Supporting Information

Testing Physical Models of Passive Membrane Permeation

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Table S1. Experimental data of examined data sets.

	$LogP_{PAMPA}$[a]							$LogP_{Caco-2}$[b]							$LogP_{MDCK}$[c]	%Abs[d]		$LogP_{app}$[e]
Molecule	Avdeef	Balimane	Bermejo	Di	Fujikawa	Li	Whitlock	Avdeef	Balimane	Bermejo	Fujikawa	Goodwin	Irvine	Li	Irvine	Balimane	Irvine	Bermjo
2,4-dichlorophenol					-3.90													
2,4-dimethylphenol					-3.58													
2,5-dichloronitrobenzene					-4.09													
2-chloroaniline					-3.61													
2-chlorophenol					-4.82													
2-methylphenol					-3.53													
2-nitroaniline					-3.64													
2-nitrophenol					-3.66													
3-chloroaniline					-3.58													
3-nitroaniline					-3.71													
3-nitrophenol					-4.16													
4-chloroaniline					-3.59													
4-cyanophenol					-4.65													
4-nitroaniline					-3.91													
Acebutalol		-5.80			-5.58				-5.40		-6.29		-5.42		-5.77	55	90	
Acetaminophen					-5.65								-4.00		-4.46		80	
Acetysalicyclic acid													-5.66		-5.13		100	
Acrivastine													-5.72		-5.66		88	
Acyclovir															-6.68		16	
Aldosterone				-5.92														
Alfentanil	-3.53							-3.49										
Alprazolam				-5.27														
Alprenolol	0.02	-4.52			-4.21			-1.75	-4.95		-4.60		-3.77		-3.80	93	93	
Amiloride		-6.30							-5.31							50		
Aminopyrine					-4.14						-4.44							
Amoxicillin													-7.68		-6.62		94	
Aniline					-3.51													
Antipyrine					-5.00								-3.82		-3.82		100	
Astemizole				-4.96														
Atenolol	-5.06			-6.10				-4.50					-5.48		-5.74		50	
Atrazine					-4.14						-4.39							
AZT													-4.55		-5.22		100	
Benthiocarb					-4.03													
Biphenyl					-4.27													
BPMC					-3.88													
Bu-ciprofloxacin			-3.52							-4.52								-3.85
Bu-norfloxacin			-3.44															-3.86
Bupropion													-3.82		-3.89		87	
Caffeine				-5.89	-4.80						-4.51							
Cefatrizine													-6.12		-5.60		76	
Cefuroxime													-6.42		-6.80		5	
Cephalexin													-6.57		-6.32		98	
Chloramphenicol					-5.24													
Chlorothiazide													-6.49		-6.52		13	

	LogP_{PAMPA}[a]							LogP_{Caco-2}[b]							LogP_{MDCK}[c]	%Abs[d]		LogP_{app}[e]
Molecule	Avdeef	Balimane	Bermejo	Di	Fujikawa	Li	Whitlock	Avdeef	Balimane	Bermejo	Fujikawa	Goodwin	Irvine	Li	Irvine	Balimane	Irvine	Bermjo
Chlorpromazine				-5.19														
Cimetidine	-6.20	-5.66						-6.44	-5.54							79		
Ciprofloxacin			-5.57							-5.54								-4.81
Clobazam				-4.77														
Clonidine				-5.28	-4.94						-4.66							
CNV97100			-5.42							-5.20								-4.51
CNV97101			-4.70							-4.66								-4.38
CNV97102			-4.29							-4.77								-4.11
CNV97103			-3.80							-4.82								-3.97
CNV97104			-3.38							-4.86								-3.90
Corticosterone				-5.29	-4.47						-4.67		-3.92		-3.85		100	
Coumarin					-3.56													
Desipramine		-4.15		-4.92	-3.81				-4.52		-4.61					95		
Dexamethasone		-4.54			-4.95				-4.87		-4.91		-4.40		-4.70	95	100	
Diazepam				-4.80														
Diazinon					-4.51						-4.32							
Diehtylpthalate					-4.33													
Dilthiazem	-1.33				-3.91			-2.88										
Dimehtylpthalate					-3.80													
Diphenylamine					-4.82						-4.40							
Diphenylamine-2-carboxylic acid					-4.61													
DMTP					-4.33						-4.32							
Dopamine				-6.70														
Enoxacin				-6.05														
Estradiol				-4.92														
Etoposide		-5.46							-5.74							50		
Fenaterol		-6.52														60		
Flumequine			-3.84							-4.54								-3.77
Fluparoxan													-3.70		-3.60		100	
Furosemide		-6.05			-6.24				-5.70				-6.85		-6.21	66	61	
Gabapentin													-8.00		-6.44		50	
Guanabenz													-4.00		-3.72		75	
Hydralazine		-4.98							-4.85							90		
Hydrochlorothiazide					-6.54						-6.29		-6.04		-6.00		67	
Hydrocortisone				-5.72	-5.07						-4.85		-4.25		-4.51		91	
Hydroquinone					-5.34													
IBP					-3.44						-4.28							
Ibuprofen					-4.14													
Imidacloprid					-5.28													
Imipramine				-4.89	-4.20													
Isoxicam				-6.52														
Ketoconazole		-4.27							-4.97							76		
Ketoprofen		-5.66			-5.40				-4.60				-4.03		-4.70	90	100	
Labetalol					-5.25						-5.03		-4.12		-4.60		95	
Lamotrigine													-3.96		-4.06		70	
Lisinopril													-6.66		-6.74		25	
Lomefloxacin				-5.96														

	LogP_{PAMPA}[a]							LogP_{Caco-2}[b]							LogP_{MDCK}[c]	%Abs[d]		LogP_{app}[e]
Molecule	Avdeef	Balimane	Bermejo	Di	Fujikawa	Li	Whitlock	Avdeef	Balimane	Bermejo	Fujikawa	Goodwin	Irvine	Li	Irvine	Balimane	Irvine	Bermjo
Loracarbef													-6.62		-6.04		100	
Mannitol													-6.24				15	
Me-ciprofloxacin			-4.43							-4.59								-4.20
Me-norfloxacin			-4.31															-4.32
MEP					-4.89													
Metformin		-6.30							-5.92							52		
Methoxyfenozide											-4.33							
Methylprednisolone													-4.60		-4.80		82	
Metoprolol	-1.17	-4.58			-4.84			-1.35	-4.92		-4.63		-3.85		-3.82	95	95	
Nadolol	-4.34				-4.49			-4.49			-5.41		-6.41		-5.85		34	
Naproxen		-5.48			-5.26				-4.52							100		
Netivudine													-6.17		-5.85		28	
Norfloxacin		-6.30	-6.15	-7.00	-6.74				-5.72	-5.74						35		-4.98
Ofloxacin			-5.20	-6.10						-4.96								-4.69
Olsalazine													-7.80		-7.32		2	
Ondansetron													-3.96		-3.96		100	
Oxazepam				-5.00														
Oxprenolol					-5.03								-3.80		-3.89		90	
Penicillin V													-6.77		-6.82		45	
Phenol					-3.83													
Phenytoin		-4.69			-4.93				-4.51		-4.57		-3.80		-3.92	90	90	
Pindolol	-1.74				-5.85			-2.58			-4.78		-4.02		-4.23		90	
Pirenzepine					-6.09						-6.36							
Piroxicam				-5.60	-4.72						-4.45							
Practolol					-6.43								-5.21		-5.89		100	
Pr-ciprofloxacin			-3.86							-4.49								-3.92
Prednisolone					-5.52													
Pr-norfloxacin			-3.88							-4.47								-4.00
Progesterone				-5.03									-4.01		-3.80		91	
Promazine				-5.06														
Propranolol	0.43	-4.39			-4.42			-1.48	-4.76		-4.66		-3.96		-3.77	90	90	
Propylthiouracil													-4.02		-4.39		75	
Pyrene					-4.32													
Ranitidine					-5.52						-6.31						50	
RH5849											-4.34							
Salicylic acid					-5.31						-4.66		-4.89		-5.00		100	
Salithion					-4.36													
Sarafloxacin			-4.85							-5.35								-4.72
Sotalol													-5.38		-5.33		95	
Sulfasalazine		-6.70							-6.40				-6.22		-6.32	12	65	
Sulpiride		-6.52							-6.30							35		
Sumatriptan															-5.72		75	
Tebufenozide											-4.44							
Tenoxicam				-7.00														
Terbutaline	-7.25	-6.52						-6.15	-5.82				-6.39		-6.00	50	60	
Testosterone				-4.77	-3.87						-4.60		-4.00		-3.85		100	
Theophylline					-5.58													

	$LogP_{PAMPA}$[a]							$LogP_{Caco-2}$[b]							$LogP_{MDCK}$[c]	%Abs[d]		$LogP_{app}$[e]
Molecule	Avdeef	Balimane	Bermejo	Di	Fujikawa	Li	Whitlock	Avdeef	Balimane	Bermejo	Fujikawa	Goodwin	Irvine	Li	Irvine	Balimane	Irvine	Bermjo
Thiopental				-4.74														
Timolol													-4.00		-4.26		90	
Trimethoprim					-5.38								-4.06		-4.28		97	
Verapamil	0.26	-4.40			-3.96			-2.07	-5.01							95		
Warfarin													-4.02		-4.36		98	
Goodwin01												-6.85						
Goodwin02												-6.60						
Goodwin03a												-6.05						
Goodwin04												-5.82						
Goodwin05a												-5.55						
Goodwin06												-5.05						
Goodwin07												-4.65						
Goodwin08												-4.60						
Goodwin09a												-4.45						
Goodwin10												-4.32						
Goodwin11a												-4.26						
Goodwin12												-4.26						
whitlock24							-4.96											
whitlock25							-4.85											
whitlock26							-4.82											
whitlock28							-5.00											
whitlock30							-4.85											
whitlock34							-4.72											
whitlock35							-5.57											
whitlock36							-5.66											
Li01						-5.18								-5.27				
Li02						-5.21								-5.39				
Li03						-4.52								-5.33				
Li04						-4.82								-5.70				
Li05						-4.90								-5.96				
Li06						-5.07								-5.57				
Li12						-4.27								-5.43				
Li15						-5.51								-6.28				
Li16						-4.53								-5.51				
Li17						-4.35								-5.44				
Li18						-4.49								-4.93				
Li19						-4.19								-4.93				
Li20						-4.49								-5.32				
Li21						-4.35								-5.35				
Li22						-5.01								-5.15				
Li23						-4.82								-5.39				
Li24						-7.00								-6.52				
Li27						-5.92								-5.89				
Li28						-7.15								-7.00				
Li29						-7.00								-6.70				
Li30						-7.05								-5.70				
Li31						-6.85								-5.30				

	LogP_{PAMPA}[a]							LogP_{Caco-2}[b]							LogP_{MDCK}[c]	%Abs[d]		LogP_{app}[e]
Molecule	Avdeef	Balimane	Bermejo	Di	Fujikawa	Li	Whitlock	Avdeef	Balimane	Bermejo	Fujikawa	Goodwin	Irvine	Li	Irvine	Balimane	Irvine	Bermjo
Li32						-6.38								-5.28				
Li33						-6.11								-6.30				
Li34						-7.15								-5.42				

[a] Logarithms of PAMPA measurements (cm/s). Avdeef: Ref. 1; Balimane: Ref. 2; Bermejo: Ref. 3; Di: Ref. 4; Fujikawa: Ref. 5; Li: Ref. 8; Whitlock: Ref. 9.

[b] Logarithms of Caco-2 cell-based assay measurements (cm/s). Avdeef: Ref. 1; Balimane: Ref. 2; Bermejo: Ref. 3; Fujikawa: Ref. 5; Goodwin: Ref. 6; Irvine: Ref. 7; Li: Ref. 8.

[c] Logarithms of MDCK cell-based assay measurements (cm/s). Irvine: Ref. 7.

[d] Percentage fraction absorbed in humans (%). Balimane: Ref. 2; Irvine: Ref. 7.

[e] Logarithms of rat *in situ* perfusion assay measurement (cm/s). Bermejo: Ref. 3.

Table S2. Predictions and compound classification of examined data sets.

	Physics-based[a]							QikProp[b]							Classification		
Molecule	$\Delta G_{transfer(LDC)}$	$\Delta G_{transfer}$	$\Delta G_{c/w}$	ΔG_{state}	ΔG_{cf}	Log $K_{barrier}$	Log P_m	MW	Vol	PSA	QPlog $P_{o/w}$	Log QPPCaco	Log QPPMDCK	QP%HOA	PGP[c]	Active[d]	QikProp[e]
2,4-dichlorophenol	3.62	3.32	5.23	0.04	1.57	-4.88	-7.48	163.00	488.78	21.61	2.83	3.54	4.00	100.00			
2,4-dimethylphenol	3.06	2.61	4.84	0.00	1.77	-4.66	-7.27	122.17	519.70	21.41	2.22	3.57	3.31	100.00			
2,5-dichloronitrobenzene	0.35	0.14	2.33	0.00	1.97	-2.86	-5.48	192.00	535.18	43.27	2.94	3.15	3.57	100.00			
2-chloroaniline	3.51	3.43	5.53	0.00	2.02	-5.02	-7.61	127.57	449.56	24.80	1.82	3.48	3.58	100.00			
2-chlorophenol	3.43	3.17	5.05	0.02	1.60	-4.65	-7.24	128.56	444.75	21.62	2.39	3.54	3.65	100.00			
2-methylphenol	3.60	2.97	5.30	0.00	1.70	-4.87	-7.47	108.14	459.75	21.41	1.94	3.57	3.31	100.00			
2-nitroaniline	3.72	3.60	5.46	0.00	1.75	-5.03	-7.63	138.13	477.31	67.55	1.38	2.66	2.32	82.59			
2-nitrophenol	3.52	3.46	5.41	0.19	1.70	-4.98	-7.58	139.11	472.48	64.37	1.87	2.71	2.38	86.36			
3-chloroaniline	3.42	3.24	5.22	0.00	1.80	-4.79	-7.39	127.57	452.41	25.88	1.81	3.42	3.54	100.00			
3-nitroaniline	3.48	3.38	5.21	0.00	1.74	-4.85	-7.45	138.13	480.88	70.81	1.28	2.50	2.15	79.18			
3-nitrophenol	3.95	3.54	5.65	0.02	1.69	-5.16	-7.76	139.11	475.81	67.50	1.91	2.55	2.21	83.85			
4-chloroaniline	3.40	3.16	5.16	0.00	1.76	-4.75	-7.34	127.57	452.28	25.84	1.88	3.42	3.54	100.00			
4-cyanophenol	4.03	3.56	5.88	0.04	1.81	-5.32	-7.91	119.12	468.59	48.35	1.60	2.79	2.47	86.32			
4-nitroaniline	3.56	3.38	5.17	0.00	1.61	-4.82	-7.43	138.13	481.15	70.87	1.58	2.50	2.15	80.87			
Acebutalol	6.81	5.92	10.92	2.32	1.79	-10.56	-13.30	336.43	1231.46	104.25	1.71	2.09	1.75	74.31	Y		Y
Acetaminophen	9.06	8.57	10.74	0.00	1.69	-9.09	-11.72	151.17	571.14	61.23	0.51	2.93	2.61	82.30			Y
Acetysalicyclic acid	7.83	5.10	13.30	3.86	4.23	-11.06	-13.70	180.16	616.59	85.10	1.19	2.09	1.82	71.38			Y
Acrivastine	5.81	5.46	14.32	6.59	1.93	-13.10	-15.83	348.44	1218.87	67.45	2.39	1.63	1.36	70.10			Y
Acyclovir	19.09	18.69	21.09	0.00	2.01	-16.98	-19.64	225.21	720.44	128.43	-1.56	1.66	1.24	47.46			Y
Aldosterone	6.94	5.44	8.83	0.00	1.89	-8.80	-11.52	360.45	1090.60	118.05	1.08	2.11	1.73	70.94	Y		
Alfentanil	2.46	2.37	8.91	4.07	2.39	-9.48	-12.24	416.52	1376.46	101.07	2.15	2.28	1.96	80.28			Y
Alprazolam	5.58	5.33	7.34	0.03	1.72	-7.41	-10.11	308.77	949.63	50.86	4.09	3.26	3.37	100.00			
Alprenolol	0.80	0.56	4.76	2.32	1.64	-5.51	-8.21	249.35	984.65	39.81	3.10	2.97	2.71	100.00	N		Y
Amiloride	21.62	21.21	27.07	3.98	1.46	-21.28	-23.93	229.63	670.86	166.40	-0.82	0.89	0.79	25.14		Y	
Aminopyrine	4.53	4.24	6.71	0.00	2.18	-6.69	-9.37	231.30	829.41	35.35	1.00	3.07	2.81	87.73			Y
Amoxicillin	24.26	22.96	32.87	6.02	2.58	-26.30	-29.01	365.40	1067.63	159.12	-2.27	-0.17	0.14	10.60		Y	Y
Aniline	2.86	2.75	4.67	0.00	1.81	-4.30	-6.88	93.13	408.26	25.86	0.93	3.42	3.15	93.61			Y
Antipyrine	3.84	3.68	5.68	0.00	1.84	-5.64	-8.30	188.23	689.27	35.20	0.38	3.50	3.23	91.80	N		Y
Astemizole	5.17	3.49	10.55	2.84	2.54	-10.77	-13.53	458.58	1418.42	36.41	6.14	3.23	3.13	100.00	Y		
Atenolol	7.09	6.80	11.28	2.32	1.86	-10.33	-13.03	266.34	977.17	94.87	0.17	1.54	1.54	55.43	N	Y	Y
Atrazine	13.71	13.68	15.17	0.00	1.46	-12.75	-15.42	215.69	765.07	56.04	2.61	3.42	3.57	100.00	N		
AZT	10.07	9.55	11.30	0.00	1.22	-10.04	-12.72	267.24	828.46	152.32	0.03	1.48	1.05	53.61			Y
Benthiocarb	0.01	-0.22	2.54	0.00	2.53	-3.75	-6.44	257.78	875.80	28.24	3.24	3.71	3.94	100.00			
Biphenyl	-1.19	-1.89	0.84	0.00	2.03	-1.93	-4.57	154.21	610.67	0.00	4.09	4.00	3.77	100.00			Y
BPMC	1.44	1.17	3.47	0.00	2.03	-4.19	-6.86	207.27	767.43	42.60	2.06	3.59	3.33	100.00			
Bu-ciprofloxacin	6.49	6.06	10.54	2.20	1.85	-10.37	-13.11	387.45	1249.57	87.49	1.55	1.38	1.24	60.62			
Bu-norfloxacin	6.71	6.13	10.81	2.20	1.90	-10.51	-13.24	375.44	1213.40	87.19	1.31	1.37	1.22	59.03			
Bupropion	0.64	0.64	2.15	1.28	0.23	-3.37	-6.06	239.74	829.00	30.60	3.02	3.09	3.22	100.00			Y
Caffeine	10.09	10.09	10.09	0.00	0.00	-8.79	-11.43	194.19	650.86	74.52	-0.07	3.01	2.71	80.49			Y
Cefatrizine	29.36	26.80	36.52	5.48	1.68	-29.26	-31.99	462.50	1278.63	204.28	-1.97	-0.87	-0.78	0.00		Y	Y
Cefuroxime	22.05	21.47	28.40	4.99	1.35	-23.31	-26.04	424.38	1194.47	201.74	0.06	0.48	0.19	22.94			Y
Cephalexin	20.25	19.70	28.09	4.91	2.93	-22.81	-25.52	347.39	1046.05	135.42	-1.09	0.59	0.68	31.22		Y	Y
Chloramphenicol	8.06	7.50	9.98	0.00	1.92	-9.24	-11.93	323.13	876.97	119.68	1.08	1.87	2.24	66.64			Y
Chlorothiazide	20.68	20.04	22.83	0.00	2.15	-18.30	-20.96	295.72	722.96	128.71	-0.42	1.51	1.37	51.42			Y

	Physics-based[a]							QikProp[b]							Classification		
Molecule	$\Delta G_{transfer(LDC)}$	$\Delta G_{transfer}$	$\Delta G_{c/w}$	ΔG_{state}	ΔG_{cf}	Log $K_{barrier}$	Log P_m	MW	Vol	PSA	QPlog $P_{o/w}$	Log QPPCaco	Log QPPMDCK	QP%HOA	PGP[c]	Active[d]	QikProp[e]
Chlorpromazine	2.47	2.30	7.94	2.95	2.51	-8.01	-10.72	318.86	993.36	6.84	5.08	3.38	3.71	100.00	Y	Y	Y
Cimetidine	10.22	9.71	12.36	0.47	1.67	-10.86	-13.55	252.34	896.19	99.00	0.42	2.36	2.14	71.58	Y	Y	Y
Ciprofloxacin	9.85	9.67	15.80	3.43	2.52	-13.74	-16.45	331.35	1003.64	97.63	0.28	1.11	0.98	48.44		Y	
Clobazam	7.40	7.16	9.17	0.09	1.68	-8.68	-11.38	300.74	914.34	56.27	2.21	3.22	3.32	100.00			
Clonidine	10.31	10.04	12.31	0.25	1.75	-10.51	-13.17	230.10	695.43	37.12	1.59	3.50	3.91	100.00	N		Y
CNV97100	9.66	9.07	15.88	3.86	2.36	-13.92	-16.64	345.37	1103.90	96.31	0.46	1.20	1.04	51.11			
CNV97101	8.43	8.16	12.96	2.11	2.42	-11.89	-14.61	359.40	1110.87	87.65	0.60	1.35	1.20	54.69			
CNV97102	7.94	7.31	12.44	2.25	2.25	-11.61	-14.34	373.43	1160.12	87.00	0.95	1.37	1.22	56.98			
CNV97103	6.55	6.26	11.24	2.28	2.42	-10.88	-13.62	387.45	1227.50	87.10	1.40	1.39	1.24	59.96			
CNV97104	5.51	5.23	10.12	2.33	2.27	-10.18	-12.92	401.48	1288.40	87.10	1.80	1.39	1.24	62.34			
Corticosterone	4.29	4.02	6.53	0.00	2.25	-7.09	-9.81	346.47	1084.31	92.79	1.94	2.42	2.06	81.54	Y		Y
Coumarin	2.27	2.27	2.27	0.00	0.00	-2.76	-5.37	146.15	515.02	40.60	1.39	3.31	3.03	94.31			
Desipramine	3.42	2.90	9.25	3.78	2.05	-8.84	-11.55	266.39	968.23	16.08	4.89	3.16	2.91	100.00	N		Y
Dexamethasone	7.61	6.39	10.13	0.00	2.52	-9.85	-12.58	392.47	1141.06	107.15	1.94	2.28	2.00	79.10	Y		Y
Diazepam	3.73	3.52	5.52	0.00	1.79	-5.96	-8.66	284.74	897.29	47.08	2.99	3.43	3.55	100.00			Y
Diazinon	7.50	6.90	9.95	0.00	2.46	-9.42	-12.13	288.28	972.75	62.40	2.02	3.65	3.41	100.00			
Diehtylpthalate	0.19	0.13	3.21	0.00	3.03	-4.13	-6.82	222.24	818.09	64.47	2.31	3.22	2.93	100.00			
Dilthiazem	3.41	2.99	8.37	2.41	2.65	-8.89	-11.63	414.52	1283.05	69.15	3.00	2.72	2.58	93.15	Y		
Dimehtylpthalate	1.65	1.48	3.58	0.00	1.93	-4.12	-6.78	194.19	695.01	65.98	1.46	3.17	2.87	92.16			
Diphenylamine	6.24	5.63	12.46	4.09	2.13	-10.71	-13.37	169.23	654.29	9.90	3.50	3.92	3.69	100.00			
Diphenylamine-2-carboxylic acid	1.77	1.28	3.47	0.00	1.70	-3.94	-6.59	213.24	726.38	56.35	4.20	2.48	2.24	95.89			
DMTP	4.99	4.29	7.01	0.00	2.02	-6.88	-9.56	302.32	826.02	70.44	2.47	3.52	4.00	100.00			
Dopamine	9.23	8.86	14.36	2.86	2.28	-11.76	-14.39	153.18	572.50	70.70	-0.98	1.83	1.48	54.04			Y
Enoxacin	11.81	11.40	17.87	3.35	2.87	-15.15	-17.85	320.32	966.45	103.60	-0.20	1.09	0.94	45.33			
Estradiol	3.28	2.85	5.01	0.00	1.74	-5.62	-8.31	272.39	911.58	43.70	4.01	3.09	2.79	100.00	Y		Y
Etoposide	15.77	14.04	17.66	0.00	1.89	-16.23	-19.00	588.56	1502.71	164.52	0.60	2.47	2.12	48.73	Y		
Fenaterol	13.93	12.14	16.77	2.63	0.20	-14.50	-17.21	303.36	1028.53	100.70	1.05	1.38	0.99	57.76		Y	
Flumequine	6.80	6.63	10.07	1.73	1.53	-9.08	-11.76	261.25	795.35	79.55	2.58	2.01	1.98	78.00			
Fluparoxan	4.49	4.49	5.45	0.96	0.00	-5.31	-7.94	195.19	612.32	33.79	1.47	3.07	3.06	90.57			Y
Furosemide	14.16	13.79	21.81	3.84	3.81	-17.93	-20.63	330.74	904.54	128.99	1.86	1.21	1.16	59.57		Y	Y
Gabapentin	4.16	4.05	13.72	7.47	2.09	-11.40	-14.04	171.24	622.64	66.71	-1.10	1.61	1.34	49.36		Y	Y
Guanabenz	6.74	6.68	14.19	5.33	2.12	-11.87	-14.52	231.08	683.67	81.76	1.13	2.55	2.82	79.27			Y
Hydralazine	10.42	10.07	12.28	0.00	1.86	-10.20	-12.82	160.18	553.99	68.37	-0.34	2.03	1.69	61.30			
Hydrochlorothiazide	19.40	18.94	21.81	0.05	2.36	-17.56	-20.23	297.73	731.85	130.90	-0.10	1.50	1.37	53.21			Y
Hydrocortisone	8.04	7.28	10.29	0.00	2.24	-9.87	-12.59	362.47	1094.96	110.47	1.60	2.13	1.75	74.40	Y		Y
Hydroquinone	7.46	6.84	9.01	0.00	1.55	-7.52	-10.10	110.11	425.79	45.07	0.80	2.96	2.65	84.58			
IBP	-0.02	-1.40	1.45	0.00	1.47	-3.13	-5.83	288.34	979.62	31.37	3.54	3.74	3.67	100.00			
Ibuprofen	0.40	-0.12	7.06	4.15	2.50	-6.88	-9.56	206.28	799.67	48.77	3.50	2.51	2.27	92.37		Y	Y
Imidacloprid	8.06	6.45	12.41	2.07	2.28	-10.71	-13.38	255.66	754.09	85.65	0.93	2.49	2.55	76.90			
Imipramine	1.10	0.86	6.77	3.14	2.40	-7.15	-9.86	280.41	1017.15	6.02	4.44	3.37	3.14	100.00	N		Y
Isoxicam	13.87	12.38	15.01	0.00	1.14	-13.05	-15.76	335.33	971.26	117.52	1.43	2.22	1.86	75.08			
Ketoconazole	5.54	4.44	7.38	0.27	1.57	-8.51	-11.28	531.44	1565.83	69.08	4.36	2.94	3.58	92.10	Y		
Ketoprofen	3.95	3.26	11.02	4.47	2.60	-9.94	-12.62	254.29	872.26	75.43	3.12	2.10	1.83	82.88			Y
Labetalol	11.21	9.78	14.49	2.23	1.06	-13.04	-15.77	328.41	1136.31	104.68	2.87	1.53	1.14	71.03	Y		Y
Lamotrigine	14.64	14.15	16.60	0.01	1.95	-13.69	-16.35	256.09	709.84	89.72	0.95	2.29	2.55	73.59			Y
Lisinopril	9.52	9.01	27.68	16.86	1.30	-23.17	-25.92	405.49	1312.41	154.68	-1.19	-1.01	-1.11	1.88		Y	Y
Lomefloxacin	8.72	8.36	15.86	4.10	3.04	-13.85	-16.56	351.35	1036.36	95.34	-0.39	1.20	1.10	46.20			

	Physics-based[a]							QikProp[b]							Classification		
Molecule	$\Delta G_{transfer(LDC)}$	$\Delta G_{transfer}$	$\Delta G_{c/w}$	ΔG_{state}	ΔG_{cf}	Log $K_{barrier}$	Log P_m	MW	Vol	PSA	QPlog $P_{o/w}$	Log QPPCaco	Log QPPMDCK	QP%HOA	PGP[c]	Active[d]	QikProp[e]
Loracarbef	15.15	14.63	23.89	5.99	2.75	-19.71	-22.42	349.77	1023.93	135.79	-1.16	0.61	0.82	31.11		Y	Y
Mannitol	13.88	13.33	14.71	0.00	0.83	-12.07	-14.70	182.17	602.16	121.16	-3.08	1.73	1.32	26.92			Y
Me-ciprofloxacin	9.13	8.88	13.42	2.01	2.32	-12.12	-14.83	345.37	1071.08	88.14	0.33	1.34	1.19	52.84			
Me-norfloxacin	9.67	9.01	14.28	2.01	2.60	-12.68	-15.39	333.36	1035.63	87.83	0.27	1.33	1.18	52.26			
MEP	1.21	0.75	3.84	0.00	2.62	-4.59	-7.27	277.23	821.26	64.16	3.27	3.17	3.25	100.00			
Metformin	14.21	14.21	15.95	1.74	0.00	-12.78	-15.39	129.16	506.32	93.16	-0.80	2.29	1.92	63.20		Y	
Methoxyfenozide	3.40	2.88	6.61	0.00	3.33	-7.50	-10.24	368.48	1242.27	63.27	4.92	3.54	3.28	100.00			
Methylprednisolone	7.71	7.08	10.32	0.00	2.60	-9.97	-12.70	374.48	1130.95	111.49	1.61	2.10	1.72	73.96			Y
Metoprolol	1.44	1.02	5.74	2.32	1.98	-6.36	-9.07	267.37	1023.93	48.98	1.88	2.93	2.67	90.48	N		Y
Nadolol	8.09	7.30	12.47	2.70	1.68	-11.43	-14.15	309.41	988.40	80.30	0.77	2.25	1.93	71.66			Y
Naproxen	3.96	3.32	10.87	4.21	2.70	-9.66	-12.33	230.26	788.16	57.05	3.18	2.51	2.27	90.52			Y
Netivudine	16.63	16.00	17.81	0.02	1.16	-14.91	-17.60	282.25	869.26	142.60	-1.15	1.64	1.23	49.60			Y
Norfloxacin	9.95	9.65	16.47	3.43	3.09	-14.16	-16.86	319.34	976.08	96.95	-1.02	1.12	0.96	40.98			
Ofloxacin	10.94	10.50	14.39	2.11	1.34	-12.83	-15.55	361.37	1067.86	92.79	-0.39	1.34	1.22	48.65		Y	
Olsalazine	18.92	18.47	35.73	14.32	2.50	-28.13	-30.82	302.24	896.26	168.28	1.15	-0.19	-0.55	30.23			Y
Ondansetron	2.67	2.31	4.08	0.31	1.10	-5.10	-7.80	293.37	982.18	43.78	3.94	3.50	3.23	100.00			Y
Oxazepam	8.95	8.53	10.95	0.00	2.01	-9.88	-12.56	286.72	863.32	78.30	2.24	2.73	2.80	88.99			Y
Oxprenolol	2.34	1.22	6.31	2.32	1.65	-6.75	-9.45	265.35	1005.22	47.11	2.18	2.94	2.68	92.43	Y		Y
Penicillin V	15.84	15.28	24.61	5.91	2.87	-20.19	-22.90	350.39	1064.80	123.72	2.08	1.09	1.47	58.61			Y
Phenol	3.39	2.93	5.16	0.00	1.77	-4.64	-7.22	94.11	403.16	22.54	1.46	3.48	3.21	100.00			Y
Phenytoin	6.98	6.80	8.91	0.00	1.93	-8.27	-10.95	252.27	815.57	71.24	2.27	2.73	2.41	89.14	Y		Y
Pindolol	7.50	7.04	11.36	2.32	1.54	-10.25	-12.95	248.32	890.05	51.56	1.84	2.82	2.54	88.18			Y
Pirenzepine	12.07	11.87	13.62	0.55	1.00	-12.30	-15.03	351.41	1113.32	85.80	0.10	1.74	1.42	58.69			Y
Piroxicam	14.15	12.15	17.11	1.50	1.47	-14.59	-17.29	331.35	954.65	108.08	0.50	2.60	2.26	76.31			Y
Practolol	7.29	7.27	11.43	2.32	1.83	-10.48	-13.18	373.43	1189.07	87.49	1.15	1.38	1.24	58.33			Y
Pr-ciprofloxacin	7.42	7.02	12.04	2.15	2.48	-11.35	-14.08	361.42	1152.81	87.19	0.85	1.37	1.22	56.37			
Prednisolone	8.74	7.78	10.94	0.00	2.20	-10.34	-13.06	266.34	994.29	79.77	1.86	2.36	2.04	80.04	N		Y
Pr-norfloxacin	7.28	7.13	12.10	2.15	2.67	-11.33	-14.06	360.45	1086.56	112.72	1.60	2.03	1.64	72.65			
Progesterone	-2.50	-2.62	-1.09	0.00	1.41	-1.43	-4.14	314.47	1047.88	55.16	3.86	3.06	2.76	100.00	N		Y
Promazine	2.88	2.51	8.16	2.95	2.32	-8.07	-10.78	284.42	949.18	9.36	4.68	3.38	3.32	100.00	Y		
Propranolol	2.61	2.47	6.27	2.32	1.35	-6.63	-9.33	259.35	987.08	40.04	3.09	2.71	2.43	93.58	Y	Y	Y
Propylthiouracil	7.07	6.83	8.62	0.17	1.38	-7.61	-10.24	170.23	590.37	64.96	0.68	3.04	3.19	85.41			Y
Pyrene	1.49	1.49	1.49	0.00	0.00	-2.57	-5.22	202.26	690.55	0.00	4.88	4.00	3.77	100.00			
Ranitidine	3.85	3.68	12.65	5.83	2.41	-11.50	-14.21	314.40	1093.64	80.96	0.71	2.25	2.10	71.33	Y		Y
RH5849	4.12	3.86	7.52	0.00	3.40	-7.66	-10.37	296.37	1001.77	59.34	3.90	3.48	3.21	100.00			
Salicylic acid	8.32	8.12	15.50	5.92	1.26	-12.40	-15.00	138.12	482.08	69.25	2.26	2.03	1.76	76.59		Y	Y
Salithion	2.24	1.80	4.05	0.00	1.82	-4.33	-6.98	216.19	635.61	24.60	2.15	4.00	4.00	100.00			
Sarafloxacin	9.14	8.77	14.93	3.59	2.20	-13.33	-16.05	385.37	1113.94	96.87	1.19	1.11	1.23	53.73			
Sotalol	11.37	10.99	17.67	3.99	2.31	-14.95	-17.65	272.36	930.79	82.81	0.24	2.02	1.68	64.48			Y
Sulfasalazine	19.85	19.10	30.80	8.51	2.44	-25.05	-27.78	398.39	1151.16	161.65	1.05	0.67	0.28	45.06	N	Y	Y
Sulpiride	12.15	11.02	16.72	2.99	1.58	-14.58	-17.30	341.42	1081.30	111.74	0.57	1.62	1.25	59.24			Y
Sumatriptan	11.03	10.47	16.15	2.68	2.44	-13.94	-16.64	295.40	984.45	71.62	1.38	2.14	1.81	73.30			Y
Tebufenozide	2.07	1.44	5.22	0.00	3.15	-6.46	-9.20	352.48	1240.68	58.20	5.23	3.48	3.21	100.00			
Tenoxicam	13.56	13.36	26.26	10.51	2.19	-21.20	-23.90	337.37	932.71	105.70	1.82	2.44	2.35	81.23			
Terbutaline	10.07	9.94	15.43	2.77	2.58	-13.07	-15.75	225.29	815.30	75.10	0.09	1.99	1.65	63.18			Y
Testosterone	-0.32	-0.40	1.47	0.00	1.79	-3.12	-5.83	288.43	960.67	50.76	3.32	3.06	2.76	100.00	N		Y
Theophylline	14.90	14.90	15.23	0.33	0.00	-12.43	-15.06	180.17	587.91	87.98	-0.02	2.64	2.31	74.09		Y	

	Physics-based[a]							QikProp[b]							Classification		
Molecule	$\Delta G_{transfer(LDC)}$	$\Delta G_{transfer}$	$\Delta G_{c/w}$	ΔG_{state}	ΔG_{cf}	Log $K_{barrier}$	Log P_m	MW	Vol	PSA	QPlog $P_{o/w}$	Log QPPCaco	Log QPPMDCK	QP%HOA	PGP[c]	Active[d]	QikProp[e]
Thiopental	7.40	6.94	9.84	0.56	1.88	-8.90	-11.57	242.34	778.28	77.37	2.05	3.34	3.51	100.00			
Timolol	6.37	6.06	10.79	2.84	1.57	-10.11	-12.82	316.42	996.29	78.38	1.83	2.61	2.61	84.33			Y
Trimethoprim	17.33	15.41	19.80	0.11	2.36	-16.49	-19.19	290.32	909.01	93.74	0.93	2.55	2.21	77.97	Y		Y
Verapamil	-2.30	-3.07	1.42	2.25	1.47	-4.38	-7.16	454.61	1558.61	59.61	3.80	2.89	2.62	100.00	Y	Y	Y
Warfarin	2.73	2.14	6.30	1.29	2.28	-6.71	-9.42	308.33	982.06	78.92	2.93	2.97	2.66	100.00			Y
Goodwin01	11.55	11.28	14.80	0.00	3.25	-12.96	-15.67	277.32	988.97	113.05	0.25	1.87	2.27	61.84			
Goodwin02	12.01	10.70	13.58	0.00	1.57	-12.02	-14.72	291.35	1046.44	109.81	0.72	2.05	2.44	67.90			
Goodwin03a	10.67	9.42	11.37	0.00	0.70	-10.61	-13.33	319.40	1140.82	104.00	1.50	2.41	2.73	78.84			
Goodwin04	9.52	8.23	10.26	0.00	0.75	-9.94	-12.67	333.43	1189.84	105.79	1.74	2.28	2.63	77.82			
Goodwin05a	10.90	9.42	12.16	0.00	1.25	-11.48	-14.21	367.45	1239.92	107.12	2.27	2.39	2.69	83.11			
Goodwin06	8.25	7.12	9.13	0.00	0.88	-9.36	-12.10	373.49	1306.92	105.69	2.48	2.31	2.65	82.83			
Goodwin07	7.03	6.82	10.69	0.00	3.66	-9.62	-12.31	220.27	837.37	78.94	0.93	2.44	2.63	76.06			
Goodwin08	6.41	5.94	9.66	0.00	3.25	-8.99	-11.68	234.30	896.96	75.70	1.40	2.60	2.78	81.60			
Goodwin09a	5.57	4.35	8.29	0.00	1.96	-8.13	-10.83	262.35	989.70	70.59	2.14	2.84	3.01	90.39			
Goodwin10	3.82	3.31	7.05	0.00	3.23	-7.41	-10.12	276.38	1051.48	71.59	2.44	2.71	2.90	89.71			
Goodwin11a	7.46	4.73	8.50	0.00	1.03	-8.29	-10.99	310.40	1117.47	72.82	3.08	2.75	2.93	94.29			
Goodwin12	3.95	2.34	6.32	0.00	2.37	-6.98	-9.70	316.44	1165.50	71.62	3.17	2.72	2.91	94.26			
whitlock24	7.57	7.26	11.90	1.46	2.87	-10.84	-13.54	320.78	991.58	78.82	2.09	2.16	2.22	77.87			
whitlock25	6.57	6.05	10.71	1.37	2.77	-10.12	-12.84	334.80	1065.98	64.67	3.08	2.67	2.78	92.84			
whitlock26	4.50	3.53	8.51	1.42	2.59	-8.61	-11.33	348.83	1116.79	55.29	3.43	2.83	2.94	100.00			
whitlock28	8.29	6.77	11.22	0.98	1.95	-10.25	-12.95	325.19	951.35	72.94	2.32	2.16	2.50	79.20			
whitlock30	4.82	3.33	7.70	0.94	1.94	-7.94	-10.66	353.25	1073.74	49.40	3.67	2.83	3.22	100.00			
whitlock34	4.25	3.06	8.52	2.30	1.97	-8.55	-11.27	332.83	1085.51	48.87	3.54	2.83	2.94	100.00			
whitlock35	8.06	6.98	12.50	2.35	2.09	-11.60	-14.33	380.89	1143.26	62.62	3.06	2.53	2.63	90.18			
whitlock36	10.48	9.35	16.53	4.27	1.79	-14.42	-17.14	354.85	1081.37	70.97	2.48	2.38	2.47	84.13			
Li01	11.27	9.64	11.69	0.00	0.89	-13.22	-16.04	726.91	2389.46	209.83	4.45	1.78	2.03	58.90			
Li02	11.45	10.92	11.98	0.00	0.53	-13.36	-16.18	712.89	2336.74	209.92	4.11	1.79	2.03	57.06			
Li03	9.03	8.38	10.11	0.02	1.06	-10.91	-13.69	506.64	1687.10	164.87	3.55	2.20	2.05	74.09			
Li04	11.80	11.49	11.91	0.00	0.11	-13.48	-16.31	744.93	2460.84	222.85	4.39	1.56	1.79	54.66			
Li05	12.90	11.16	13.00	0.00	0.09	-14.20	-17.02	742.91	2403.70	223.56	4.07	1.61	1.84	53.61			
Li06	10.86	10.78	12.29	0.00	1.43	-13.79	-16.61	738.92	2427.68	217.16	4.53	1.51	1.79	54.58			
Li12	10.73	9.77	11.79	0.02	1.05	-12.70	-15.50	653.82	2077.90	187.61	5.28	2.34	2.09	60.87			
Li15	9.64	9.36	11.42	0.02	1.76	-12.86	-15.68	653.82	2108.39	197.99	5.15	1.69	1.58	48.43			
Li16	10.19	9.24	11.80	0.02	1.32	-13.08	-15.89	653.82	2137.99	198.75	5.31	1.59	1.54	47.72			
Li17	10.39	9.37	11.89	0.02	1.48	-13.24	-16.06	671.81	2012.42	190.28	4.90	2.26	2.21	70.21			
Li18	5.83	4.77	7.43	0.00	1.87	-10.33	-13.16	709.92	2282.87	170.38	6.65	2.81	2.60	77.25			
Li19	5.89	5.08	7.57	0.00	1.67	-10.12	-12.93	647.85	2129.95	170.85	5.60	2.95	2.75	73.68			
Li20	10.48	9.19	12.15	0.02	1.66	-13.27	-16.08	679.86	2142.71	188.33	5.63	2.20	1.99	60.36			
Li21	10.46	9.56	11.86	0.02	1.37	-12.96	-15.77	631.81	2014.56	189.12	4.72	2.33	2.13	70.37			
Li22	9.43	8.84	11.19	0.02	1.73	-12.62	-15.43	645.84	2044.11	184.10	4.95	2.42	2.18	73.39			
Li23	9.90	8.89	11.40	0.02	1.48	-12.71	-15.52	645.84	2056.77	187.90	4.98	2.33	2.11	71.84			
Li24	15.55	14.59	20.91	3.99	1.32	-19.14	-21.93	563.69	1819.68	205.15	3.26	0.79	0.68	21.22			
Li27	15.13	14.79	21.16	4.62	1.40	-19.38	-22.17	563.69	1805.20	213.52	3.09	0.67	0.54	18.25			
Li28	15.38	14.81	21.79	4.55	1.86	-20.19	-22.99	623.75	1933.04	210.98	4.26	0.90	0.80	29.20			
Li29	15.06	14.13	21.19	4.55	1.58	-19.84	-22.65	637.78	1966.19	208.58	4.53	1.00	0.88	32.54			
Li30	15.26	14.44	21.05	4.62	1.18	-19.31	-22.11	563.69	1786.89	209.13	3.12	0.91	0.75	22.71			
Li31	13.28	11.86	19.44	4.51	1.65	-18.68	-21.49	653.82	2090.67	191.01	5.45	1.56	1.48	47.95			

	Physics-based[a]							QikProp[b]							Classification		
Molecule	$\Delta G_{transfer(LDC)}$	$\Delta G_{transfer}$	$\Delta G_{c/w}$	ΔG_{state}	ΔG_{cf}	Log $K_{barrier}$	Log P_m	MW	Vol	PSA	QPlog $P_{o/w}$	Log QPPCaco	Log QPPMDCK	QP%HOA	PGP[c]	Active[d]	QikProp[e]
Li32	12.66	10.09	18.25	4.51	1.07	-17.93	-20.75	667.84	2128.26	188.91	5.66	1.54	1.46	48.88			
Li33	11.72	10.47	18.17	4.51	1.94	-17.95	-20.77	667.84	2151.16	192.33	5.78	1.50	1.41	48.72			
Li34	11.03	9.87	17.11	4.51	1.42	-16.86	-19.66	605.77	1979.82	189.15	4.51	1.48	1.38	53.86			

[a] Physics-based permeability predictions. The $\Delta G_{transfer(LDC)}$ is based on the low dielectric conformation. The $\Delta G_{transfer}$, $\Delta G_{c/w}$. and Log P_m values are the optimal values produced by the conformer ensemble, i.e. the minimum value for free energy measures or the maximum value for Log P_m. Therefore, each of these values may not correspond to the same conformation. The ΔG_{cf} and Log $K_{barrier}$ values correspond to the conformation that produced the highest Log P_m value.

[b] Physiochemical descriptors and permeability predictions by QikProp.

[c] For "PGP", Y indicates a P-glycoprotein substrate and N indicates a non-substrate.[10-12]

[d] For "Active", Y indicates an active transport protein substrate.[13-18]

[e] For "QikProp", Y indicates that the compound is part of the QikProp training sets (i.e. QPlog $P_{o/w}$, QPPCaco, QPPMDCK, and QP%HOA).[7,19-21]

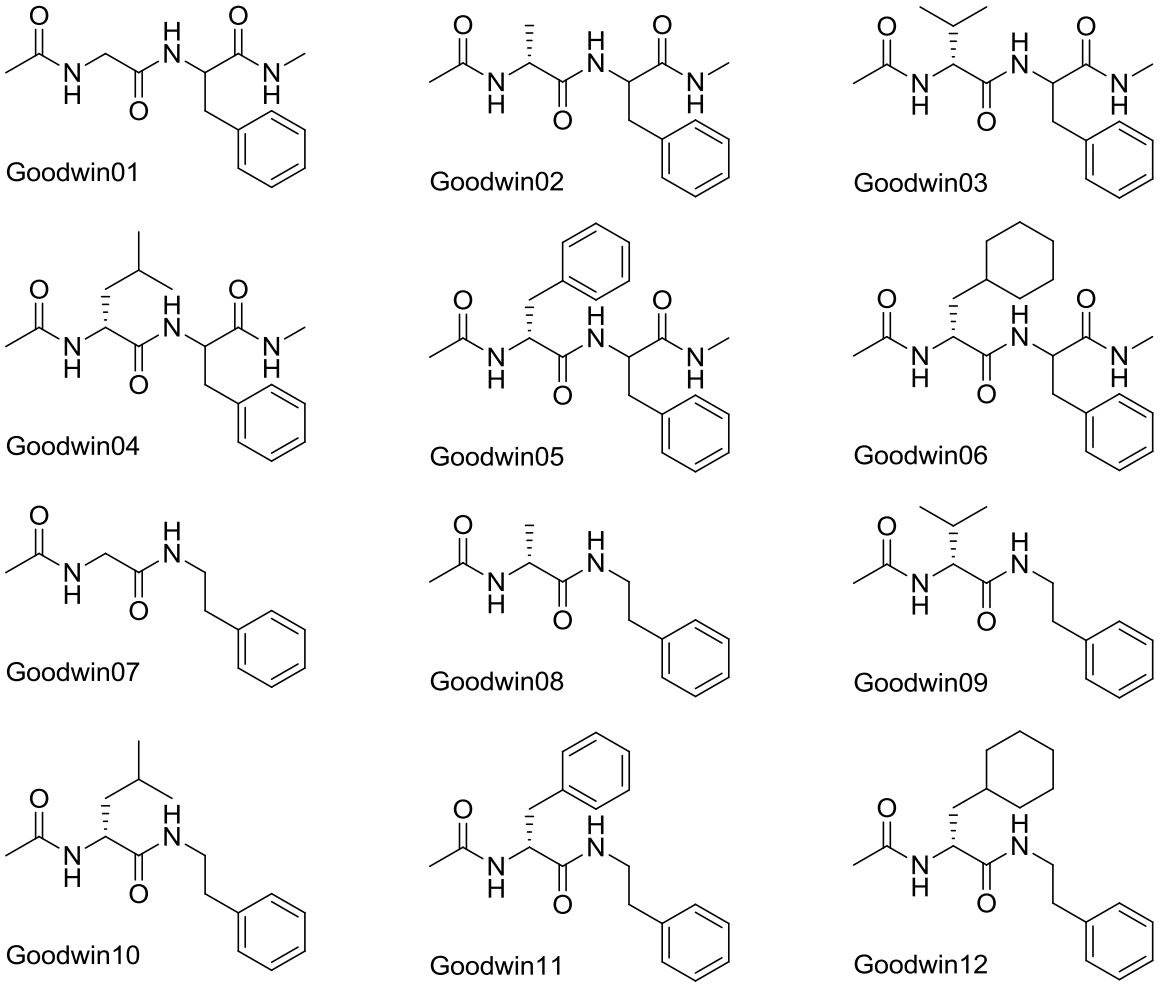

Figure S1. Compounds from the Goodwin set.

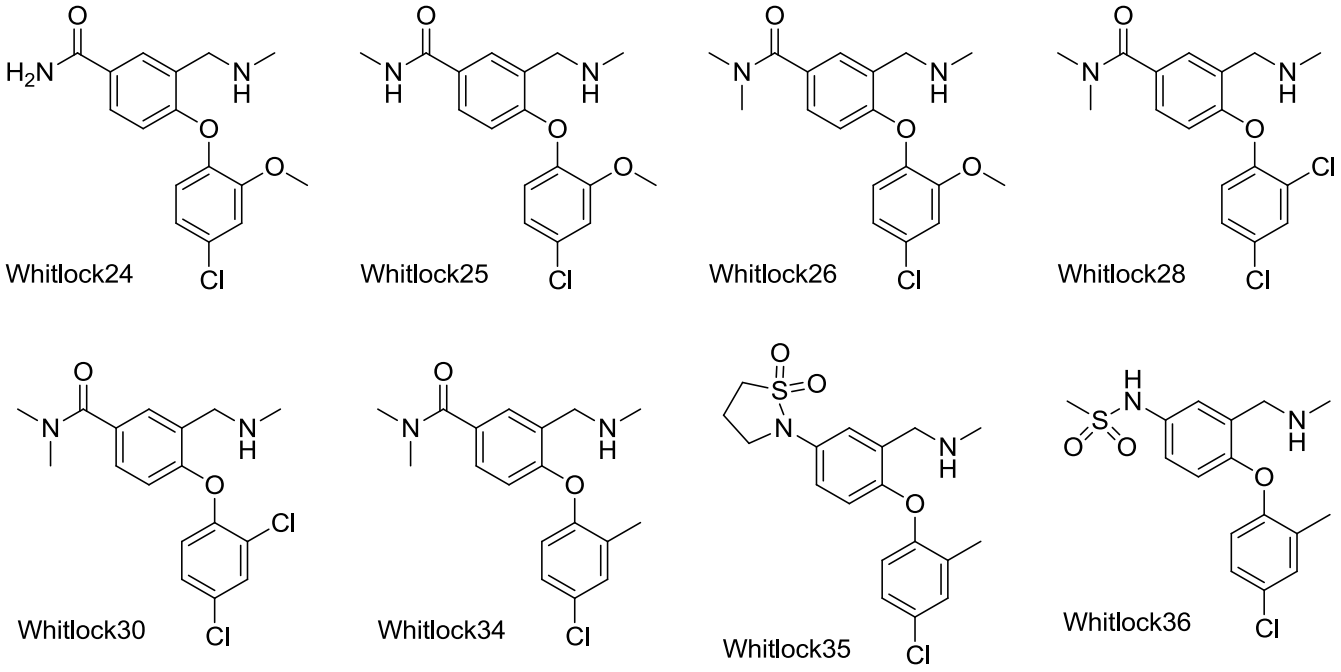

Figure S2. Compounds from the Whitlock set.

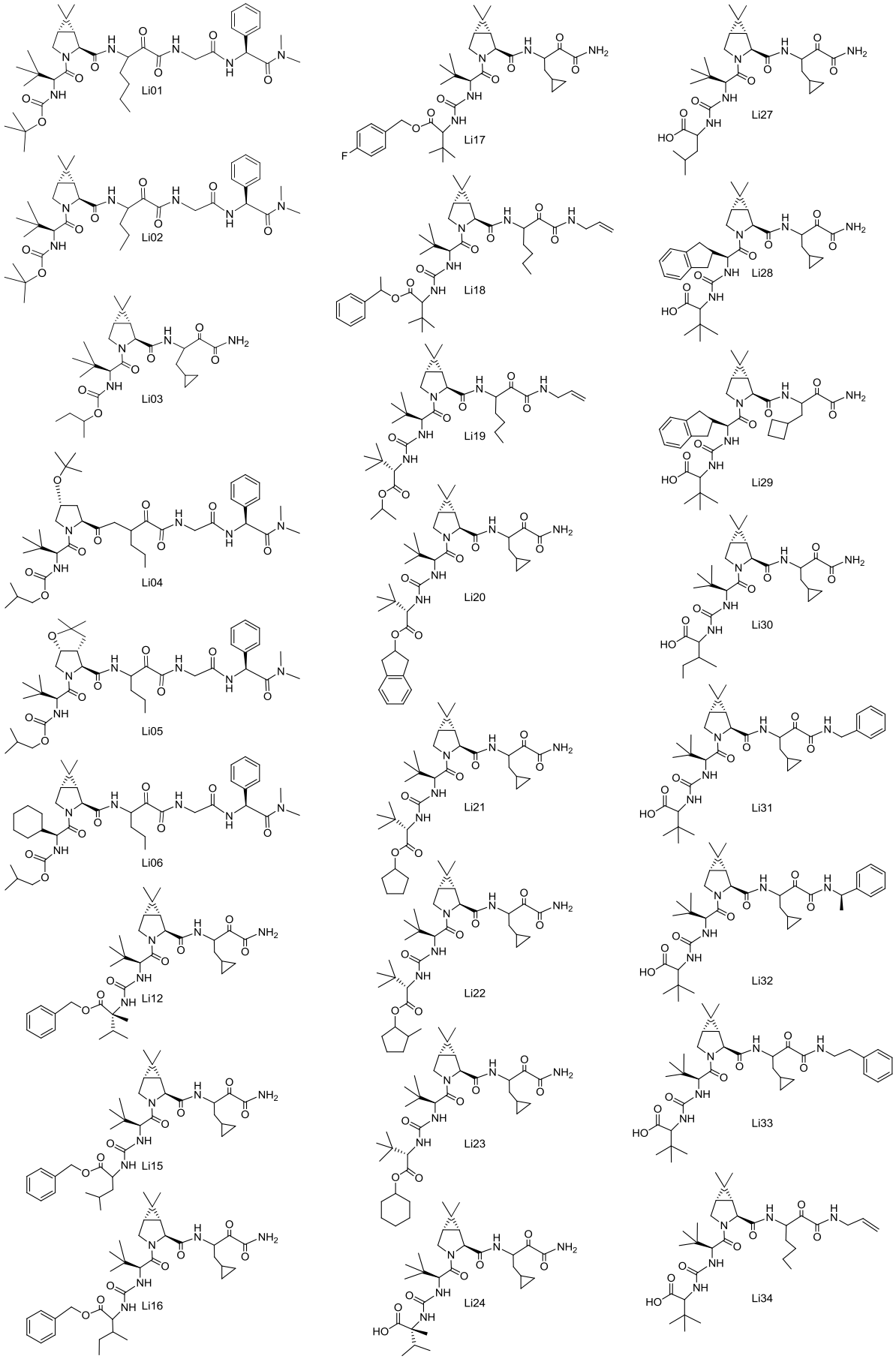

Figure S3. Compounds from the Li set.

Table S3. The correlation coefficients from linear regression analyses between cell-based assay data and physics-based permeability predictions with all compounds.

prediction[a]	Model's Component						Correlation Coefficient (r^2)[b]													
	Conf. search	Conf. ensemble	State penalty	Conf. penalty	Size selectivity	Membrane diffusion	Avdeef (Caco-2)		Balimane (Caco-2)		Bermejo (Caco-2)		Fujikawa (Caco-2)		Goodwin (Caco-2)	Irvine (Caco-2)		Irvine (MDCK)		Li (Caco-2)
							All	Passive	All	Passive	All	Passive	All	Passive	All	All	Passive	All	Passive	All
Log $K(\Delta G_{transfer(LDC)})$	×						0.70	0.67	0.48	0.56	0.39	0.39	0.15	0.32	0.83	0.43	0.59	0.49	0.68	0.49
Log $K(\Delta G_{transfer})$	×	×					0.70	0.70	0.47	0.55	0.39	0.37	0.16	0.33	0.88	0.44	0.57	0.51	0.67	0.55
Log $K(\Delta G_{transfer}+\Delta G_{state})$	×	×	×				0.66	0.80	0.49	0.55	0.62	0.58	0.24	0.35	0.88	0.60	0.68	0.65	0.74	0.49
Log $K(\Delta G_{transfer}+\Delta G_{cf})$	×	×		×			0.73	0.75	0.47	0.53	0.48	0.44	0.15	0.30	0.82	0.44	0.61	0.51	0.70	0.54
Log $K(\Delta G_{c/w})$	×	×	×	×			0.69	0.83	0.48	0.50	0.66	0.61	0.24	0.32	0.82	0.60	0.69	0.65	0.75	0.45
Log $K_{barrier}$	×	×	×	×	×		0.71	0.84	0.51	0.55	0.64	0.59	0.28	0.34	0.86	0.60	0.70	0.65	0.77	0.45
Log P_m	×	×	×	×	×	×	0.72	0.84	0.51	0.56	0.64	0.59	0.29	0.34	0.86	0.60	0.70	0.65	0.77	0.45

[a] Optimal values were determined from the refined conformational ensemble for each type of permeability prediction, except for Log $K(\Delta G_{transfer(LDC)})$, which were computed using the LDC, and Log $K_{barrier}$, which was computed using the conformation with the optimal Log P_m value.

[b] "All" indicates the all compounds in the data set. "Passive" indicates the passive permeation subset. Models with $\Delta r^2 \geq 0.05$ and $\Delta r^2 \leq -0.05$ relative to Log $K(\Delta G_{transfer(LDC)})$ are highlighted in green and red, respectively.

Table S4. The Spearman's rank correlation coefficients between cell-based assay data and physics-based permeability predictions with all compounds.

prediction[a]	Model's Component						Spearman's Rank Correlation Coefficient (ρ)[b]													
	Conf. search	Conf. ensemble	State penalty	Conf. penalty	Size selectivity	Membrane diffusion	Avdeef (Caco-2)		Balimane (Caco-2)		Bermejo (Caco-2)		Fujikawa (Caco-2)		Goodwin (Caco-2)	Irvine (Caco-2)		Irvine (MDCK)		Li (Caco-2)
							All	Passive	All	Passive	All	Passive	All	Passive	All	All	Passive	All	Passive	All
Log $K(\Delta G_{transfer(LDC)})$	×						0.79	0.89	0.64	0.44[c]	0.64	0.50[c]	0.35[c]	0.35[c]	0.89	0.71	0.77	0.75	0.83	0.61
Log $K(\Delta G_{transfer})$	×	×					0.78	0.89	0.64	0.44[c]	0.60	0.45[c]	0.32[c]	0.35[c]	0.96	0.70	0.75	0.74	0.83	0.69
Log $K(\Delta G_{transfer}+\Delta G_{state})$	×	×	×				0.84	0.89	0.67	0.56[c]	0.68	0.52[c]	0.45	0.43[c]	0.96	0.81	0.80	0.82	0.84	0.66
Log $K(\Delta G_{transfer}+\Delta G_{cf})$	×	×		×			0.83	0.89	0.67	0.54[c]	0.65	0.47[c]	0.33[c]	0.30[c]	0.92	0.72	0.78	0.76	0.84	0.65
Log $K(\Delta G_{c/w})$	×	×	×	×			0.81	0.89	0.67	0.56[c]	0.71	0.55[c]	0.46	0.41[c]	0.92	0.82	0.82	0.82	0.84	0.64
Log $K_{barrier}$	×	×	×	×	×		0.85	0.89	0.71	0.56[c]	0.71	0.55[c]	0.48	0.37[c]	0.95	0.82	0.81	0.83	0.84	0.66
Log P_m	×	×	×	×	×	×	0.85	0.89	0.71	0.56[c]	0.71	0.55[c]	0.48	0.37[c]	0.95	0.82	0.81	0.83	0.84	0.66

[a] Optimal values were determined from the refined conformational ensemble for each permeability prediction, except for Log $K(\Delta G_{transfer(LDC)})$, which were computed using the LDC, and Log $K_{barrier}$, which was computed using the conformation with the optimal Log P_m value.

[b] "All" indicates the all compounds in the data set. "Passive" indicates the passive permeation subset. Models with $\Delta\rho \geq 0.05$ and $\Delta\rho \leq -0.05$ relative to Log $K(\Delta G_{transfer(LDC)})$ are highlighted in green and red, respectively.

[c] The p-value is greater than 0.05.

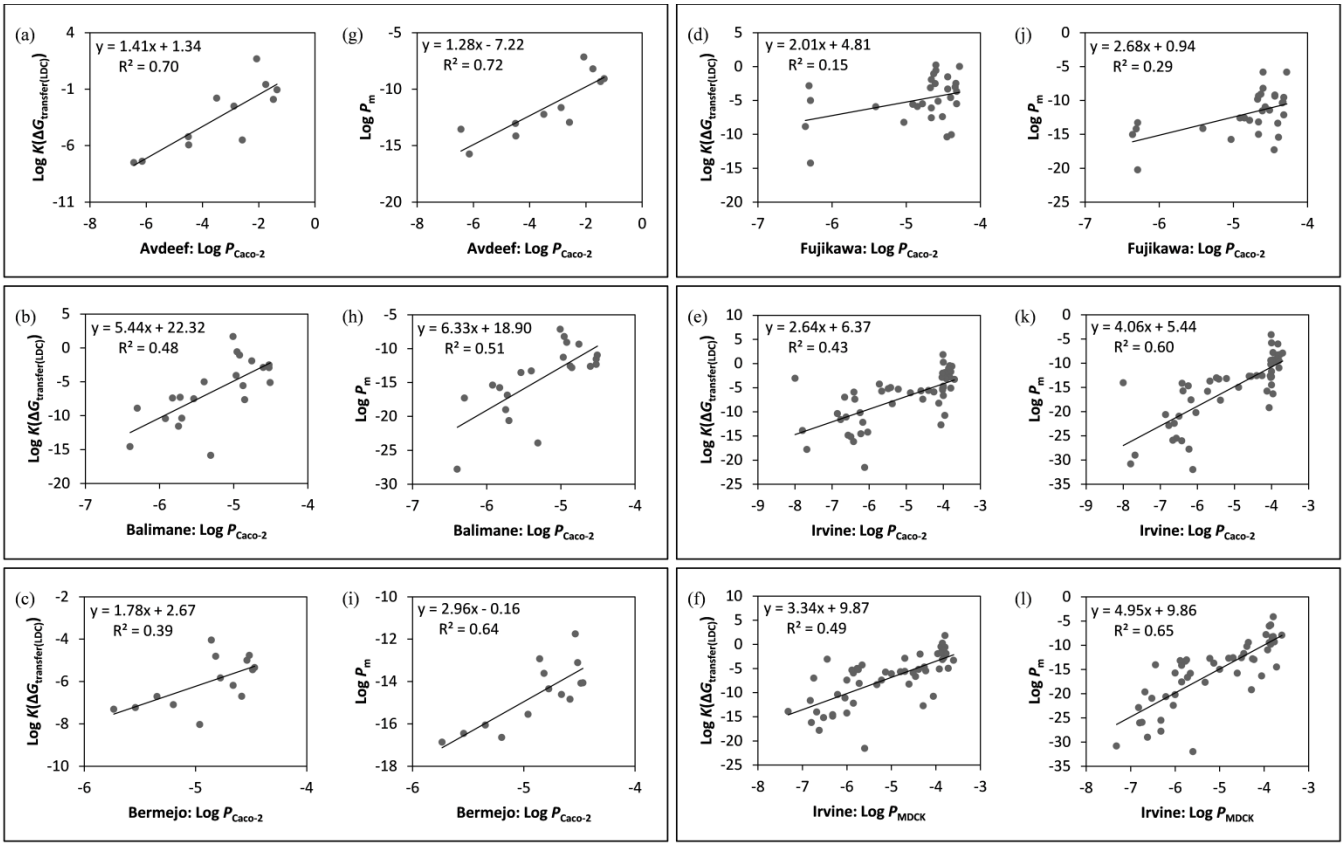

Figure S4. The linear regression analyses between cell-based assay data and physics-based permeability predictions with all compounds. Predictions based on Log $K(\Delta G_{\text{transfer(LDC)}})$: (a) Avdeef set (Caco-2), (b) Balimane set (Caco-2), (c) Bermejo set (Caco-2), (d) Fujikawa set (Caco-2), (e) Irvine set (Caco-2), and (f) Irvine set (MDCK). Predictions based on Log P_{m}: (g) Avdeef set (Caco-2), (h) Balimane set (Caco-2), (i) Bermejo set (Caco-2), (j) Fujikawa set (Caco-2), (k) Irvine set (Caco-2), and (l) Irvine set (MDCK).

Table S5. The correlation coefficients from linear regression analyses between *in vivo* data and physics-based permeability predictions with all compounds.

prediction[a]	Model's Component						Correlation Coefficient (r^2)[b]					
	Conf. search	Conf. ensemble	State penalty	Conf. penalty	Size selectivity	Membrane diffusion	Balimane (%Abs)		Bermejo (P_{app})		Irvine (%Abs)	
							All	Passive	All	Passive	All	Passive
Log $K(\Delta G_{transfer(LDC)})$	×						0.60	0.63	0.77	0.73	0.21	0.65
Log $K(\Delta G_{transfer})$	×	×					0.59	0.63	0.79	0.75	0.23	0.66
Log $K(\Delta G_{transfer}+\Delta G_{state})$	×	×	×				0.65	0.72	0.91	0.88	0.28	0.62
Log $K(\Delta G_{transfer}+\Delta G_{cf})$	×	×		×			0.59	0.65	0.81	0.78	0.20	0.63
Log $K(\Delta G_{c/w})$	×	×	×	×			0.64	0.69	0.89	0.88	0.25	0.59
Log $K_{barrier}$	×	×	×	×	×		0.68	0.76	0.87	0.86	0.24	0.58
Log P_m	×	×	×	×	×	×	0.68	0.76	0.86	0.86	0.24	0.58

[a] Optimal values were determined from the refined conformational ensemble for each type of permeability prediction, except $\Delta G_{transfer(LDC)}$, which were computed using the LDC, and Log $K_{barrier}$, which was computed based on the conformation with the optimal Log P_m value.

[b] "All" indicates the all compounds in the data set. "Passive" indicates the passive permeation subset. Models with $\Delta r^2 \geq 0.05$ and $\Delta r^2 \leq -0.05$ relative to Log $K(\Delta G_{transfer(LDC)})$ are highlighted in green and red, respectively.

Table S6. The Spearman's rank correlation coefficients between *in vivo* data and physics-based permeability predictions with all compounds.

prediction[a]	Model's Component						Spearman's Rank Correlation Coefficient (ρ)[b]					
	Conf. search	Conf. ensemble	State penalty	Conf. penalty	Size selectivity	Membrane diffusion	Balimane (%Abs)		Bermejo (P_{app})		Irvine (%Abs)	
							All	Passive	All	Passive	All	Passive
Log $K(\Delta G_{transfer(LDC)})$	×						0.76	0.66[c]	0.89	0.87	0.41	0.74
Log $K(\Delta G_{transfer})$	×	×					0.77	0.66[c]	0.89	0.89	0.44	0.76
Log $K(\Delta G_{transfer}+\Delta G_{state})$	×	×	×				0.79	0.84	0.95	0.94	0.50	0.74
Log $K(\Delta G_{transfer}+\Delta G_{cf})$	×	×		×			0.79	0.76	0.93	0.91	0.42	0.74
Log $K(\Delta G_{c/w})$	×	×	×	×			0.79	0.84	0.96	0.96	0.49	0.72
Log $K_{barrier}$	×	×	×	×	×		0.82	0.84	0.96	0.96	0.50	0.73
Log P_m	×	×	×	×	×	×	0.82	0.84	0.96	0.96	0.50	0.73

[a] Optimal values were determined from the refined conformational ensemble for each type of permeability prediction, except $\Delta G_{transfer(LDC)}$, which were computed using the LDC, and Log $K_{barrier}$, which was computed based on the conformation with the optimal Log P_m value.

[b] "All" indicates the all compounds in the data set. "Passive" indicates the passive permeation subset. Models with $\Delta\rho \geq 0.05$ relative to Log $K(\Delta G_{transfer(LDC)})$ are highlighted in green.

[c] The p-value is greater than 0.05.

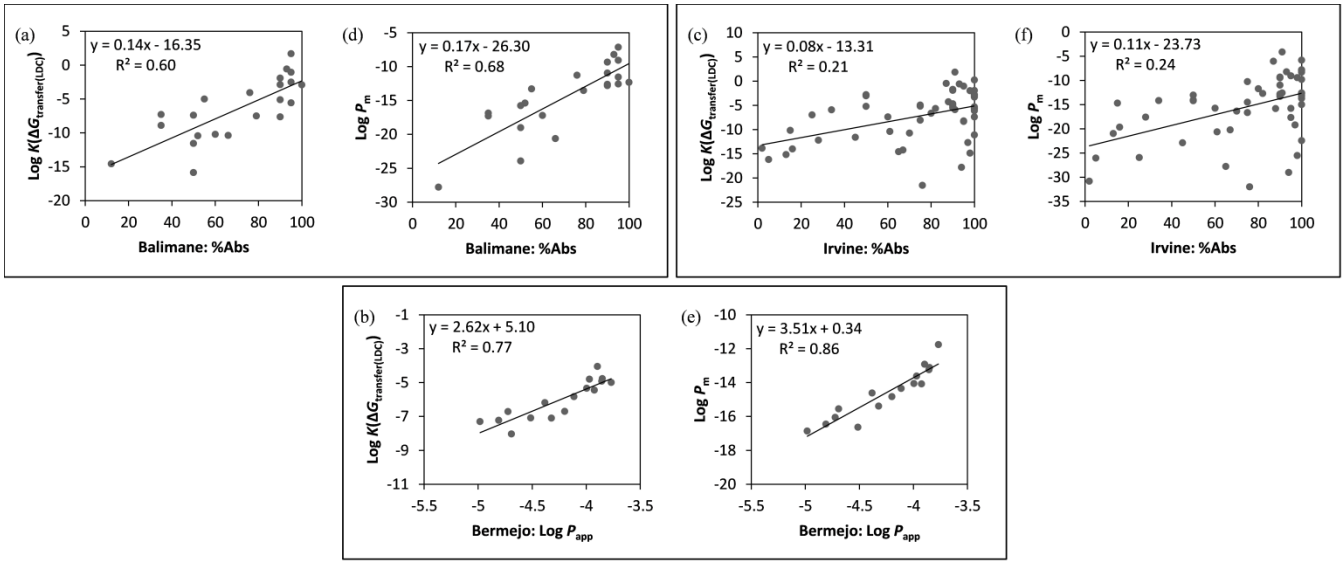

Figure S5. The linear regression analyses between *in vivo* data and physics-based permeability predictions with all compounds. Predictions based on Log $K(\Delta G_{transfer(LDC)})$: (a) Balimane set, (b) Bermejo set, and (c) Irvine set. Predictions based on Log P_m: (d) Balimane set, (e) Bermejo set, and (f) Irvine set.

Estimation of $K_{barrier}$ from air/water partition. The passive diffusion model developed by Seelig *et al.* to study permeation across blood-brain barrier provides an alternative to estimate $K_{barrier}$. Instead of using organic solvent as a reference medium for the barrier, this approach employs the air/water partition $K_{a/w}$, to approximate the membrane/water partition. Experimentally, $K_{a/w}$ can be obtained from Gibbs adsorption isotherm measurements, which provide the change in solute concentration between air and water based on the change in surface tension at the interface.[22,23] The contribution from the cavity creation in the membrane barrier to accommodate the permeant is evaluated by the membrane insertion potential, ΔW, which is presumed to be proportional to the lateral packing density of the membrane, π_m, and the cross-sectional area of the permeant, A_p:[24-26]

$$\Delta W = \pi_m A_p, \qquad \text{(S1)}$$

Similar to the function form of the barrier domain model (Eq. 3), $K_{barrier}$ is estimated from the air/water partition coefficient, $K_{a/w}$, and the shape-dependent insertion factor, ξ_A, as shown in Eq. S2.

$$K_{barrier} = K_{a/w}\xi_A, \qquad \text{(S2)}$$

where

$$\xi_A = e^{\frac{-\pi_m A_p}{k_B T}} \qquad \text{(S3)}$$

In our implementation, $K_{a/w}$ is calculated from the air/water partition free energy, $\Delta G_{a/w}$, which is estimated from the free energy of solvation, ΔG_{solv}, of the permeant membranephilic conformation. Analogous to the formulation of the chloroform/water partition energy $\Delta G_{c/w}$ (Eq. 7), $\Delta G_{a/w}$ is expressed in terms of ΔG_{solv}, the state penalty, ΔG_{state}, and conformational penalty, ΔG_{cf}:

$$\Delta G_{a/w} = -\Delta G_{solv} + \Delta G_{state} + \Delta G_{cf} \qquad \text{(S4)}$$

Subsequently, $K_{a/w}$ can be calculated from $\Delta G_{a/w}$:

$$K_{a/w} = 10^{\Delta G_{a/w}/-2.3RT} \qquad \text{(S5)}$$

Like the size-dependent ξ_V (Eq. 4), the insertion factor, ξ_A, is also defined by properties from both the membrane and the permeant (Eq. S3). The membrane environment is described by π_m, which is assumed to be 35 mN/m.[26] The molecular shape of the permeant is assessed by its molecular cross-

sectional area, A_p. With the shape-dependent ξ_A, the partition coefficient decreases exponentially as A_p increases.

In the current implementation, the computation protocol is identical to that of the barrier domain model. In order to estimate A_p, the compound's orientation for insertion was determined by performing principal component analysis of the molecular coordinates. Assuming the first principle axis is parallel to the normal of the membrane, the first, second, and third principal axes are treated as the z-, y-, x-axes, respectively. The molecular projection on the xy-plane was measured as A_p with the atomic radii derived from the Lennard-Jones parameters of the OPLS2005 force field. The permeability coefficient based on $K_{a/w}$, $P_{m(a/w)}$, was calculated for each conformation in the low-energy conformation ensemble of the permeant, and the optimal predicted values were subsequently determined.

The correlation coefficients (r^2) from linear regression analyses and the Spearman's rank correlation coefficients (ρ) of the examined data sets obtained from the barrier domain model and the passive diffusion model are summarized in Tables S7–S12. For PAMPA (Tables S7 & S8) and cell-based assay data (Tables S9 & S10), the chloroform/water-based predictions of the barrier domain model generally deliver higher r^2 than those based on the air/water partition of the passive diffusion model. The Log P_m values yield higher r^2 and ρ than Log $P_{m(a/w)}$ values for most *in vitro* data sets. Results for the *in vivo* data (Tables S11 & S12) indicate that the predictions by both models are similar in accuracy.

The slopes from the linear regression analyses between physics-based predictions and different experimental data are listed in Tables S13–S15. Similar to the results from the barrier domain approach, the shape-based insertion factor and the diffusion coefficient have little effects on the slope of the linear regression model. For most of the *in vitro* data sets, the slopes of the linear regression models derived from the air/water partition values are steeper than those from the chloroform/water partition values. Both formulations of P_m yield predictions with similar slopes for *in vivo* data. Overall, the performance of both physics-based permeability models is demonstrated to be comparable. The barrier domain model, however, does produce higher correlation coefficients than those of the passive diffusion model for most *in vitro* data sets.

Table S7. The correlation coefficients from linear regression analyses between PAMPA data and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a higher r^2 is highlighted in green.

	Correlation Coefficient (r^2)						
prediction	Avdeef	Balimane	Bermejo	Di	Fujikawa	Li	Whitlock
Log $K(\Delta G_{transfer})$	0.73	0.57	0.80	0.49	0.43	0.52	0.62
Log $K(\Delta G_{c/w})$	0.78	0.64	0.88	0.57	0.56	0.82	0.74
Log P_m	0.80	0.61	0.81	0.56	0.58	0.83	0.78
Log $K(-\Delta G_{solv})$	0.84	0.52	0.43	0.40	0.57	0.45	0.83
Log $K(\Delta G_{a/w})$	0.77	0.55	0.54	0.54	0.62	0.74	0.88
Log $P_{m(a/w)}$	0.70	0.50	0.47	0.50	0.59	0.74	0.88

Table S8. The Spearman's rank correlation coefficients between PAMPA data and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a higher ρ is highlighted in green.

	Spearman's Rank Correlation Coefficient (ρ)						
prediction	Avdeef	Balimane	Bermejo	Di	Fujikawa	Li	Whitlock
Log $K(\Delta G_{transfer})$	0.83	0.75	0.95	0.68	0.63	0.71	0.89
Log $K(\Delta G_{c/w})$	0.88	0.83	0.95	0.72	0.73	0.76	0.85
Log P_m	0.91	0.83	0.95	0.70	0.74	0.81	0.87
Log $K(-\Delta G_{solv})$	0.94	0.78	0.86	0.66	0.76	0.58	0.87
Log $K(\Delta G_{a/w})$	0.88	0.78	0.92	0.71	0.77	0.70	0.81
Log $P_{m(a/w)}$	0.83	0.74	0.92	0.69	0.75	0.70	0.81

Table S9. The correlation coefficients from linear regression analyses between cell-based assay data and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a higher r^2 is highlighted in green.

prediction	Correlation Coefficient (r^2)[a]													
	Avdeef (Caco-2)		Balimane (Caco-2)		Bermejo (Caco-2)		Fujikawa (Caco-2)		Goodwin (Caco-2)	Irvine (Caco-2)		Irvine (MDCK)		Li (Caco-2)
	All	Passive	All	Passive	All	Passive	All	Passive	All	All	Passive	All	Passive	All
Log $K(\Delta G_{transfer})$	0.70	0.70	0.47	0.55	0.39	0.37	0.16	0.33	0.88	0.44	0.57	0.51	0.67	0.55
Log $K(\Delta G_{c/w})$	0.69	0.83	0.48	0.50	0.66	0.61	0.24	0.32	0.82	0.60	0.69	0.65	0.75	0.45
Log P_m	0.72	0.84	0.51	0.56	0.64	0.59	0.29	0.34	0.86	0.60	0.70	0.65	0.77	0.45
Log $K(-\Delta G_{solv})$	0.84	0.82	0.63	0.81	0.26	0.27	0.26	0.43	0.83	0.44	0.60	0.54	0.73	0.45
Log $K(\Delta G_{a/w})$	0.72	0.76	0.61	0.69	0.51	0.49	0.36	0.42	0.84	0.56	0.68	0.65	0.80	0.40
Log $P_{m(a/w)}$	0.67	0.73	0.60	0.70	0.48	0.47	0.38	0.43	0.82	0.55	0.68	0.64	0.81	0.39

[a] "All" indicates the all compounds in the data set. "Passive" indicates the passive permeation subset.

Table S10. The Spearman's rank correlation coefficients between cell-based assay data and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a higher ρ is highlighted in green.

predicted permeability	Spearman's Rank Correlation Coefficient (ρ)[a]													
	Avdeef (Caco-2)		Balimane (Caco-2)		Bermejo (Caco-2)		Fujikawa (Caco-2)		Goodwin (Caco-2)	Irvine (Caco-2)		Irvine (MDCK)		Li (Caco-2)
	All	Passive	All	Passive	All	Passive	All	Passive	All	All	Passive	All	Passive	All
Log $K(\Delta G_{transfer})$	0.78	0.89	0.64	0.44[b]	0.60	0.45[b]	0.32[b]	0.35[b]	0.96	0.70	0.75	0.74	0.83	0.69
Log $K(\Delta G_{c/w})$	0.81	0.89	0.67	0.56[b]	0.71	0.55[b]	0.46	0.41[b]	0.92	0.82	0.82	0.82	0.84	0.64
Log P_m	0.85	0.89	0.71	0.56[b]	0.71	0.55[b]	0.48	0.37[b]	0.95	0.82	0.81	0.83	0.84	0.66
Log $K(-\Delta G_{solv})$	0.95	0.94	0.78	0.62[b]	0.56	0.40[b]	0.38	0.30[b]	0.87	0.73	0.78	0.78	0.85	0.55
Log $K(\Delta G_{a/w})$	0.83	0.89	0.73	0.50[b]	0.67	0.50[b]	0.54	0.30[b]	0.90	0.81	0.83	0.84	0.88	0.51
Log $P_{m(a/w)}$	0.83	0.89	0.73	0.46[b]	0.67	0.50[b]	0.51	0.28[b]	0.90	0.80	0.83	0.83	0.88	0.49

[a] "All" indicates the all compounds in the data set. "Passive" indicates the passive permeation subset.

[b] The p-value is greater than 0.05.

Table S11. The correlation coefficients from linear regression analyses between *in vivo* data and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a higher r^2 is highlighted in green.

prediction	Correlation Coefficient (r^2)					
	Balimane (%Abs)		Bermejo (P_{app})		Irvine (%Abs)	
	All	Passive	All	Passive	All	Passive
Log $K(\Delta G_{transfer})$	0.59	0.63	0.79	0.75	0.23	0.66
Log $K(\Delta G_{c/w})$	0.64	0.69	0.89	0.88	0.25	0.59
Log P_m	0.68	0.76	0.86	0.86	0.24	0.58
Log $K(-\Delta G_{solv})$	0.72	0.84	0.63	0.58	0.21	0.63
Log $K(\Delta G_{a/w})$	0.74	0.82	0.71	0.70	0.23	0.59
Log $P_{m(a/w)}$	0.73	0.83	0.67	0.66	0.22	0.58

[a] "All" indicates the all compounds in the data set. "Passive" indicates the passive permeation subset.

Table S12. The Spearman's rank correlation coefficients between *in vivo* data and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a higher ρ is highlighted in green.

prediction	Spearman's Rank Correlation Coefficient (ρ)[a]					
	Balimane (%Abs)		Bermejo (P_{app})		Irvine (%Abs)	
	All	Passive	All[c]	Passive[c]	All	Passive
Log $K(\Delta G_{transfer})$	0.77	0.66[b]	0.89	0.89	0.44	0.76
Log $K(\Delta G_{c/w})$	0.79	0.84	0.96	0.96	0.49	0.72
Log P_m	0.82	0.84	0.96	0.96	0.50	0.73
Log $K(-\Delta G_{solv})$	0.84	0.84	0.90	0.89	0.44	0.72
Log $K(\Delta G_{a/w})$	0.82	0.76	0.96	0.96	0.45	0.70
Log $P_{m(a/w)}$	0.83	0.71	0.96	0.96	0.46	0.70

[a] "All" indicates the all compounds in the data set. "Passive" indicates the passive permeation subset.

[b] The p-value is greater than 0.05.

[c] Log P_m and Log $P_{m(a/w)}$ give identical ρ.

Table S13. Slopes from linear regression analyses between PAMPA data and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a slope closer to 1 is highlighted in green.

	Slope of Linear Regression Model ($\|m\|$)						
prediction	Avdeef	Balimane	Bermejo	Di	Fujikawa	Li	Whitlock
Log $K(\Delta G_{transfer})$	0.96	3.88	1.23	3.04	2.56	1.31	3.68
Log $K(\Delta G_{c/w})$	0.99	4.73	1.77	4.35	3.29	2.83	5.08
Log P_m	0.90	4.53	1.60	4.26	3.53	2.74	5.19
Log $K(-\Delta G_{solv})$	1.07	4.99	0.89	3.50	4.59	1.61	5.53
Log $K(\Delta G_{a/w})$	1.09	5.93	1.36	4.92	5.42	3.36	7.26
Log $P_{m(a/w)}$	1.03	5.68	1.35	4.67	5.60	3.29	7.27

Table S14. Slopes from linear regression analyses between cell-based assay data (active-transport compounds excluded) and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a slope closer to 1 is highlighted in green.

	Slope of Linear Regression Model ($\|m\|$)							
prediction	Avdeef (Caco-2)	Balimane (Caco-2)	Bermejo (Caco-2)	Fujikawa (Caco-2)	Goodwin (Caco-2)	Irvine (Caco-2)	Irvine (MDCK)	Li (Caco-2)
Log $K(\Delta G_{transfer})$	1.33	3.61	1.55	3.72	2.14	3.00	3.52	2.65
Log $K(\Delta G_{c/w})$	1.52	3.47	3.10	3.49	1.79	4.16	4.65	4.15
Log P_m	1.49	3.69	2.95	3.49	1.83	4.20	4.71	4.00
Log $K(-\Delta G_{solv})$	1.70	6.33	2.17	5.30	2.67	4.77	5.70	3.19
Log $K(\Delta G_{a/w})$	1.90	6.43	3.62	5.21	2.91	6.02	7.01	4.87
Log $P_{m(a/w)}$	1.84	6.38	3.10	5.31	3.01	6.04	7.06	4.68

Table S15. Slopes from linear regression analyses between *in vivo* data (active-transport compounds excluded) and permeability predictions based on chloroform/water and air/water partition values. For each data set, the P_m prediction with a slope closer to 1 is highlighted in green.

prediction	Slope of Linear Regression Model ($\|m\|$)		
	Balimane (%Abs)	Bermejo (P_{app})	Irvine (%Abs)
Log $K(\Delta G_{transfer})$	0.09	2.43	0.12
Log $K(\Delta G_{c/w})$	0.10	3.97	0.14
Log P_m	0.10	3.73	0.14
Log $K(-\Delta G_{solv})$	0.15	2.17	0.18
Log $K(\Delta G_{a/w})$	0.17	3.62	0.20
Log $P_{m(a/w)}$	0.16	3.76	0.20

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