

**Suppl. Table 1.**

Parameters of the WT P2X3R Markov model (see Fig. 1) for  $\alpha,\beta$ -meATP as agonist and TNP-ATP and A314791 as antagonists

Rate constants	TNP					A317491			
	from	to	k	std	equilibrium	k	std	equilibrium	
3a <sub>1</sub>	1	2	5.76	0	1,582	5.76	0	1.582	
a <sub>-1</sub>	2	1	3.64	0	0,6319	3.64	0	0.6319	
2a <sub>1</sub>	2	3	3.84	0	0,5275	3.84	0	0.5275	
2a <sub>-1</sub>	3	2	7.28	0	1,896	7.28	0	1.896	
a <sub>1</sub>	3	4	1.92	0	0,1758	1.92	0	0.1758	
3a <sub>-1</sub>	4	3	10.92	0	5,687	10.92	0	5.687	
3k <sub>1</sub>	1	5	0.04751	4.68E-06	0,6358	20.06	0.0582	42.94	
<b>k<sub>-1</sub></b>	<b>5</b>	<b>1</b>	<b>0.05597</b>	<b>6.10E-06</b>	<b>1,573</b>	<b>0.4672</b>	<b>0.001365</b>	<b>0.02329</b>	
2k <sub>1</sub>	5	8	0.03167	3.12E-06	0,2119	13.37	0.0388	14.31	
2k <sub>-1</sub>	8	5	0.1119	1.22E-05	4,718	0.9344	0.00273	0.06987	
2k <sub>1</sub>	2	6	0.03167	3.12E-06	0,2119	13.37	0.0388	28.62	
k <sub>-1</sub>	6	2	0.05597	6.10E-06	4,718	0.4672	0.001365	0.03494	
<b>k<sub>1</sub></b>	<b>3</b>	<b>7</b>	<b>0.01584</b>	<b>1.56E-06</b>	<b>0,07064</b>	<b>6.687</b>	<b>0.0194</b>	<b>14.31</b>	
k <sub>-1</sub>	7	3	0.05597	6.10E-06	14,16	0.4672	0.001365	0.06987	
2a <sub>1</sub>	5	6	3.84	0	0,5275	3.84	0	1.055	
a <sub>-1</sub>	6	5	3.64	0	1,896	3.64	0	0.9479	
a <sub>1</sub>	6	7	1.92	0	0,1758	1.92	0	0.2637	
2a <sub>-1</sub>	7	6	7.28	0	5,687	7.28	0	3.792	
a <sub>1</sub>	8	9	1.92	0	0,1758	1.92	0	0.5275	
a <sub>-1</sub>	9	8	3.64	0	5,687	3.64	0	1.896	
k <sub>1</sub>	6	9	0.01584	1.56E-06	0,07064	6.687	0.0194	7.156	
2k <sub>-1</sub>	9	6	0.1119	1.22E-05	14,16	0.9344	0.00273	0.1397	
k <sub>1</sub>	8	10	0.01584	1.56E-06	0,07064	6.687	0.0194	4.771	
3k <sub>-1</sub>	10	8	0.1679	1.83E-05	14,16	1.402	0.004095	0.2096	
d <sub>-1</sub>	11	1	273.4	0	713,9	273.4	0	713.9	
d <sub>1</sub>	1	11	0.3829	0	0,001401	0.3829	0	0.001401	
d <sub>-2</sub>	12	2	8.1	0	1,247	8.1	0	1.247	
d <sub>2</sub>	2	12	6.498	0	0,8022	6.498	0	0.8022	
d <sub>-3</sub>	13	3	0.03762	0	0,002175	0.03762	0	0.002175	
d <sub>3</sub>	3	13	17.3	0	459,8	17.3	0	459.8	
d <sub>-4</sub>	14	4	8.28E-05	0	3,80E-06	8.28E-05	0	3.80E-06	
d <sub>4</sub>	4	14	21.81	0	2,63E+05	21.81	0	2.63E+05	
3a <sub>1</sub>	11	12	5.76	0	906,8	5.76	0	906.8	
1a <sub>-1</sub>	12	11	0.006352	0	0,001103	0.006352	0	0.001103	
2a <sub>1</sub>	12	13	3.84	0	302,3	3.84	0	302.3	
2a <sub>-1</sub>	13	12	0.0127	0	0,003308	0.0127	0	0.003308	
a <sub>1</sub>	13	14	1.92	0	100,8	1.92	0	100.8	
3a <sub>-1</sub>	14	13	0.01906	0	0,009925	0.01906	0	0.009925	
d <sub>-1</sub>	15	5	273.4	0	713,9	273.4	0	713.9	
d <sub>1</sub>	5	15	0.3829	0	0,001401	0.3829	0	0.001401	
d <sub>-2</sub>	16	6	8.1	0	1,247	8.1	0	1.247	
d <sub>2</sub>	6	16	6.498	0	0,8022	6.498	0	0.8022	
d <sub>-3</sub>	17	7	0.03762	0	0,002175	0.03762	0	0.002175	
d <sub>3</sub>	7	17	17.3	0	459,8	17.3	0	459.8	
2a <sub>1</sub>	15	16	3.84	0	302,3	3.84	0	604.5	
a <sub>-1</sub>	16	15	0.006352	0	0,003308	0.006352	0	0.001654	
a <sub>1</sub>	16	17	1.92	0	100,8	1.92	0	151.1	
2a <sub>-1</sub>	17	16	0.0127	0	0,009925	0.0127	0	0.006617	
3k <sub>1</sub>	11	15	0.04751	4.68E-06	0,6358	20.06	0.0582	42.94	
k <sub>-1</sub>	15	11	0.05597	6.10E-06	1,573	0.4672	0.001365	0.02329	
2k <sub>1</sub>	12	16	0.03167	3.12E-06	0,2119	13.37	0.0388	28.62	

			TNP			A317491		
Rate constants	from	to	k	std	equilibrium	k	std	equilibrium
k <sub>-1</sub>	16	12	0.05597	6.10E-06	4,718	0.4672	0.001365	0.03493
k <sub>1</sub>	13	17	0.01584	1.56E-06	0,07064	6.687	0.0194	14.31
k <sub>-1</sub>	17	13	0.05597	6.10E-06	14,16	0.4672	0.001365	0.06987
a <sub>1</sub>	18	19	1.92	0	100,8	1.92	0	302.3
a <sub>-1</sub>	19	18	0.006352	0	0,009925	0.006352	0	0.003308
d <sub>-2</sub>	19	9	8.1	0	1,247	8.1	0	1.247
d <sub>2</sub>	9	19	6.498	0	0,8022	6.498	0	0.8022
d <sub>-1</sub>	18	8	273.4	0	713,9	273.4	0	713.9
d <sub>1</sub>	8	18	0.3829	0	0,001401	0.3829	0	0.001401
2k <sub>1</sub>	15	18	0.03167	3.12E-06	0,2119	13.37	0.0388	14.31
2k <sub>-1</sub>	18	15	0.1119	1.22E-05	4,718	0.9344	0.00273	0.06987
k <sub>1</sub>	16	19	0.01584	1.56E-06	0,07064	6.687	0.0194	7.156
2 k <sub>-1</sub>	19	16	0.1119	1.22E-05	14,16	0.9344	0.00273	0.1397
d <sub>-1</sub>	20	10	273.4	0	713,9	273.4	0	713.9
d <sub>1</sub>	10	20	0.3829	0	0,001401	0.3829	0	0.001401
k <sub>1</sub>	18	20	0.01584	1.56E-06	0,07064	6.687	0.0194	4.771
3k <sub>-1</sub>	20	18	0.1679	1.83E-05	14,16	1.402	0.004095	0.2096
o <sub>1</sub>	7	23	1.00E+04	0	10	1.00E+04	0	10
o <sub>-1</sub>	23	7	1000	0	0,1	1000	0	0.1
k <sub>-1</sub>	23	21	0.05597	6.10E-06	14,18	0.4672	0.001365	0.07006
k <sub>1</sub>	21	23	0.01579	1.56E-06	0,07051	6.669	0.01935	14.27
o <sub>-1</sub>	21	3	1000	0	0,1	1000	0	0.1
o <sub>1</sub>	3	21	1.00E+04	0	10	1.00E+04	0	10
o <sub>1</sub>	4	22	1.00E+04	0	10	1.00E+04	0	10
o <sub>-1</sub>	22	4	1000	0	0,1	1000	0	0.1
3a <sub>-1</sub>	22	21	10.92	0	5,688	10.92	0	5.688
a <sub>1</sub>	21	22	1.92	0	0,1758	1.92	0	0.1758

Constraints:

- ScaleRate: 1 2 2 3
- ScaleRate: 1 2 3 4
- ScaleRate: 1 2 21 22
- ScaleRate: 1 2 11 12
- ScaleRate: 1 2 12 13
- ScaleRate: 1 2 13 14
- ScaleRate: 2 1 3 2
- ScaleRate: 2 1 4 3
- ScaleRate: 2 1 22 21
- ScaleRate: 12 11 13 12
- ScaleRate: 12 11 14 13
- ScaleRate: 1 11 2 12
- ScaleRate: 1 11 3 13
- ScaleRate: 1 11 4 14
- ScaleRate: 11 1 12 2
- ScaleRate: 11 1 13 3
- ScaleRate: 11 1 14 4
- ScaleRate: 1 2 5 6
- ScaleRate: 1 5 2 6
- ScaleRate: 1 5 3 7
- ScaleRate: 1 5 11 15
- ScaleRate: 1 5 12 16
- ScaleRate: 1 5 13 17
- ScaleRate: 5 1 6 2
- ScaleRate: 5 1 7 3
- ScaleRate: 5 1 15 11
- ScaleRate: 5 1 16 12

ScaleRate: 5 1 17 13  
ScaleRate: 2 1 6 5  
ScaleRate: 1 11 5 15  
ScaleRate: 11 1 15 5  
ScaleRate: 12 11 16 15  
ScaleRate: 5 6 6 7  
ScaleRate: 5 6 15 16  
ScaleRate: 5 6 16 17  
ScaleRate: 6 5 7 6  
ScaleRate: 16 15 17 16  
ScaleRate: 5 15 6 16  
ScaleRate: 5 15 7 17  
ScaleRate: 15 5 16 6  
ScaleRate: 15 5 17 7  
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ScaleRate: 2 1 9 8  
ScaleRate: 1 5 5 8  
ScaleRate: 1 5 6 9  
ScaleRate: 1 5 15 18  
ScaleRate: 1 5 16 19  
ScaleRate: 1 11 8 18  
ScaleRate: 11 1 18 8  
ScaleRate: 5 1 8 5  
ScaleRate: 5 1 9 6  
ScaleRate: 5 1 18 15  
ScaleRate: 5 1 19 16  
ScaleRate: 12 11 19 18  
ScaleRate: 8 9 18 19  
ScaleRate: 8 18 9 19  
ScaleRate: 18 8 19 9  
ScaleRate: 1 11 10 20  
ScaleRate: 11 1 20 10  
ScaleRate: 1 5 8 10  
ScaleRate: 1 5 18 20  
ScaleRate: 5 1 10 8  
ScaleRate: 5 1 20 18  
FixRate: 3 21  
FixRate: 21 3  
FixRate: 7 23  
ScaleRate: 1 5 21 23  
ScaleRate: 5 1 23 21  
FixRate: 23 7  
FixRate: 4 22  
FixRate: 22 4  
LoopBal: 3 2 12 13 14 4  
FixRate: 1 2  
FixRate: 2 1  
FixRate: 1 11  
FixRate: 11 1