Supplemental Information

Supplemental Table 1

Compounds inhibiting KCNJ5^{G151R} with >33.3% effect in primary and confirmatory screening.

Compound ID	Supplier	Supplier ID	Drug Name	% effect (1)	% effect (2)	mean % effect
YU225283	Microsource	1503276	Roxithromycin	107.6	107.0	107.3
YU199271	ChemDiv	G118-0224		83.9	102.3	93.1
YU156201	ChemDiv	3132-1065		100.5	81.0	90.7
YU156312	ChemDiv	3232-1884		109.1	70.3	89.7
YU200104	ChemDiv	G281-1947		87.9	90.9	89.4
YU194148	ChemDiv	F471-0857		68.2	110.6	89.4
YU170857	ChemDiv	3572-5949		79.4	98.0	88.7
YU194117	ChemDiv	F471-0014		80.3	96.1	88.2
YU195258	ChemDiv	F580-0413		98.0	74.1	86.1
YU164410	ChemDiv	D089-0525		72.1	99.3	85.7
YU192559	ChemDiv	F351-0044		106.7	61.8	84.2
YU186983	ChemDiv	E612-0759		100.6	63.9	82.3
YU221968	NCI	NSC645033	Pyrimidine	77.2	86.6	81.9
YU156202	ChemDiv	3132-1071		107.1	49.8	78.5
YU156203	ChemDiv	3132-1074		83.6	68.5	76.1
YU155936	ChemDiv	2434-0130		80.2	70.7	75.5
YU164355	ChemDiv	D089-0323		82.5	68.3	75.4
YU214474	ChemDiv	L437-0030		41.7	108.8	75.3
YU186982	ChemDiv	E612-0750		83.3	64.8	74.1
YU205248	ChemDiv	G764-0071		84.3	62.8	73.6
YU176999	ChemDiv	C700-2077		80.3	66.2	73.2
YU034553	Microsource	1501176	Erythromycin	91.9	54.2	73.0
YU173899	ChemDiv	C200-9149		70.1	75.5	72.8
YU039827	Microsource	2300165	Amiodarone hydrochloride	77.8	65.9	71.8
YU200116	ChemDiv	G281-2440		54.5	87.7	71.1
YU164429	ChemDiv	D089-0725		65.8	75.6	70.7
YU182169	ChemDiv	D393-0253		63.3	77.5	70.4
YU163288	ChemDiv	C620-0363		70.5	68.6	69.5
YU164416	ChemDiv	D089-0533		53.7	82.7	68.2
YU214875	ChemDiv	L491-0661		84.0	52.1	68.1

Compound ID	Supplier	Supplier ID	Drug Name	% effect (1)	% effect (2)	mean % effect
YU165270	ChemDiv	D297-0001		94.9	40.9	67.9
YU164350	ChemDiv	D089-0310		81.9	50.4	66.1
YU039449	NCC	SAM001246981	Indatraline	70.6	61.3	65.9
YU171244	ChemDiv	5340-0013		58.6	73.1	65.8
YU155938	ChemDiv	2434-0134		83.4	47.9	65.7
YU195274	ChemDiv	F580-1522		74.6	49.9	62.3
YU156667	ChemDiv	3534-0434		68.1	56.0	62.0
YU164338	ChemDiv	D089-0264		54.7	69.0	61.9
YU164351	ChemDiv	D089-0311		77.7	44.0	60.8
YU164423	ChemDiv	D089-0559		66.6	54.9	60.8
YU200600	ChemDiv	G345-0648		84.8	36.5	60.6
YU164347	ChemDiv	D089-0297		64.9	56.2	60.6
YU164343	ChemDiv	D089-0287		55.9	64.5	60.2
YU171246	ChemDiv	5340-1529		49.4	70.7	60.0
YU225090	Enzo	CA-305	Phenoxybenzamine -HCl	67.8	52.1	59.9
YU161687	ChemDiv	8017-3019		65.0	53.9	59.4
YU177007	ChemDiv	C700-2100		63.5	54.8	59.2
YU170768	ChemDiv	3141-0464		75.7	40.9	58.3
YU158463	ChemDiv	5137-3628		58.7	57.6	58.2
YU223483	NCI	NSC341196		48.0	68.3	58.1
YU159856	ChemDiv	6456-0125		62.8	53.1	58.0
YU224116	Enzo	KC-159	U-37883A-HCl	49.9	65.8	57.9
YU223163	NCI	NSC33823		43.9	65.7	54.8
YU200092	ChemDiv	G281-1685		47.4	60.1	53.8
YU164352	ChemDiv	D089-0316		55.1	52.4	53.7
YU164430	ChemDiv	D089-0731		39.2	68.3	53.7
YU033748	Enzo	DL-247	Clemastine	60.8	44.6	52.7
YU207124	ChemDiv	G856-5896		47.7	57.8	52.7
YU164420	ChemDiv	D089-0547		62.5	42.4	52.4
YU221408	NCI	NSC719276	Fulvestrant	65.0	39.6	52.3
YU164426	ChemDiv	D089-0562		59.6	44.2	51.9
YU199273	ChemDiv	G118-0292		64.8	38.0	51.4
YU175883	ChemDiv	C530-0280		68.9	33.7	51.3
YU164362	ChemDiv	D089-0344		62.7	39.1	50.9
YU155939	ChemDiv	2434-0139		66.0	35.2	50.6
YU199272	ChemDiv	G118-0226		48.2	49.4	48.8
YU158681	ChemDiv	5320-4034		48.2	48.9	48.5
YU209326	ChemDiv	J006-1570		48.1	48.9	48.5
YU187648	ChemDiv	E762-2304		59.9	35.0	47.4

Compound ID	Supplier	Supplier ID	Drug Name	% effect (1)	% effect (2)	mean % effect
YU164400	ChemDiv	D089-0499		41.7	52.7	47.2
YU188170	ChemDiv	E864-1074		38.5	55.1	46.8
YU179100	ChemDiv	D089-0253		53.5	40.0	46.8
YU197082	ChemDiv	F788-0051		35.9	57.3	46.6
YU040261	Enzo	DL-566	Nelfinavir mesylate	42.0	51.2	46.6
YU158754	ChemDiv	5465-0013		54.8	35.9	45.4
YU161684	ChemDiv	8017-2854		36.2	53.5	44.9
YU164332	ChemDiv	D089-0232		49.5	39.4	44.4
YU164421	ChemDiv	D089-0554		35.1	51.3	43.2
YU207147	ChemDiv	G856-6079		35.0	50.5	42.8
YU205819	ChemDiv	G786-2333		46.8	38.7	42.8
YU034516	Enzo	AC-124	Propafenone	39.7	45.5	42.6
YU161686	ChemDiv	8017-3017		42.8	42.4	42.6
YU226705	Microsource	1502084	Proadifen HCl	43.3	41.0	42.1
YU164427	ChemDiv	D089-0563		36.0	48.0	42.0
YU206375	ChemDiv	G809-0126		39.2	44.3	41.8
YU224113	Enzo	ALX-550-253	Loperamide-HCl	35.2	47.6	41.4
YU177904	ChemDiv	C796-1275		46.7	34.9	40.8
YU212319	ChemDiv	L150-0457		38.4	40.5	39.4
YU226729	Microsource	1503118	Triflupromazine HCl	39.5	39.2	39.4
YU225091	Microsource	1500591	Trifluoperazine HCl	41.9	35.6	38.7
YU224969	Microsource	1503106	Bepridil HC	33.4	43.9	38.7
YU156360	ChemDiv	3258-0337		34.1	39.8	36.9

Compounds with >33.3% effect in initial and confirmatory screen are shown. Data are sorted by mean % effect (see Methods).

Supplemental Table 2

$KCNJ5^{G151R}$, $KCNJ5^{L168R}$ and $KCNJ5^{WT}$ inhibition characteristics of 98 compounds tested in dose-response assays

				G151R					L168R					WT					
Compound ID	**Supplier**	**Supplier ID**	**Name**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**mean IC50 G151R / L168R**
YU225283	Microsource	1503276	Roxithromycin	0.37	2.25	11.58	0.96	97.14	0.39	20.09	7.15	0.97	75.52	No Fit	NA	NA	NA	NA	0.76
YU228064	Toronto Research	R700852	Roxithromycin-D7	0.58	1.26	1.67	0.9	96.22	0.68	4.37	3.95	0.96	70.07	No Fit	NA	NA	NA	NA	1.26
YU223163	NCI	NSC18883		0.44	12.87	5.54	0.98	69.05	1.06	-9.84	10.55	0.71	1.09	No Fit	NA	NA	NA	NA	1.5
YU228063	Toronto Research	D231265	N-demethyl Roxithromycin	0.82	1.84	4.5	0.95	96.2	1.18	2.68	1.12	0.99	76.95	No Fit	NA	NA	NA	NA	2
YU164430	ChemDiv	D089-0731		1.13	37.2	3.4	0.84	53.42	2.73	3.29	-1.11	0.95	49.45	5.1	1.74	-4.67	0.82	80	3.86
YU224116	Enzo	KC-159	U-37883A hydrochloride	1.07	7.58	12.84	0.92	60.42	3.28	3.86	0.14	0.97	6.81	NA	NA	NA	NA	NA	4.36
YU164429	ChemDiv	D089-0725		0.51	5.25	9.58	0.92	64.38	4.76	1.54	0.39	0.99	59.85	4.09	1.52	12.04	0.87	75	5.27
YU158463	ChemDiv	5137-3628		0.68	1.98	9.85	1	68.87	5.04	2.84	0.83	0.96	12	NA	NA	NA	NA	NA	5.72
YU158681	ChemDiv	5320-4034		2.05	2.33	11.42	0.99	73.8	3.85	3.92	-0.16	0.96	14.06	NA	NA	NA	NA	NA	5.91
YU228018	Toronto Research	E650010	Erythromycin A Oxime (Roxithromycin Impurity C)	1.45	1.05	-3.29	0.97	110.11	4.59	2.35	1.01	0.97	47	No Fit	NA	NA	NA	NA	6.04
YU164352	ChemDiv	D089-0316		4.05	1.88	2.68	0.95	58.32	2.31	1.26	0.06	0.93	3.6	4.9	1.74	16.74	0.72	50	6.36
YU040261	Enzo	DL-566	Nelfinavir mesylate	5.72	4.11	3.67	0.98	70	1.77	1.06	-0.35	0.86	10	NA	NA	NA	NA	NA	7.49
YU170857	ChemDiv	3572-5949		3.24	1.97	3.79	0.99	97.9	4.25	8.14	1.61	0.99	21.04	3.84	1.83	10.69	0.95	65	7.49
YU164426	ChemDiv	D089-0562		2.08	1.23	1.27	0.92	59.28	5.5	1.24	0.1	0.74	8.88	0.92	1.6	13.89	0.91	39.54	7.58
YU039827	Microsource	2300165	Amiodarone hydrochloride	4.31	2.37	12.29	0.97	80	3.35	3.08	1	0.92	5.49	NA	NA	NA	NA	NA	7.66
YU223483	NCI	NSC341196		2.06	3.6	2.12	0.98	71.07	5.61	3.23	2.85	0.9	32	No Fit	NA	NA	NA	NA	7.67
YU164347	ChemDiv	D089-0297		3.98	1.45	2.77	0.99	75.58	3.87	8.97	0.37	0.77	4.26	4.59	5.49	8.8	0.88	59.58	7.85
YU226705	Microsource	1502084	Proadifen hydrochloride	4.87	3.33	9.56	0.97	60	3.94	8.36	0.85	0.85	5.6	NA	NA	NA	NA	NA	8.81

				G151R					L168R					WT					
Compound ID	**Supplier**	**Supplier ID**	**Name**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**mean IC50 G151R / L168R**
YU164423	ChemDiv	D089-0559		3	1.47	1.57	0.93	73.86	5.88	2.9	0.26	0.91	10	4.15	1.13	18.43	0.71	100	8.88
YU156203	ChemDiv	3132-1074		5.28	1.45	9.73	0.99	100	3.74	3.11	0.17	0.91	7.57	NA	NA	NA	NA	NA	9.02
YU161687	ChemDiv	8017-3019		5.14	3.68	7.74	0.97	60	3.9	7.88	0.85	0.88	6.41	NA	NA	NA	NA	NA	9.04
YU164420	ChemDiv	D089-0547		4.24	1.46	0.2	0.92	84.54	4.95	3.66	-2.23	0.84	5.35	No Fit	NA	NA	NA	NA	9.19
YU164427	ChemDiv	D089-0563		4.31	2.28	6.73	0.98	70	4.97	3.01	0.94	0.84	8	4.95	1.38	11.99	0.85	80	9.28
YU156202	ChemDiv	3132-1071		4.4	1.43	9.01	0.95	88.62	5.58	4.08	0.5	0.86	9	NA	NA	NA	NA	NA	9.97
YU200116	ChemDiv	G281-2440		5.3	4.05	4.54	0.99	80	5.06	6.58	0.84	0.92	20.2	No Fit	NA	NA	NA	NA	10.36
YU207147	ChemDiv	G856-6079		3.62	2.72	2.76	0.9	50.26	7.41	6.31	0.81	0.93	8.45	No Fit	NA	NA	NA	NA	11.03
YU040325	Enzo	DL-357	Clarithromycin	8.38	1.55	4.77	0.99	100	2.98	1.8	0.27	0.94	10	NA	NA	NA	NA	NA	11.36
YU171244	ChemDiv	5340-0013		5.79	3.93	6.15	0.99	70	6.22	29.13	1.52	0.76	5.26	No Fit	NA	NA	NA	NA	12.01
YU164410	ChemDiv	D089-0525		5.52	4.96	1.23	0.93	60.3	6.5	9.82	0.2	1	41.02	No Fit	NA	NA	NA	NA	12.02
YU155936	ChemDiv	2434-0130		7.48	2.11	8.92	1	100	5.24	3.9	0.76	0.98	18	NA	NA	NA	NA	NA	12.71
YU034553	Microsource	1501176	Erythromycin estolate	7.85	1.52	8.8	0.98	75.76	6.64	1.84	2.28	0.9	8	NA	NA	NA	NA	NA	14.49
YU194117	ChemDiv	F471-0014		6.44	3.92	2.41	0.96	100	9.08	77.1	-0.03	0.92	12.53	6.69	3.4	4.06	0.69	30.41	15.52
YU164416	ChemDiv	D089-0533		6.87	1.76	0.49	0.97	91.29	9.01	6.67	-1.13	0.79	12.23	No Fit	NA	NA	NA	NA	15.88
YU159856	ChemDiv	6456-0125		8.37	1.5	7.88	0.99	100	9.06	19	0.22	0.88	14	NA	NA	NA	NA	NA	17.43
YU155502	Microsource	1500280	Erythromycin	10.53	1.4	3.55	0.87	90	11.76	1.31	0.71	0.94	25	No Fit	NA	NA	NA	NA	22.29
YU221968	NCI	NSC645033	Pyrimidine	1.42	2.71	5.43	0.98	64.56	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU164338	ChemDiv	D089-0264		1.72	1.42	5.91	0.84	17.84	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU221408	NCI	NSC719276	Fulvestrant	1.93	1.15	-1.21	0.9	40.71	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU176999	ChemDiv	C700-2077		2.92	1.57	4.14	0.95	59.77	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU187648	ChemDiv	E762-2304		3.66	4.41	3.35	0.98	33.46	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU161684	ChemDiv	8017-2854		3.75	1.91	10.14	0.96	60	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU164421	ChemDiv	D089-0554		3.94	1.47	2.29	0.97	64.01	No Fit	NA	NA	NA	NA	1.12	16.58	17.97	0.93	35.28	NA

				G151R					L168R					WT					
Compound ID	**Supplier**	**Supplier ID**	**Name**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**mean IC50 G151R / L168R**
YU195258	ChemDiv	F580-0413		4.05	11.03	3.39	1	65	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU212319	ChemDiv	L150-0457		4.05	15.94	1.6	0.98	35.53	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU179100	ChemDiv	D089-0253		4.1	4.46	3.25	0.92	24.95	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU164362	ChemDiv	D089-0344		4.13	4.35	3.37	0.96	31.22	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU164351	ChemDiv	D089-0311		4.15	3.31	3.75	0.98	71.94	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU156667	ChemDiv	3534-0434		4.19	1.34	2.76	0.86	57.23	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU200092	ChemDiv	G281-1685		4.34	5.25	3.41	0.88	23.31	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU173899	ChemDiv	C200-9149		4.48	2.07	6.28	0.97	80	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU224969	Microsource	1503106	Bepridil hydrochloride	4.56	7.01	5.2	0.99	64.13	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU155939	ChemDiv	2434-0139		4.59	5.97	0.64	0.97	47.39	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU034516	Enzo	AC-124	Propafenone	4.71	5.3	1.02	0.97	50	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU200104	ChemDiv	G281-1947		4.88	6.01	4.69	0.76	57.8	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU199271	ChemDiv	G118-0224		4.89	4.99	2.71	0.99	95	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU163288	ChemDiv	C620-0363		4.9	2.94	9.78	0.97	50	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU225091	Microsource	1500591	Trifluoperazine hydrochloride	4.97	2.42	5.78	0.96	40	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU205248	ChemDiv	G764-0071		5.03	2.37	2.03	0.86	58.52	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU164343	ChemDiv	D089-0287		5.05	2.4	5.78	0.94	65	No Fit	NA	NA	NA	NA	5.16	2.41	11.67	0.84	120	NA
YU164400	ChemDiv	D089-0499		5.09	2.05	2.87	0.9	26.98	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU161686	ChemDiv	8017-3017		5.14	2.23	3.27	0.9	30	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU188170	ChemDiv	E864-1074		5.14	6.8	1.3	0.99	25.45	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU171246	ChemDiv	5340-1529		5.29	5.14	3.04	0.71	38.01	No Fit	NA	NA	NA	NA	3.61	3.66	1.27	0.89	29.78	NA
YU194148	ChemDiv	F471-0857		5.3	2.91	3.15	0.98	82.52	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU170768	ChemDiv	3141-0464		5.37	5.69	3.75	0.99	60	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA

				G151R					L168R					WT					
Compound ID	**Supplier**	**Supplier ID**	**Name**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**mean IC50 G151R / L168R**
YU039449	NCC	SAM001246981	Indatraline	5.37	1.7	9.85	0.99	100	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU175883	ChemDiv	C530-0280		5.44	6.28	2.07	0.98	36	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU209326	ChemDiv	J006-1570		5.47	1.96	2.24	0.91	42	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU195274	ChemDiv	F580-1522		5.55	3.52	4.46	0.97	30	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU156201	ChemDiv	3132-1065		5.56	1.67	7.49	0.99	100	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU207124	ChemDiv	G856-5896		5.62	3.19	3.56	0.97	72	No Fit	NA	NA	NA	NA	0.17	-0.79	-16.77	0.76	1.2	NA
YU192559	ChemDiv	F351-0044		5.64	5.27	0.99	1	50	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU197082	ChemDiv	F788-0051		5.82	1.94	4.93	0.92	60	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU205819	ChemDiv	G786-2333		5.89	3.57	-2.2	0.98	50	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU206375	ChemDiv	G809-0126		6.16	3.05	3.12	0.98	52	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU177904	ChemDiv	C796-1275		6.23	1.86	3.12	0.94	25	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU182169	ChemDiv	D393-0253		6.35	3.7	1.13	0.97	60	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU226729	Microsource	1503118	Trifluprom azine hydrochloride	6.42	1.64	5.54	0.91	50	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU225090	Enzo	CA-305	Phenoxy-benzamine hydrochloride	6.5	3.6	5.01	1	100	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU164350	ChemDiv	D089-0310		6.71	1.91	1.29	0.78	22	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU033748	Enzo	DL-247	Clemastine	6.82	1.91	7.65	0.99	86.42	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU177007	ChemDiv	C700-2100		7.19	1.98	3.89	0.77	42	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU164355	ChemDiv	D089-0323		7.19	2.52	3.08	0.85	50	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU164332	ChemDiv	D089-0232		7.43	1.31	2.25	0.96	43.1	No Fit	NA	NA	NA	NA	6.1	2.28	19.63	0.8	80	NA
YU158754	ChemDiv	5465-0013		7.53	1.15	5.58	0.98	49.02	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU186983	ChemDiv	E612-0759		7.71	3.97	4.2	0.9	80	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU214474	ChemDiv	L437-0030		8.04	2.72	0.98	0.71	31.17	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU156312	ChemDiv	3232-1884		9.02	8.17	8.04	0.81	38.16	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

				G151R					L168R					WT					
Compound ID	**Supplier**	**Supplier ID**	**Name**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**IC_{50}**	**Hill**	**Minimum inhibition (%)**	**r^2**	**Maximum inhibition (%)**	**mean IC50 G151R / L168R**
YU200600	ChemDiv	G345-0648		9.38	9.03	2.71	0.67	30.59	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU224113	Enzo	ALX-550-253	Loperamide hydrochloride	9.51	2.99	6.37	0.94	99.75	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU155938	ChemDiv	2434-0134		No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
YU228017	Toronto Research	D226800	Decladinose Roxithromycin (Roxithromycin Impurity B)	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU165270	ChemDiv	D359-0544		No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU186982	ChemDiv	E612-0750		No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU199272	ChemDiv	G118-0226		No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU199273	ChemDiv	G118-0292		No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU214875	ChemDiv	L491-0661		No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA
YU156360	ChemDiv	3258-0337		No Fit	NA	NA	NA	NA	No Fit	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Inhibition data were obtained at 0.12 µM, 0.37 µM, 1.1 µM, 3.3 µM and 10 µM compound concentration in technical duplicates (see methods) for $KCNJ5^{G151R}$, $KCNJ5^{L168R}$ and $KCNJ5^{WT}$. IC_{50}, half maximal inhibitory concentration; Hill, Hill coefficient; LD_{50}, median lethal dose. Data are sorted by mean IC_{50} in G151R and L168R, then by IC_{50} in L168R, then by IC_{50} in G151R.

Supplemental Table 3

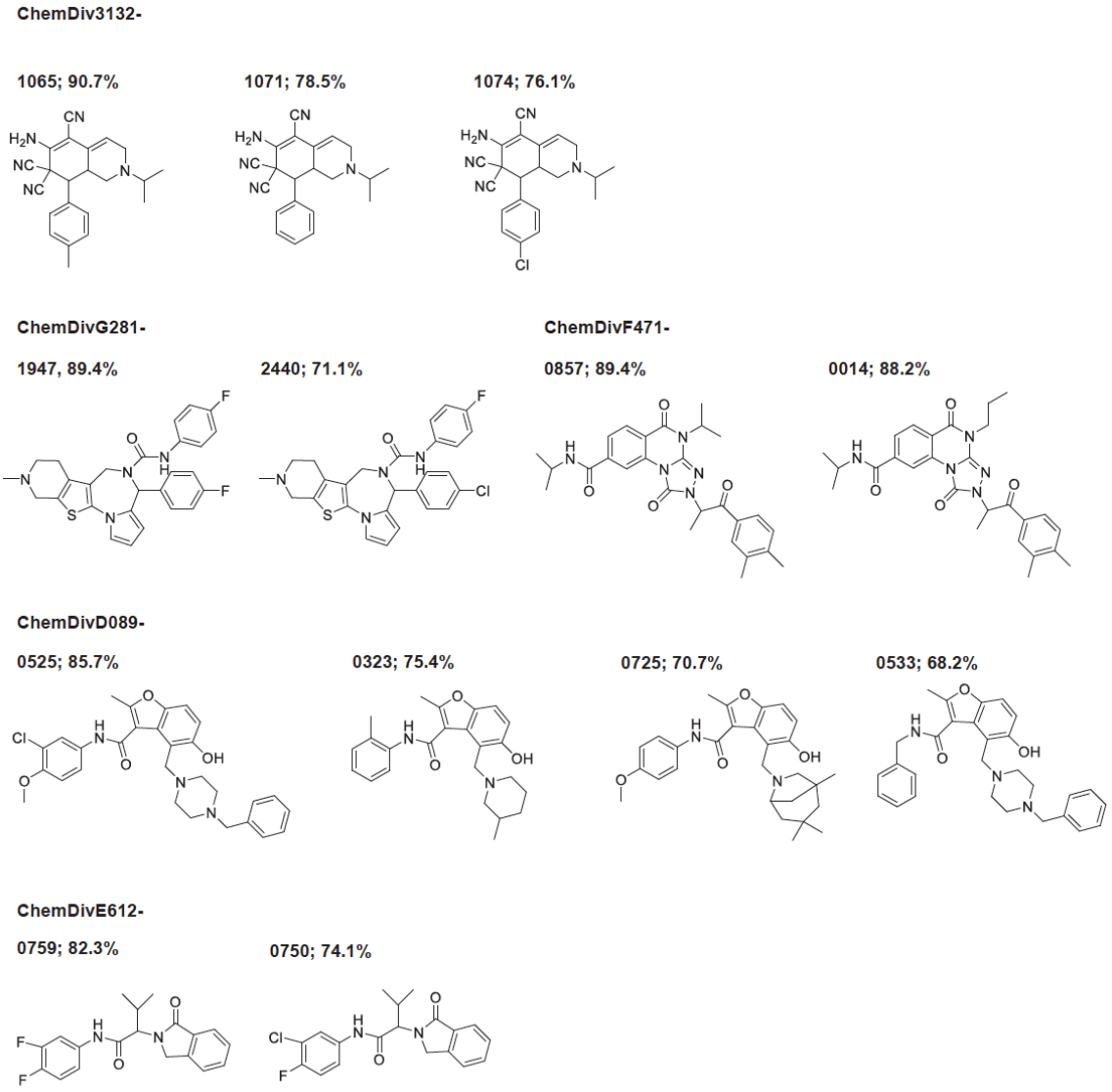
KCNJ5^{G151R} and ^{L168R} inhibition characteristics of idremcinal and synthesized macrolide derivatives

		G151R					L168R				
Compound ID	**Kirby Bauer zone diameter (mm)**	**IC_{50}**	**Hill**	**minimum inhibition (%)**	**r^2**	**maximum inhibition (%)**	**IC_{50}**	**Hill**	**minimum inhibition (%)**	**r^2**	**maximum inhibition (%)**
Idremcinal (EM574)	NA	0.54	2.88	5.47	0.89	73.81	1.99	2.09	-1.28	0.97	66.69
PLUX38	0	0.58	2.42	6.36	0.92	89.18	1.15	1.83	4.40	0.91	58.96
PLUX36	0	1.03	1.81	4.30	0.96	82.77	6.16	1.30	4.33	0.92	72.00
PLUX37	0	1.11	2.60	0.90	0.94	72.22	3.72	1.95	2.90	0.94	85.03
PLUX33	0	1.93	2.89	2.85	0.96	60.43	2.41	3.38	4.93	0.81	39.18
PLUX41	15	2.07	1.86	3.07	0.93	75.31	4.70	1.89	3.67	0.74	34.50
PLUX40	0	3.18	1.94	1.60	0.97	73.98	10.34	2.16	3.15	0.87	55.00
PLUX32	0	3.62	1.39	3.63	0.98	91.44	5.70	1.82	-0.35	0.99	67.94
PLUX30B	23	9.94	2.78	3.41	0.97	70.00	12.81	3.93	-0.41	0.98	22.00
PLUX34	0	10.24	2.19	1.33	0.76	12.93	No Fit	0.00	0.00	0.00	0.00
PLUX31A	13	11.00	3.00	3.48	0.93	30.00	No Fit	0.00	0.00	0.00	0.00
PLUX35A	18	11.33	1.52	0.56	0.86	38.00	No Fit	1.68	0.00	0.72	7.50
PLUX39	0	16.84	3.96	2.72	0.75	60.00	12.91	5.14	2.42	0.91	34.00
PLUX42	0	No Fit	No Fit	No Fit	No Fit	No Fit	No Fit	No Fit	No Fit	No Fit	No Fit

Synthesized macrolide derivatives were tested as in Supplemental Table 2. No KCNJ5^{WT} inhibition was observed for any of the compounds shown.

Supplemental Figure 1

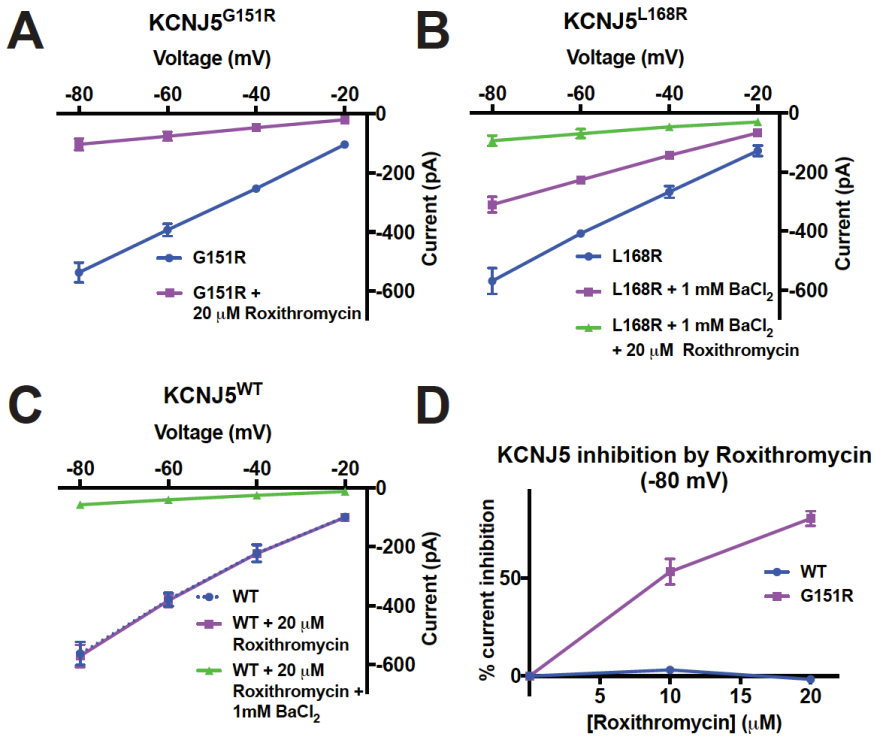
Structural series of compounds showing significant inhibition of KCNJ5^{G151R}.



Recurrent structural elements from compounds with >66.6% mean effect in primary screen and confirmatory testing. Mean % effect at 10 μM is indicated for each compound. Macrolide structures are shown in Figure 1.

Supplemental Figure 2

Inhibition of KCNJ5 homotetramers by Roxithromycin



Cation currents were measured with the perforated whole cell recording technique (140 mM NaCl/5mM KCl bath solution, 140mM KCl pipette solution for $KCNJ5^{G151R}$; 140 mM NaCl/5mM KCl bath solution, 140mM KCl, 1.8 mM $MgCl_2$ pipette solution for $KCNJ5^{L168R}$; 140 mM KCl bath and pipette solution for $KCNJ5^{WT}$). (**A**-**C**) Current-voltage plots of KCNJ3/$KCNJ5^{G151R}$, ^{L168R} and ^{WT} heterotetramers before and 10 minutes after addition of 20 μM Roxithromycin and 1 mM $BaCl_2$ are shown. N=3 (L168R), N=4 (WT), or N=5 (G151R). (**D**), Dose-dependent inhibition of $KCNJ5^{G151R}$ currents at -80 mV by increasing roxithromycin concentrations. In contrast, WT currents are not inhibited. Data were normalized to current before addition of roxithromycin, and % inhibition was calculated. N=3 for 10 μM (G151R and WT), N=4 (20 μM WT), N=5 (20 μM G151R). Data reflect mean ± SEM.