

**Extension of the mechanistic tissue distribution model of Rodgers & Rowland by systematic incorporation of lysosomal trapping: impact on K<sub>p</sub> and volume of distribution predictions in the rat**

Schmitt MV, Reichel A, Xiaohui L, Fricker G, Lienau P

#DMD-AR-2020-000161

**Table S1: Compound specific parameters of LC-MS/MS quantification**

Compound	Eluent	Gradient	Mode	MRM transitions
Afatinib	acid	2	positive	387.200 → 356.100
Axitinib	basic	2	positive	387.200 → 356.100
Bosutinib	basic	2	negative	528.100 → 335.800
Cediranib	acid	2	positive	451.000 → 112.100
Crizotinib	basic	2	positive	450.000 → 260.200
Dasatinib	acid	2	positive	488.200 → 401.100
Erlotinib	acid	2	positive	394.100 → 278.100
Gefitinib	acid	2	positive	447.226 → 128.200
Ibrutinib	acid	2	positive	441.000 → 138.000
Imatinib	basic	2	positive	494.300 → 394.200
Lapatinib	acid	2	negative	579.300 → 470.100
Linsitinib	acid	1	positive	422.000 → 364.300
Masitinib	basic	2	negative	497.100 → 362.300
Motesanib	acid	2	positive	374.300 → 212.000
Nilotinib	acid	3	positive	530.300 → 289.100
Nintedanib	acid	2	positive	540.200 → 070.200
Olaparib	basic	2	positive	435.000 → 281.300
Pazopanib	acid	2	positive	438.744 → 357.700
Quizartinib	acid	2	positive	561.200 → 421.100
Regorafenib	acid	2	negative	481.000 → 193.900
Saracatinib	basic	2	positive	542.200 → 127.200
Selumetinib	acid	2	positive	459.350 → 396.900
Sunitinib	basic	2	positive	399.200 → 283.100
Tandutinib	basic	2	positive	563.300 → 126.100
Vandetanib	acid	2	negative	474.900 → 455.000
N-(4-chlorophenyl)-2-[(4-pyridinylmethyl)amino]-benzamid (IS)	acid basic	1-3	positive negative	338.130 → 211.100 336.072 → 264.900

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**Table S2: Gradients of high performance liquid chromatography**

Gradient	Time [min]	Eluent A [%]	Eluent B [%]	Flow [mL/min]
1	0.00	90	10	1.00
	0.60	5	95	1.00
	0.61	5	95	1.20
	0.80	90	10	1.20
	0.81	90	10	1.00
	1.20	90	10	1.00
2	0.00	95	5	0.60
	1.50	5	95	0.60
	2.50	5	95	0.60
	2.51	95	5	0.60
	3.50	95	5	0.60
3	0.00	40	60	0.20
	2.00	40	60	0.20
In vivo PK studies	0.00	95	5	0.60
	1.50	5	95	0.60
	2.50	5	95	0.60
	2.51	95	5	0.60
	3.50	95	5	0.60

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**Table S3: Physicochemical properties of 26 compounds to predict distribution to lysosomes in rat hepatocytes. Properties were predicted using ADMET Predictor™ (Simulations Plus Inc.).**

Compound	pK <sub>a,1</sub>	pK <sub>a,2</sub>	logP
Afatinib	8.4	3.9	4.5
Axitinib	4.5	1.7	1.5
Bosutinib	8.3	4.1	5.1
Canertinib	6.9	3.9	4.9
Cediranib	9.1	3.4	5.3
Crizotinib	9.7	4.1	4.3
Dasatinib	6.9	3.9	2.5
Erlotinib	4.5	-	4.3
Gefitinib	6.9	4.1	5.6
Ibrutinib	3.8	1.7	4.1
Imatinib	8.2	4.5	4.5
Lapatinib	6.5	4.1	6.0
Linsitinib	5	3.9	4.0
Masitinib	8.1	4.2	5.0
Motesanib	4.9	3.6	3.4
Nilotinib	5.5	4.5	5.8
Nintedanib	7.9	2.6	3.1
Olaparib	0.2	-	1.2
Pazopanib	5.1	3.1	3.7
Quizartinib	6.2	3.8	6.6
Regorafenib	5.8	-	5.2
Saracatinib	8.1	5	4.1
Selumetinib	3.3	-	3.9
Sunitinib	9	-	3.0
Tandutinib	8.9	4.6	5.5
Vandetanib	8.8	4.2	5.8

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**Table S4: Tissue:Plasma water partition coefficients (K<sub>p</sub>) and Volume of Distributions at steady state (V<sub>U,ss</sub>) in rat for 28 moderate to strong bases. [continued on next page]**

K <sub>p</sub> and V <sub>U,ss</sub> predicted via equation 3 followed by K <sub>p</sub> predicted according to Rodgers et al. (2007), for experimental values refer to Rodgers et al. (2007)														
Compound	Adipose	Bone	Brain	Gut	Heart	Kidney	Liver	Lung	Muscle	Pancreas	Skin	Spleen	Thymus	V <sub>U,ss</sub> [L/kg]
Acebutolol-R	1.05; 1.02	2.35; 2.35	4.16; 2.55	7.87; 6.43	6.46; 6.08	13.9; 11.8	12.4; 11.0	11.3; 9.48	4.97; 4.84	5.22; 5.22	4.03; 3.84	14.4; 8.18	6.44; 6.44	5.09; 4.77
Acebutolol-S	0.91; 0.88	2.10; 2.10	4.01; 2.40	6.99; 5.55	5.64; 5.26	12.0; 9.97	10.8; 9.29	9.83; 8.05	4.41; 4.28	4.61; 4.61	3.55; 3.36	13.3; 7.02	5.60; 5.60	4.51; 4.19
Betaxolol-R	7.63; 7.60	13.0; 13.0	10.6; 8.99	46.0; 44.6	42.0; 41.6	93.3; 91.2	84.4; 83.0	73.0; 71.2	29.1; 29.0	31.7; 31.7	25.1; 24.9	64.6; 58.4	42.8; 42.8	30.7; 30.4
Betaxolol-S	6.61; 6.58	11.3; 11.3	9.57; 7.97	39.9; 38.4	36.3; 35.9	80.4; 78.4	72.8; 71.3	63.0; 61.3	25.2; 25.1	27.4; 27.4	21.7; 21.5	56.5; 50.3	36.9; 36.9	26.6; 26.2
Biperiden	88.0; 88.0	26.0; 26.0	37.9; 36.4	78.5; 77.1	57.7; 57.4	115; 113	107; 105	97.4; 95.7	40.1; 40.0	64.3; 64.3	68.9; 68.7	77.6; 71.6	60.3; 60.3	52.3; 51.9
Bisoprolol-R	1.83; 1.80	3.62; 3.62	4.92; 3.32	12.4; 11.0	10.7; 10.3	23.4; 21.3	21.1; 19.6	18.7; 16.9	7.86; 7.74	8.40; 8.40	6.55; 6.36	20.4; 14.2	10.8; 10.8	8.16; 7.84
Bisoprolol-S	1.83; 1.80	3.62; 3.62	4.92; 3.32	12.4; 11.0	10.7; 10.3	23.4; 21.3	21.1; 19.6	18.7; 16.9	7.86; 7.74	8.40; 8.40	6.55; 6.36	20.4; 14.2	10.8; 10.8	8.16; 7.84
Carvediolol-R	330; 330	99.2; 99.2	136; 135	301; 300	225; 225	452; 450	419; 418	380; 378	154; 154	247; 247	264; 264	288; 283	235; 235	202; 202
Carvediolol-S	325; 324	90.3; 90.3	131; 130	269; 268	195; 195	385; 384	359; 358	328; 326	134; 134	225; 225	246; 246	246; 240	205; 205	180; 179
Fentanyl	35.4; 35.4	13.4; 13.4	18.7; 17.1	41.9; 40.4	32.3; 31.9	66.2; 64.2	60.9; 59.4	54.9; 53.2	22.6; 22.5	32.9; 32.9	33.2; 33.0	47.1; 41.0	33.4; 33.4	27.8; 27.5
Imipramine	78.4; 78.4	27.5; 27.5	33.6; 32.0	87.8; 86.3	70.3; 69.9	147; 145	135; 133	120; 118	48.6; 48.4	68.0; 68.0	66.9; 66.7	97.9; 91.7	72.7; 72.7	58.9; 58.5
Inaperisone	25.2; 25.2	27.1; 27.1	21.8; 20.3	94.6; 93.2	85.2; 84.9	188; 186	171; 169	148; 146	58.6; 58.4	66.8; 66.8	55.5; 55.3	124; 118	87.2; 87.2	63.2; 62.9
Lidocaine	8.45; 8.43	8.92; 8.92	9.23; 7.94	30.3; 29.1	26.4; 26.1	57.3; 55.6	52.0; 50.8	45.5; 44.1	18.5; 18.4	21.7; 21.7	18.5; 18.4	40.7; 35.7	27.0; 27.0	20.1; 19.9
Metorolol-R	2.51; 2.48	4.75; 4.75	5.60; 4.00	16.5; 15.1	14.5; 14.1	31.9; 29.8	28.8; 27.3	25.3; 23.5	10.5; 10.3	11.2; 11.2	8.78; 8.59	25.8; 19.6	14.7; 14.7	10.9; 10.6
Metorolol-S	2.40; 2.37	4.57; 4.57	5.50; 3.89	15.9; 14.4	13.9; 13.6	30.5; 28.5	27.6; 26.1	24.2; 22.5	10.0; 9.92	10.8; 10.8	8.43; 8.24	25.0; 18.7	14.1; 14.1	10.5; 10.1
Nicotine	0.41; 0.39	0.89; 0.89	2.78; 1.62	2.49; 1.45	1.62; 1.34	2.85; 1.36	2.52; 1.45	2.66; 1.38	1.58; 1.48	1.69; 1.69	1.39; 1.25	5.97; 1.46	1.54; 1.54	1.58; 1.34
Oxrenolol-R	2.20; 2.17	4.18; 4.18	5.27; 3.67	14.4; 13.0	12.6; 12.2	27.5; 25.5	24.8; 23.4	21.9; 20.1	9.13; 9.00	9.80; 9.80	7.67; 7.48	23.0; 16.8	12.7; 12.7	9.60; 9.28
Oxrenolol-S	1.34; 1.30	2.74; 2.74	4.41; 2.80	9.25; 7.81	7.73; 7.36	16.7; 14.6	15.0; 13.5	13.5; 11.7	5.83; 5.70	6.19; 6.19	4.82; 4.63	16.2; 9.97	7.74; 7.74	6.07; 5.75
Pentazocine	18.6; 18.6	11.3; 11.3	13.7; 12.2	37.0; 35.6	30.5; 30.1	64.6; 62.7	59.0; 57.6	52.3; 50.6	21.3; 21.2	27.7; 27.7	25.8; 25.6	45.9; 40.1	31.3; 31.3	24.4; 24.1
Phencyclidine	128; 128	16.8; 16.8	38.9; 37.3	40.6; 39.2	17.5; 17.1	20.9; 18.9	22.2; 20.7	26.6; 24.8	12.8; 12.7	41.3; 41.3	56.7; 56.5	17.9; 11.7	19.6; 19.6	27.5; 27.1
Pindolol-R	3.04; 3.01	5.51; 5.51	6.02; 4.47	19.2; 17.8	17.0; 16.7	37.4; 35.5	33.8; 32.4	29.6; 27.9	12.1; 12.0	13.1; 13.1	10.3; 10.1	29.1; 23.1	17.3; 17.3	12.7; 12.4
Pindolol-S	2.68; 2.65	4.91; 4.91	5.66; 4.11	17.0; 15.6	15.0; 14.6	32.9; 30.9	29.7; 28.3	26.1; 24.4	10.8; 10.6	11.6; 11.6	9.14; 8.95	26.3; 20.3	15.2; 15.2	11.3; 10.9

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**Table S4 [continued]:** Tissue:Plasma water partition coefficients (K<sub>pu</sub>) and Volume of Distributions at steady state (V<sub>u,ss</sub>) in rat for 28 moderate to strong bases.

Compound	K <sub>pu</sub> and V <sub>u,ss</sub> predicted via equation 3 followed by K <sub>pu</sub> predicted according to Rodgers et al. (2007), for experimental values refer to Rodgers et al. (2007)													
	Adipose	Bone	Brain	Gut	Heart	Kidney	Liver	Lung	Muscle	Pancreas	Skin	Spleen	Thymus	V <sub>u,ss</sub> [L/kg]
Procainamide	0.46; 0.42	1.37; 1.37	3.54; 1.95	4.35; 2.92	3.19; 2.81	6.54; 4.51	5.80; 4.34	5.57; 3.81	2.74; 2.61	2.79; 2.79	2.10; 1.91	9.73; 3.57	3.10; 3.10	2.73; 2.41
Propranolol-R	62.3; 62.3	99.7; 99.7	63.3; 61.6	357; 356	332; 331	740; 738	671; 670	576; 575	226; 226	248; 248	197; 196	474; 468	339; 339	241; 241
Propranolol-S	18.3; 18.3	26.0; 26.0	19.3; 17.7	92.4; 90.9	84.6; 84.2	188; 186	170; 169	147; 145	58.1; 58.0	64.3; 64.3	51.7; 51.5	124; 118	86.4; 86.4	61.9; 61.6
Quinidine	7.31; 7.18	11.7; 11.7	14.9; 8.36	45.9; 40.0	38.9; 37.3	89.8; 81.5	80.2; 74.1	71.0; 63.7	26.6; 26.1	28.6; 28.6	23.3; 22.5	77.7; 52.2	38.4; 38.4	28.7; 27.4
Timolol-S	11.3; 1.48	4.30; 4.30	492; 5.22	447; 10.7	124; 10.1	640; 18.8	465; 17.8	554; 15.2	47.9; 8.73	9.37; 9.37	65.1; 6.26	1902; 13.6	11.1; 11.1	106; 8.26
Verapamil	62.6; 62.6	34.3; 34.3	36.2; 34.7	113; 112	95.1; 94.7	203; 201	186; 184	163; 162	65.4; 65.3	85.0; 85.0	79.2; 79.0	133; 127	98.0; 98.0	75.9; 75.6
Procainamide	0.46; 0.42	1.37; 1.37	3.54; 1.95	4.35; 2.92	3.19; 2.81	6.54; 4.51	5.80; 4.34	5.57; 3.81	2.74; 2.61	2.79; 2.79	2.10; 1.91	9.73; 3.57	3.10; 3.10	2.73; 2.41

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**Table S5:** Tissue:Plasma water partition coefficients (K<sub>pu</sub>) and unbound volume of distributions at steady state (V<sub>u,ss</sub>) in rat for 13 moderate-to-strong protein kinase inhibitors.

Compound	K <sub>pu</sub> and V <sub>u,ss</sub> predicted via equation 3 followed by K <sub>pu</sub> predicted according to Rodgers et al. (2007)													
	Adipose	Bone	Brain	Gut	Heart	Kidney	Liver	Lung	Muscle	Pancreas	Skin	Spleen	Thymus	V <sub>u,ss</sub> [L/kg]
Afatinib	111; 111	97; 97	77; 76	335; 333	299; 299	656; 654	597; 596	517; 515	204; 204	240; 240	205; 205	420; 414	307; 307	224; 223
Bosutinib	184; 184	48; 48	76; 74	141; 139	97; 97	188; 186	176; 174	163; 161	67; 67	120; 120	135; 135	123; 116	103; 103	93; 93
Cediranib	50; 50	39; 39	34; 32	134; 133	119; 118	260; 258	237; 235	205; 204	81; 81	97; 97	83; 83	170; 164	122; 122	90; 90
Crizotinib	34; 34	54; 54	36; 34	194; 192	179; 179	400; 397	362; 361	312; 309	122; 122	134; 134	106; 106	259; 252	183; 183	130; 130
Dasatinib	861; 861	150; 150	315; 314	375; 374	182; 182	256; 255	261; 260	283; 283	127; 127	375; 375	503; 502	155; 153	202; 202	245; 245
Gefitinib	446; 446	86; 86	176; 176	218; 217	111; 111	164; 163	164; 164	174; 173	77; 77	215; 215	284; 284	101; 99	122; 122	142; 142
Imatinib	447; 447	139; 139	181; 179	429; 427	329; 328	671; 668	620; 618	558; 555	225; 225	346; 346	361; 360	427; 420	342; 342	288; 288
Lapatinib	5010; 5010	674; 674	1518; 1518	1607; 1607	667; 667	742; 742	816; 816	995; 995	469; 469	1685; 1685	2359; 2359	428; 427	761; 761	1085; 1085
Mastatinib	2042; 2042	252; 252	570; 568	602; 601	251; 250	280; 278	307; 306	374; 372	176; 176	631; 631	882; 882	167; 161	285; 285	411; 411
Saracatinib	52; 52	55; 55	44; 41	195; 192	175; 174	386; 383	351; 348	304; 300	119; 119	137; 137	115; 115	254; 242	179; 179	130; 129
Sunitinib	94; 94	156; 156	96; 95	558; 557	520; 520	1162; 1160	1053; 1052	904; 902	354; 354	387; 387	306; 306	740; 734	532; 532	375; 375
Tandutinib	100; 100	36; 36	46; 43	114; 112	90; 89	186; 183	171; 169	153; 151	62; 62	89; 89	89; 89	125; 116	93; 93	76; 75
Vandetanib	188; 187	73; 73	82; 80	235; 233	191; 191	403; 401	370; 368	327; 325	131; 131	181; 181	176; 176	260; 253	198; 198	157; 157