

Supporting Information

Table S1: Measured values and s.e.m. of EP and TP, and calculated OP values, for 14 piperazine derivatives at three concentrations

		EP						TP						OP					
		10 mM		30 mM		100 mM		10 mM		30 mM		100 mM		10 mM		30 mM		100 mM	
		EP	Error	EP	Error	EP	Error	TP	Error	TP	Error	TP	Error	OP	Error	OP	Error	OP	Error
A	piperazine	0.07	0.04	1.00	0.00	1.00	0.00	0.06	0.08	0.00	0.15	0.72	0.03	0.01	0.09	1.00	0.15	0.28	0.03
B	1-methylpiperazine	0.10	0.07	1.00	0.02	1.00	0.00	0.00	0.08	0.00	0.12	0.68	0.03	0.10	0.10	1.00	0.12	0.32	0.03
C	1-ethylpiperazine	0.23	0.05	0.98	0.00	1.00	0.01	0.01	0.06	0.00	0.17	0.69	0.08	0.21	0.08	0.98	0.17	0.31	0.08
D	(S)-(+)-2-methylpiperazine	0.19	0.06	0.84	0.08	1.00	0.00	0.00	0.07	0.00	0.08	0.71	0.02	0.19	0.09	0.84	0.11	0.29	0.02
E	trans-2,5-dimethylpiperazine	0.13	0.09	0.94	0.01	1.00	0.00	0.00	0.14	0.00	0.01	0.70	0.05	0.31	0.17	0.94	0.02	0.30	0.05
F	2,6-dimethylpiperazine	0.10	0.03	1.00	0.00	1.00	0.04	0.00	0.14	0.00	0.15	0.79	0.04	0.10	0.14	1.00	0.15	0.21	0.06
G	1-allylpiperazine	0.19	0.02	0.91	0.01	0.99	0.01	0.00	0.02	0.00	0.04	0.63	0.17	0.00	0.03	0.91	0.04	0.36	0.17
H	1,4-dimethylpiperazine	0.08	0.07	0.57	0.07	0.96	0.00	0.00	0.07	0.00	0.07	0.00	0.12	0.08	0.10	0.57	0.10	0.96	0.12
I	1-isopropylpiperazine	0.72	0.03	0.94	0.02	1.00	0.00	0.00	0.16	0.00	0.11	0.69	0.07	0.72	0.16	0.94	0.11	0.31	0.07
J	1,4-diethylpiperazine	0.27	0.10	0.88	0.02	0.98	0.00	0.03	0.02	0.00	0.10	0.43	0.10	0.09	0.11	0.88	0.10	0.55	0.10
K	1-isopropyl-2-methylpiperazine	0.24	0.06	0.45	0.05	0.73	0.02	0.04	0.08	0.00	0.09	0.97	0.07	0.20	0.10	0.45	0.10	0.00	0.07
L	2,5-diethylpiperazine	0.33	0.07	0.90	0.03	0.99	0.01	0.00	0.07	0.11	0.03	0.49	0.14	0.33	0.10	0.79	0.04	0.50	0.14
M	1-butylpiperazine	0.06	0.21	0.85	0.08	0.98	0.01	0.15	0.06	0.34	0.05	0.71	0.10	0.00	0.22	0.51	0.09	0.27	0.10
N	1,4-diallylpiperazine	0.16	0.17	0.45	0.03	0.98	0.01	0.04	0.06	0.03	0.02	0.07	0.13	0.11	0.18	0.42	0.04	0.92	0.13

Table S2: Measured values of pKa and pH at three concentrations for 14 piperazine derivatives								
		10 mM	30 mM	100mM	pKa 1	pKa 1	pKa 2	pKa 2
		pH	pH	pH	pKa 1	s.e.m.	pKa 2	s.e.m.
A	piperazine	9.07	9.43	10.31	5.40	0.02	9.59	0.01
B	1-methylpiperazine	8.85	9.12	9.83	4.59	0.04	8.97	0.02
C	1-ethylpiperazine	8.91	9.35	9.93	4.87	0.02	9.10	0.02
D	(S)-(+)-2-methylpiperazine	9.01	9.49	10.20	5.25	0.03	9.53	0.01
E	trans-2,5-dimethylpiperazine	8.95	9.55	10.09	5.16	0.04	9.57	0.03
F	2,6-dimethylpiperazine	8.85	9.46	10.09	5.28	0.01	9.62	0.04
G	1-allylpiperazine	8.76	9.19	9.75	4.34	0.12	9.07	0.05
H	1,4-dimethylpiperazine	8.55	8.88	9.25	4.01	0.05	8.19	0.01
I	1-isopropylpiperazine	8.97	9.41	10.07	5.03	0.06	9.37	0.02
J	1,4-diethylpiperazine	8.63	9.09	9.46	4.43	0.13	8.72	0.03
K	1-isopropyl-2-methylpiperazine	8.90	9.44	10.11	5.04	0.06	9.55	0.07
L	2,5-diethylpiperazine	9.03	9.55	10.24	5.15	0.11	9.63	0.06
M	1-butylpiperazine	8.81	9.31	9.85	4.92	0.05	9.31	0.03
N	1,4-diallylpiperazine	8.57	8.73	9.12	N/A	N/A	7.80	0.05

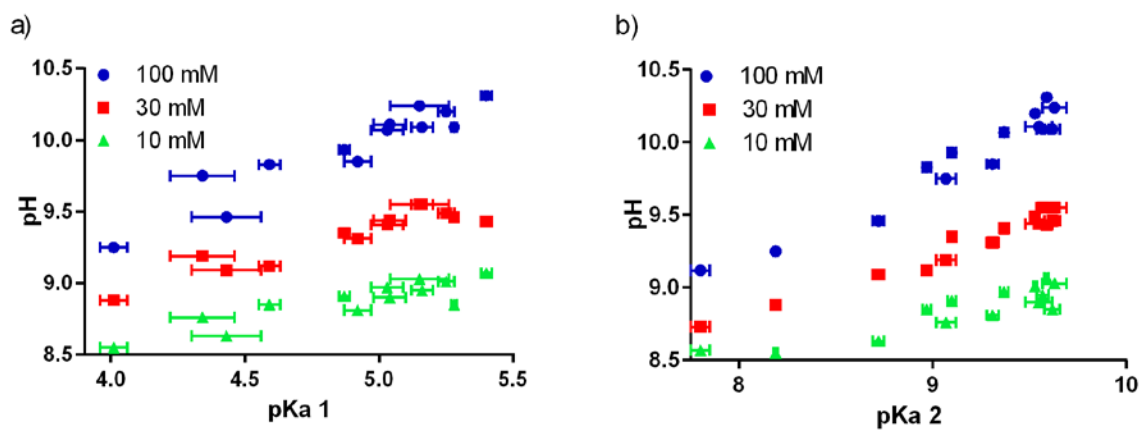


Figure S1. The pH of piperazine derivatives increases with increasing pKa.

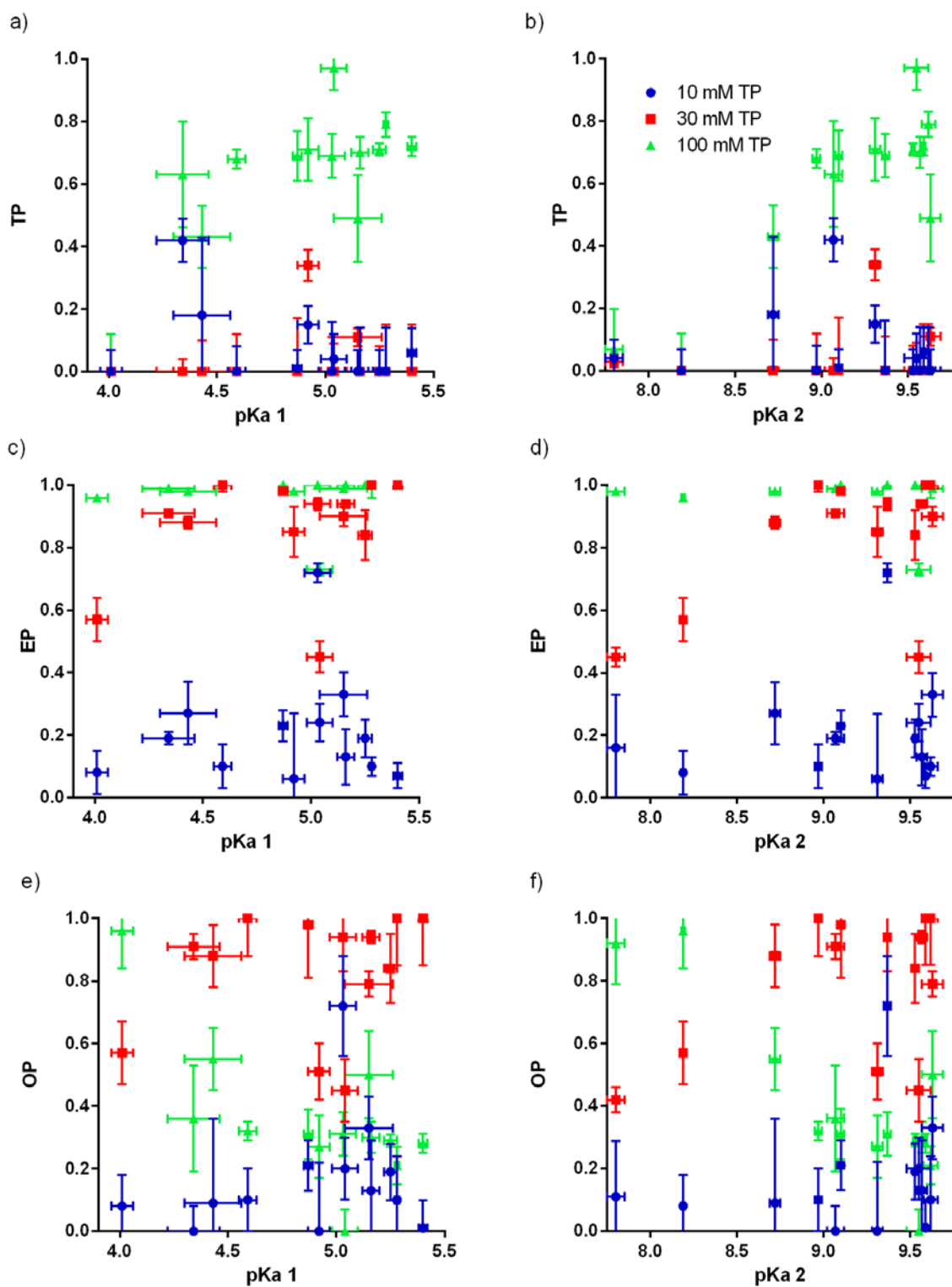


Figure S2. No strong relationships exist between potentials of piperazine derivatives as permeation enhancers and their pKas.

Table S3: EP, TP, and OP values with s.e.m. for non-piperazine amines

		EP						TP						OP					
		3mM	3mM	10	10	30	30	3mM	3mM	10	10	30	30	3mM	3mM	10	10	30	30
		EP	Error	EP	Error	EP	Error	TP	Error	TP	Error	TP	Error	OP	Error	OP	Error	OP	Error
P	1-aminohexane	0.25	0.16	0.77	0.02	0.95	0.00	0.03	0.02	0.00	0.04	1.00	0.00	0.22	0.17	0.77	0.04	0.00	0.01
Q	1,6-diaminohexane	0.54	0.02	0.75	0.05	0.96	0.01	0.00	0.03	0.07	0.04	1.00	0.03	0.54	0.04	0.68	0.04	0.00	0.03
R	ethylbutylamine	0.16	0.10	0.29	0.05	0.97	0.00	0.07	0.05	0.05	0.04	0.79	0.01	0.09	0.11	0.24	0.06	0.18	0.01
S	1,2-bis(methylamino)ethane	0.00	0.06	0.41	0.07	0.97	0.00	0.02	0.03	0.00	0.04	0.00	0.05	0.00	0.07	0.41	0.08	0.97	0.05
T	triethylamine	0.00	0.04	0.28	0.03	0.98	0.00	0.00	0.03	0.00	0.02	0.03	0.04	0.00	0.05	0.28	0.04	0.95	0.04
U	1,2-bis(dimethylamino)ethane	0.20	0.10	0.39	0.03	0.97	0.00	0.00	0.03	0.00	0.03	0.00	0.03	0.20	0.10	0.39	0.04	0.97	0.03

Table S4: Measured values of pH at three concentrations for six non-piperazine amines				
		3mM pH	10 mM pH	30 mM pH
P	1-aminohexane	8.10	9.09	9.93
Q	1,6-diaminohexane	8.61	9.66	10.71
R	ethylbutylamine	8.30	8.99	9.95
S	1,2-bis(methylamino)ethane	8.43	9.14	9.96
T	triethylamine	8.03	8.98	9.82
U	1,2-bis(dimethylamino)ethane	8.14	9.06	9.60