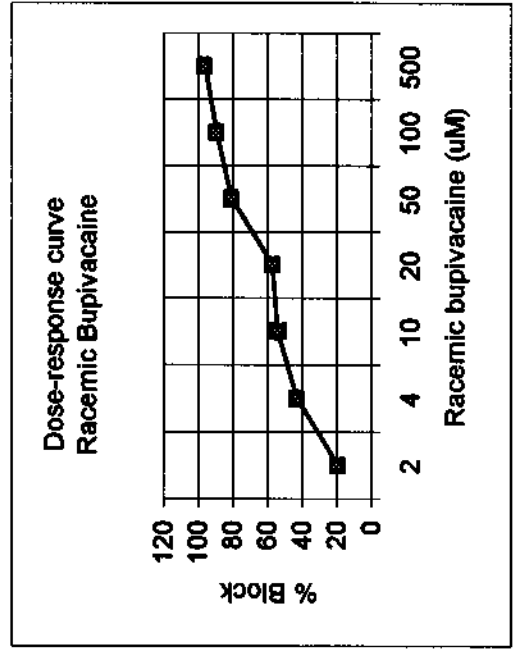


**Worksheet of data of the effects of racemic  
bupivacaine on hKv1.5 channels**

**Percentage of block induced by racemic Bupivacaine on HK2**

Exp.	2	4	10	20	50	100	500
T9O01A				64,7			
T9O01B				52,8			
T9O05A				52,7			
T9O22A					74,2	89	97,9
T9O22B					77,7	88,9	98,1
T9O26A	24,1	43,2	61,5				93,1
T9O05B				58,9			
T9N12A					85,4	93	
T9N12B					87	88	
M9N11A	20			52,6			
T9N12D	15			48,7			



N	3	1	3	4	4	4	3
Mean	19,7	43,2	54,26667	57,275	81,075	89,725	96,36667
SD	4,557412	#jDIV/0!	6,560742	5,736651	6,12284	2,229163	2,830783
SEM	2,631223	#jDIV/0!	3,787846	2,868326	3,06142	1,114581	1,634353



**Time dependence: inactivation with racemic bupivacaine.**

Exp.	TaoB	[D]	1/TaoB	k	l
T9O01B	0,012396	20	80,67118	2,881114	10,88111
T9O01A	0,01038	20	96,33911	3,440683	11,44068
T9O05A	0,01303	20	76,74597	2,740928	10,74093
T9O05B	0,00941	20	106,2699	3,795354	11,79535
T9O22A	0,011912	50	83,94896	1,447396	9,447396
T9O22A	0,007275	100	137,457	1,27275	9,27275
T9O22A	0,004243	500	235,6823	0,463942	8,463942
T9O22B	0,013095	50	76,36502	1,316638	9,316638
T9O22B	0,009226	100	108,3893	1,003605	9,003605
T9O22B	0,006496	500	153,9409	0,303033	8,303033
T9O26A	0,022931	10	43,60909	2,422727	10,42273
T9N12A	0,006034	50	165,7275	2,857371	10,85737
T9N12A	0,005136	100	194,704	1,802815	9,802815
T9N12B	0,005903	50	169,4054	2,920783	10,92078
T9N12B	0,005069	100	197,2776	1,826644	9,826644
T9N12D	0,011687	10	85,56516	4,75362	12,75362

N	Mean	SD	SEM
16	2,203088	1,235866	0,308967
16	10,20309	1,235866	0,308967

**Activation kinetics**

Exp.	Control		Racemic Bupivacaine (20 uM)	
	Tao (0)	Tao (+60)	Tao (0)	Tao (+60) Conc.
T9O01B		1,303		1,032
T9O01A		1,371		0,979
T9O05A		1,732		1,431
T9O05B		1,386		1,298

N	Mean	SD	SEM	t-test
4	1,448	0,192747	0,096373	
4	1,185	0,215352	0,107676	
			0,025829	P<0.05

**Time dependence: inactivation of racemic IQB-9302.**

Exp.	TaoB	[D]	1/TaoB	k	l
T9629A	0,0077	10	129,8701	3,607504	93,79509
T9630A	0,0131	10	76,33588	2,120441	55,13147
T9630A	0,00364	100	274,7253	2,180359	56,68934
T9630B	0,01033	10	96,80542	2,689039	69,91503
T9630B	0,00426	100	234,7418	1,86303	48,43878
T9701A	0,02362	2	42,337	1,512036	39,31293
T9701A	0,00427	50	234,192	3,081474	80,11833
T9701B	0,01385	2	72,20217	2,578649	67,04487
T9701B	0,00739	50	135,318	1,7805	46,293
T9922A	0,016554	20	60,40836	1,313225	34,14386

N	Mean	SD	SEM	t-test
10	0,010471	0,006404	0,002025	
10	2,272626	0,718313	0,22715	
10	59,08827	18,67614	5,905913	
		0,873446	1,66E-10	

**Percentage of washout**

Exp.	[D]	%washout
T9O01A	20	96,7
T9O01B	20	97,1
T9O05A	20	90,2
T9O22B	500	83
T9N12A	100	88,6
T9N12B	100	82,4
N		6
Mean		89,66667
SD		6,377983
SEM		2,603801

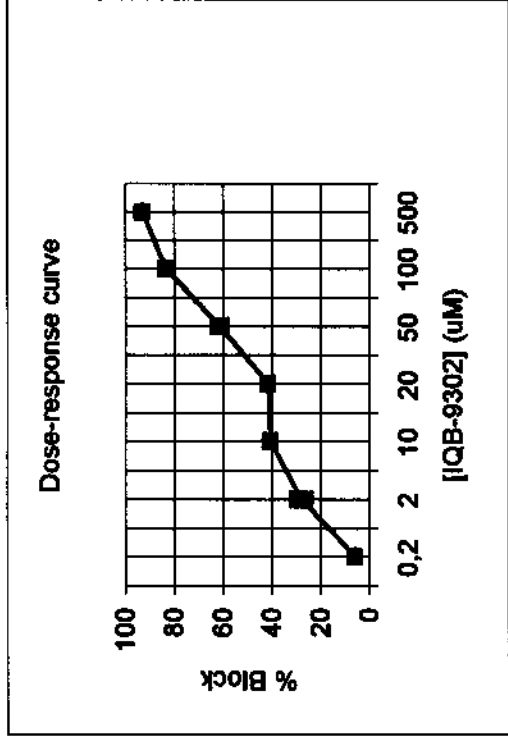
**KD\* for each experiment**

Exp.	Delta	KD	KD*
T9O01A	0,15	23,3000	33,39658
T9O01B	0,16	17,9000	26,2798
T9O05A	0,17	17,9500	26,99334
T9N12A	0,16	8,5	12,47924
T9N12A	0,22	7,5	12,71653
T9N12B	0,22	7,5	12,71653
T99O26A	0,17	5,2	7,819797
T99O26A	0,22	6,3	10,68189
T9N12D	0,1	10,5	13,34812
T9O22A	0,23	17,4	30,21898
T9O22A	0,26	12,4	23,1431
T9O22B	0,28	14,4	28,19736
T9O22B	0,33	12,5	27,5976
T9O05B	0,16	13,96	20,49531
N		14	14
Mean		12,52214	20,43458
SD		5,313171	8,533782
SEM		1,420005	2,280749
t-test			7,43E-06
			P<0.001

**Worksheet of data of the effects of racemic  
IQB-9302 on hKv1.5 channels**

**Percentage of block induced by racemic IQB-9302 in hKv1.5 channels**

Exp.	0,2	2	10	20	50	100	500
T9507A				45,8			
T9511D				36,1	51,9		
T9512A				47	65,2		
T9629A			41,4			84,2	
T9630A			34			83,3	
T9630B			39,7				
T9701A		20,4			65		
T9701B		40			63,8		
T9706A		39,1					
T9706B		20	40,7				
T9706D		21,7	48				
T9709A		6					
T9921A				38,8			
T9922A				45,3			
T9922B				53,4			
T9001A				46,2			
T9001B				29,3			
T8005A				35,2			
T8005B				39,3			
T8026A							93,1



N	1	6	5	10	4	2	1
Mean	6	28,24	40,76	41,64	61,475	83,75	93,1
SD	#DIV/0!	10,34857	4,991292	7,121985	6,413203	0,636396	#DIV/0!
SEM	#DIV/0!	4,224788	2,232174	2,252169	3,206601	0,45	#DIV/0!

**Voltage dependence: delta**

Exp.	Delta	Conc.
T9507A	0,25	20
T8512A	0,16	20
T8701A	0,17	50
T9821A	0,15	20
T9822A	0,16	20
T9001A	0,2	20
T9001B	0,13	20
T9005A	0,24	20
T9005B	0,13	20
T9701B	0,13	50

N 10  
 Mean 0,172  
 SD 0,044171  
 SEM 0,013968

**Time dependence: deactivation.**

Exp.	Control					Racemic IQB-9302 20uM						
	Tf	Ts	Af	As	Af+As	Af/(Af+As)	Tf	Ts	Af	As	Af+As	Af/(Af+As)
T9512A	14,8	25	99,3	70,1	169,4	0,586187	35,2	243,4	114	27,2	141,2	0,807365
T9921A	12,893	39,183	331,353	264,499	595,852	0,5561	23,444	64,789	154,776	221,15	375,926	0,411719
T9922A	13,876	44,368	119,126	232,189	351,315	0,339086	20,71	84,149	37,359	161,646	199,005	0,187729
T9922B	23,441	70,956	222,156	136,739	358,895	0,619	27,339	79,683	45,511	108,402	153,913	0,295693
T9507A	30,15315	109,9934	119,9934	30,59373	150,5871	0,796837	34,17799	90,4212	11,30325	87,96757	99,27082	0,113863

N 5 5 5 5 5  
 Mean 19,03263 57,90008 178,3857 146,8241 325,2088 0,579442 28,1742 112,4884 72,58985 121,2731 193,863 0,363274  
 SD 7,505011 33,54114 98,09531 100,7873 180,1618 0,163697 6,40691 73,78915 59,58164 73,70556 107,8082 0,272558  
 SEM 3,356343 15,00005 43,86955 45,07346 80,57082 0,073208 2,865257 32,99851 26,64572 32,96213 48,2133 0,121892  
 t-test 0,040589 0,264775

**P<0.05 NS**

Exp.	Control					Racemic IQB-9302 10uM						
	Tf	Ts	Af	As	Af+As	Af/(Af+As)	Tf	Ts	Af	As	Af+As	Af/(Af+As)
T9630A	12,5	35,3	89,2	61,7	150,9	0,59112	34,3	20,2	101,2	20,2	121,4	0,833608
T9630B	15	43	241,4	227,8	469,2	0,514493	21,7	155,7	106,9	155,7	262,6	0,407083



**Time dependence: inactivation.**

Exp.	TaoB	[D]	1/TaoB	k	l
T9629A	0,0077	10	129,8701	3,607504	93,79509
T9630A	0,0131	10	76,33588	2,120441	55,13147
T9630A	0,00364	100	274,7253	2,180359	56,68934
T9630B	0,01033	10	96,80542	2,689039	69,91503
T9630B	0,00426	100	234,7418	1,86303	48,43878
T9701A	0,02362	2	42,337	1,512036	39,31293
T9701A	0,00427	50	234,192	3,081474	80,11833
T9701B	0,01385	2	72,20217	2,578649	67,04487
T9701B	0,00739	50	135,318	1,7805	46,293
T9822A	0,016554	20	60,40836	1,313225	34,14386
N		10			10
Mean	0,010471			2,272626	59,08827
SD	0,006404			0,718313	18,67614
SEM	0,002025			0,22715	5,905913

**Activation Kinetics**

Exp.	Control		Racemic IQB-9302		Conc.
	Tao (0)	Tao (+60)	Tao (0)	Tao (+60)	
T9507A	9,881	1,404	8,637	0,987	20
T9511D	7,0496	1,269	6,815	0,8101	20
T9512A	5,225	0,9636	7	0,5542	20
T9921A		1,472		0,901	20
N	3	4	3	4	
Mean	7,3852	1,27715	7,484	0,813075	
SD	2,346072	0,225416	1,002803	0,187088	
SEM	1,354505	0,112708	0,578968	0,093544	
t-test			0,949743	0,001116	
			NS		
					<b>P&lt;0.01</b>

**Percentage of washout:**

Exp.	[D]	%washout
T9630A	100	83,4
T9630B	100	79,4
T9701A	50	77,5
T9701B	50	61,6
T9706D	10	83,5
T9709A	20	99,6
T9821A	20	88,8
T9922A	20	85,1
T9922B	20	80,2

N	9
Mean	82,12222
SD	10,1001
SEM	3,366699

**KD\* for each experiment**

Exp.	Delta	KD	KD*
T9507A	0,25	23,7000	43,18422
T9512A	0,16	22,6000	33,18009
T9701A	0,17	26,9000	40,45241
T9921A	0,12	31,55	42,08004
T9922A	0,12	24,2	32,27693
T9O01A	0,15	23,3	33,39658
T9O01B	0,13	48,3	65,98527
T9O05A	0,13	36,8	50,27449
T9O05B	0,13	30,9	42,21418

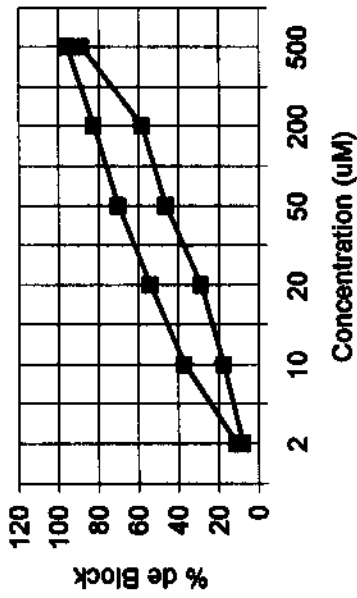
N	9	9
Mean	29,80558	42,56047
SD	8,415701	10,55421
SEM	2,805234	3,51807

**Worksheet of data of the effects of the IQB-9302  
enantiomers on hKv1.5 channels**

## Effects of IQB-9302 enantiomers on hKv1.5 channels

		<u>Percentage of block induced by R(+) enantiomer</u>						<u>Percentage of block induced by S(-) enantiomer</u>					
Exp.	2	10	20	50	200	500	Exp.	2	10	20	50	100	500
98D15B		43,2					T9210B	14,1				61,1	
98N25A		31					T9210A	10,6				52,7	
98N25B		37,5					T9208D				29,3		
98D15A		47					T9209A				39,2		
98D15D		44,3					T9205A				54,1		
98D16A	13,7		53,4	75			T9204A		9,3		37		
T9202B		38,4					T9203D		34,1				
T9205A				62,2			T9202A		13,7				
T9202A		18,5					T9406A					55,5	
T9422B				74,8			T9407A						
T9423A			58,6				T9407B					64,1	
T9427A	3,6						T9413A	0		25,4			
T9427B	13,6						T9415A	8		23			
T9504A	13,6		50,5				T9416A			29,1			85,9
T9504B			54,3				T9420A						91
T9505B				69,4			T9421B		13,4				
T9506A					77,6		T9422B				48,5		
T9508B					87,3		T9608A			38,8			
T9506D						95,8	T9720A			29			
							T9720B				38,6		
							T9721A				53		
							T9727A				58,9		
							T9727B				49,4		
											57,1		
N	4	4	7	4	4	2	1 N	4	4	5	10	4	2
Mean	11,125	37,12857	54,2	70,35	82,45	95,8	Mean	8,175	17,625	29,02	46,51	58,35	88,45
SD	5,016888	9,764513	3,351617	6,020797	6,858936	#DIV/0!	SD	5,995762	11,16524	5,939865	9,890113	5,185557	3,606245
SEM	2,508444	3,690639	1,675808	3,010399	4,85	0 SEM	SEM	2,997861	5,562618	2,656369	3,127528	2,592778	2,55
t-test							t-test	0,040422	0,000136	0,000808			

Block induced by R- y S-IQB-9302



**Voltage dependence: delta**

Exp.	R-IQB-9302		S-IQB-9302	
	Delta	Conc.	Delta	Conc.
98D15B	0,16	10 T9209D	0,16	50
98N25A	0,2	10 T9209A	0,14	50
98N25B	0,16	10 T9203D	0,35	10
98D15A	0,14	10 T9204A	0,27	50
T9202B	0,29	10 T9407A	0,13	20
98D16A	0,24	2 T8413A	0,25	20
T9504A	0,11	2 T9416A	0,13	20
T9505B	0,1	50 T9205A	0,14	50
T9422B	0,2	50 T9422B	0,16	50
T9423A	0,21	20 T9721A	0,13	50
		T9727A	0,1	50
		T9727B	0,11	50

N	10	N	12
Mean	0,181	Mean	0,1725
SD	0,058775	SD	0,076292
SEM	0,018586	SEM	0,022024
t-test			0,776412
			NS

**Time dependence: deactivation**

Exp.	Control					S-IQB-9302 (100 $\mu$ M)							
	Tf	Ts	Af	As	Af+As	Af/(Af+As)	Tao	Tf	Ts	Af	As	Af+As	Af/(Af+As)
T9210A	16,3	42	150,9	94	244,9	0,61617	85,2						
T9210B	22	61,7	43,2	130,4	173,6	0,249848	166,4						
T9406A	17,2	59,7	50,4	7,9	58,3	0,864494	57,1						
T9407B	16	55,5	171,9	218,7	390,6	0,440092	100						
N	4	4	4	4	4	4	4						
Mean	17,875	54,725	104,1	112,75	216,85	0,542401	102,175						
SD	2,796873	8,868061	66,78218	87,33462	139,0258	0,261933	46,36625						
SEM	1,398437	4,43403	33,39109	43,66731	69,51291	0,130966	23,18313						
t-test							0,119962						

Exp.	Control					S-IQB-9302 (20 $\mu$ M)						
	Tf	Ts	Af	As	Af+As	Af/(Af+As)	Tf	Ts	Af	As	Af+As	Af/(Af+As)
T9416A	24,6	70,5	18,2	45,7	63,9	0,28482	33,13	233,21	18,03	49,67	67,7	0,266322
T9407A	10,6	40,6	371,9	173,7	545,6	0,681635	19,1	61,6	166,2	363,6	529,8	0,313703
T9608A	17,6	52	60,7	194,2	254,9	0,238133	44,2	206,2	107,8	58,8	166,6	0,647059
T9413A	26,1	100,2	96,9	39,4	136,3	0,710932	30,2	195,1	25,1	98,6	123,7	0,20291
T9720A	10,8	29,8	61,4	44	105,4	0,582543	29,4	141	68,5	2,6	71,1	0,963432
N	5	5	5	5	5	5	5	5	5	5	5	5
Mean	17,94	58,62	121,82	99,4	221,22	0,498612	31,206	167,422	77,126	114,654	191,78	0,478685
SD	7,346972	27,70004	142,5521	77,55704	194,764	0,223144	8,991311	67,98684	61,53967	143,2921	193,3171	0,320818
SEM	3,285666	12,38783	63,75121	34,68456	87,10109	0,099793	4,021037	30,40911	27,52137	64,06219	86,45402	0,143474
t-test							0,031691	0,012764				0,916554

P<0.05 P<0.05

Exp.	Control						R-IQB-9302 (10 $\mu$ M)					
	Tf	Ts	Af	As	Af+As	Af/(Af+As)	Tf	Ts	Af	As	Af+As	Af/(Af+As)
98D15B	22,2	56,4	172,9	129,9	302,8	0,571004	36,2	91,8	43,9	132,7	176,6	0,248584
T9202B	10,3	28,6	131,2	100,3	231,5	0,568739	20,2	73,7	79,4	77,1	156,5	0,507348
T9202A	13,3	37,2	258,6	137,9	394,5	0,650444	12,9	41,1	136	202	338	0,402367
98N25B	25,1	59	57,5	76,7	134,2	0,428465	30,8	84	6,9	82	88,9	0,077615
98D15A	22,7	61	277,4	228,8	508,2	0,548005	40	74,3	101,9	156	257,9	0,395114
N	5	5	5	5	5	5	5	5	5	5	5	5
Mean	18,72	48,44	179,12	134,72	313,84	0,552931	28,02	72,98	73,62	129,96	203,58	0,326206
SD	6,498615	14,59959	90,53804	57,95569	143,7713	0,079909	11,26863	19,32762	50,14795	52,36815	96,32672	0,166721
SEM	2,906269	6,529135	40,48984	25,91857	64,29646	0,035737	5,039484	8,643576	22,42685	23,41975	43,07862	0,07456
t-test							0,040342	0,0294				0,013772
							P<0.05	P<0.05				P<0.05

Exp.	Control						S-IQB-9302 (50 $\mu$ M)					
	Tf	Ts	Af	As	Af+As	Af/(Af+As)	Tf	Ts	Af	As	Af+As	Af/(Af+As)
T9422B	19,4	55,3	240,9	176,6	417,5	0,577006	16,6	81,5	46,6	193,6	240,2	0,194005
T9720B	16	49,8	150,4	97,9	248,3	0,605719	31,9	169,2	95,1	19,5	114,6	0,829843
T9721A	14,054	38,32	194,194	133,6	327,794	0,592427	35,39	1195,808	131,271	111,906	243,177	0,539817
T9727A	15,254	49,525	91,86	352,616	444,476	0,20667	44,473	504,944	150,868	193,768	344,636	0,43776
T9727B	13,234	83,713	139,84	83,713	223,553	0,625534	32,233	197,52	71,478	28,385	99,663	0,715761
N	5	5	5	5	5	5	5	5	5	5	5	5
Mean	15,5884	55,3316	163,4388	168,8858	332,3246	0,521471	32,1192	429,7944	99,0634	109,4318	208,4952	0,543437
SD	2,382599	17,02362	56,56094	108,8058	98,41837	0,176879	10,05262	457,0542	42,57381	84,94015	101,6853	0,247491
SEM	1,065531	7,613194	25,29482	48,65941	44,01404	0,079103	4,495671	204,4008	19,03959	37,98639	45,47505	0,110681
t-test							0,035794	0,147721				
							P<0.05	NS				

**Time dependence: inactivation. Rate constants**

**R-1QB-9302: kinetics**

Exp.	TaoB	[D]	1/TaoB	k	l
T9506D	0,00346	500	289,0173	0,557303	10,36584
T9506B	0,00256	200	390,625	1,78894	33,23708
T9506A	0,00275	200	363,6364	1,663478	30,9407
T9505B	0,00457	50	218,8184	3,189772	59,32977
98D15A	0,00891	10	112,2334	3,924246	72,99098
T95423A	0,00749	20	133,5113	3,458843	64,33448
98D15B	0,00646	10	154,7988	5,412544	100,6733
N				7	7
Mean	0,005171			2,856161	53,12459
SD	0,002483			1,633039	30,37452
SEM	0,000938			0,617231	11,48049

**S-1QB-9302: kinetics**

Exp.	TaoB	[D]	1/TaoB	k	l
T9422B	0,00868	50	149,7006	1,378459	80,77767
T9416A	0,00681	500	146,8429	0,262877	15,40457
T9420A	0,00684	500	146,1988	0,261724	15,33701
T9406A	0,0132	100	75,75758	0,477664	27,98113
T9205A	0,01279	50	78,18608	0,719946	42,18881
T9407B	0,00716	100	139,2758	0,878157	51,46002
T9608A	0,01492	20	67,02413	0,852724	49,96964
T9720A	0,01797	20	55,6463	0,707994	41,48843
T9720A	0,01621	50	61,69031	0,568051	33,28778
T9720B	0,02224	50	44,98403	0,414033	24,26236
T9721A	0,022919	50	43,63192	0,401767	23,54356
T9727A	0,011171	50	89,5175	0,824286	48,30318
T9727B	0,015506	50	64,49116	0,593841	34,7991

N		13	13
Mean	0,013418	0,641656	37,60102
SD	0,005627	0,305372	17,89478
SEM	0,001561	0,084695	4,96312
T-TEST		0,00013	0,164074
		P<0.01	NS



**Activation kinetics with and without IQB-9302 enantiomers**

Exp.	Control		S-IQB-9302 (50 $\mu$ M)	
	Tao (0)	Tao (+60)	Tao (0)	Tao (+60)
T9422B		1,418		1,182
T9205A		0,848		0,735
T9204A		1,486		1,201
T9209A		1,683		1,636
T9209D		1,552		1,272
T9720B		0,963		0,946
T9727A		0,997		0,692
T9727B		1,285		0,817

N	8	8
Mean	1,279	1,060125
SD	0,308242	0,321732
SEM	0,10898	0,113749
t-test		0,186407
		NS

Exp.	Control		R-IQB-9302 (10 $\mu$ M)	
	Tao (0)	Tao (+60)	Tao (0)	Tao (+60)
98N25B		1,761		1,365
98N25A		2,723		1,338
98D15B		1,503		1,335
98D15D		1,605		1,098
98D15A		1,454		1,21
T9202A		1,372		1,293

N	6	6
Mean	1,736333	1,273167
SD	0,50165	0,101515
SEM	0,204798	0,041443
t-test		0,050983
		NS

**Percentage of washout:**

**R-IQB-9302**

Exp.	[D]	%washout
98N25A	10	100
98N25B	10	90
98D15A	10	94,3
98D15B	10	98,1
98D15D	10	100
T9422B	50	99,1
T9202B	10	89,6
T9423A	20	96,7
T9427A	2	100

**S-IQB-9302**

Exp.	[D]	%washout
T9203D	10	89,7
T8204A	50	99,4
T9205A	50	81,8
T9209A	50	87,8
T9209D	50	89,1
T9210A	100	100
T9210B	100	84,7
T9422B	50	91,2
T9608A	20	99
T9720B	50	91,2
T9720A	50	97,2
T9721A	50	86,9
T9727A	50	75,9
T9727B	50	91

N	9
Mean	96,42222
SD	4,194573
SEM	1,398191

N	14
Mean	90,35
SD	6,977188
SEM	1,864732

***Washout of all experiments***

N	23
Mean	92,72609
SD	6,659253
SEM	1,36855

**KD\* for each experiment**

**R-IQB-9302**

Exp.	Delta	KD	KD*
98D16A	0,24	17,4000	30,95301
T9505B	0,1	22,0000	27,96748
T9504A	0,11	18,6000	25,52171
T9205A	0,14	30,4000	42,53991
T9202B	0,29	16	32,09142
98D15B	0,16	13,2	19,37952
98N25B	0,16	16,7	24,51803
98N25A	0,2	22,2	39,4938
T9423A	0,21	14,1	25,0839
T9422B	0,2	16,8	29,8872

N	10
Mean	28,7436
SD	7,017596
SEM	2,219159

**S-IQB-9302**

Exp.	Delta	KD	KD*	KD*
T9721A	0,13	34,9	47,6788	47,6788
T9721B	0,26	50	93,31893	93,31893
T9422B	0,16	53,1	77,95852	77,95852
T9416A	0,13	48,7	66,53173	66,53173
T9413A	0,23	58,7	101,9456	101,9456
T9407A	0,13	172,3	235,3885	
T9209D	0,16	120,6	177,0583	
T9209D	0,14	77,6	108,5887	
T9204A	0,27	85,1	162,6868	162,6868
T9203D	0,35	19,3	44,70588	44,70588
T9727A	0,1	51,2	65,08796	65,08796
T9727B	0,11	37,6	48,96002	48,96002

N	12	9
Mean	102,4925	78,76361
SD	59,90153	37,3231
SEM	17,29208	26,2546