inhibition of cAMP accumulation was measured after the stimulation with investigated compounds. Pooled data of three to nine experiments performed in triplicate are shown as mean values ± SEM; n.a. – not available

Supplemental Table 3. The *p*EC_{50} values and the efficacies for the stimulation of ERK1/2 phosphorylation mediated by D_{2L} wild type, D_{2L} His393$^{6.55}$Ala and D_{2L} His393$^{6.55}$Phe. Serum-starved cells expressing D_{2L} wild type, D_{2L} His393$^{6.55}$Ala and D_{2L} His393$^{6.55}$Phe receptor were stimulated with investigated compounds for 5 min at 37^{o}C. The level of phosphorylated ERK1/2 was detected by ELISA. Pooled data of three to four experiments are shown as mean values ± SEM. Legend: n.a. – not available, n.d. – not done

Supplemental Table 4: Log(τ/K_A), Δ log(τ/K_A) and biased values for the inhibition of cAMP accumulation and the stimulation of ERK1/2 phosphorylation by D_{2L} wild type. s_{pooled} = 0.1861, degree of error = 41, T = 2.01954 (for one tail, 0.975), [a] 95% confidence interval, n.a. – not available, the compound was an antagonist

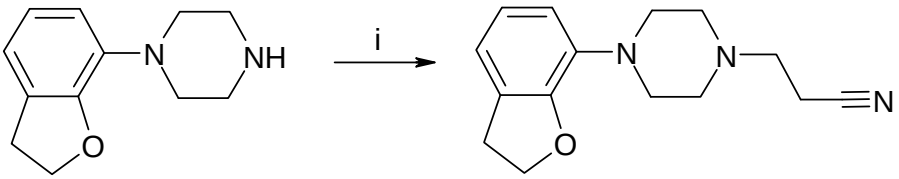
Supplemental Table 5: Log(τ/K_A), Δ log(τ/K_A) and biased values for the inhibition of cAMP accumulation and the stimulation of ERK1/2 phosphorylation by D_{2L} His393$^{6.55}$Ala. s_{pooled} = 0.2415, degree of error = 49, T =2.00958 (for one tail, 0.975), [a] 95% confidence interval.

Supplemental Table 6: Log(τ/K_A), Δ log(τ/K_A) and biased values for inhibition of cAMP accumulation by D_{2L} wild type and D_{2L} His393$^{6.55}$Ala. s_{pooled} = 0.250, degree of error = 52, T = 2.00665 (for one tail, 0.975), [a] 95% confidence interval, n.a. – not available, the compound was an antagonist

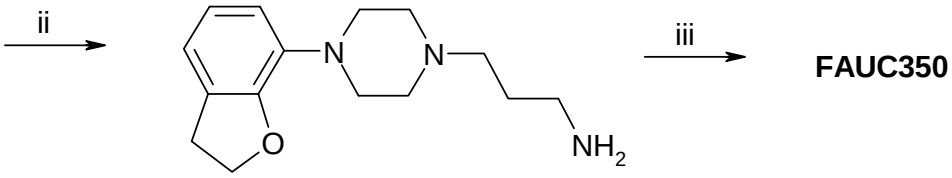
Supplemental Table 7: Log(τ/K_A), Δ log(τ/K_A) and biased values for the stimulation of ERK1/2 phosphorylation by D_{2L} wild type and D_{2L} His393$^{6.55}$Ala. s_{pooled} = 0.164, degree of error = 38, T = 2.02439 (for one tail, 0.975), [a] 95% confidence interval.

Supplemental Figure 1: The short-term stimulus of the D_{2L} wild type, D_{2L} His393$^{6.55}$Ala and D_{2L} His393$^{6.55}$Phe receptor fuels only the pertussis toxin sensitive $G_{i/o}$ protein mediated stimulation of ERK1/2 phosphorylation. Cells incubated over night in the serum free media with and without pertussis toxin (PTX, 25 ng/mL) were stimulated with 1 μM of selected compounds for 5 min at 37^{o}C. The level of phosphorylated ERK1/2 was detected by ELISA. The mean values with error bars representing the SEM of three to four experiments are shown.

Supplemental Scheme 1



1 **2**

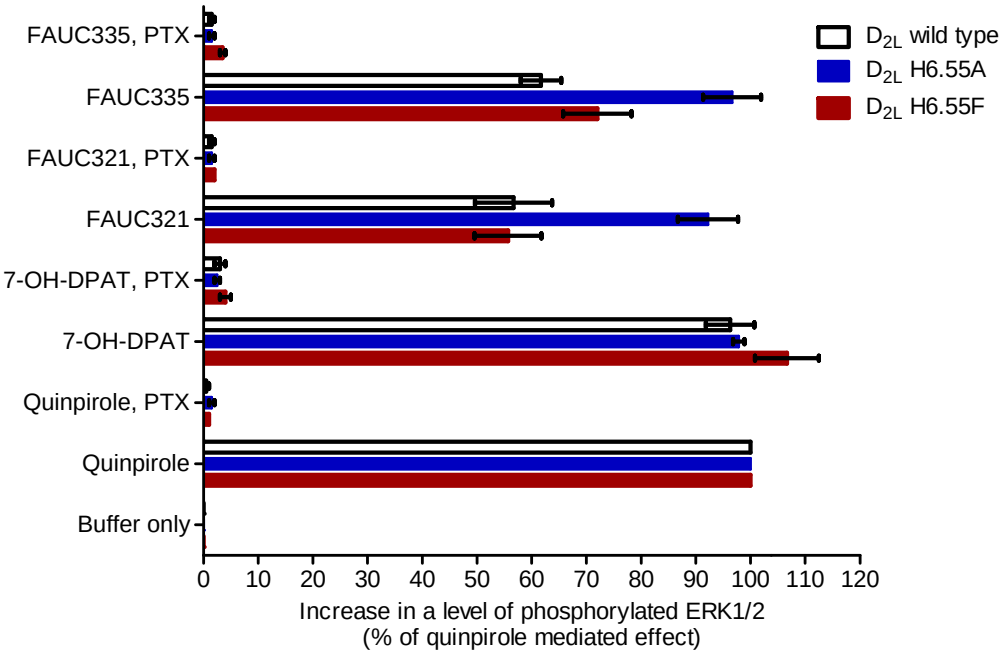


3

Supplemental Table 1

Compound	pK_i measured	pK_i for D_{2L} wild type	pK_i for D_{2L}His393$^{6.55}$Lys
FAUC335	$pK_{0.5}$	8.85 ± 0.04[b] *(-0.71)*[c]	9.17 ± 0.05 [b] (-0.83) [c]
FAUC321	$pK_{0.5}$	8.43 ± 0.03[b] *(-0.89)*[c]	8.33 ± 0.04 [b] (-1.05) [c]
FAUC350	$pK_{0.5}$	7.41 ± 0.03[b] (*-0.92*)[c]	8.26 ± 0.06 [b] (-0.92) [c]
Dopamine	$pK_{0.5}$	6.35 ± 0.05[b] *(-0.43)*[c]	5.32 ± 0.09 [b] (-0.67) [c]
	pK_{high}	8.08 ± 0.12[b] (*31%)*[d]	6.58 ± 0.45 [b] (19%) [d]
	pK_{low}	5.70 ± 0.09[b]	4.45 ± 0.09 [b]
Quinpirole	$pK_{0.5}$	6.21 ± 0.04[b] (*-0.44*)[c]	5.51 ± 0.14 [b] (-0.51) [c]
	pK_{high}	7.89 ± 0.12[b] *(31%)*[d]	7.71 ± 0.44 [b] (25%) [d]
	pK_{low}	5.68 ± 0.08[b]	5.18 ± 0.21 [b]

Supplemental Figure 1



Supplemental Table 2

	D_{2L} Wild Type		D_{2L} His393$^{6.55}$Ala		D_{2L} His393$^{6.55}$Phe	
Compound	*pEC$_{50}$*	Efficacy (%)	*pEC$_{50}$*	Efficacy (%)	*pEC$_{50}$*	Efficacy (%)
Quinpirole	8.24 ± 0.09	100	6.60 ± 0.10	100	7.55 ± 0.08	100
Dopamine	7.72 ± 0.10	111 ± 5	6.26 ± 0.11	101 ± 4	7.06 ± 0.23	97 ± 8
7-OH-DPAT	8.64 ± 0.11	84 ± 4	7.71 ± 0.12	84 ± 4	7.86 ± 0.13	81 ± 4
Aripiprazole	7.49 ± 0.15	62 ± 5	6.79 ± 0.20	47 ± 4	8.15 ± 0.94	-5 ± 3
FAUC335	7.94 ± 0.19	46 ± 4	6.70 ± 0.16	40 ± 3	6.18 ± 0.39	8 ± 4
FAUC321	8.09 ± 0.17	35 ± 2	8.17 ± 0.26	41 ± 3	6.56 ± 0.92	-6 ± 3
FAUC350	n.a	0	8.03 ± 0.24	41 ± 4	5.94 ± 0.61	10 ± 4
FAUC346	7.77 ± 0.64	4 ± 1	7.69 ± 0.30	10 ± 1	5.74 ± 0.39	-34 ± 5
CPD1	n.a	0	7.88 ± 0.20	54 ± 5	6.21 ± 0.38	-28 ± 5
Haloperidol	8.68 ± 0.27	-8 ± 1	8.66 ± 0.74	-2 ± 1	8.20 ± 0.24	-18 ± 2
Buspirone	8.50 ± 0.57	-7 ± 2	7.91 ± 0.49	-3 ± 1	8.14 ± 0.42	-15 ± 2

Supplemental Table 3

	D_{2L} Wild Type		D_{2L} His393$^{6.55}$Ala		D_{2L} His393$^{6.55}$Phe	
Compound	*pEC$_{50}$*	Efficacy (%)	*pEC$_{50}$*	Efficacy (%)	Conc. (nM)	Efficacy (%)
Quinpirole	8.37 ± 0.05	100	7.37 ± 0.07	100	10 000	100
Dopamine	7.76 ± 0.11	106 ± 4	6.45 ± 0.10	98 ± 4	10 000	101 ± 7
7-OH-DPAT	9.04 ± 0.08	98 ± 2	8.22 ± 0.07	94 ± 3	10 000	107 ± 6
Aripiprazole	6.96 ± 0.17	62 ± 5	7.23 ± 0.10	79 ± 3	1000	78 ± 8
FAUC335	7.45 ± 0.11	68 ± 4	7.66 ± 0.09	99 ± 5	1000	72 ± 6
FAUC321	8.41 ± 0.14	55 ± 4	8.22 ± 0.07	94 ± 3	1000	56 ± 6
FAUC350	7.46 ± 0.10	55 ± 3	8.13 ± 0.11	90 ± 4	1000	75 ± 3
FAUC346	6.93 ± 0.33	11 ± 2	7.55 ± 0.15	79 ± 6	1000	-9 ± 2
CPD1	6.51 ± 0.11	37 ± 3	7.00 ± 0.14	78 ± 6	1000	18 ± 3
Haloperidol	n.a.	0	n.a.	0	n.d.	n.d.
Buspirone	n.a.	0	n.a.	0	n.d.	n.d.

Supplemental Table 4

	Inhibition of cAMP accumulation				Stimulation of ERK1/2 phosphorylation				Bias calculation	
	N	Mean $\log(\tau/K_A)$	$s^2 \log(\tau/K_A)$	$\Delta\log(\tau/K_A)_{quin}$	N	Mean $\log(\tau/K_A)$	$s^2 \log(\tau/K_A)$	$\Delta\log(\tau/K_A)_{quin}$	Log Bias	Bias
Quinpirole	4	8.68 (8.46 – 8.90) [a]	0.061	0.00	3	8.41 (8.30 – 8.52) [a]	0.013	0.00	0.00	1
Dopamine	3	8.70 (8.48 – 8.92) [a]	0.049	0.02 (-0.26 – 0.30) [a]	4	8.62 (8.51 – 8.73) [a]	0.021	0.21 (-0.10 – 0.52) [a]	-0.19 (-0.61 – 0.23) [a]	0.6 (0.2 – 1.7) [a]
7-OH-DPAT	3	8.73 (8.51 – 8.95) [a]	0.016	0.05 (-0.26 – 0.36) [a]	3	9.17 (8.98 – 9.36) [a]	0.026	0.76 (0.45 – 1.07) [a]	-0.71 (-1.14 – -0.28) [a]	0.2 (0.1 – 0.5) [a]
Aripiprazole	3	7.16 (6.94 – 7.38) [a]	0.095	-1.52 (-1.83 – -1.21) [a]	3	6.67 (6.56 – 6.78) [a]	0.036	-1.74 (-2.05 – -1.43) [a]	0.22 (-0.21 – 0.65) [a]	1.6 (0.6 – 4.5) [a]
FAUC335	4	7.13 (6.91 – 7.35) [a]	0.058	-1.55 (-1.86 – -1.24) [a]	3	7.29 (7.18 – 7.40) [a]	0.009	-1.12 (-1.43 – -0.81) [a]	-0.43 (-0.86 – 0.00) [a]	0.4 (0.1 – 1) [a]
FAUC321	4	7.70 (7.52 – 7.88) [a]	0.040	-0.98 (-1.26 – -0.70) [a]	4	8.19 (8.08 – 8.30) [a]	0.005	-0.22 (-0.53 – 0.09) [a]	-1.20 (-1.62 – -0.78) [a]	0.2 (0.1 – 0.5) [a]
FAUC350	3	n.a	n.a.	n.a.	3	7.41 (7.30 – 7.52) [a]	0.018	-1.00 (-1.31 – -0.69) [a]	n.a.	n.a.
CPD1	3	n.a.	n.a.	n.a.	3	5.84 (5.73 – 5.95) [a]	0.003	-2.57 (-2.88 – -2.26) [a]	n.a.	n.a.
FAUC346	3	6.18 (5.96 – 6.40) [a]	0.047	-2.50 (-2.81 – -2.19) [a]	3	5.91 (5.80 – 6.02) [a]	0.021	-2.50 (-2.81 – -2.19) [a]	0 (-0.43 – 0.43) [a]	1 (0.4 – 2.7) [a]

Supplemental Table 5

	Inhibition of cAMP accumulation				Stimulation of ERK1/2 phosphorylation				Bias calculation	
	N	Mean $\log(\tau/K_A)$	$s^2 \log(\tau/K_A)$	$\Delta\log(\tau/K_A)_{quin}$	N	Mean $\log(\tau/K_A)$	$s^2 \log(\tau/K_A)$	$\Delta\log(\tau/K_A)_{quin}$	Log Bias	Bias
Quinpirole	6	6.69	0.039	0.00	3	7.36	0.001	0.00	0.00	1
		(6.49 – 6.89) [a]				(7.08 – 7.64) [a]				
Dopamine	7	6.75	0.018	0.06	3	6.45	0.001	-0.91	0.97	9.3
		(6.57 – 6.93) [a]		(-0.33 – 0.21) [a]		(6.17 – 6.73) [a]		(-1.30 – -0.52) [a]	(0.49 – 1.45) [a]	(3 – 28) [a]
7-OH-DPAT	3	7.55	0.075	0.86	3	7.71	0.065	0.35	0.51	3.2
		(7.27 – 7.83) [a]		(0.52 – 1.20) [a]		(7.43 – 7.99) [a]		(-0.04 – 0.74) [a]	(-0.01 – 1.03) [a]	(0.5 – 11) [a]
Aripiprazole	5	6.25	0.089	-0.44	3	6.91	0.049	-0.45	0.01	1
		(6.03 – 6.47) [a]		(-0.73 – -0.15) [a]		(6.63 – 7.19) [a]		(-0.84 – -0.06) [a]	(-0.48 – 0.50) [a]	(0.3 – 3.0) [a]
FAUC335	5	7.06	0.221	0.38	3	7.53	0.011	0.17	0.21	1.6
		(6.84 – 7.28) [a]		(0.09 – 0.67) [a]		(7.25 – 7.81) [a]		(-0.22 – 0.56) [a]	(-0.28 – 0.70) [a]	(0.5 – 5.0) [a]
FAUC321	5	7.78	0.072	1.09	3	8.26	0.023	0.90	0.19	1.6
		(7.56 – 8.00) [a]		(0.80 – 1.38) [a]		(8.07 – 8.79) [a]		(0.51 – 1.29) [a]	(-0.30 – 0.68) [a]	(0.5 – 4.8) [a]
FAUC350	3	7.21	0.005	0.52	3	8.40	0.024	1.04	-0.52	0.3
		(6.93 – 7.49) [a]		(0.18 – 0.86) [a]		(8.12 – 8.68) [a]		(0.65 – 1.43) [a]	(-1.04 – 0.00) [a]	(0.09 – 1) [a]
CPD1	3	7.59	0.019	0.90	3	6.78	0.085	-0.58	1.48	30
		(7.31 – 7.87) [a]		(0.56 – 1.24) [a]		(6.50 – 7.06) [a]		(-0.97 – -0.19) [a]	(0.96 – 1.97) [a]	(9.1 – 93) [a]
FAUC346	3	6.96	0.066	0.27	3	7.48	0.091	0.12	0.15	1.4
		(6.68 – 7.49) [a]		(-0.07 – 0.61) [a]		(7.20 – 7.76) [a]		(-0.27 – 0.51) [a]	(-0.37 – 0.67) [a]	(0.4 –4.7) [a]

Supplemental Table 6

	D_{2L} wild type				D_{2L} His393$^{6.55}$Ala				Bias calculation	
	N	Mean $\log(\tau/K_A)$	s^2 $\log(\tau/K_A)$	$\Delta\log(\tau/K_A)_{quin}$	N	Mean $\log(\tau/K_A)$	s^2 $\log(\tau/K_A)$	$\Delta\log(\tau/K_A)_{quin}$	Log Bias	Bias
Quinpirole	4	8.68	0.061	0.00	6	6.69	0.039	0.00	0.00	1
		(8.43 – 8.93) [a]				(6.48 – 6.90) [a]				
Dopamine	3	8.70	0.049	0.02	7	6.75	0.018	0.06	0.04	1
		(8.41 – 8.99) [a]		(-0.36 – 0.40) [a]		(6.56 – 6.94) [a]		(-0.22 – 0.34) [a]	(-0.43 – 0.51) [a]	(0.4 – 3) [a]
7-OH-DPAT	3	8.73	0.016	0.05	3	7.55	0.075	0.86	0.81	6
		(8.44 – 9.02) [a]		(-0.33 – 0.43) [a]		(7.26 – 7.84) [a]		(0.51 – 1.21) [a]	(0.29 – 1.33) [a]	(2 – 21) [a]
Aripiprazole	3	7.16	0.095	-1.52	5	6.25	0.089	-0.44	1.08	12
		(6.87 – 7.41) [a]		(-1.90 – -1.14) [a]		(6.03 – 6.47) [a]		(-0.79 – -0.09) [a]	(0.59 – 1.57) [a]	(4 – 37) [a]
FAUC335	4	7.13	0.058	-1.55	5	7.06	0.221	0.38	1.93	85
		(6.88 – 7.38) [a]		(-1.90 – -1.20) [a]		(6.84 – 7.28) [a]		(0.08 – 0.68) [a]	(1.47 – 2.39) [a]	(30 – 245) [a]
FAUC321	4	7.70	0.040	-0.98	5	7.78	0.072	1.09	2.07	117
		(7.45 – 7.95) [a]		(-1.33 – -0.63) [a]		(7.56 – 8.00) [a]		(0.79 – 1.39) [a]	(1.61 – 2.53) [a]	(41 – 339) [a]
FACU350	3	n.a.	n.a.	n.a.	3	7.21	0.005	n.a.	n.a.	n.a.
						(6.92 – 7.50) [a]				
CPD1	3	n.a.	n.a.	n.a.	3	7.59	0.019	n.a.	n.a.	n.a.
						(7.30 – 7.88) [a]				
FAUC346	3	6.18	0.047	-2.50	3	6.96	0.066	0.27	2.77	589
		(5.89 – 6.47) [a]		(-2.88 – -2.12) [a]		(6.67 – 7.50) [a]		(-0.08 – 0.62) [a]	(2.25 – 3.29) [a]	(178 – 1950) [a]

Supplemental Table 7

	D_{2L} wild type				D_{2L} His393$^{6.55}$Ala				Bias calculation	
	N	Mean $\log(\tau/K_A)$	s^2 $\log(\tau/K_A)$	$\Delta\log(\tau/K_A)_{quin}$	N	Mean $\log(\tau/K_A)$	s^2 $\log(\tau/K_A)$	$\Delta\log(\tau/K_A)_{quin}$	Log Bias	Bias
Quinpirole	3	8.41	0.013	0.00	3	7.36	0.001	0.00	0.00	1
		(8.22 – 8.60) [a]				(7.17 – 7.55) [a]				
Dopamine	4	8.62	0.021	0.21	3	6.45	0.001	-0.91	-1.12	0.08
		(8.45 – 8.79) [a]		(-0.04 – 0.46) [a]		(6.26 – 6.64) [a]		(-1.18 – -0.64) [a]	(-1.51 – -0.75) [a]	(0.03 – 0.18) [a]
7-OH-DPAT	3	9.17	0.026	0.76	3	7.71	0.065	0.35	-0.41	0.4
		(8.98 – 9.36) [a]		(0.49 – 1.03) [a]		(7.52 – 7.90) [a]		(0.08 – 0.62) [a]	(-0.79 – -0.03) [a]	(0.2 – 0.9) [a]
Aripiprazole	3	6.67	0.036	-1.74	3	6.91	0.049	-0.45	1.30	20
		(6.48 – 6.68) [a]		(-2.01 – -1.47) [a]		(6.72 – 7.10) [a]		(-0.72 – -0.18) [a]	(0.92 – 1.68) [a]	(8.3 – 48) [a]
FAUC335	3	7.29	0.009	-1.12	3	7.53	0.011	0.17	1.29	19.5
		(7.00 – 7.48) [a]		(-1.39 – -0.85) [a]		(7.34 – 7.72) [a]		(-0.10 – 0.44) [a]	(0.90 – 1.68) [a]	(7.9 – 48) [a]
FAUC321	4	8.19	0.005	-0.22	3	8.26	0.023	0.90	1.12	13.2
		(8.02 – 8.36) [a]		(-0.47 – 0.03) [a]		(8.07 – 8.79) [a]		(0.63 – 1.17) [a]	(0.75 – 1.49) [a]	(5.6 – 31) [a]
FAUC350	3	7.41	0.018	-1.00	3	8.40	0.024	1.04	2.04	110
		(7.22 – 7.60) [a]		(-1.27 – -0.73) [a]		(8.21 – 8.59) [a]		(0.77 – 1.31) [a]	(1.66 – 2.42) [a]	(46 – 263) [a]
CPD1	3	5.84	0.003	-2.57	3	6.78	0.085	-0.58	1.99	98
		(5.65 – 6.03) [a]		(-2.84 – -2.30) [a]		(6.59 – 6.97) [a]		(-0.85 – -0.31) [a]	(1.61 – 2.37) [a]	(40 – 234) [a]
FAUC346	3	5.91	0.021	-2.50	3	7.48	0.091	0.12	2.62	417
		(5.72 – 6.10) [a]		(-2.77 – -2.23) [a]		(7.29 – 7.67) [a]		(-0.15 – 0.39) [a]	(2.24 – 3.00) [a]	(174 – 1000) [a]