Supporting Information

Estimation of volume of distribution in humans from high throughput HPLC-based measurements of human serum albumin (HSA) binding and immobilized artificial membrane (IAM) partitioning

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No	DRUG	CAS number	VD L/kg	Comment	PPB %	logK PPB	ClogP	pKa acid class	pKa base class	Ref (VD)	Ref (PPB)
1	ACECAINIDE	32795-44-1	1.5	ss, IV	10	0.38	1.64	0	7	63	61
2	ACETAMINOPHEN	103-90-2	0.95	ss, IV	1	0.14	0.49	1	0	72	63
3	ACETANILIDE	103-84-4	0.7	a, IV	na	na	1.16	0	0	59	Na
4	ACETAZOLAMIDE	59-66-5	0.2	a, IV	95	3.32	-1.13	2	0	59	61
5	ALCLOFENAC	22131-79-9	0.1	a, IV	99	5.44	2.73	7	0	59	61
6	ALOSETRON HCl	122852-69-1	1.1	a, IV	na	na	1.74	0	2	61	Na
7	AMANTADINE	768-94-5	6.6	ss, IV	67	1.34	2.00	0	7	72	61
8	AMILORIDE	2609-46-3	5.0	a, IV	40	0.83	-0.55	0	5	59	59
9	AMOXAPINE	14028-44-5	16.0	a, PO, 36	na	na	4.62	0	6	61	Na
10	AMOXICILLIN	26787-78-0	0.27	ss, IV	18	0.51	-1.87	7	2	72	61
11	AMPICILLIN	69-53-4	0.29	ss, IV	18	0.51	-1.20	7	3	72	61
12	APOMORPHINE HCl	314-19-2	2.0	a, IV	na	na	2.49	1	2	61	Na
13	ASPIRIN	50-78-2	0.15	ss, IV	70	1.42	1.02	7	0	45	61
14	BAMETHAN	3703-79-5	3.7	a, IV	na	na	1.50	1	7	59	Na
15	BETAMETHASONE	378-44-9	1.3	ss, IV	64	1.27	1.79	0	0	72	66
16	BROMAZEPAM	1812-30-2	0.9	ss, IV	52	1.03	1.70	0	1	72	61
17	BROMOCRIPTIN	25614-03-3	3.0	a, IV	90	2.48	6.59	1	1	59	61
18	BUDESONIDE	51333-22-3	3.9	ss, IV	88	2.29	2.91	0	0	72	61
19	BUMETANIDE	28395-03-1	0.14	ss, IV	96	3.61	3.37	7	1	72	61
20	CARBAMAZEPINE	298-46-4	1.4	a, PO, 70	75	1.58	1.98	0	0	63	61
21	CEFAZOLINE	25953-19-9	0.10	ss, IV	89	2.39	-1.14	7	1	63	67
22	CEFIXIME	79350-37-1	0.24	ss, IV7	67	1.34	0.45	7	1	72	67
23	CEPHALEXIN	15686-71-2	0.30	ss, PO, 90	14	0.45	-1.64	7	3	72	67
24	CHLORPHENIRAMINE	132-22-9	3.2	ss, IV	72	1.48	3.15	0	6	72	59
25	CHLORPROPAMIDE	94-20-2	0.19	ss, IV	90	2.49	2.35	7	0	72	59
26	CHLORPROTHIXENE	113-59-7	15.0	ss, IV	na	na	5.48	0	6	72	Na
27	CINOXACIN	28657-80-9	0.33	ss, IV	63	1.25	1.50	7	0	61	63
28	CLONAZEPAM	1622-61-3	2.8	ss, IV	85	2.07	2.38	0	1	72	63
29	CLONIDINE	4205-90-7	2.1	ss,IV	20	0.54	1.43	0	5	72	63
30	CLOXACILLIN	61-72-3	0.12	ss, PO, 43	95	3.32	2.52	7	1	72	63

31	COLCHICINE	64-86-8	5.20	ss, IV	31	0.70	1.20	0	0	72		58
32	CYTARABINE	147-94-4	2.5	a, IV	13	0.44	-2.20	0	1	61		59
33	DIAZEPAM	439-14-5	1.3	ss, IV	98	4.55	3.17	0	1	72		63
34	DIAZOXIDE	364-98-7	0.24	ss, IV	94	3.09	1.20	1	7	72		63
35	DICLOFENAC	15307-86-5	0.17	ss, IV	99	5.44	4.73	7	0	72		59
36	DIFLUNISAL	22494-42-4	0.1	ss, IV	99	5.44	4.40	7	0	72		63
37	DILTIAZEM	33286-22-5	3.1	ss, IV	98	4.55	3.65	0	5	72		63
38	DIPHENHYDRAMINE	58-73-1	4.5	ss, IV	99	5.44	3.54	0	6	72		63
39	DIPROPHYLLINE	479-18-5	0.8	a, PO, 90	na	na	-1.29	0	1	61	Na	
40	DIPYRIDAMOLE	58-32-2	2.5	a, IV	na	na	2.53	0	1	61	Na	
41	DOXEPIN	1668-19-5	11.7	a, PO, 30	83	1.94	4.09	0	6	61		61
42	DROPERIDOL	548-73-2	2.0	a, IV	na	na	3.26	0	2	61	Na	
43	ENCAINIDE	66778-36-7	2.7	a, IV	75	1.58	3.52	0	7	61		59
44	ETHINYL ESTRADIOL	57-63-6	4.33	ss, IV	97	3.99	3.86	1	0	72		62
45	FAMOTIDINE	76824-35-6	1.2	ss, IV	17	0.50	-1.20	1	7	72		63
46	FELBAMATE	25451-15-4	0.75	ss, IV	29	0.67	0.50	0	0	61		61
47	FELODIPINE	72509-76-3	10.0	ss, IV	99	5.44	5.58	0	0	67		63
48	FENCLOFENAC	34645-84-6	0.2	a, IV	na	na	4.71	7	1	61	Na	
49	FENOPROFEN	31879-05-7	0.09	a, IV	99	5.44	3.82	7	0	61		61
50	FINASTERIDE	98319-26-7	1.10	ss, IV	90	2.49	3.01	0	0	61		61
51	FLOXACILLIN	5250-39-5	0.15	a, IV	93	2.90	2.66	7	1	61		61
52	FLUMAZENIL	78755-81-4	1.10	ss, IV	45	0.91	1.09	0	1	72		61
53	FLUNARIZINE	52468-60-7	43.0	a, IV	90	2.49	6.34	0	4	61		61
54	FLUNITRAZEPAM	1622-62-4	1.9	ss, IV	78	1.70	2.14	0	1	72		63
55	FLUOXETINE	54910-89-3	31.0	a, PO, 95	99	5.44	4.57	0	7	61		61
56	FLURAZEPAM	17617-23-1	3.4	a, IV	97	3.99	4.42	0	7	61		61
57	FLURBIPROFEN	5104-49-4	0.12	ss, IV	99	5.44	3.75	7	0	72		61
58	FUROSEMIDE	54-31-9	0.13	ss, IV	97	3.99	1.90	7	0	72		63
59	GEMFIBROZIL	25812-30-0	0.14	a, PO, 98	97	3.99	4.16	7	0	60		61
60	GLIPIZIDE	29094-61-9	0.16	ss, IV	98	4.55	2.57	7	0	72		61
61	GRISEOFULVIN	126-07-8	1.5	a, IV	84	2.00	1.77	0	0	61		61
62	HEXOBARBITAL	56-29-1	1.2	ss, IV	47	0.94	1.53	0	0	72		63

63	HYDRALAZINE	86-54-4	1.4	ss, IV	89	2.39	1.02	0	3	72	59
64	HYDROCHLOROTHIAZIDE	58-93-5	3.0	a, PO, 70	40	0.83	-0.37	1	1	61	61
65	HYDROCORTISONE	50-23-7	0.44	ss, IV	85	2.07	1.70	0	0	72	59
66	IMIPRAMINE	50-49-7	23.0	ss, IV	89	2.39	5.04	0	7	72	63
67	INDOMETHACIN	53-86-1	0.10	ss, IV	90	2.49	4.18	7	0	72	63
68	INDORAMIN	26844-12-2	7.0	a, IV	na	na	2.84	0	6	61	Na
69	ISRADIPINE	75695-93-1	1.5	Ss, IV	95	3.32	4.20	0	1	72	61
70	KETOCONAZOLE	65277-42-1	2.4	a, IV	99	5.44	2.58	0	2	61	63
71	KETOPROFEN	22071-15-4	0.15	ss, IV	94	3.09	2.76	7	0	72	63
72	LABETALOL	36894-69-6	4.8	ss, IV	50	0.99	2.50	2	7	72	63
73	LEVAMISOL	14769-73-4	1.4	a, IV	NA	NA	1.84	0	2	61	Na
74	LEVONORGESTREL	797-63-7	2.9	a, IV	94	3.09	3.31	0	0	61	59
75	LIGNOCAINE	137-58-6	1.5	a, IV	60	1.18	1.95	0	5	67	61
76	LORAZEPAM	846-49-1	1.5	ss, IV	90	2.49	2.37	0	1	72	59
77	MAPROTILINE	10262-69-8	43	ss, IV	88	2.29	4.52	0	7	72	61
78	MEBENDAZOLE	31431-39-7	2.0	a, IV	90	2.49	3.08	4	1	61	61
79	METHYLPREDNISOLONE	83-43-2	1.2	ss, IV	83	1.91	1.74	0	0	72	63
80	METRONIDAZOLE	443-48-1	0.74	ss, IV	20	0.54	-0.46	0	1	72	63
81	MIANSERIN	24219-97-4	6.3	a, IV	95	3.32	4.27	0	6	61	59
82	MINOXIDIL	38304-91-5	3.0	a, IV	1	0.14	0.54	0	3	61	59
83	N - DEALKYLFLURAZEPAM	17617-59-3	0.7	a, IV	98	4.55	2.81	0	1	61	59
84	NABUMETONE	42924-53-8	0.79	a, PO, 35	99	5.44	2.98	0	0	61	61
85	NADOLOL	42200-33-9	1.9	ss, IV	28	0.66	0.38	0	7	72	61
86	NAPROXEN	22204-53-1	0.16	a, IV	99	5.44	2.82	7	0	75	63
87	NEOSTIGMINE	59-99-4	0.74	ss, IV	na	na	-2.81	0	0	72	Na
88	NICARDIPINE	55985-32-5	0.98	ss, IV	95	3.32	5.51	0	3	72	63
89	NIFEDIPINE	21829-25-4	0.78	ss, IV	96	3.61	3.41	0	1	72	63
90	NISOLDIPINE	63675-72-9	5.0	a, IV	99	5.44	4.86	0	0	61	61
91	NITRAZEPAM	146-22-5	1.9	ss, IV	87	2.21	2.32	0	1	72	63
92	NITRENDIPINE	39562-70-4	5.2	ss, IV	99	5.44	4.02	0	0	72	59
93	NITROFURANTOIN	67-20-9	0.58	ss, IV	40	0.83	-0.47	2	0	72	61
94	NIZATIDINE	76963-41-2	1.2	ss, IV	35	0.76	-0.20	0	6	72	61

95	NORDAZEPAM	1088-11-5	0.87	ss, PO, 99	97	3.99	3.02	0	1	61		63
96	NORTRIPTYLINE	72-69-5	19.1	ss, IV	93	2.90	4.32	0	7	72		61
97	ONDANSETRON	99614-02-5	1.9	ss, IV	73	1.52	2.72	0	2	72		59
98	OXACILLIN	66-79-5	0.06	ss, IV	94	3.09	2.05	7	1	72		63
99	OXAZEPAM	604-75-1	0.59	ss, IV	95	3.32	2.31	0	1	72		63
100	PAPAVERINE	58-74-2	1.5	a, IV	87	2.21	3.78	0	2	61		61
101	PENTOBARBITAL	76-74-4	1.0	a, IV	55	1.08	1.42	0	0	61		61
102	PENTOXIFYLLINE	6493-05-6.	4.2	ss, IV	na	na	0.12	0	1	72	Na	
103	PERPHENAZINE	58-39-9	2.0	ss, IV	na	na	4.31	0	5	72	Na	
104	PHENYTOIN	57-41-0	0.64	a, PO, 90	90	2.49	2.09	2	0	61		63
105	PINDOLOL	13523-86-9	2.0	ss, PO, 75	50	0.99	1.67	0	7	72		63
106	PIPERACILLIN	61477-96-1	0.26	ss, IV	22	0.57	1.70	7	1	72		63
107	PIROXICAM	36322-90-4	0.14	a, IV	99	5.44	1.89	0	1	61		61
108	PRAZOSIN	19216-56-9	0.67	ss, IV	94	3.09	1.21	0	4	72		63
109	PREDNISOLONE	50-24-8	0.52	ss, IV	78	1.70	1.42	0	0	72		63
110	PREDNISONE	53-03-2	0.97	ss, IV	78	1.70	1.66	0	0	72		63
111	PRIMIDONE	125-33-7	0.6	a, IV	20	0.54	0.88	0	0	61		61
112	PROBENECID	57-66-9	0.13	ss, IV	89	2.39	3.37	7	0	72		63
113	PROCAINAMIDE	614-39-1	1.9	ss, IV	15	0.47	1.42	0	7	72		63
114	PROCYCLIDINE	77-37-2	0.74	ss, IV	na	na	4.59	0	7	72	Na	
115	PROPRANOLOL	525-66-6	4.0	ss, IV	93	2.90	2.75	0	7	72		63
116	PROPYLTHIOURACIL	51-52-5	0.4	a, IV	80	1.79	2.87	2	1	61		61
117	PROTRYPTYLINE	438-60-8	22.0	a, PO, 82.5	na	na	4.47	0	7	61	Na	
118	PROXYPHYLLINE	603-00-9	0.6	a, IV	na	na	-0.56	0	1	61	Na	
119	QUINIDINE	56-54-2	3.5	ss, IV	90	2.49	2.79	0	7	72		63
120	QUININE	130-95-0	1.6	ss, PO, 90	93	2.90	2.79	0	7	66		63
121	RANITIDINE	66357-35-5	1.3	ss, IV	15	0.47	0.63	0	6	72		63
122	SULFACHLORPYRIDAZINE	80-32-0	0.1	a, IV	na	na	0.56	5	1	61	Na	
123	SULFAMETER	651-06-9	0.25	a, IV	87	2.21	0.65	2	1	61		61
124	SULFAMETHOXYPYRIDAZINE	80-35-3	0.2	a, IV	65	1.29	0.41	3	1	61		61
125	SULFAMETOPYRAZINE	152-47-6	0.25	a, IV	na	na	1.05	3	1	61	Na	
126	SULFAPYRIDINE	144-83-2	0.4	a, IV	na	na	0.84	2	1	61	Na	

127	SULFINPYRAZONE	57-96-5	0.10	ss, IV	98	4.55	1.66	7	0	72	63
128	SULFISOXAZOLE	127-69-5	0.19	ss, IV	88	2.29	0.22	5	1	72	63
129	SULPHADIMETHOXINE	122-11-2	0.15	a, IV	99	5.44	1.98	5	1	61	61
130	SULPHADIMIDINE	57-68-1	0.6	a, IV	80	1.79	1.10	3	1	61	61
131	SULPIRIDE	15676-16-1	2.5	a, IV	40	0.83	1.11	1	7	61	61
132	TAMOXIFEN	10540-29-1	55.0	a, PO, 23	99	5.44	6.82	0	5	61	61
133	TEMAZEPAM	846-50-4	0.8	ss, IV	97	3.99	2.55	1	1	72	63
134	TERBUTALINE	23031-32-5	1.8	ss, IV	25	0.62	0.48	1	7	72	61
135	THEOBROMINE	83-67-0	0.75	ss, IV	na	na	-0.67	1	1	61	Na
136	TINIDAZOLE	19387-91-8	0.7	a, PO, 90	12	0.42	-0.32	0	1	61	61
137	TOLBUTAMIDE	64-77-7	0.14	ss, IV	95	3.32	2.50	7	0	72	63
138	TOLFENAMIC ACID	13710-19-5	0.16	a, IV	99	5.44	5.66	7	0	61	61
139	TOLMETIN	26171-23-3	0.10	a, IV	99	5.44	2.21	7	0	61	63
140	TRAMADOL	27203-92-5	2.8	ss, IV	4	0.25	3.10	0	7	72	601
141	TRAZODONE	19794-93-5	1.0	ss, IV	93	2.90	3.17	0	7	72	603
142	TRIMETHOPRIM	738-70-5	1.6	ss, IV	45	0.91	0.98	0	3	72	63
143	VILOXAZINE	46817-91-8	1.0	a, IV	na	na	na	0	6	61	na
144	VINBLASTINE	865-21-4	35.0	a, IV	70	1.42	5.23	1	7	58	61
145	VINCRISTINE	57-22-7	11.0		70	1.42	4.04	1	7	58	48
146	WARFARIN	81-81-2	0.14	ss, PO, 93	99	5.44	2.90	7	0	61	63
147	ZIDOVUDINE	30516-87-1	1.7	ss, IV	25	0.62	0.04	1	0	72	63
148	ZOLMITRIPTAN	139264-17-8	1.8	ss, IV	18	0.51	1.29	0	7	72	61
149	ZOLPIDEM	82626-48-0	0.54	ss. IV	93	2.82	2.83	0	2	72	63

na = not available
a = VD area
ss = VD ss
IV = intravenous admin.
PO = oral admin.
number = percent of bioavailability

Table 1b Literature and calculated data for drug molecules in the test set. (VD : literature volume of distribution; PPB: literature plasma protein binding; $\log K_{PPB}$: logarithm of association constant for plasma protein binding calculated from the % binding data as $e^{\log(\%PPB/(101-\%PPB))}$; ClogP: calculated octanol/water partition coefficient; pKa acid class and pKa base class: classification based on the pKa values of acidic and basic groups – higher number means higher % of ionization)

No	DRUG	CAS number	VD L/kg	Comment	PPB %	logKPPB	ClogP	pKa acid class	pKa base class	Ref (VD)	Ref (PPB)
1	ACYCLOVIR	59277-89-3	0.71	ss, IV	15	0.47	-2.42	0	1	72	58
2	AMINOGLUTETHIMIDE	125-84-8	1.4	a, IV	24	0.6	0.77	1	1	60	67
3	ANTIPYRINE	60-80-0	0.6	ss, IV	13	0.43	0.20	0	1	72	61
4	CEFTAZIDIME	78439-06-2	0.43	ss, IV	21	0.56	-3.26	7	1	72	68
5	CHLORPHENTERMINE	461-78-9	2.4	A, IV	na	na	2.85	0	7	60	na
6	CIMETIDINE	51481-61-9	1.0	ss, IV	20	0.54	0.35	0	2	72	61
7	DAUNORUBICIN	20830-81-3	23	a, IV	na	na	0.06	1	6	72	na
8	DEXAMETHASONE	50-02-2	0.82	ss, IV	77	1.66	1.79	0	0	72	60
9	DICLOXACILLIN	3116-76-5	0.89	ss, IV	98	4.55	2.98	7	1	59	67
10	DOMPERIDONE	57808-66-9	5.7	ss, IV	na	na	4.27	0	6	62	na
11	DOTHIEPIN	113-53-1	70	ss, IV	na	na	4.53	0	6	72	na
12	FLUNISOLIDE	03/03/3385	1.8	a, PO, 42	80	1.79	2.41	0	0	72	58
13	GANCICLOVIR	82410-32-0	0.7	ss, IV	1	0.14	-2.55	0	1	72	58
14	GLYBURIDE	10283-21-8	0.14	a, IV	99	5.44	4.24	7	0	72	61
15	HALOPERIDOL	52--86-8	18	ss, IV	90	2.49	3.85	0	5	72	61
16	IBUPROFEN	15687-27-1	0.15	ss, IV	99	5.44	3.68	7	0	72	61
17	INDOPROFEN	31842-01-0	0.1	ss, IV	98	4.55	2.74	7	1	72	65
18	MEPHOBARBITAL	115-38-8	2.5	A, PO, 70	na	na	1.55	0	0	60	na
19	METOCLOPRAMIDE	364-62-5	3.4	ss, IV	40	0.83	2.23	0	7	72	61
20	NIMODIPINE	66085-59-4	1.5	a, IV	95	3.32	4.14	0	0	72	61
21	PHENACETIN	62-44-2	1.5	a, IV	33	0.73	1.77	0	0	60	61
22	PHENOBARBITAL	50-06-6	0.63	ss, IV	50	0.99	0.67	1	0	72	61
23	PHENYLBUTAZONE	50-33-9	0.17	a, IV	99	5.44	3.65	1	0	60	61
24	PROPAFENONE	54063-53-5	3.6	a, IV	95	3.32	3.64	0	7	72	61
25	PYRIMETHAMINE	58-14-0	0.43	ss, IV	85	2.07	3.00	0	2	72	61
26	RIFAMPIN	13292-46-1	0.38	ss, IV	80	1.79	3.77	1	7	72	61
27	SAQUINAVIR	127779-20-8	10	ss, IV	98	4.55	4.73	0	3	72	61
28	TETROXOPRIM	53808-87-0	0.8	a, IV	15	0.47	0.73	0	3	60	61
29	VANCOMYCIN	1404-90-6	0.39	ss, IV	30	0.69	-1.14	0	0	63	61
30	VERAPAMIL	52-53-9	4.7	ss, IV	90	2.49	4.47	0	5	72	601

na = not available
a = VD area
ss = VD ss
IV = intravenous admin.
PO = oral admin.
number = percent of bioavailability

Supporting information on the literature volume of distribution data

We have checked each and every value of volume of distribution data to the original references. When the data were obtained after oral administration the bioavailability data were taken into account for the estimate of the volume. When using pharmacokinetics to make drug dosing decisions, the difference between VDarea and VDss is not usually clinically significant. (Wilkinson, G. R. (2001) Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman, J. G. Limbird, L. E., Gillman, A. G. (eds) Goodman& Gillman's the pharmacological basis of therapeutics. 10th edn. McGraw-Hill, New York, pp 20 22). However, we have recalculated the equations for two subsets of compounds with the VDarea and the VDss data. The coefficients and the statistics are not significantly different as is shown below.

Model for compounds with the steady state volume of distribution (VDss) data:

$$\log VDss = 0.42 \log K(IAM) - 0.19 \log K(HSA) - 0.74 \quad (1)$$

$n = 65$ $r^2 = 0.62$ $s = 0.35$ $F = 51$

Model for compounds with VDarea values:

$$\log VDarea = 0.41 \log K(IAM) - 0.22 \log K(HSA) - 0.54 \quad (2)$$

$n = 114$ $r^2 = 0.80$ $s = 0.32$ $F = 217$

Model for the combined data set:

$$\log VD = 0.42 \log K(IAM) - 0.21 \log K(HSA) - 0.61 \quad (3)$$

$n = 180$ $r^2 = 0.76$ $s = 0.33$ $F = 274$

Based on the above equations there were no significant differences between the models for the steady state and the apparent volumes of distribution.

The effect of plasma protein binding other than albumin on the volume of distribution

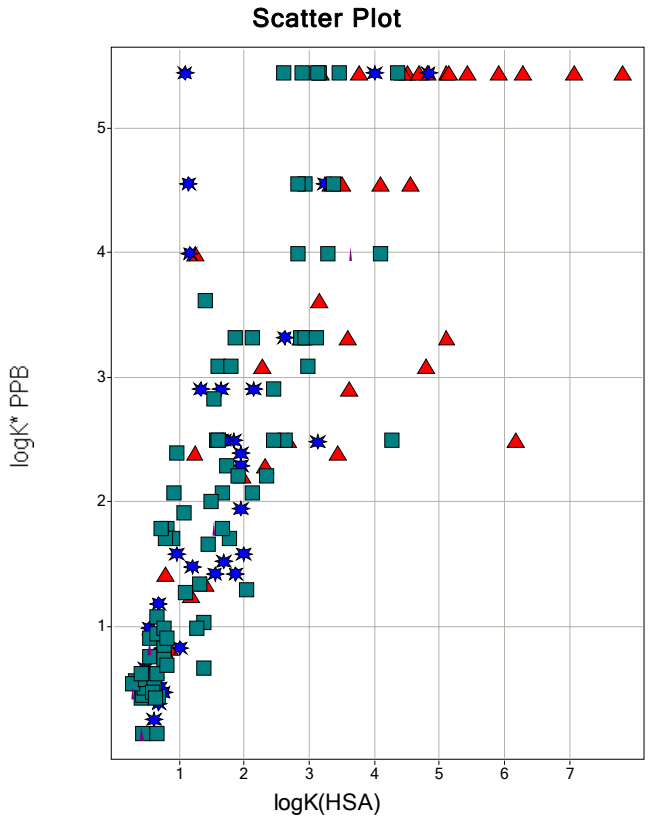
We have tried to use directly the literature plasma protein binding data in the model as well, to check whether HSA binding alone is enough to take into consideration in modeling volume of distribution. The statistical characteristic of the regression equation was slightly worse as shown by equation 6 in the paper.

$$LogVD_{ss}=0.44(\pm0.02)logK(IAM)-0.19(\pm0.02)logK^{*}(PPB)-0.65 \qquad (4)$$

N=152 r^2 = 0.72 s= 0.36 F= 182

It is worth mentioning that the regression coefficients were not statistically different from our model. When we compared our measured HSA binding data with the literature plasma protein binding, it was found that plasma protein binding is normally similar or higher than HSA binding (see figure below). The higher plasma protein binding is probably due to compound's binding to other than albumin, such as alpha-1-acid glycoprotein (AGP) or globulins.

The plot of logK (HSA) vs logK*(PPB).



The worse statistical characteristic of the model when plasma protein binding was included can also be explained by the observation that compounds binding primarily to HSA were restrictive binders, while compounds binding to other plasma proteins (for example alpha-1-acidglycoprotein) showed non-restrictive binding. We have observed that the IAM binding and AGP binding showed good correlation with each other (positively charged lipophilic compounds tend to bind strongly for both), thus reducing the difference between the tissue and plasma protein binding.