Kainic acid-based agonists of glutamate receptors – SAR analysis and guidelines for analogs design

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Supporting Information

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1. Relative activity scale for kainoids

The literature values of binding, activity or affinity of KAR agonists are reported using a wide range of biochemical and biological assays. In order to compare the activity of kainic acid derivatives presented in different studies, a qualitative scale was established. Glutamate, kainic acid and domoic acid were set as benchmarks for this scale system.

Table S1. Qualitative scale of relative activity for kainoid analogs

Relative Activity (RA)	Grade	Notes
Inactive	--	Inactive
$0 < RA < 0.065$	-	Weaker than L-Glu, but active
$0.065 \leq RA < 1$	+	Between L-Glu and KA
$1 \leq RA < 2.89$	++	Between KA and DA
$2.89 \leq RA$	+++	Being equal as or stronger than DA

The activity of each compound was first normalized to the positive control used in a given study (typically, glutamic acid or kainic acid). Since the activity date were collected from various sources, which were obtained from different assays. Some assays are based on neuron activity, such as effects on neurons, which might be combined consequences of AMPARs and KARs. In this article, we are mainly interested in KARs, when a compound was tested in more than one assay, priority was given to data from KARs (eg. GluK2) binding assay (K_i or IC_{50}). Otherwise, data from [^{3}H]-KA displacement assays was used for calculations. If those data were not available, calculations were performed with the reported activity in neurons or in animal experiments. Data from those experiments might not be only the contribution of KARs. When multiple data were available for a single agonist, the most recent data is used.

Calculation methods:

1. Relative activity = K_i (or EC_{50}) of KA / K_i (or EC_{50}) of compounds

2. Relative activity = Effect of compounds / effect of KA

3. Relative activity (iso-DAs) = (K_i of DA / K_i of iso-DAs) * RA of DA (Ki of KA / Ki of DA)

2. Calculated relative activity values of kainoids

Table S2. **Relative activity values of kainic acid analogues.**

Compound	Relative activity (Relative to KA)	Activity Level	Ref.
Kainic acid (1) – Reference	1	++	1-18
Domoic acid (2)	2.89	+++	14
L-Glu (3)	0.065	+	12
4	Inactive	--	3
5a	Inactive	--	3
5b	Inactive	--	3
6	Inactive	--	2
7	Inactive	--	2
8a	Inactive	--	7
8b	Inactive	--	7
9a	Inactive	--	7
9b	Inactive	--	7
10	0.049	-	14
11	0.0063	-	7
12a	1	++	9
12b	Inactive	--	9
13	0.00063	-	7
14a	Inactive	--	5
14b	Inactive	--	5
15a	0.013	-	4
15b	0.00065	-	4
15c	Inactive	--	4
16a	Inactive	--	5
16b	Inactive	--	5
16c	Inactive	--	5
16d	Inactive	--	5
17	Inactive	--	9
18	Inactive	--	9
19	Inactive	--	9
20	0.68	+	9
21	Inactive	--	9
22	Inactive	--	11
23	Inactive	--	9
24a	Inactive	--	10
24b	Inactive	--	10
25a	0.22	+	8
25b	0.043	-	8
Acro A (26)	2.2	++	12
Acro B (27)	7.2	+++	12
MPPA (28)	0.31	+	12
HMPPA (29)	0.68	+	12
CPPA (30)	0.87	+	12
CNOPA (31)	0.27	+	12
32a	0.34	+	13
32b	4.0	+	13
32c	0.85	+	13
32d	0.03	-	13
32e	1.6	++	12
33a	5.67	+++	13
33b	0.12	+	13
33c	6.8	+++	13
33d	2.13	++	13
34a	Inactive	--	15
34b	Inactive	--	15
35a	0.016	-	15
35b	0.023	-	15
35c	0.017	-	15
35d	0.001	-	15
36a	2.3	++	15
36b	1.7	++	15
36c	1.4	++	15
36d	1.1	++	15
36e	0.95	+	15
36f	0.95	+	15
36g	1.4	++	15
36h	1.6	++	15
36i	0.40	+	15
36j	1.94	++	15
36k	0.48	+	15
36l	1.02	++	15
36m	1.94	++	15
36n	0.20	+	15
36o	1.02	++	15
36p	0.41	+	15
36q	1.76	++	15
36r	0.41	+	15
36s	0.16	+	15
36t	1.32	++	15
36u	0.31	+	15
36v	0.23	+	15
36w	0.59	+	15
36x	0.029	-	15
36y	0.018	-	15
36z	0.041	-	15
36aa	0.41	+	15
36ab	0.08	+	15
iso DA A (37)	1.62	++	18
iso DA B (38)	0.001	-	18
iso DA C (39)	0.040	-	18
iso DA D (40)	0.004	-	18
iso DA E (41)	0.004	-	18
iso DA F (42)	0.10	+	18

*These relative activity values were calculated based on the original data listed in Tables S3 and S4.

Table S3. **Original literature data for the activity of kainic acid analogs in functional assays.**

Compound	Potency relative to L-Glu[1]	Mimimum effective concentration (μM) [2]		Potency relative to KA neurotoxicity (%)[3]			Potency relative to L-Glu[4]	Effect in rat cerebellar slices (KA in 1 mM) [5]		Binding to GluK2[6]	[3H] kainate binding to KA Receptors Ki (μM) [7]
		Depolarization	Potentiation	Retina	Striatum	Electrophysiology		EC_{50} (mM)	KA Antagonist IC_{50} (mM)		
KA (**1**)	8 -80	0.3	0.05	1.0	1.0	1.0	8.0	1.0	–		0.01
DA (**2**)		0.006	0.003								
L-Glutamic acid (**3**)	1	0.03	Inactive[a]	0.3	< 0.1	1.0	1.0				
Kainic acid dimethyl ester (**4**)		Inactive[a]	Inactive[a]	< 1.0	< 2.0	Inactive[a]					
N-acetyl kainic acid (**5a**)		Inactive[a]	Inactive[a]	< 1.0	< 2.0	Inactive[a]					
N-Boc kainic acid (**5b**)		Inactive[a]	Inactive[a]								
allo – KA (**6**)		Inactive[a]	Inactive[a]								
β-KA (**7**)		Inactive[a]	Inactive[a]								
8a										Inactive	
8b										Inactive	
9a										Inactive	
9b										Inactive	
Pyroglutamic acid (**10**)	0.7 – 0.8										
CPAA (11)											1.6
Kainic acid methyl ketone (**12a**)		0.01	0.003				5.2				
allo – kainic acid methyl ketone (**12b**)							4.6				
DHK (**13**)	0.06 - 0.6	Inactive[a]	Inactive[a]	< 1.0	< 2.0	Inactive[a]					16
Carboxyl kainic acid (**14a**)							2.5	Inactive	Inactive		
Carboxyl *allo* – kainic acid (**14b**)							2.3	Inactive	Inactive		
Hydroxyl kainic acid (**15a**)							0.2				
Dihydroyl kainic acid (**15b**)							0.1				
Phenylthio-hydroxyl kainic acid (**15c**)							0.1				
Kainic acid lactone (**16a**)		Inactive[a]	Inactive[a]					--	3 (KA 0.1 mM)[6]		
Kainic acid hydroxy-lactone (mixed isomers) (**16b**)								Inactive[b]	2.0[b]		
Kainic acid iodolactone (**16c**)								Isomer A Very weak Isomer B Inactive	Isomer A Inactive Isomer B 0.3		
Kainic acid phenylthiolactone (**16d**)								Inactive	0.5		

Notes: (a) Inactive at a concentration less than 1 μM. (b) Isomer mixture.

Table S4. **Original literature data for the activity of kainic acid analogs in functional assays. (Continued)**

Compounds	IC50 (Displacement by kainate analogue of bound [3H] KA (20 nm)) (nM)[8]	Effect on neurons[9]		Insecticidal Activity[10]	IC_{50} for KA receptors (M)[11]	Mean molar potency ratios, relative to KA[12]		Ki (μ M) against kainate receptors[13]	[3H] kainate binding Ki (nM)[14]		Binding to Gluk2 Ki (nM)[15]	In vivo potencies[16,17]			Synaptosomal KA BRA Ki (nM)[18]
		Minimum effective or used concentration (mM)	Effects			Dorsal root fibers	Motoneurones		HumGluK 2 receptors	Rat forebrain receptors		Spike amplitude EC50 (nM)	Spike area EC50 (nM)	Gluk2 binding assay Ki (nM)	
KA (1)	17.8	0.3 - 0.03	Effective			1	1		53.0 ± 23.6	3.7 ± 0.20					
DA (2)		0.3 – 0.03	Effective			34 ± 2.4	2.2 ± 0.08		18.3 ±10.2		4.9 ± 0.29	228	237	3.35	2.4
L-Glu (3)		0.68	Inactive			0.11 ± 0.01	0.02 ± 0.003								
***allo*-KA (6)**		0.47	Inactive												
12a		0.3 – 0.03	Effective												
12b		0.47	Inactive												
DHKA (13)	645.6	0.47	Inactive			< 0.01	< 0.01								
17		0.28	Inactive												
18		0.26	Inactive												
19		0.2	Inactive												
20		0.24	Inactive												
21		0.24	Inactive												
22					> 100										
23		0.19	Inactive												
Domoilactone A (24a)				Inactive											
Domoilactone B (24b)				Inactive											
25a	79.4														
25b	416.8														
Acro A (26)						1.7 ± 0.08	2.7 ± 0.1								
Acro B (27)						13 ± 0.7	1.4 ± 0.04								
MPPA (28)						0.045 ± 0.006	0.57 ± 0.05								
HMPPA (29)						0.45 ± 0.04	0.91 ± 0.04								
CPPA (30)						0.91 ± 0.12	0.82 ± 0.04								
CNOPA (31)						0.29 ± 0.06	0.22 ± 0.02								
32a						0.22 ± 0.03	0.45 ± 0.33	0.006							
32b						4.2 ± 0.29	3.8 ± 0.12	0.29							
32c								0.005							
32d								0.016							
32e						1.3 ± 0.13	1.9 ± 0.12								
33a								0.1							
33b								0.01							
33c								0.04							
33d								1.3							

34a		> 100,000	NA					
34b		> 100,000	NA					
35a		6969.0 ± 1330.8	230.0 ± 38.3					
35b		2303.3 ± 802.5	230.0 ± 38.3					
35c		3109.2 ± 934.3	NA					
35d		> 100, 000	3000 ± 100					
36a		29.8 ± 6.9	1.6 ± 0.25					
36b		122.5 ± 40.9	2.2 ± 0.25					
36c		41.1 ±1.8	2.6 ±0.87					
36d		93.5 ± 21.5	3.5 ± 0.45					
36e		57.4 ± 15.4	3.9 ±1.61					
36f		31.7 ± 5.4	3.9 ± 0.41					
36g		38.4 ± 21.7	2.7 ± 0.49					
36h		107.8 ± 20.4	2.3 ± 0.90					
36i		169.3 ± 23.6	9.5 ± 1.43					
36j		54.3 ± 16.2	1.9 ± 0.63					
36k		82.2 ± 24.3	7.7 ± 3.02					
36l		146.8 ±46.4	3.6 ±2.80					
36m		145.6 ± 26.2	1.9 ±0.63					
36n		262.7 ± 59.7	18.5 ± 12.75					
36o		131.5 ± 46.2	3.6 ± 0.59					
36p		288.0 ± 105.0	9.0 ± 0.83					
36q		90.6 ± 10.9	2.1 ± 0.57					
36r		130.6 ± 29.8	9.1 ± 3.18					
36s		275.3 ± 498.5	23.3 ± 0.47					
36t		146.6 ± 52.0	2.8 ± 0.64					
36u		209.6 ± 60.9	11.9 ± 2.29					
36v		667.0 ± 259.8	16.0 ± 6.52					
36w		126.2 ± 40.3	6.2 ± 1.10					
36x		1295.7 ± 272.2	126.0 ± 34.9					
36y		2423.3 ± 300.2	210.3 ± 59.3					
36z		1284 ± 131.5	NA					
36aa		129.3 ± 13.6	NA					
36ab		663.3 ± 300.1	NA					
Iso-DA A (37)	Effective				887	939	130	4.4
Iso-DA B (38)	Effective							5000
Iso-DA C (39)	Effective			1176 ± 70	3712	4626	1176	171
Iso-DA D (40)								600
Iso-DA E (41)								600
Iso-DA F (42)								67

Table S5. **Agonists activity of Glu, KA and DA at KARs (GluK1–5).**

	GluK1		GluK2		GluK3	GluK4	GluK5
Glu	EC_{50} = 917 μM	K_i = 140 nm	EC_{50} = 9 ± 1 μM	K_i = 331 nm	K_i = 494 nm	–	–
KA	EC_{50} = 51 μM	K_i = 75.9 nm	EC_{50} = 1.1 ± 0.1 μM	K_i = 12.7 nm	K_i = 32.8 nm	K_d = 1.9 nm	K_i = 15 nm
DA	EC_{50} = 13 μM	K_i = 1.11 nm	EC_{50} = 0.07 ± 0.01 μM	K_i = 6.04 nm	K_i = 3.84 nm	K_i = 25 nm	–
Ref	Neurochem. Int. **2012**, 61, 536.	J. Med. Chem. **2008**, 51, 4093	Neuropharmacology. **2004**, 46, 793.	J. Med. Chem. **2008**, 51, 4093	J. Med. Chem. **2008**, 51, 4093	Structure, **2016**, 24, 1582.	Nature, **1992**, 8, 775.

3. Effect of aromatic substituents on the binding of kainoids

Hammett and electrophilic coefficients were tabulated for each aromatic compound reported.[19,20] These constants are only available for *meta* and *para* substituents, consequently, some kainoids were ignored in the graphs presented in the manuscript.

Table S6. Correlation of the binding affinity of analogs of compounds **34**, **35**, and **36** with the Hammett constants of their aromatic substituents.

Compound	∑ σ (Hammett substituent constants)	∑ σ⁺ (Electrophilic substituent constants)	[³H] Kainate binding K_i (nM)	$Log_{10}Ki$
1	-	-	53 ± 23.6	1.7 ± 1.4
2	-	-	18.3 ± 10.2	1.3 ± 1.0
34a	-	-	>100,000	> 5
34b	-	-	>100,000	> 5
35a	-	-	6,969 ± 1331	3.8 ± 3.1
35b	-	-	2,303 ± 802	3.4 ± 2.9
35c	-	-	3,109 ± 934	3.5 ± 3.0
35d	-	-	>100,000	
36a	0	0	29.8 ± 6.9	1.5 ± 0.8
36b	-0.069	-0.066	122.5 ± 40.9	2.1 ± 1.6
36c	-0.170	-0.311	41.1 ± 1.8	1.6 ± 0.3
36d	0.115	0.047	93.5 ± 21.5	2.0 ± 1.3
36e	-0.268	-0.778	57.4 ± 15.4	1.8 ± 1.2
36f	0.277	0.114	31.7 ± 5.4	1.5 ± 0.7
36g	0.062	-0.073	38.4 ± 21.7	1.6 ± 1.3
36h	-0.239	-0.377	107.8 ± 20.4	2.0 ± 1.3
36i	-0.138	-0.132	169.3 ± 23.6	2.2 ± 1.4
36j	-0.007	-0.139	54.3 ± 16.2	1.7 ± 1.2
36k	-0.151	-0.295	82.2 ± 24.3	1.9 ± 1.4
36l	-	-	146.8 ± 46.4	2.2 ± 1.7
36m	-	-	145.6 ± 26.2	2.2 ± 1.4
36n	-	-	262.7 ± 59.7	2.4 ± 1.8
36o	-	-	131.5 ± 46.2	2.1 ± 1.7
36p	-	-	288.0 ± 105.0	2.5 ± 2.0
36q	-0.010	0.109	90.6 ± 10.9	2.0 ± 1.0
36r	0.060	-0.179	130.6 ± 29.8	2.1 ± 1.5
36s	0.100	-	275.3 ± 598.5	2.4 ± 2.8
36t	-0.320	-	146.6 ± 52.0	2.2 ± 1.7
36u	-0.320	-0.500	209.6 ± 60.9	2.3 ± 1.8
36v	-	-	667 ± 259	2.8 ± 2.4
36w	-	-	126.2 ± 40.3	2.1 ± 1.6
36x	-	-	1,296 ± 272	3.1 ± 2.4
36y	-	-	2,423 ± 300	3.4 ± 2.5
36z	-	-	1,284 ± 131	3.1 ± 2.1
36aa	-	-	129.3 ± 13.6	2.1 ± 1.1
36ab		-	663 ± 300	2.8 ± 2.5

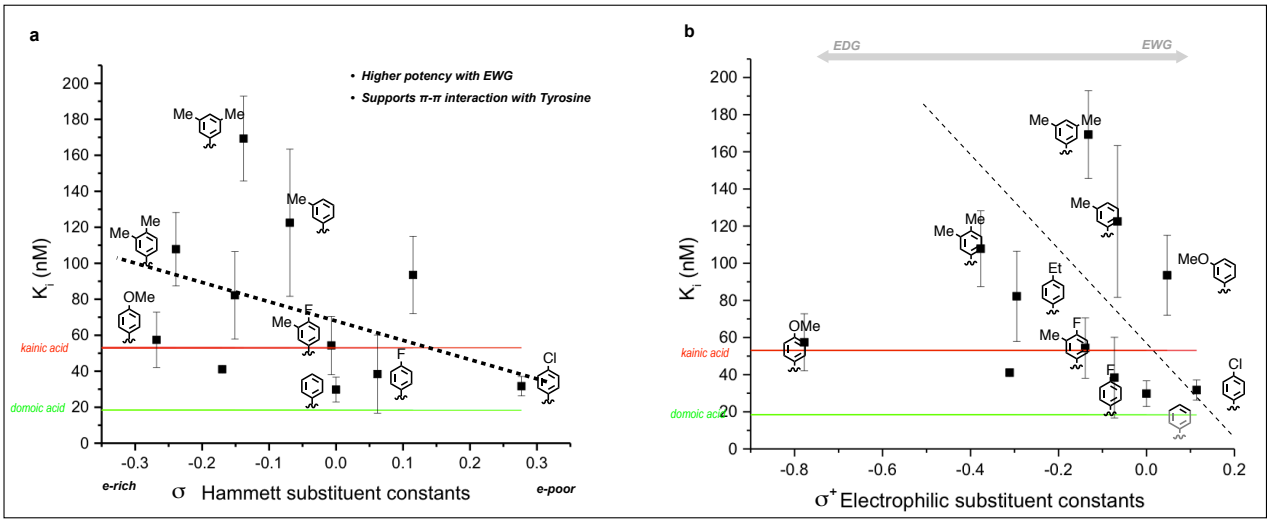

Figure S1. **Plots of kainoid analogs 36's inhibitory constants as a function of the Hammett σ (A) and σ⁺ (B) coefficients of their aromatic substituents**. Potential trends are manually indicated by a dashed line. Reference K_i values of kainic acid and domoic acid are shown as red and green lines, respectively.

The analogs series **36** make it tempting to analyze the electronic density of the aromatic susbstituents to reveal the extent of a π–π interaction. However, plotting the potency of derivatives **36** against their Hammett constants shows no clear trend in terms of electronic factors (Fig. S1). Yet, compounds with K_i's lower than KA have substituents only in the *para* position. In contrast, compounds with *meta* substituents are less potent than KA. A slightly lower activity can be detected for more electron-rich aromatic compounds (suggesting a potential destabilizing interaction with a tyrosine)—however, this is admittedly a weak correlation. A similar weak correlation is also observed when the electrophilic constant parameters are used (Figure S1b). This analysis rules out a cation–π interaction, but may still support a π–π stacking contribution. On the other hand, the relatively bulky and hydrophobic aromatic groups favor the hydrophobic interactions with KARs. This was confirmed by higher thermal stability of KA with GluK4 compared to that of Glu since thermal stability is highly correlated with hydrophobic forces. [21] But agonists with hydrophilic groups on aromatic ring stills display high affinity, such as **26**, **27** and **31**. Thus, we believe that the activity of agonists might be a sum of all these factors (π–π stacking and hydrophobic force).

4. 3D structures of domoic acid and isodomoic acids

3D structures of domoic acid are presented bound to the GluK2 kainate receptor. The coordinate files were obtained from the protein data bank (GluK2, 1yae).[22] 3D structures of domoids were created with Chemdraw3D, then their conformational energies were minimized to generate sets of plausible poses (Figure S2). All structures were visualized in Pymol.

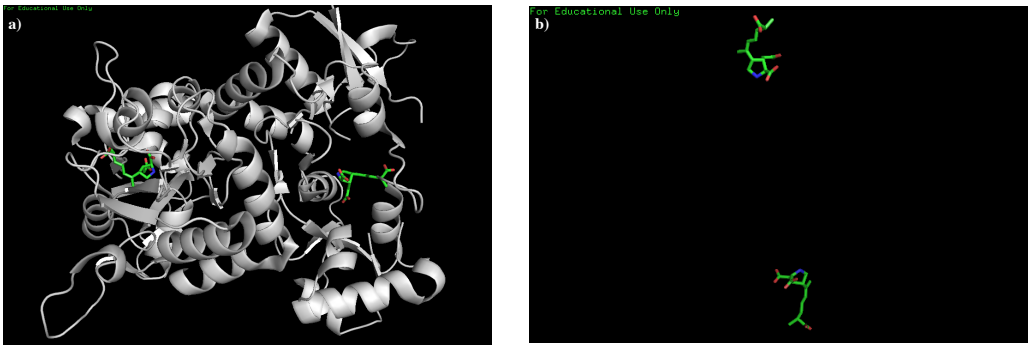

Figure S2. (A) X-ray crystal structure of GluK2 bound to domoic acid (PDB: 1yae). (B) The protein chains were omitted for clarity**.**

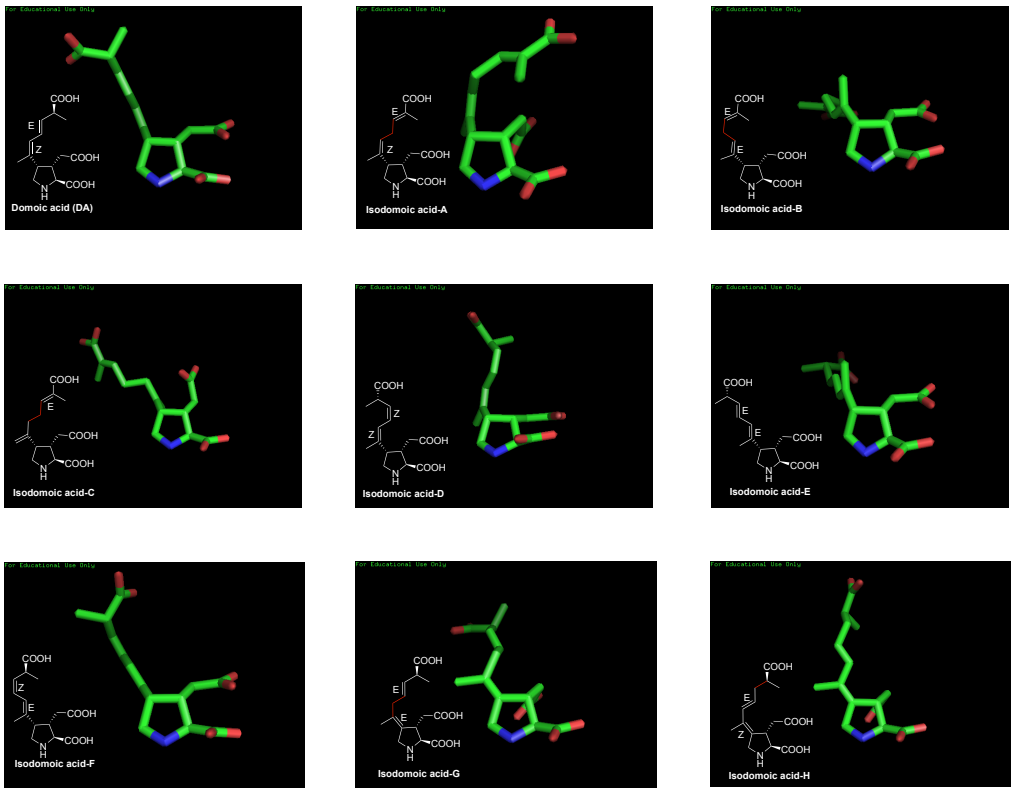

Figure S3. **Domoic acid analogs in their energy-minimized, ground state conformation.** 3D structures of domoic acid analogs were produced by Chemdraw in ground state to provide visual comparison. Rotatable sp^3 C-C bond on C4 sidechain were highlighted with red since the rotation may led to configuration change of C4 side chain.

5. Homology Analysis of kainate receptors

Table S7. **Kainate receptors reference sequences for the most commonly used organisms (mouse, rat, and humans).**

Ionotropic glutamate receptor	*organism*	Catalogued name	Accession number	Protein size (# a.a.)
GluK1	*mus musculus*	m.m.	Q60934.2	836
(GluR5)		m.m. isoform a	NP_666184.2	934
		m.m. isoform b	NP_034478.1	905
		m.m. isoform c	NP_001333893.1	903
	rattus norvegicus	r.n.	P22756.3	949
		r.n. isoform 1	NP_001104587.1	949
		r.n. isoform 2	NP_058937.1	920
		r.n. isoform 3	NP_001104584.1	905
	homo sapiens	h.s.	P39086.1	918
		h.s. isoform 1	NP_000821.1	918
		h.s. isoform 2	NP_783300.1	905
		h.s. isoform 3	NP_001307545.1	920
		h.s. isoform 4	NP_001307547.1	781
		h.s. isoform 5	NP_001307550.1	763
		h.s. isoform 7	NP_001317922.1	934
		h.s. isoform 8	NP_001317923.1	949
GluK2	*mus musculus*	m.m. isoform 1	NP_001104738.1	908
(GluR6)		m.m. isoform 2	NP_034479.2	869
	ratus norvegicus	r.n.	P42260.2	908
		r.n.	NP_062182.1	908
	homo sapiens	h.s. isoform 1	NP_068775.1	908
		h.s. isoform 2	NP_786944.1	869
		h.s. isoform 3	NP_001159719.1	892
GluK3	*mus musculus*	m.m.	NP_001074566.1	919
(GluR7)	*rattus norvegicus*	r.n.	P42264.1	919
		r.n. isoform 1	NP_001106187.1	919
		r.n. isoform 2	NP_852038.2	910
	homo sapiens	h.s.	NP_000822.2	919
GluK4	*mus musculus*	m.m	NP_780690.2	956
(KA1)	*rattus norvegicus*	r.n.	Q01812.1	956
		r.n.	NP_036704.1	956
	homo sapiens	h.s. isoform 1	NP_001269399.1	956
		h.s. isofrom 2	NP_001269402.1	956
GluK5	*mus musculus*	m.m.	NP_032194.2	979
(KA2)	*rattus norvegicus*	r.n.	NP_113696.1	979
	homo sapiens	h.s. isoform 1	NP_001287959.1	981
		h.s. isoform 2	NP_002079.3	980

Notes: The GluK2 protein reference that is used throughout this review to number the amino acids is highlighted in yellow.

Table S8. **Homology analysis of GluK1 between mouse, rat, and human isoforms.**

Homology Analysis of **GluK1** between mouse, rat, and human isoforms

GluK1	*mus musculus* m.m. Q60934.2 838 aa	m.m. isoform a NP_666184.2 934 aa	m.m. isoform b NP_034478.1 905	m.m. isoform c NP_001333853.1 903	*rattus norvegicus* r.n. P22756.3 949 aa	r.n. isoform 1 NP_001104587.1 949	r.n. isoform 2 NP_058937.1 920	r.n. isoform 3 NP_001104584.1 905	*homo sapiens* h.s. P39086.1 918 aa	h.s. isoform 1 NP_000821.1 918	h.s. isoform 2 NP_783300.1 905	h.s. isoform 3 NP_001307545.1 920	h.s. isoform 4 NP_001307547.1 781	h.s. isoform 5 NP_001307550.1 763	h.s. isoform 7 NP_001317922.1 934	h.s. isoform 8 NP_001317923.1 949
Q60934.2		89.2% (89.4%)	86.1% (86.3%)	88.3% (88.4%)	86.5% (87.5%)	86.9% (87.8%)	84.0% (84.8%)	85.3% (86.2%)	85.2% (86.8%)	85.2 (86.8%)	84.7% (86.2%)	83.4% (84.8%)	71.5% (72.9%)	81.9% (83.0%)	87.4% (89.1%)	86.0% (87.7%)
NP_666184.2	89.2% (89.4%)	*numbering reference*	96.9% (96.9%)	91.4% (91.4%)	96.9% (97.9%)	97.4% (98.2%)	94.4% (95.3%)	95.9% (96.8%)	96.1% (98.2%)	96.1% (98.2%)	94.8% (96.8)	93.3% (95.3%)	81.6% (83.5%)	94.4% (96.1%)	97.4% (9.7%)	95.9% (98.1%)
NP_034478.1	86.1% (86.3%)	96.9% (96.9%)		99.7% (99.8%)	94.0% (94.9%)	94.4% (95.3%)	97.4% (98.3%)	99.0% (99.9%)	96.8% (97.9%)	96.8% (97.9%)	97.8% (99.9%)	96.2% (98.3%)	84.2% (86.2%)	98.2% (100.0%)	94.8% (96.8%)	93.3% (95.3%)
NP_001333853.1	88.3% (88.4%)	91.4% (91.4%)	99.7% (99.8%)		96.8% (97.8%)	97.2% (98.2%)	96.9% (97.9%)	98.6% (99.7%)	95.8% (98.0%)	95.8% (98.0%)	97.4% (99.7%)	95.8% (97.9%)	83.1% (85.2%)	97.8% (99.7%)	97.8% (99.9%)	96.1% (98.2%)
P22756.3	86.5% (87.5%)	96.9% (97.9%)	94.0% (94.9%)	96.8% (97.8%)		99.6% (99.7%)	96.5% (96.6%)	94.9% (95.0%)	95.7% (99.4%)	96.7% (99.4%)	92.3% (94.8%)	93.8% (96.4%)	79.5% (81.8%)	91.7% (93.8%)	95.0% (97.8%)	96.5% (99.4%)
NP_001104587.1	86.9% (87.8%)	97.4% (98.2%)	94.4% (95.3%)	97.2% (98.2%)	99.6% (99.7%)		**96.9%** (96.9%)	95.4% (95.4%)	**97.1%** (99.8%)	97.1% (99.8%)	92.7% (95.2%)	**94.2%** (96.7%)	79.8% (82.1%)	92.2% (94.1%)	95.5% (98.1%)	**96.9%** (99.7%)
NP_058937.1	84.0% (84.8%)	94.4% (95.3%)	97.4% (98.3%)	96.9% (97.9%)	96.5% (96.6%)	96.9% (96.9%)		98.4% (98.4%)	**96.8%** (99.5%)	96.8% (99.5%)	95.7% (98.2%)	**97.2%** (99.8%)	82.3% (84.7%)	96.8% (97.8%)	92.7% (95.2%)	**94.2%** (96.7%)
NP_001104584.1	86.3% (86.2%)	95.9% (96.8%)	99.0% (99.9%)	98.6% (99.7%)	94.9% (95.0%)	95.4% (95.4%)	98.4% (98.4%)		95.2% (97.8%)	95.2% (97.8%)	97.2% (99.8%)	95.7% (98.2%)	83.6% (86.1%)	97.8% (99.9%)	94.2% (96.7%)	92.7% (95.2%)
P39086.1	85.2% (86.8%)	96.1% (98.2%)	95.8% (97.9%)	95.8% (98.0%)	96.7% (99.4%)	97.1% (99.8%)	96.8% (99.5%)	95.2% (97.8%)		21.9% (62.5%) ???	97.9% (98.1%)	99.7% (99.8%)	83.7% (83.8%)	96.0% (95.9%)	98.3% (98.3%)	100.0% (100.0%)
NP_000821.1	85.2 (86.8%)	96.1% (98.2%)	95.8% (97.9%)	95.8% (98.0%)	96.7% (99.4%)	97.1% (99.8%)	96.8% (99.5%)	95.2% (97.8%)	21.9% (62.5%) ???		97.9% (98.1%)	99.7% (99.8%)	83.7% (83.8%)	95.0% (95.9%)	98.3% (98.3%)	100.0% (100.0%
NP_783300.1	84.7% (86.2%)	94.8% (96.8)	97.8% (99.9%)	97.4% (99.7%)	92.3% (94.8%)	92.7% (95.2%)	95.7% (98.2%)	97.2% (99.8%)	97.9% (98.1%)	97.9% (98.1%)		98.4% (98.4%)	86.3% (86.3%)	97.6% (98.4%)	96.9% (96.9%)	95.4% (95.4%)
NP_001307545.1	83.4% (84.8%)	93.3% (95.3%)	96.2% (98.3%)	95.8% (97.9%)	93.8% (96.4%)	94.2% (96.7%)	97.2% (99.8%)	96.7% (98.2%)	99.7% (99.8%)	99.7% (99.8%)	98.4% (98.4%)		84.9% (84.9%)	95.7% (96.5%)	95.4% (95.4%)	96.9% (96.9%)
NP_001307547.1	71.5% (72.9%)	81.6% (83.5%)	84.2% (86.2%)	83.1% (85.2%)	79.5% (81.8%)	79.8% (82.1%)	82.3% (84.7%)	83.6% (86.1%)	83.7% (83.8%)	83.7% (83.8%)	86.3% (86.3%)	84.9% (84.9%)		81.9% (81.9%)	83.6% (83.6%)	82.3% (82.3%)
NP_001307550.1	81.9% (83.0%)	94.4% (96.1%)	98.2% (100.0%)	97.8% (99.7%)	91.7% (93.8%)	92.2% (94.1%)	96.8% (97.8%)	97.8% (99.9%)	95.0% (95.9%)	95.0% (95.9%)	97.6% (98.4%)	95.7% (96.5%)	81.9% (81.9%)		94.0% (94.7%)	92.2% (92.9%)
NP_001317922.1	87.4% (89.1%)	97.4% (9.7%)	94.8% (96.8%)	97.8% (99.9%)	95.0% (97.8%)	95.5% (98.1%)	92.7% (95.2%)	94.2% (96.7%)	98.3% (98.3%)	98.3% (98.3%)	96.9% (96.9%)	95.4% (95.4%)	83.6% (83.6%)	94.0% (94.7%)		98.4% (98.4%)
NP_001317923.1	86.0% (87.7%)	95.9% (98.1%)	93.3% (95.3%)	96.1% (98.2%)	96.5% (98.4%)	96.9% (99.7%)	94.2% (96.7%)	92.7% (95.2%)	100.0% (100.0%	100.0% (100.0%	95.4% (95.4%)	96.9% (96.9%)	82.3% (82.3%)	92.2% (92.9%)	98.4% (98.4%)	

Table S9. **Homology analysis of GluK2, GluK3, GluK4, and GluK5 between mouse, rat, and human isoforms.**

Homology Analysis of **GluK2** between mouse, rat, and human isoforms

GluK2	*mus musculus* **m.m. isoform 1** NP_001104738.1 908	**m.m. isoform 2** NP_034479.2 869	*ratus norvegicus* **r.n.** P42260.2 908	**r.n.** NP_062182.1 908	*homo sapiens* **h.s. isoform 1** NP_068775.1 908	**h.s. isoform 2** NP_786944.1 869	**h.s. isoform 3** NP_001159719.1 892
NP_001104738.1	*numbering reference*	99.9% (100.0%)	99.6% (99.9%)	99.9% (100.0%)	98.7% (99.6%)	98.5% (99.5%)	98.5% (99.5%)
NP_034479.2	99.9% (100.0%)		99.4% (99.9%)	99.8% (100.0%)	98.5% (99.5%)	98.6% (99.5%)	97.7% (99.0%)
P42260.2	99.6% (99.9%)	99.4% (99.9%)	*numbering reference*	99.7% (99.9%)	99.1% (99.7%)	98.9% (99.6)	98.9% (99.6%)
NP_062182.1	99.9% (100.0%)	99.8% (100.0%)	99.7% (99.9%)		98.8% (99.6%)	98.6% (99.5%)	98.6% (99.5%)
NP_068775.1	98.7% (99.6%)	98.5% (99.5%)	99.1% (99.7%)	98.8% (99.6%)		99.9% (100.0%)	99.9% (100.0%)
NP_786944.1	98.5% (99.5%)	98.6% (99.5%)	98.9% (99.6)	98.6% (99.5%)	99.9% (100.0%)	*numbering reference*	99.9% (100.0%)
NP_001159719.1	98.5% (99.5%)	97.7% (99.0%)	98.9% (99.6%)	98.6% (99.5%)	99.9% (100.0%)	99.9% (100.0%)	

Note: The amino acid numbering reference used in this review is highlighted in yellow (GluK2_rat, P42260).

Homology Analysis of **GluK3** between mouse, rat, and human isoforms

GluK3	*mus musculus* **m.m.** NP_001074566.1 919	*rattus norvegicus* **r.n.** P42264.1 919	**r.n. isoform 1** NP_001106187.1 919	**r.n. isoform 2** NP_852038.2 910	*homo sapiens* **h.s.** NP_000822.2 919
NP_001074566.1		99.5% (99.7%)	99.8% (100.0%)	99.8% (100.0%)	99.0% (99.9%)
P42264.1	99.5% (99.7%)		99.7% (99.7%)	99.6% (99.6%)	98.7% 99.6%
NP_001106187.1	99.8% (100.0%)	99.7% (99.7%)	[REF]	100.0% (100.0%)	99.0% 99.9%
NP_852038.2	99.8% (100.0%)	99.6% (99.6%)	100.0% (100.0%)		99.2% (99.9%)
NP_000822.2	99.0% (99.9%)	98.7% 99.6%	99.0% 99.9%	99.2% (99.9%)	

Homology Analysis of **GluK4** between mouse, rat, and human isoforms

GluK4	*mus musculus* **m.m** NP_780690.2 956	*rattus norvegicus* **r.n.** Q01812.1 956	**r.n.** NP_036704.1 956	*homo sapiens* **h.s. isoform 1** NP_001269399.1 956	**h.s. isofrom 2** NP_001269402.1 956
NP_780690.2		99.5% (99.9%)	99.6% (100.0%)	97.9% (99.7%)	98.3% (99.6%)
Q01812.1	99.5% (99.9%)		99.9% (99.9%)	97.8% (99.6%)	98.2% (99.5%)
NP_036704.1	99.6% (100.0%)	99.9% (99.9%)		97.9% (99.7%)	98.3% (99.6%)
NP_001269399.1	97.9% (99.7%)	97.8% (99.6%)	97.9% (99.7%)		99.5% (99.6%)
NP_001269402.1	98.3% (99.6%)	98.2% (99.5%)	98.3% (99.6%)	99.5% (99.6%)	

Homology Analysis of **GluK5** between mouse, rat, and human isoforms

GluK5	*mus musculus* **m.m.** NP_032194.2 979	*rattus norvegicus* **r.n.** NP_113696.1 979	*homo sapiens* **h.s. isoform 1** NP_001287959.1 981	**h.s. isoform 2** NP_002079.3 980
NP_032194.2		100.0% (100.0%)	99.5% (99.9%)	98.9% (99.6%)
NP_113696.1	100.0% (100.0%)		99.5% (99.9%)	98.9% (99.6%)
NP_001287959.1	99.5% (99.9%)	99.5% (99.9%)		100.0% (100.0%)
NP_002079.3	98.9% (99.6%)	98.9% (99.6%)	100.0% (100.0%)	

Table S10. **Reported crystallized protein structures of ionotropic glutamate receptors: kainate receptors (GluK1-5).** GluKs with Glu, KA or DA complex are highlight with grey. PDB IDs of dimer crystal structures are shown in blue, tetramers are in red and monomers are in black.

		PDB #	Amino acids	Resolution (Å)	Year	Lab	Citation
KAINATE receptors							
GluK1	GluR5 + drug	6fz4	257	1.85	2019	Johansen	ACS Chem. Neurosci. **2019**, 10, 1814.
	GluR5 + drug	5nf5	514	2.85	2017	Kastrup	ACS Chem. Neurosci. **2017**, 8, 2056.
	GluR5 + drug	5neb	514	2.05	2017	Kastrup	ACS Chem. Neurosci. **2017**, 8, 2056.
	GluR5 + drug + KA	5mfq	514	1.90	2017	Mulle	Mol. Pharmacol. **2017**, 91, 576.
	GluR5 + drug + KA	5mfv	514	2.18	2017	Mulle	Mol. Pharmacol. **2017**, 91, 576.
	GluR5 + drug + KA	5mfw	514	2.10	2017	Mulle	Mol. Pharmacol. **2017**, 91, 576.
	GluR5 + drug	5m2v	514	3.18	2017	Bunch	J.Med. Chem. **2017**, 60, 441.
	GluR5 + drug	4YMB	514	1.93	2015	Kastrup	J.Med. Chem. **2015**, 58, 6163.
	GluR5 + drug	4QF9	771	2.28	2015	Kastrup	ACS Chem. Neurosci. **2015**, 6, 845
h	GluR5 + drug	4MF3	522	3.00	2014	Ornstein	Bioorg. Med. Chem. Lett. **2013**, 23, 6463.
	GluR5 + KA	4E0X	514	2.00	2012	Kastrup	Neurochem. Int. **2012**, 61, 536.
	GluR5 + drug	4DLD	514	2.00	2012	Kastrup	ChemMedChem. **2012**, 7, 1793.
	GluR5 + drug	3s2v	514	2.50	2011	Kastrup	J.Med. Chem. **2011**, 54, 4793.
h	GluR5 + drug	3FVO	256	1.50	2010	Ikeda-Saito	To be published
h	GluR5 + drug	3FVN	512	1.50	2010	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
h	GluR5 + drug	3FVK	512	1.50	2010	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
h	GluR5 + drug	3FVG	512	1.50	2010	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
h	GluR5 + toxin	3FV2	512	1.50	2010	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
h	GluR5 + toxin	3FV1	512	1.50	2010	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
h	GluR5 + Glu	3FUZ	512	1.65	2010	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
	GluR5 + drug	3gbb	514	2.10	2009	Kastrup	J. Biol. Chem. **2009**, 284, 14219.
	GluR5 + toxin	3gba	1028	1.35	2009	Kastrup	J. Biol. Chem. **2009**, 284, 14219.
h	GluR5 + toxin	2ZNU	256	1.80	2009	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
h	GluR5 + toxin	2ZNT	256	1.60	2009	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
h	GluR5 + Glu	2ZNS	256	2.00	2009	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
	GluR5 + drug	2wky	516	2.20	2009	Kastrup	J. Med. Chem. **2009**, 52, 4911.
	GluR5 + KA + drug	3C36	516	1.68	2008	Mayer	Neuron, **2008**, 58, 720.
	GluR5 + KA + drug	3C35	516	1.97	2008	Mayer	Neuron, **2008**, 58, 720.
	GluR5 + KA + drug	3C34	516	1.82	2008	Mayer	Neuron, **2008**, 58, 720.
	GluR5 + KA + drug	3C33	516	1.72	2008	Mayer	Neuron, **2008**, 58, 720.
	GluR5 + KA + drug	3C32	516	1.72	2008	Mayer	Neuron, **2008**, 58, 720.
	GluR5 + KA + drug	3C31	516	1.49	2008	Mayer	Neuron, **2008**, 58, 720.
	GluR5 + drug	2qs4	1032	1.58	2008	Mayer	Neuropharmacology, **2011**, 60, 126.
	GluR5 + drug	2qs3	516	1.76	2008	Mayer	Neuropharmacology, **2009**, 56, 121.
	GluR5 + drug	2qs2	516	1.80	2008	Mayer	Neuropharmacology, **2011**, 60, 126.
	GluR5 + drug	2qs1	516	1.80	2008	Mayer	Neuropharmacology, **2011**, 60, 126.
	GluR5 + DA	2PBW	514	2.50	2007	Kastrup	J. Biol. Chem. **2007**, 282, 25726
	GluR5 + drug	1VSO	257	1.85	2007	Kastrup	J. Biol. Chem. **2007**, 282, 25726
	GluR5 + Glu	2f36	1032	2.11	2006	Mayer	J. Neurosci. **2006**, 26, 2852.
	GluR5 + drug	2f35	516	1.87	2006	Mayer	J. Neurosci. **2006**, 26, 2852.
	GluR5 + drug	2f34	516	1.74	2006	Mayer	J. Neurosci. **2006**, 26, 2852.
	GluR5 + Glu	1ycj	514	1.95	2005	Kastrup	Febs Lett. **2005**, 579, 1154.
	GluR5 + Glu	1txf	258	2.10	2005	Mayer	Neuron, **2005**, 45, 539.

Table S10. **Reported crystallized protein structures of ionotropic glutamate receptors: kainate receptors (GluK1-5) (Continued).** GluKs with Glu, KA or DA complex are highlight with grey. PDB IDs of dimer crystal structures are shown in blue, tetramers are in red and monomers are in black.

GluK2	GluR6 full length + drug	5kuf	3508	3.8	2016	Subramaniam	Nature **2016**, 537, 567.
	GluR6 + drug	5kuh	3028	11.6	2016	Subramaniam	Nature **2016**, 537, 567.
	GluR6 + glu	5cmk	518	1.8	2016	Subramaniam	Nature **2016**, 537, 567.
	GluR6 + drug	5cmm	259	1.27	2016	Subramaniam	Nature **2016**, 537, 567.
	GluR6 full length + glu	4UQQ	3528	7.60	2014	Mayer	Nature **2014**, 514, 328
	GluR6 mut + glu	4BDL	522	1.75	2013	Green	Open Biol. **2013**, 3, 0051.
	GluR6 mut + KA	4BDM	1044	3.40	2013	Green	Open Biol. **2013**, 3, 0051.
	GluR6 mut + Glu	4BDN	1044	2.50	2013	Green	Open Biol. **2013**, 3, 0051.
	GluR6 mut + KA	4BDO	1044	2.55	2013	Green	Open Biol. **2013**, 3, 0051.
	GluR6 mut + Glu	4BDQ	522	1.90	2013	Green	Open Biol. **2013**, 3, 0051.
	GluR6 mut + KA	4BDR	522	1.65	2013	Green	Open Biol. **2013**, 3, 0051.
	GluR6 + Azobenzene-Glu	4H8I	518	2.00	2013	Trauner / Schiefer	Biochemistry, **2013**, 52, 8972.
h	GluR6 + toxin	3QXM	516	1.65	2011	Ikeda-Saito	J. Mol. Biol. **2011**, 413, 667.
	GluR6 + Glu	2XXR	522	1.60	2011	Green	J. Neurosci. **2011**, 31, 2916.
	GluR6 + KA	2XXT	522	1.90	2011	Green	J. Neurosci. **2011**, 31, 2916.
	GluR6 mut + Glu	2XXU	522	1.50	2011	Green	J. Neurosci. **2011**, 31, 2916.
	GluR6 mut + KA	2XXV	522	1.70	2011	Green	J. Neurosci. **2011**, 31, 2916.
	GluR6 mut + Glu	2XXW	522	2.30	2011	Green	J. Neurosci. **2011**, 31, 2916.
	GluR6 mut + Glu	2XXX	1044	2.10	2011	Green	J. Neurosci. **2011**, 31, 2916.
	GluR6 mut + KA	2XXY	1044	3.00	2011	Green	J. Neurosci. **2011**, 31, 2916.
	GluR6 + drug	3QLT	790	2.99	2011	Mayer	Neuron. **2011**, 71, 319.
	GluR6 / KA2 dimer	3qlu	1576	2.91	2011	Mayer	Neuron. **2011**, 71, 319.
	GluR6 / KA tetramer	3qlv	3940	3.94	2011	Mayer	Neuron. **2011**, 71, 319.
	GluR6 + Glu	3g3f	518	1.38	2009	Mayer	Embo J. **2009**, 28, 1518.
	GluR6 mut + Glu	3g3g	518	1.30	2009	Mayer	Embo J. **2009**, 28, 1518.
	GluR6 mut + Glu	3g3h	518	1.50	2009	Mayer	Embo J. **2009**, 28, 1518.
	GluR6 mut + Glu	3g3i	518	1.37	2009	Mayer	Embo J. **2009**, 28, 1518.
	GluR6 mut + Glu	3g3j	518	1.32	2009	Mayer	Embo J. **2009**, 28, 1518.
	GluR6 mut + Glu	3g3k	518	1.24	2009	Mayer	Embo J. **2009**, 28, 1518.
	GluR6	3h6g	790	2.70	2009	Mayer	Nat. Struct. Mol. Biol. **2009**, 16, 631.
	GluR6	3h6h	790	2.90	2009	Mayer	Nat. Struct. Mol. Biol. **2009**, 16, 631.
	GluR6 mut	2I0B	777	1.96	2007	Mayer	Nat. Struct. Mol. Biol. **2006**, 13, 1120.
	GluR6 mut	2I0C	518	2.25	2006	Mayer	Nat. Struct. Mol. Biol. **2006**, 13, 1120.
	GluR6 + Glu	1s50	259	1.65	2005	Mayer	Neuron. **2005**, 45, 539.
	GluR6 + Glu	1s7y	518	1.75	2005	Mayer	Neuron. **2005**, 45, 539.
	GluR6 + drug	1s9t	518	1.80	2005	Mayer	Neuron. **2005**, 45, 539.
	GluR6 + Glu	1sd3	518	1.80	2005	Mayer	Neuron. **2005**, 45, 539.
	GluR6 mut + DA	1tt1	518	1.93	2005	Mayer	Neuron. **2005**, 45, 539.
	GluR6 mut + DA	1YAE	1872	3.11	2005	Heinemann	PNAS. **2005**, 102, 1708

Table S10. **Reported crystallized protein structures of ionotropic glutamate receptors: kainate receptors (GluK1-5) (Continued).** GluKs with Glu, KA or DA complex are highlight with grey. PDB IDs of dimer crystal structures are shown in blue, tetramers are in red and monomers are in black.

GluK3	GluR7 full length	6jfy	3236	7.40	2019	Kumar	Sci. Rep. **2019**, 9, 10254.
	GluR7 full length + drug	6jfz	3236	7.60	2019	Kumar	Sci. Rep. **2019**, 9, 10254.
	GluR7 + drug	6jmv	514	1.83	2019	Kumar	Sci. Rep. **2019**, 9, 10254.
	GluR7 + drug	6f28	516	2.40	2018	Pickering	J. Med. Chem. **2018**, 61, 2124.
	GluR7 + drug	6f29	258	2.60	2018	Pickering	J. Med. Chem. **2018**, 61, 2124.
	GluR7 + drug	5nf6	516	2.55	2017	Kastrup	ACS Chem. Neurosci. **2017**, 8, 2056.
	GluR7 + drug	5o4f	516	2.10	2017	Kastrup	ACS Chem. Neurosci. **2017**, 8, 2056.
	GluR7 + drug	4NWC	258	2.01	2014	Kastrup	ChemMedChem, **2014**, 9, 2254
	GluR7 + drug	4NWD	258	2.60	2014	Kastrup	ChemMedChem, **2014**, 9, 2254
	GluR7 + glu	4MH5	258	1.65	2013	Kastrup	J. Struct. Biol. **2011**, 176, 307.
	GluR7 + drug	4IGR	258	2.65	2013	Kastrup	J. Med. Chem. **2013**, 56, 1614.
	GluR7 + KA	3U92	514	1.90	2012	Mayer	Neuron, **2012**, 76, 565.
	GluR7 + glu	3U93	514	1.88	2012	Mayer	Neuron, **2012**, 76, 565.
	GluR7 + glu	3U94	1028	1.96	2012	Mayer	Neuron, **2012**, 76, 565.
	GluR7 + drug	4G8N	258	2.30	2012	Kastrup	J. Struct. Biol. **2012**, 180, 39.
	GluR7 + KA	4eow	258	2.35	2012	Kastrup	Biochem. J. **2012**, 447, 205.
	GluR7 + glu	3s9e	516	1.60	2011	Kastrup	J. Struct. Biol. **2011**, 176, 307.
	GluR7	3olz	796	2.75	2010	Mayer	J. Mol. Biol. **2010**, 404, 680.
GluK4	GluK4 + KA	5ikb	257	2.05	2016	Kastrup	Structure, **2016**, 24, 1582.
GluK5	KA2 dimer	3qlz	796	2.91	2011	Mayer	J. Mol. Biol. **2010**, 404, 680.
	KA2 / GluR6 dimer	3qlu	1576	2.91	2011	Mayer	Neuron. **2011**, 71, 319.
	KA2 / GluR6 tetramer	3qlv	3940	3.94	2011	Mayer	Neuron. **2011**, 71, 319.
	KA2	3om0	393	1.40	2010	Mayer	J. Mol. Biol. **2010**, 404, 680.
	KA2	3om1	786	1.68	2010	Mayer	J. Mol. Biol. **2010**, 404, 680.

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