

Title: Probing the Metabotropic Glutamate Receptor 5 (mGlu5) Positive Allosteric Modulator (PAM) Binding Pocket: Discovery of Point Mutations that Engender a “Molecular Switch” in PAM Pharmacology

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Supplementary Table 1: Potency and operational model parameters for glutamate stimulated Ca^{++} mobilization at HEK293A-mGlu₅-wt and mutants in the absence and presence of MPEP. Data represent mean \pm s.e.m from 3-6 independent determinations performed in duplicate.

	pEC ₅₀ ^a	log τ _A ^b	n ^c	E _m ^d	basal ^e
R5-wt (poly)	6.49 \pm 0.09	0.52 \pm 0.04	3.7 \pm 1.0	101.5 \pm 5.3	0.6 \pm 2.5
F585I	6.31 \pm 0.09	0.37 \pm 0.06	4.0 \pm 0.7	109.6 \pm 3.8	0.8 \pm 0.7
R647A	6.11 \pm 0.17	0.13 \pm 0.12*	3.0 \pm 0.4	167.0 \pm 24.5	5.2 \pm 3.1
I650A	6.44 \pm 0.11	0.57 \pm 0.05	3.7 \pm 0.4	104.6 \pm 1.3	1.5 \pm 0.6
G651F	6.35 \pm 0.10	0.37 \pm 0.06	2.5 \pm 0.3	114.4 \pm 0.3	-3.0 \pm 2.9
P654S	6.41 \pm 0.03	0.46 \pm 0.01	3.1 \pm 0.3	100.1 \pm 1.7	0.2 \pm 1.7
P654F	6.48 \pm 0.03	0.44 \pm 0.02	3.2 \pm 0.3	106.5 \pm 7.9	3.3 \pm 1.3
S657C	6.36 \pm 0.07	0.41 \pm 0.04	2.4 \pm 0.3	111.2 \pm 3.7	0.9 \pm 1.2
Y658V	6.51 \pm 0.08	0.52 \pm 0.04	3.6 \pm 0.8	103.8 \pm 2.2	1.3 \pm 1.5
P742S	5.90 \pm 0.08*	0.19 \pm 0.05*	5.0 \pm 1.2	119.3 \pm 13.1	0.6 \pm 0.9
L743V	6.52 \pm 0.11	0.52 \pm 0.06	2.6 \pm 0.4	95.7 \pm 2.9	2.6 \pm 1.3
N746A	6.55 \pm 0.06	0.56 \pm 0.04	3.8 \pm 0.3	98.0 \pm 1.8	1.5 \pm 2.2
G747V	6.50 \pm 0.10	0.50 \pm 0.05	3.5 \pm 0.8	102.3 \pm 3.2	2.6 \pm 0.4
T779A	6.63 \pm 0.06	0.57 \pm 0.03	2.3 \pm 0.3	108.6 \pm 1.8	1.9 \pm 1.6
T780A	6.68 \pm 0.02	0.58 \pm 0.03	2.4 \pm 0.6	104.1 \pm 5.4	0.8 \pm 0.5
W784A	6.15 \pm 0.14	0.35 \pm 0.05	3.7 \pm 0.3	103.9 \pm 1.3	2.9 \pm 1.2
V788A	6.32 \pm 0.06	0.38 \pm 0.04	3.0 \pm 0.6	107.4 \pm 3.6	0.8 \pm 0.8
F792A	6.64 \pm 0.07	0.61 \pm 0.09	2.5 \pm 0.3	107.0 \pm 6.9	-0.4 \pm 0.9
S806A	6.66 \pm 0.04	0.58 \pm 0.05	2.0 \pm 0.2	102.4 \pm 4.5	3.2 \pm 0.2
S808A	6.76 \pm 0.08	0.71 \pm 0.07	3.0 \pm 0.5	101.8 \pm 0.5	1.5 \pm 0.8
S808T	6.72 \pm 0.06	0.71 \pm 0.06	2.8 \pm 0.2	103.1 \pm 1.6	1.0 \pm 1.1
A809V	6.28 \pm 0.23	0.38 \pm 0.07	3.0 \pm 0.6	110.1 \pm 4.9	-1.4 \pm 1.7
A809G	6.15 \pm 0.14	0.31 \pm 0.08	3.3 \pm 0.4	115.2 \pm 8.0	1.2 \pm 1.1
T810A	6.40 \pm 0.05	0.36 \pm 0.04	2.1 \pm 0.1	111.2 \pm 4.1	1.5 \pm 0.7
C815A	6.22 \pm 0.06	0.36 \pm 0.04	4.5 \pm 0.5	100.5 \pm 0.5	0.7 \pm 0.6

* denotes significantly different from wild type value, p<0.05, one-way ANOVA, Dunnett’s post-test.

^a negative logarithm of the concentration of agonist that elicits a half maximal response

^b logarithm of the coupling efficiency of glutamate.

^c the transducer function that links occupancy to response

^d the maximal possible system response

^e basal denotes the baseline level (ligand-independent) of the system response