Supporting Information

Simple Predictive Models of Passive Membrane Permeability Incorporating Size-Dependent Membrane-Water Partition

Siegfried S. F. Leung[†], *Daniel Sindhikara*[‡], *and Matthew P. Jacobson*[†,*]

[†]Department of Pharmaceutical Chemistry, University of California, San Francisco, California, 94158.

[‡]Schrödinger, Inc. 120 West 45th Street, 17th Floor, New York, New York, 10036.

* To whom correspondence should be addressed. E-mail: matt.jacobson@ucsf.edu

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Table S1. RRCK data sets and predictions.

	Data Set	Compound[a]	MW	RRCK: Log P_{app}	Log D	PAMPA: Log P_m	V (Å^3)	CSA (Å^2)	SASA (Å^2)	ΔG_{trans}	ΔG_{deslv}	ΔG_{state}	MLR set[b]	Predicted Log $P_{app(RRCK)}$	Ref.
1	1	White 01	712.93	-5.74			2082.66	120.49	944.18	-0.34	7.86	0.00	training	-5.44	1
2	1	White 02	712.93	-6.30			2057.89	118.50	895.64	0.72	9.66	0.00	test	-5.51	1
3	1	White 03L1S	728.93	-5.72			2140.96	118.85	976.27	0.44	10.20	0.00	training	-5.60	1
4	1	White 03L4S	728.93	-6.12			2155.27	97.99	983.95	1.21	12.39	0.00	training	-5.72	1
5	1	White 04	769.04	-5.39			2261.10	120.54	1004.84	-4.43	3.50	0.00	test	-5.36	1
6	1	White 05	783.06	-5.46			2299.55	102.33	1008.03	-3.94	7.04	0.00	training	-5.56	1
7	1	White 06	783.06	-5.21			2283.79	121.25	991.43	-4.98	2.28	0.00	test	-5.31	1
8	2	Stepan 01	520.89	-5.26	4.7		1258.22	57.54	636.42	1.52	7.94	0.00	test	-4.84	2
9	2	Stepan 03	492.90	-4.71	3.8		1276.61	75.70	674.04	3.38	14.01	0.00	test	-5.15	2
10	2	Stepan 07	449.88	-4.52	4.1		1185.53	72.51	641.70	1.66	11.63	0.00	test	-4.96	2
11	2	Stepan 08	459.87	-4.71	4.3		1169.48	56.27	594.94	0.74	6.38	0.00	training	-4.69	2
12	2	Stepan 09	477.86	-4.73	3.8		1193.89	59.73	634.01	0.55	6.79	0.00	training	-4.73	2
13	2	Stepan 10	397.80	-4.99	2.3		1064.24	61.72	595.94	1.30	9.06	0.00	training	-4.75	2
14	2	Stepan 11	411.83	-4.56	2.6		1057.21	53.18	564.83	1.16	8.65	0.00	training	-4.72	2
15	2	Stepan 12	425.85	-4.62	2.7		1182.38	73.85	660.32	1.04	9.37	0.00	training	-4.85	2
16	2	Stepan 13	423.84	-4.67	2.7		1131.61	58.66	615.99	1.07	7.79	0.00	training	-4.73	2
17	2	Stepan 14	423.84	-5.00	2.7		1119.67	58.13	607.62	1.50	10.39	0.00	training	-4.85	2
18	2	Stepan 15	437.86	-4.62	3.2		1179.30	76.23	639.85	1.12	9.69	0.00	training	-4.86	2
19	2	Stepan 16	437.86	-4.60	2.9		1186.62	66.85	653.03	0.99	9.42	0.00	training	-4.86	2
20	2	Stepan 17	451.89	-4.66	3.7		1222.33	74.16	661.57	0.88	8.88	0.00	training	-4.86	2
21	2	Stepan 18	451.89	-4.59	3.8		1215.24	75.83	648.89	0.84	9.29	0.00	training	-4.87	2
22	2	Stepan 19	423.84	-4.52	2.7		1123.03	71.02	608.25	1.36	9.53	0.00	training	-4.81	2
23	2	Stepan 20	465.92	-4.84	4.0		1254.86	71.45	673.95	0.25	7.93	0.00	training	-4.83	2
24	2	Stepan 21	465.92	-4.80	4.0		1246.89	75.93	660.56	0.16	7.36	0.00	test	-4.80	2
25	2	Stepan 22	440.82	-4.53	2.5		1157.51	65.27	640.50	2.95	11.22	0.00	training	-4.92	2
26	2	Stepan 23	454.85	-4.50	2.9		1211.32	70.33	666.19	2.54	10.48	0.00	training	-4.93	2
27	2	Stepan 24	466.86	-4.79	3.7		1161.35	73.08	607.94	1.00	5.20	0.00	test	-4.63	2
28	2	Stepan 25	480.89	-4.85	3.2		1267.32	74.73	685.37	2.85	11.60	0.00	training	-5.02	2
29	3	acetaminophen	151.17	-4.91	0.4	-5.82	567.70	23.52	368.96	3.08	10.08	0.00	test	-4.43	3, 4
30	3	acyclovir	225.21	-6.52			705.82	38.30	433.57	6.62	18.29	0.00	excluded	-4.94	3
31	3	amiloride	229.63	-5.42		-8.70	668.06	28.78	425.69	7.75	14.67	0.58	training	-4.83	3
32	3	amitriptyline	277.41	-5.39		-0.79	1014.99	54.99	562.45	-1.81	0.00	2.33	training	-4.65	3
33	3	antipyrine	188.23	-4.51	0.3	-5.70	689.40	32.75	422.86	1.42	4.76	0.00	training	-4.26	3, 4
34	3	atenolol	266.34	-5.82	-2.0	-7.22	943.56	44.27	546.91	2.80	7.94	2.53	training	-5.03	3, 5
35	3	atorvastatin	558.65	-5.70			1632.96	88.20	825.11	-2.58	4.44	3.70	excluded	-5.56	3
36	3	atropine	289.37	-5.21	-0.2		1001.56	48.27	571.73	-0.94	2.66	2.75	training	-4.84	3, 4
37	3	azithromycin	748.99	-6.15	0.3		2043.24	102.31	891.73	-4.24	0.49	4.87	training	-5.86	3, 5
38	3	bidisomide	407.98	-6.10			1298.68	70.91	687.94	0.78	6.90	2.84	training	-5.29	3
39	3	buspirone	385.51	-4.56		-2.89	1296.85	51.44	722.90	3.59	11.16	0.28	training	-5.07	3
40	3	caffeine	194.19	-4.51	0.0	-5.55	648.96	32.75	400.16	4.43	8.89	0.00	test	-4.43	3, 4
41	3	carbamazepine	236.27	-4.41	1.8	-3.73	779.95	39.89	459.98	1.76	6.71	0.00	training	-4.42	3, 4
42	3	carvedilol	406.48	-5.92	3.5	-0.63	1290.05	69.54	687.64	1.60	6.18	0.97	test	-4.93	3, 5
43	3	cetirizine	388.89	-5.54		-4.23	1207.13	71.20	670.36	2.08	24.77	0.89	training	-5.78	3
44	3	chloroquine	319.88	-5.29	0.9	-3.42	1063.34	58.59	560.84	-1.64	-0.01	4.01	training	-4.97	3, 5
45	3	chlorothiazide	295.72	-5.89	-0.1		725.62	38.00	441.89	8.69	24.57	0.60	training	-5.37	3, 5
46	3	chlorpheniramine	274.79	-4.55	1.6		961.10	52.10	559.42	-1.69	0.75	3.54	training	-4.85	3, 4

47	3	chlorpromazine	318.86	-4.99	3.2	-0.22	1017.39	50.65	583.49	-0.10	2.48	2.97	test	-4.88	3, 4
48	3	cimetidine	252.34	-6.10	0.4	-6.30	840.50	41.16	489.57	3.99	10.61	6.90	excluded	-5.81	3, 4
49	3	ciprofloxacin	331.35	-5.85	-1.1	-5.52	992.12	45.79	553.78	2.61	8.83	3.20	training	-5.22	3, 5
50	3	cisapride	465.95	-5.12			1431.73	69.05	795.06	2.83	7.69	0.66	training	-5.06	3
51	3	danazol	337.46	-5.12		-1.79	1069.01	50.50	580.87	-0.75	3.30	0.00	test	-4.47	3
52	3	desipramine	266.39	-5.15	1.3	-1.01	965.77	62.61	547.41	-0.91	1.33	4.14	training	-4.99	3, 4
53	3	diazepam	284.74	-4.44	3.0	-2.44	895.64	52.36	524.64	1.15	5.72	0.00	test	-4.46	3, 4
54	3	diclofenac	296.15	-4.75	1.3	-4.64	848.52	47.48	495.19	1.07	5.73	3.86	training	-5.07	3, 5
55	3	dicloxacillin	470.33	-5.85			1195.88	67.79	618.62	6.80	23.22	6.01	excluded	-6.55	3
56	3	diflunisal	250.20	-4.65	0.4		743.16	31.93	452.26	1.47	6.51	6.16	training	-5.42	3, 5
57	3	digoxin	780.95	-5.82		-5.77	2223.89	63.91	1109.69	0.41	11.54	0.00	excluded	-5.73	3
58	3	diltiazem	414.52	-4.59	2.0	-2.04	1275.09	60.49	671.31	0.66	5.52	1.45	test	-4.97	3, 4
59	3	diphenhydramine	255.36	-4.51	1.4	-2.41	976.12	55.18	567.20	-1.95	0.24	1.58	excluded	-4.51	3, 4
60	3	disopyramide	339.48	-5.62	-1.2	-4.06	1169.85	68.24	631.14	-1.79	1.57	3.04	test	-4.96	3, 4
61	3	doxycycline	444.44	-5.74	0.2	-4.77	1209.25	61.62	649.82	6.31	16.10	8.92	excluded	-6.70	3, 5
62	3	enalapril	376.45	-5.92		-7.52	1190.88	59.48	613.33	0.79	6.59	6.65	excluded	-5.83	3
63	3	ephedrine	165.24	-4.65	-0.8		656.33	31.72	405.58	0.47	3.77	1.93	training	-4.51	3, 5
64	3	ergonovine	325.41	-4.70	1.5	-4.26	1068.07	52.55	612.80	3.67	10.92	0.14	training	-4.87	3, 5
65	3	erthromycin	733.94	-6.15	1.1	-3.82	2064.21	110.38	933.14	-3.59	2.35	1.82	excluded	-5.46	3, 5
66	3	ethambutol	204.31	-6.10			819.99	38.71	485.00	0.73	5.00	9.10	training	-5.89	3
67	3	ethinylestradiol	296.41	-4.54	3.4	-2.99	978.94	46.26	547.49	-0.33	4.50	0.00	test	-4.46	3, 5
68	3	famotidine	337.43	-6.15	-0.6	-8.00	926.70	50.39	544.00	7.44	17.49	2.18	training	-5.43	3, 5
69	3	fexofenadine	501.66	-6.30		-5.31	1532.94	83.13	759.16	-1.70	13.20	0.01	excluded	-5.30	3
70	3	fluoxetine	309.33	-5.30			1007.70	59.59	589.48	-1.81	0.69	3.53	training	-4.88	3
71	3	flurbiprofen	244.27	-4.80	0.9	-5.00	821.73	34.55	491.88	-0.49	4.17	4.45	training	-5.07	3, 5
72	3	fluvastatin	411.47	-4.94	1.1		1294.11	70.00	714.38	-1.16	5.34	3.82	excluded	-5.37	3, 5
73	3	furosemide	330.74	-6.15	-0.2	-7.70	868.71	48.72	493.87	6.02	18.53	3.84	excluded	-5.71	3, 5
74	3	ganciclovir	255.23	-6.30			756.67	43.19	446.23	6.99	20.62	0.97	excluded	-5.25	3
75	3	glipizide	445.54	-5.25			1294.10	79.35	659.92	6.04	16.22	3.06	training	-5.78	3
76	3	glyburide	494.00	-4.77		-4.06	1360.72	82.61	681.99	4.48	13.86	3.07	excluded	-5.72	3
77	3	griseofulvin	352.77	-4.52	2.2	-3.61	1032.65	58.58	583.33	1.58	7.01	0.00	training	-4.62	3, 4
78	3	hydrochlorothiazide	297.73	-6.05	-0.2	-8.30	729.16	38.09	430.02	7.39	20.12	0.05	training	-5.06	3, 5
79	3	ibuprofen	206.28	-4.52	1.4	-4.92	800.00	34.01	478.32	-1.68	1.49	4.15	excluded	-4.87	3, 5
80	3	imipramine	280.41	-4.74	2.0	-1.13	1025.93	62.85	580.64	-1.89	0.35	3.00	training	-4.79	
81	3	indinavir	613.80	-5.47		-3.60	1824.56	93.46	861.61	1.32	9.50	0.02	test	-5.33	3
82	3	indomethacin	357.79	-4.71	0.7	-4.48	1064.61	54.39	603.35	0.33	5.84	4.33	training	-5.31	3, 5
83	3	itraconazole	705.64	-4.82		-0.29	1772.29	82.62	804.54	-0.74	4.26	0.00	training	-5.03	3
84	3	ketoconazole	531.44	-5.38	3.8	-1.46	1467.36	78.01	755.24	1.71	8.76	0.27	training	-5.08	3, 5
85	3	ketoprofen	254.29	-4.61	-0.1	-5.96	863.19	48.21	503.83	-0.32	4.75	4.47	excluded	-5.13	3, 5
86	3	labetalol	328.41	-4.89	1.1	-5.28	1061.65	56.28	585.05	2.41	7.45	1.84	training	-4.97	3, 5
87	3	lansoprazole	369.36	-4.63		-3.89	990.43	56.14	534.46	0.27	6.16	0.35	training	-4.61	3
88	3	levodopa	197.19	-3.78		-7.52	641.05	33.35	398.44	9.99	46.32	0.01	excluded	-6.28	3
89	3	levofloxacin	361.37	-5.57			1064.57	45.70	585.29	2.20	7.04	2.15	excluded	-5.01	3
90	3	lidocaine	234.34	-4.35	1.7	-2.08	871.41	43.67	491.86	0.68	4.71	2.21	training	-4.76	3, 5
91	3	lisinopril	405.49	-6.30		-6.70	1175.51	63.18	592.34	6.03	40.36	0.29	training	-6.43	3
92	3	losartan	422.92	-6.05			1247.64	62.11	660.63	2.02	10.47	3.95	training	-5.61	3
93	3	lovastatin	404.55	-4.97			1297.20	68.35	657.26	-1.70	5.20	0.00	training	-4.73	3
94	3	mebendazole	295.30	-4.61	3.3		957.46	32.32	574.88	2.90	9.77	0.58	training	-4.80	3, 5
95	3	methotrexate	454.44	-5.68	-2.9	-9.00	1225.25	64.82	619.72	9.40	19.73	9.04	excluded	-6.91	3, 5

96	3	methyldopa	211.22	-6.05		-5.29	682.03	36.80	410.41	8.99	43.01	0.01	training	-6.15	3
97	3	metoclopramide	299.80	-4.63	0.7		970.74	49.59	549.73	2.91	7.03	2.74	training	-5.04	3, 4
98	3	metoprolol	267.37	-4.59	-0.6	-3.33	993.51	45.88	571.87	-0.05	3.07	2.53	training	-4.82	3, 4
99	3	metronidazole	171.16	-4.94	0.1		570.67	32.82	360.79	0.47	5.54	0.00	training	-4.21	3, 4
100	3	midazolam	325.77	-4.57			968.62	55.50	554.76	-0.47	6.99	0.12	test	-4.59	3
101	3	minocycline	457.48	-5.74		-4.12	1301.68	67.33	700.29	6.12	15.00	8.13	excluded	-6.58	3
102	3	nadolol	309.41	-5.82	-1.4	-6.70	1063.84	54.32	597.35	1.10	6.91	2.92	training	-5.13	3, 5
103	3	naproxen	230.26	-4.44	0.1	-5.39	785.56	34.75	467.50	0.41	4.86	4.16	training	-5.03	3, 5
104	3	nifedipine	346.34	-4.05	2.8	-3.35	1062.72	65.59	594.91	1.22	6.27	0.00	test	-4.61	3, 4
105	3	ofloxacin	361.37	-5.34	-0.3	-5.27	1060.54	44.49	588.46	2.23	7.06	2.15	test	-5.01	3, 5
106	3	oxaprozin	293.32	-4.62			971.56	51.16	574.19	-0.59	3.60	3.83	training	-5.05	3
107	3	phenazopyridine	213.24	-4.70	3.3	-2.67	738.08	23.99	457.94	3.74	7.74	0.00	training	-4.44	3, 5
108	3	phenobarbital	232.24	-4.67	1.5		700.17	42.51	400.11	5.78	12.22	0.64	training	-4.74	3, 5
109	3	phenytoin	252.27	-4.55	2.2	-4.41	781.04	50.43	450.30	4.05	9.40	0.20	test	-4.59	3, 5
110	3	piroxicam	331.35	-4.49	0.0	-5.49	952.52	51.92	539.91	4.92	14.78	3.81	training	-5.59	3, 5
111	3	pravastatin	424.53	-5.68			1304.07	71.31	665.84	0.32	10.65	3.67	excluded	-5.62	3
112	3	prednisolone	360.45	-5.26	1.6	-4.46	1083.35	49.21	578.48	0.18	7.43	0.01	training	-4.68	3, 4
113	3	prednisone	358.43	-4.83	1.2	-4.34	1065.95	45.99	569.68	0.17	7.58	0.01	test	-4.68	3, 4
114	3	primaquine	259.35	-4.96	1.2	-2.06	922.05	53.79	527.86	1.15	4.43	3.84	training	-5.06	3, 5
115	3	promazine	284.42	-5.41			972.85	47.07	559.05	-0.27	2.36	2.97	training	-4.85	3
116	3	propranolol	259.35	-4.82	0.9	-1.70	932.19	52.25	538.86	-0.06	2.60	2.53	excluded	-4.75	3, 4
117	3	quinidine	324.42	-4.76	1.5	-2.74	1032.42	59.43	561.98	-0.48	2.81	1.48	excluded	-4.66	3, 4
118	3	ranitidine	314.40	-6.15	-0.5	-6.10	995.94	56.45	547.92	2.27	6.15	5.83	training	-5.53	3, 4
119	3	rifampin	822.95	-4.92	1.0		2160.98	110.79	948.21	2.18	8.70	1.23	excluded	-5.75	3, 5
120	3	ritonavir	724.98	-5.08		-1.68	1959.47	102.32	850.63	4.61	15.27	0.00	excluded	-5.72	3
121	3	rosiglitazone	357.43	-4.52			1085.48	48.25	606.74	5.64	13.62	0.35	training	-5.05	3
122	3	saquinavir	670.85	-6.05		-3.79	2020.29	97.13	1006.72	3.22	9.75	0.15	training	-5.51	3
123	3	tacrolimus	804.03	-5.21			2262.01	126.10	994.87	-3.16	3.21	0.11	training	-5.36	3
124	3	talinolol	363.50	-6.10			1294.23	49.82	736.61	3.43	10.07	2.92	training	-5.46	3
125	3	tamoxifen	371.52	-4.16	4.2	0.78	1302.69	60.01	719.86	-3.41	-1.65	1.38	training	-4.62	3, 5
126	3	tetracycline	444.44	-6.15		-5.54	1208.70	63.31	637.04	6.35	17.23	8.35	excluded	-6.66	3
127	3	theophylline	180.17	-4.94	0.0	-6.00	586.89	29.56	370.11	6.32	12.88	0.14	excluded	-4.61	3, 5
128	3	trimethoprim	290.32	-4.90	0.6	-3.57	924.10	53.27	530.68	5.86	12.57	0.07	training	-4.83	3, 4
129	3	valsartan	435.53	-6.22			1328.38	61.11	677.82	1.36	8.60	8.84	training	-6.40	3
130	3	verapamil	454.61	-4.89	2.5	-1.41	1467.12	64.95	721.57	-2.86	1.24	2.13	excluded	-5.01	3, 5
131	3	warfarin	308.33	-4.53	1.1	-5.00	978.87	58.76	558.32	-0.02	5.05	1.23	training	-4.69	3, 5
132	3	zidovudine	267.24	-5.21		-5.80	809.78	34.89	476.64	3.80	10.57	0.00	excluded	-4.63	3
133	4	Rand 01	755.01	-5.31	4.4		2301.34	138.70	1076.13	-3.10	5.54	0.00	training	-5.49	6
134	4	Rand 02	728.93	-5.80	2.6		2096.97	124.64	949.42	-1.98	6.57	0.00	test	-5.39	6
135	4	Rand 03	742.95	-5.33	3.2		2166.30	117.86	990.92	-0.90	9.17	0.00	training	-5.57	6
136	4	Rand 04	755.01	-5.49	4.6		2258.57	128.96	1019.96	-3.71	4.42	0.00	training	-5.40	6
137	4	Rand 05	712.93	-5.26	3.6		2108.20	118.45	968.54	-2.05	6.64	0.00	test	-5.40	6
138	4	Rand 06	805.03	-5.89	3.8		2318.68	112.34	1036.98	-0.91	9.04	0.00	training	-5.67	6
139	4	Rand 07	789.03	-5.24	4.5		2289.49	115.66	1018.56	-3.15	5.88	0.00	training	-5.50	6
140	4	Rand 08	828.06	-6.70	4.1		2372.35	116.53	1066.71	-0.95	9.19	0.00	excluded	-5.72	6
141	4	Rand 09	756.94	-6.40	0.5		2202.41	125.19	1027.77	-1.70	9.56	4.64	training	-6.39	6
142	4	Rand 10	770.02	-6.52	0.7		2292.47	106.42	1036.56	0.50	11.20	4.50	training	-6.51	6
143	4	Rand 11	784.05	-6.70	0.7		2399.86	137.73	1114.94	-1.93	7.82	4.12	test	-6.36	6
144	4	Rand 12	795.07	-6.70	5.1		2426.83	128.64	1136.69	-3.69	4.30	0.00	excluded	-5.52	6

145	4	Rand 13	810.09	-6.15	2.2	2426.81	132.81	1105.68	-2.98	5.58	4.48	test	-6.33	6
146	4	Rand 14	824.07	-5.85	3.8	2428.52	141.40	1108.51	-0.78	10.85	0.00	training	-5.84	6
147	4	Rand 15	812.06	-5.92	2.8	2386.49	122.51	1107.52	-1.88	7.31	0.06	training	-5.65	6
148	4	Rand 16	826.04	-6.22	2.8	2388.45	125.22	1097.28	0.62	13.37	0.00	training	-5.94	6
149	5	Guzman-Perez 18	474.48	-6.22	1.3	1360.14	67.20	702.27	2.24	10.34	4.18	training	-5.73	7
150	5	Guzman-Perez 19	474.48	-5.40	1.9	1449.69	84.66	807.29	2.41	9.58	4.18	test	-5.76	7
151	5	Guzman-Perez 20	475.47	-5.34	2.1	1439.18	82.12	802.42	3.23	10.52	4.20	training	-5.80	7
152	5	Guzman-Perez 21	475.47	-6.10	1.3	1447.02	64.30	811.43	3.96	12.30	4.18	test	-5.89	7
153	5	Guzman-Perez 22	476.46	-6.10	1.3	1427.94	83.57	799.55	4.33	13.25	4.18	training	-5.92	7
154	5	Guzman-Perez 23	502.54	-5.57	2.2	1558.17	88.97	857.83	1.10	8.05	4.18	training	-5.76	7
155	5	Guzman-Perez 24	475.47	-5.64	1.6	1454.16	81.83	816.30	2.63	14.72	4.18	training	-6.02	7
156	5	Guzman-Perez 25	475.47	-5.51	2.4	1453.69	80.91	816.11	1.56	8.87	4.18	test	-5.73	7
157	5	Guzman-Perez 26	476.45	-5.47	2.6	1452.86	78.77	829.68	1.83	8.62	4.18	training	-5.71	7
158	6	Filipski 03	440.51	-5.36	4.1	1396.87	59.71	785.47	4.29	13.93	0.00	training	-5.23	8
159	6	Filipski 04	399.46	-4.74	2.8	1245.99	60.38	710.08	4.44	14.03	0.00	training	-5.13	8
160	6	Filipski 21	400.45	-4.03	2.3	1233.66	60.44	703.29	4.70	14.58	0.00	training	-5.15	8
161	6	Filipski 25	400.45	-4.62	2.1	1237.14	61.28	707.01	4.42	14.24	0.10	training	-5.15	8
162	6	Filipski 26	414.48	-4.77	2.7	1295.41	61.73	737.36	4.09	13.59	0.09	training	-5.16	8
163	6	Filipski 27	414.48	-5.32	2.4	1303.74	64.21	750.55	4.53	14.37	0.08	test	-5.20	8
164	6	Filipski 30	395.42	-5.15	1.0	1248.81	62.32	700.31	5.94	13.96	0.10	test	-5.14	8
165	6	Filipski 36	430.48	-5.55	1.4	1243.87	57.18	669.45	4.68	14.67	0.10	training	-5.17	8
166	6	Filipski 37	428.50	-5.40	3.1	1350.71	65.12	765.91	3.77	13.14	0.09	test	-5.18	8
167	6	Filipski 39	430.48	-5.41	2.2	1318.20	74.73	753.13	4.42	15.21	0.73	training	-5.36	8
168	6	Filipski 40	434.89	-5.08	2.0	1280.48	62.91	730.12	4.75	14.57	0.65	training	-5.29	8
169	6	Filipski 42	415.46	-4.82	2.6	1248.85	60.50	693.22	5.69	16.45	0.10	training	-5.27	8
170	6	Filipski 43	412.42	-4.89	1.5	1288.40	61.80	734.53	4.94	12.47	0.10	test	-5.10	8
171	6	Filipski 44	395.42	-4.80	1.3	1259.75	66.63	720.16	6.02	14.18	0.10	training	-5.16	8
172	6	Filipski 45	423.47	-4.77	1.9	1332.01	68.04	713.35	4.55	12.42	1.30	training	-5.33	8
173	6	Filipski 46	421.46	-4.85	1.7	1288.07	60.02	701.25	6.03	13.90	0.10	training	-5.17	8
174	6	Filipski 47	411.42	-6.09	0.0	1242.76	57.75	681.29	6.94	16.22	0.10	test	-5.25	8
175	6	Filipski 48	425.44		0.4	1303.74	64.07	715.30	5.48	12.71	0.10		-5.12	8
176	6	Filipski 51	409.44	-4.96	1.5	1307.11	63.70	730.73	5.74	13.48	0.09	test	-5.16	8
177	6	Filipski 52	425.44	-5.66	0.8	1316.41	69.40	735.27	5.34	12.37	0.10	training	-5.11	8
178	6	Filipski 53	459.52	-4.85	2.3	1398.51	71.24	780.41	4.68	15.55	0.09	training	-5.33	8
179	6	Filipski 54	445.49	-5.80	2.0	1298.84	58.35	706.44	6.16	17.21	0.09	test	-5.34	8
180	7	Dow 01	396.45	-6.00		1208.68	41.84	658.11	4.31	11.63	3.40	training	-5.55	9
181	7	Dow 19	270.29	-4.48		845.33	35.84	492.48	4.72	9.74	0.00	training	-4.62	9
182	7	Dow 20	312.37	-4.55		1011.10	41.27	562.89	3.58	8.31	0.00	training	-4.67	9
183	7	Dow 25	410.47	-5.40		1262.90	43.26	685.35	3.95	11.22	3.37	training	-5.57	9
184	7	Dow 28	410.47	-4.77		1287.90	42.56	703.60	3.99	10.23	0.00	test	-4.97	9
185	7	Dow 29	395.46	-5.40		1215.70	41.48	661.62	6.14	14.64	0.00	training	-5.14	9
186	7	Dow 30	423.51	-4.89		1357.66	47.62	746.32	5.96	14.28	0.00	training	-5.22	9
187	7	Dow 31	463.58	-4.66		1479.86	55.76	803.11	5.72	13.82	0.00	test	-5.29	9
188	7	Dow 32	481.59	-5.40		1522.78	50.66	811.62	5.44	14.47	0.00	training	-5.35	9
189	7	Dow 33	449.55	-4.62		1417.14	43.00	764.72	5.42	12.71	0.00	test	-5.19	9
190	7	Dow 34	465.55	-5.70		1439.69	44.33	777.40	6.20	15.83	0.00	test	-5.36	9
191	7	Dow 35	465.55	-4.96		1414.82	44.99	748.80	5.68	13.58	0.00	training	-5.23	9
192	7	Dow 36	492.58	-5.70		1511.50	52.97	810.95	8.12	18.89	0.00	training	-5.56	9
193	7	Dow 37	493.61	-4.66		1536.97	53.37	823.11	5.24	13.30	0.00	training	-5.31	9

194	7	Dow 39	381.43	-5.30		1174.32	44.08	642.85	6.28	14.08	0.00	training	-5.08	9
195	7	Dow 40	409.49	-4.80		1284.73	48.15	696.10	5.47	13.00	0.00	training	-5.11	9
196	7	Dow 41	425.49	-5.22		1286.66	54.85	680.45	6.15	13.48	0.00	training	-5.13	9
197	7	Dow 42	449.55	-4.68		1403.08	55.62	752.80	5.13	12.47	0.00	test	-5.17	9
198	7	Dow 43	451.52	-5.52		1357.01	54.69	721.68	6.36	15.04	0.00	training	-5.26	9
199	7	Dow 44	465.55	-6.00		1422.77	57.06	762.31	5.94	15.40	0.00	test	-5.33	9
200	7	Dow 46	443.50	-4.72		1347.29	55.24	728.51	6.01	13.76	0.00	training	-5.19	9
201	7	Dow 47	434.45	-4.85		1281.74	50.98	697.47	7.46	16.00	0.00	test	-5.25	9
202	7	Dow 48	434.45	-4.80		1279.81	50.00	695.48	7.66	15.99	0.00	training	-5.25	9
203	7	Dow 49	377.45	-4.57		1188.15	42.18	649.98	3.84	11.38	0.00	training	-4.95	9
204	7	Dow 50	410.52	-4.64		1305.97	42.61	702.00	3.21	9.26	0.00	test	-4.94	9
205	7	Dow 51	409.53	-5.70		1306.99	44.59	698.59	4.17	9.94	3.96	training	-5.63	9
206	7	Dow 52	434.50	-4.41		1340.22	45.32	727.17	5.11	12.74	0.00	training	-5.13	9
207	7	Dow 53	434.50	-4.92		1335.75	48.08	724.20	5.35	13.74	0.00	training	-5.18	9
208	7	Dow 54	450.56	-4.96		1368.03	50.06	740.88	5.37	13.04	0.00	training	-5.17	9
209	7	Dow 55	433.51	-5.22		1342.53	45.57	728.86	6.47	16.02	0.43	training	-5.37	9
210	7	Dow 56	447.54	-6.22		1392.45	51.64	749.63	5.40	15.48	0.00	training	-5.31	9
211	7	Dow 57	448.52	-4.66		1403.95	43.14	765.65	4.98	12.64	0.00	test	-5.18	9
212	8	Griffith 01	407.47	-5.01	1.4	1252.08	66.72	653.38	3.14	11.39	0.01	training	-5.00	10
213	8	Griffith 02	376.41	-5.10	2.5	1144.50	51.91	639.16	5.81	14.54	0.01	training	-5.08	10
214	8	Griffith 05	406.49	-6.15	1.0	1287.84	42.04	720.39	5.64	17.20	0.01	training	-5.32	10
215	8	Griffith 06	434.54	-6.30	1.5	1404.34	48.69	780.42	5.51	16.59	0.01	training	-5.37	10
216	8	Griffith 07	420.51	-6.22	1.1	1360.52	47.75	764.60	6.00	17.38	0.01	test	-5.38	10
217	8	Griffith 08	432.52	-5.80	1.4	1384.37	47.33	778.10	6.56	18.53	0.01	training	-5.45	10
218	8	Griffith 09	448.57	-5.92	1.7	1453.51	51.20	805.38	4.94	16.01	0.01	training	-5.38	10
219	8	Griffith 10	434.54	-4.82	2.6	1391.28	50.84	764.28	4.72	13.70	0.01	training	-5.22	10
220	8	Griffith 11	420.51	-5.15	1.7	1352.41	48.71	756.70	5.26	14.55	0.01	training	-5.23	10
221	8	Griffith 14	448.57	-5.57	1.4	1442.69	55.12	786.26	4.48	14.62	0.01	training	-5.30	10
222	8	Griffith 15	474.49	-5.82	2.5	1382.88	46.77	769.67	4.70	15.79	0.01	test	-5.32	10
223	8	Griffith 16	440.93	-5.85	1.8	1330.53	45.11	743.09	6.13	17.85	0.01	training	-5.38	10
224	8	Griffith 17	439.94	-5.40	2.6	1343.79	45.30	750.03	5.20	16.35	0.00	training	-5.31	10
225	8	Griffith 18	439.94	-5.38	3.5	1376.66	42.09	784.98	5.31	16.10	0.00	training	-5.33	10
226	8	Griffith 19	440.93	-6.10	1.4	1330.79	41.77	742.93	6.45	19.69	0.00	training	-5.47	10
227	8	Griffith 20	447.54	-5.01	1.6	1413.29	43.14	779.74	4.58	15.04	0.00	test	-5.30	10
228	8	Griffith 21	447.54	-4.96	2.2	1416.74	46.40	784.40	4.25	14.31	0.00	training	-5.27	10
229	8	Griffith 22	447.54	-5.01	2.0	1422.33	52.83	787.12	4.26	13.95	0.00	training	-5.25	10
230	8	Griffith 23	446.55	-5.82	1.5	1435.34	46.04	798.99	5.53	16.71	0.00	training	-5.40	10
231	8	Griffith 24	446.55	-6.05	1.5	1431.75	47.26	794.63	5.89	16.93	0.05	test	-5.42	10
232	8	Griffith 26	474.61	-5.60	2.1	1556.01	45.96	865.41	5.18	15.33	0.00	training	-5.42	10
233	8	Griffith 27	460.58	-5.21	1.9	1492.88	46.97	825.80	4.89	15.54	0.01	training	-5.39	10

[a] Numbering of compounds is consistent with original publication.

[b] Subsets for MLR modeling of physics-based descriptors to predict RRCK permeability. The "excluded" set contains compound with reported influx mechanisms[11-17] or low recovery in RRCK assays (Rand 08 and Rand 12).

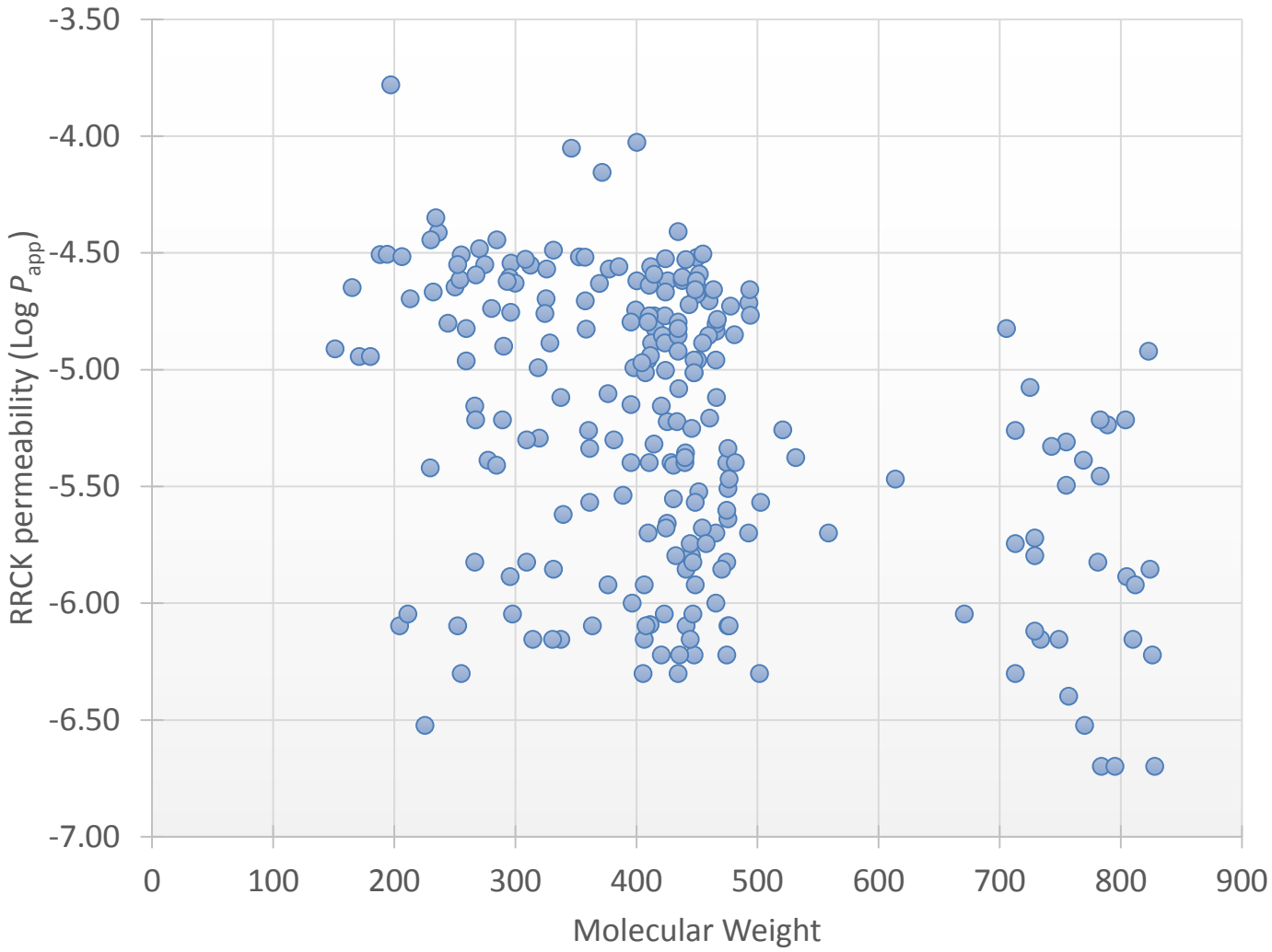


Figure S1. Experimental RRCK permeability vs. molecular weight.

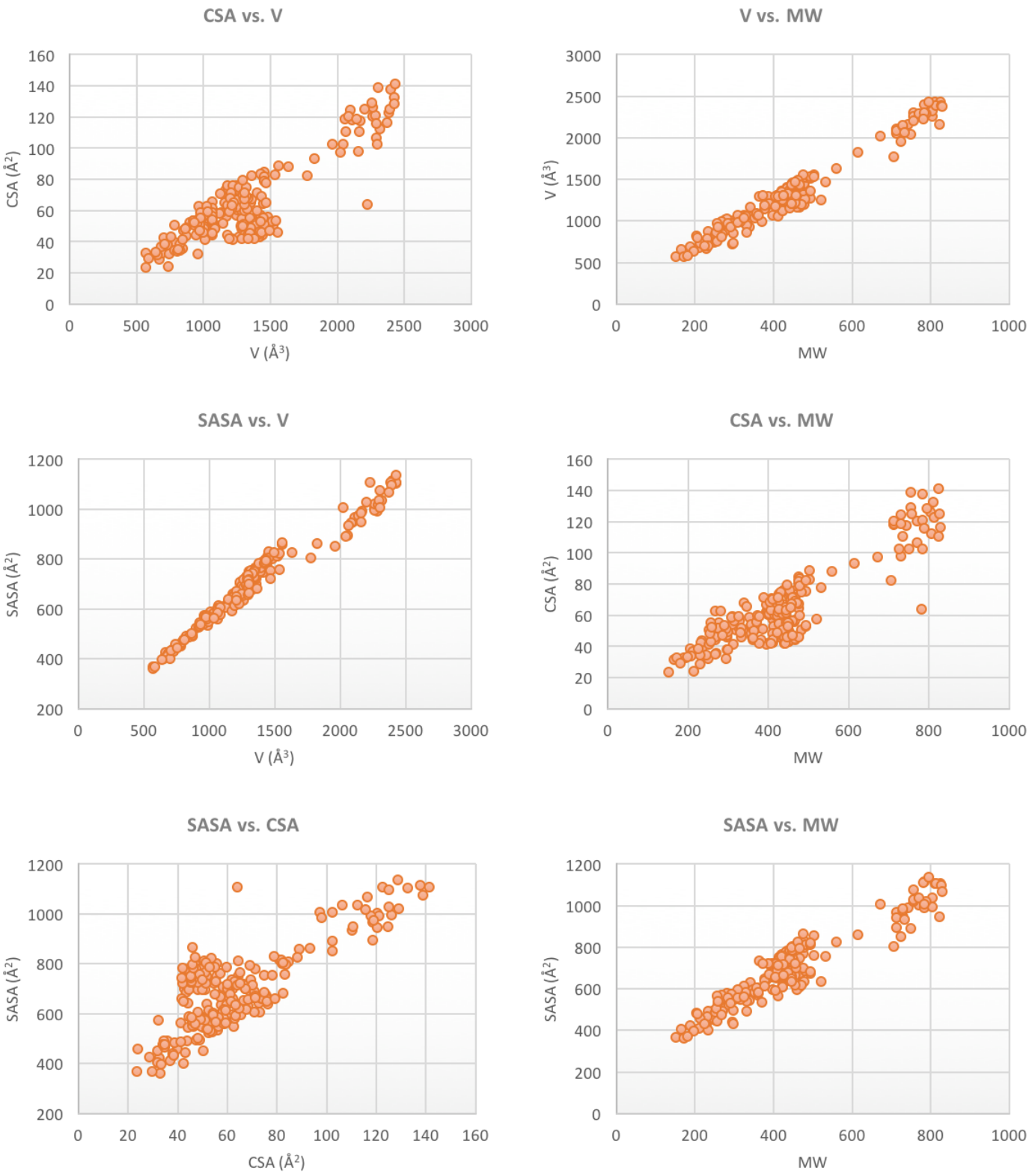


Figure S2. Comparison of size descriptors.

Table S2. MLR analysis for predicting RRCK permeability from *in silico* descriptors.

	Descriptor							Training set (n=151)				Test set (n=50)		
Model	ΔG_{deslv}	ΔG_{state}	$\Delta G_{deslv} + \Delta G_{state}$	V	CSA	SASA	MW	SD	r^2	F	P	RMSE	q^2	r-Pearson
1	✓							0.56	0.10	16.56	7.63E-05	0.59	0.04	0.21
2			✓					0.53	0.18	32.76	5.55E-08	0.57	0.11	0.35
3	✓	✓						0.50	0.26	26.09	1.97E-08	0.54	0.20	0.51
4	✓	✓		✓				0.41	0.51	51.42	8.70E-23	0.43	0.50	0.72
5	✓	✓			✓			0.45	0.42	35.76	2.05E-17	0.44	0.45	0.70
6	✓	✓				✓		0.42	0.49	46.24	4.17E-21	0.44	0.46	0.69
7	✓	✓					✓	0.42	0.49	47.12	2.14E-21	0.43	0.48	0.71

Table S3. Correlation coefficients (r^2 and q^2 (shown in parenthesis)) from MLR analyses between RRCK permeability ($P_{app(RRCK)}$) and different size-dependent partition models that are based on calculated partition free energies and size descriptors.[a] All MLR models share the functional form of size-dependent partition model: $\mathrm{Log}P_{app(RRCK)} = (\sum a_i \Delta G_i) + b$ (Size descriptor).

		Size Descriptor			
		/	b V	b CSA	b SASA
Partition Free Energy[b]	/		0.21 (0.17)	0.12 (0.08)	0.21 (0.17)
	$a\,\Delta G_{transfer}$	0.00 (0.00)			
	$a\,(\Delta G_{transfer}+\Delta G_{state})$	0.03 (0.09)	0.39 (0.39)	0.33 (0.41)	0.33 (0.35)
	$a_1\,\Delta G_{transfer} + a_2\,\Delta G_{state}$	0.10 (0.07)	0.45 (0.41)	0.34 (0.40)	0.40 (0.37)
	$a\,\Delta G_{desolv}$	0.05 (0.18)			
	$a\,(\Delta G_{desolv}+\Delta G_{state})$	0.12 (0.27)	0.38 (0.42)	0.32 (0.42)	0.34 (0.41)
	$a_1\,\Delta G_{desolv} + a_2\,\Delta G_{state}$	0.22 (0.31)	0.51 (0.50)	0.41 (0.48)	0.47 (0.50)

[a] Total: N = 201/232 (excluded compounds with known influx transport or low recovery in RRCK assay); Training set (75%): N = 151; Test set (25%): N = 50

[b] ΔG_{desolv} estimates free energy of partitioning between water and vacuum; $\Delta G_{transfer}$ estimates free energy of partitioning between water and chloroform, a low dielectric solvent.[18]

Table S4. Correlation coefficients (Pearson's correlation, r^2, and Spearman's rank correlation, ρ) for each compound series between RRCK permeability and predictions by Model 3 (free-energy-based partition model) and Model 4 (size-dependent partition model).

	Compound series	Congeneric	N	$P_{app(RRCK)}$ Range (Log 10^{-6} cm/s)	Volume Range (Å^3)	Model 3 r^2 (ρ)	Model 4 r^2 (ρ)	Ref.
1	Drug-like	Yes	21	2.06 (-6.09 – -4.03)	165 (1234 – 1399)	0.05 (0.14)	0.08 (0.33)	8
2	Drug-like	Yes	9	0.88 (-6.22 – -5.34)	198 (1360 – 1558)	0.20 (0.39)	0.09 (0.31)	7
3	Drug-like	Yes	21	0.75 (-5.26 – -4.50)	219 (1057 – 1277)	0.05 (-0.36)	0.02 (-0.29)	2
4	Cyclic peptides	Yes	21	1.48 (-6.70 – -5.21)	371 (2058 – 2429)	0.72 (0.84)	0.66 (0.80)	1,6
5	Drug-like	Yes	22	1.48 (-6.30 – -4.82)	412 (1145 – 1556)	0.61 (0.84)	0.45 (0.68)	10
6	Drug-like	Yes	32	1.81 (-6.22 – -4.41)	692 (845 – 1537)	0.50 (0.81)	0.42 (0.69)	9
7	Drugs	No	75	2.25 (-6.30 – -4.05)	1694 (568 – 2262)	0.32 (0.48)	0.46 (0.62)	3

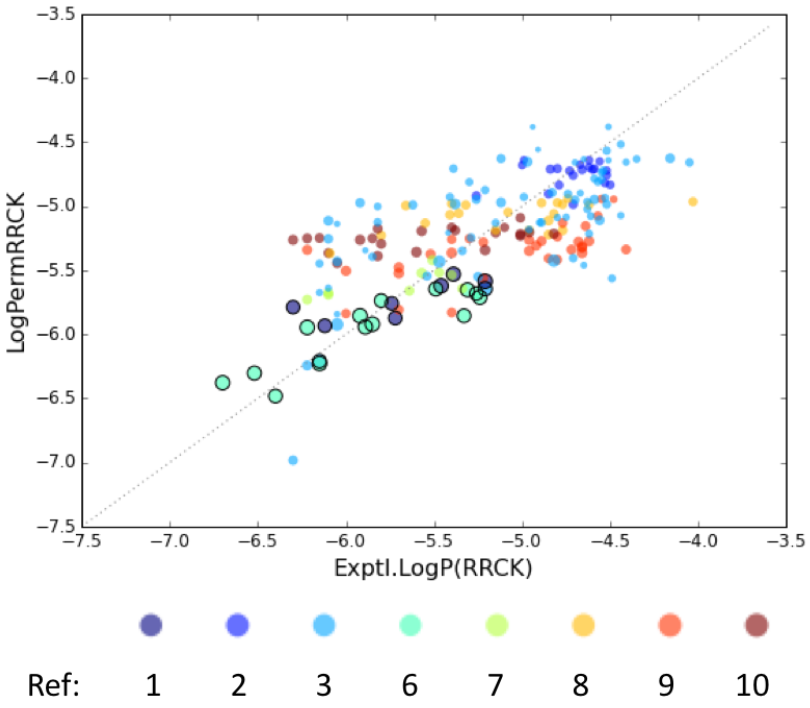
Computational RRCK permeability model implemented by Schrödinger

The computational model for predicting RRCK permeability via the size-dependent partition approach (Model 4) was implemented as the RRCK permeability predictor in the physics-based permeability prediction module within the Schrödinger's Small-Molecule Drug Discovery Suite. The computational workflow was automated with slight modifications:

1) Neutralize input molecule.
2) Identify lowest state penalty neutral form (EPIK).
3) Detect cyclic and linear structures.
4) Perform conformational prediction using either Prime ligand sampling for non-macrocycles or Prime macrocycle sampling for macrocycles in conjunction with the use of OPLS2005 force field and an implicit solvent model of chloroform (PRIME).
5) Calculate energy in high dielectric environment and volume for top conformers (PRIME).
6) Calculate $\Delta G_{transfer}$ and select conformer with the lowest $\Delta G_{transfer}$..
7) Calculate permeability by:

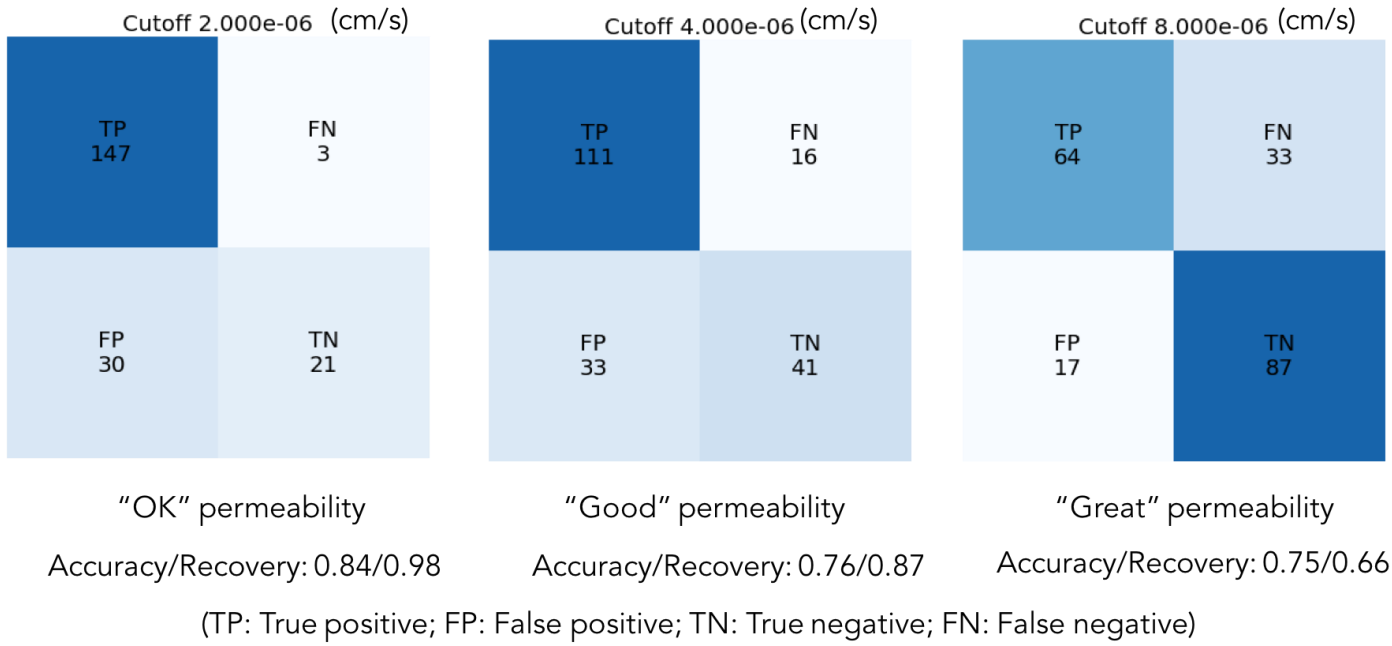
$$\mathrm{Log}P_{app(RRCK)\text{-}calc} = \text{-}4.25e\text{-}2\ \Delta G_{transfer} - 0.136\ \Delta G_{state} - 8.61e\text{-}4\ V - 3.87$$

This workflow utilizes $\Delta G_{transfer}$ (based on partition between water and chloroform), instead of ΔG_{desolv} (based on partition between water and vacuum) as in Model 4, for computing permeability, which has produced good correlation with the RRCK permeability measurements[1-3,6-10] as well as other permeability data,[18] including PAMPA and Caco-2 measurements. Conformation selection is also based on $\Delta G_{transfer}$. As shown in Figure S3, the predictive performance of this implementation for modeling RRCK permeability ($r^2 = 0.49$) is similar to that of Model 4.



r^2	0.49
RMSE (log_{10}(cm/s))	0.42
r^2 (Small Mol)	0.41
RMSE (Small Mol)	0.42
r^2 (macrocycles)	0.72
RMSE (macrocycles)	0.28

Symbol size by volume
Ringed circles O are macrocycles



"OK" permeability
Accuracy/Recovery: 0.84/0.98

"Good" permeability
Accuracy/Recovery: 0.76/0.87

"Great" permeability
Accuracy/Recovery: 0.75/0.66

(TP: True positive; FP: False positive; TN: True negative; FN: False negative)

Figure S3. Predictive performance of computational RRCK permeability model (Schrödinger's implementation).

Table S5. Correlation coefficients between Caco-2 permeability measurements and predictions by computational RRCK permeability model (Schrödinger's implementation).

	Compound series	Congeneric	N	r^2	Reference
1	Drugs	No	11	0.40	19
2	Peptidomimetics	Yes	12	0.61	20
3	Peptidomimetics	Yes	25	0.41	21

Table S6. MLR analysis for predicting RRCK permeability from Log *D* and *in silico* descriptors.

	Descriptor								
Model	Log *D*	V	CSA	SASA	MW	SD	r^2	F	P
8	✓					0.58	0.07	9.73	2.21E-03
9		✓				0.51	0.29	54.67	1.35E-11
10			✓			0.56	0.12	19.18	2.37E-05
11				✓		0.50	0.30	58.53	3.40E-12
12					✓	0.52	0.25	44.83	5.29E-10
13	✓	✓				0.41	0.53	75.95	8.89E-23
14	✓		✓			0.50	0.31	29.78	2.00E-11
15	✓			✓		0.40	0.55	82.50	4.42E-24
16	✓				✓	0.41	0.54	77.51	4.30E-23

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