

Supporting Information

Predicting efflux ratios and blood-brain barrier penetration from chemical structure: combining passive permeability with active efflux by P-glycoprotein

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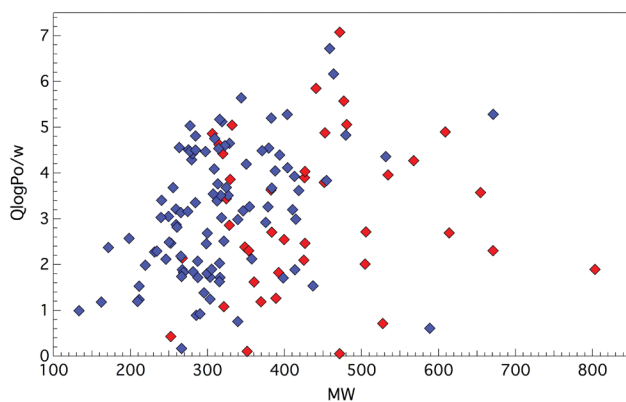


Figure 1. QlogP vs MW for compounds with experimental ER > 3 (red) and ER < 3 (blue).

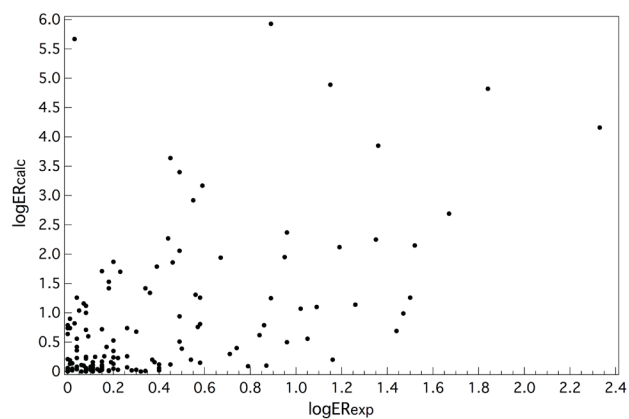


Figure 2. Calculated vs. experimental efflux ratio values.

Table S1.

Compound	Efflux Ratio								Papp (nm/s)						logPmcw2	GlideXP	Excluded
	Doan	Polli	Wager	Carrara	Feng	Chen	Average	St.dev.	Doan	Polli	Wager	Carrara	Feng	Chen			
Acrivastine	3.71						4.7		11.7						-15.8	-13.3	
Actinomycin		>80					>80			< 0.21					-	-	MW > 800
Alprazolam			1.4				1.4								-10.2	-10.2	
Alprenolol	1.01						1.0		461						-8.3	-10.4	
Amantadine	0.95	0.84					0.9	0.1	427	186					-11.1	-10.6	ER < 1
Amfebutamone (Bupropion)			1.2				1.2				321				-6.2	-10.1	
Amisulpride			9.2				9.2				11				-18.1	-12.1	
Amitriptylline	1.34						1.3		474						-7.8	-13.0	
Amprenavir	29	32.4		20.9			27.4	5.9	28.8	21.7		18			-12.4	-12.9	
Aniracetam			1.1				1.1								-10.6	-10.2	
Antipyrine	0.94			0.73			0.8	0.1	792			658			-8.3	-9.4	ER < 1
Apomorphine			6.9				6.9				27				-12.4	-12.6	
Aprepitant			5.5				5.5				44				-10.4	-14.1	
Astemizole	2.22			2.16			2.2	0.0	184			50			-13.3	-15.9	
Atenolol	1.24			0.8			1.0	0.3	2.56			10			-13.0	-10.0	
Atomoxetine			2.5				2.5				167				-9.0	-10.7	
Biperiden	0.95						1.0		515						-8.6	-13.5	
Bromazepam			1.2				1.2				275				-11.6	-11.7	
Bromocriptine	1.26		5.8				3.5	3.2	194		55				-18.7	-13.1	
Brotizolam			1.3				1.3				308				-9.9	-10.6	
Bufuralol	0.78						0.8		641						-10.7	-13.4	ER < 1
Buspirone	0.95		1.3	0.48	0.8		0.9	0.3	547		300	689	233		-15.9	-9.7	ER < 1
Cabergoline			14.3				14.3				13				-9.6	-13.7	
Caffeine				0.51	0.6		0.6	0.1			374	482	306		-11.5	-9.7	ER < 1
Carbamazepine	0.98		1		0.7		0.9	0.2	602		361		294		-10.7	-11.4	ER < 1
Carisoprodol			1.2		0.7		1.0	0.4					25.6		-9.6	-8.1	
Cetirizine	8.65					5.8	7.2	2.0	25.1						-11.7	-14.5	
Chloroquine		3.83					3.8			44.9					-13.0	-12.7	
Chlorpheniramine	0.93	1.14		0.77			0.9	0.2	468	562		303			-9.9	-11.8	ER < 1
Chlorpromazine	1.27	1.09	5.7		1.5		2.4	2.2	303	438			41		-10.8	-11.8	
Chlorprothixene	1.26						1.3		260						-9.2	-12.5	
Cimetidine	4.77	2.19		3.55			3.5	1.3	3.96	12.3		11			-13.6	-9.5	
Citalopram			1.9		1.3		1.6	0.4			151		183		-8.5	-12.5	
Clarythromycin		31.3					31.3			10.8					-14.0	-13.2	
Clemastine fumarate	1.29						1.3		331						-8.2	-13.6	
Clomipramine	1.42		10.9				6.2	6.7	369		19				-9.6	-12.2	
Clonazepam			1.3				1.3				311				-10.7	-11.9	
Clonidine	0.99						1.0		529						-13.2	-9.6	
Clozapine			2.5				2.5				68				-25.5	-11.0	
Colchicine		11.34					11.3			17.9					-12.9	-11.9	
Cyclobenzaprine	0.97		2.8		0.5		1.4	1.2	385				122		-8.2	-12.2	
Cyclosporine		9.61					9.61			15.9							MW > 800
Daunorubicin		14.2					14.2			5.47					-23.2	-14.8	
Desipramine	1.03			0.59			0.8	0.3	551			342			-11.6	-12.3	ER < 1
Dexamethasone		12.4					12.4			43.5					-12.6	-14.8	
Diazepam				0.7			0.7						277		-8.7	-11.6	ER < 1
Diltiazem	1.53	1.64					1.6	0.1	430	413					-11.7	-12.2	
Diphenhydramine	0.91					0.9	0.9	0.0	698						-9.5	-11.7	ER < 1
Dipyridamole		22.7					22.7			28.5					-20.9	-13.6	
Domperidone	31.2			62.8			47.0	22.3	18.5			5			-17.4	-14.2	

Donepezil			1.6				1.6			219					-11.1	-13.9	
Dopamine				0.25			0.3								-14.5	-9.9	ER < 1
Doxapram (Sinequan)	1.41		2				1.4		451		104		4		-8.5	-13.1	
Doxepin	1.15						1.6	0.6	451						-8.5	-12.7	
Doxorubicin		0.67					0.7			14.5					-25.6	-14.4	ER < 1
Doxylamine	0.84						0.8		359						-12.0	-11.8	ER < 1
Duloxetine			1.8				1.8								-10.5	-12.9	
Eletriptan	44.7	31.5	22.6				32.9	11.1	14.8	18.4	91				-15.3	-16.0	
Emetine		29.2					29.2			9.61					-12.0	-16.1	
Enoxacin				0.91			0.9						23		-17.9	-10.8	ER < 1
Erythromycin		14.4					14.4			0.94							# rot.b. >= 11
Escitalopram			2				2.0				161				-8.5	-11.9	
Ethosuximide					0.8		0.8						268		-10.8	-9.1	ER < 1
Etoposide		2.8					2.8			21.4					-19.3	-17.7	
Famciclovir	3.17						3.2		71.2						-13.8	-10.3	
Flumazenil	0.92		1.1				1.0	0.1	597		308				-14.2	-11.2	
Fluoxetine	1.18		5.2	0.68	0.6		1.9	2.2	521		21	179	63		-7.4	-12.7	
Flurazepam	0.88						0.9		705						-9.7	-13.4	ER < 1
Fluvoxamine	1.2		3.1		0.7		1.7	1.3	317		75		130		-7.2	-13.6	
Galantamine			1				1.0				156				-13.1	-12.5	
Guanabenz	0.91						0.9		598						-23.3	-8.9	ER < 1
Guanfacine	1.23						1.2		130						-13.1	-11.8	
Haloperidol	1.04			0.5	0.8		0.8	0.3	556			323	123		-10.5	-14.9	ER < 1
Hoechst 33342		7.75					7.75			3.35					-26.1	-14.7	
Hydrocodone			1.3		0.9		1.1	0.3			295		200		-11.8	-11.4	
Hydroxyzine					0.6		0.6						161		-7.6	-12.8	ER < 1
Imipramine	1.05						1.1		393						-9.8	-12.6	
Indeloxazine			1.4				1.4				252				-10.3	-11.4	
Indinavir	24.6	20.3					22.5	3.0	10.9	8.69					-15.6	-16.1	
Indomethacin	0.97			0.46			0.7	0.4	616			291			-15.4	-12.5	ER < 1
Itraconazole		0.97					1.0			571					-14.7	-15.9	
Ketamine	0.93						0.9		748						-8.5	-10.3	ER < 1
Ketoconazole		1.02					1.0			316					-11.7	-15.9	
Labetolol	8.85						8.9		40.9						-15.0	-14.9	
Lamotrigine			1.1		0.7		0.9	0.3			247		229		-16.2	-11.6	ER < 1
Levetiracetam			1.3				1.3								-10.9	-7.8	
Levomeprazine	1.54						1.5		347						-11.3	-11.4	
Lidocaine	0.83	0.99		0.55			0.8	0.2	664	842		716			-10.5	-10	ER < 1
Lofexidine			1.2				1.2								-11.4	-8.6	
Loperamide	9.94	7.77			9.4		9.0	1.1	77.7	99.8			27		-10.3	-15.6	
Loratidine		1.9			0.9		1.4	0.7		264			89		-9.1	-12.1	
Lorazepam			1.2				1.2				247				-12.4	-14.4	
Lorcainide	1.45						1.5		448						-10.4	-13	
Mannitol	0.88	0.82					0.9	0.0	8,29	11.3					-14.6	-10.4	ER < 1
Maprotiline	1.05						1.1		455						-9.3	-11.7	
Mebendazole		0.91					0.9			714					-15.2	-13.4	ER < 1
Mephentermine	0.87						0.9		537						-8.5	-9.9	ER < 1
Meprobamate	0.97						1.0		344						-11.2	-8.8	
Mequitazine	2.81						2.8		260						-12.5	-9.9	
Metergoline	1.21						1.2		179						-12.9	-14.3	
Methotrexate		0.67					0.7			10.5					-34.6	-9.8	ER < 1
Methylphenidate			1.1		0.8		1.0	0.2			283		247		-9.5	-10.5	
Methysergide	4.33			1.81			3.1	1.8	174			200			-12.3	-14.3	
Metoclopramide					1.1		1.1						177		-13.8	-11.0	

Metoprolol	1.21						1.2		296						-8.8	-11.3	
Mexilitene	0.87						0.9		682						-9.2	-9.6	ER < 1
Midazolam	1.01	0.81			0.7		0.8	0.2	609	701			225		-12.8	-12.4	ER < 1
Minaprine			1.2				1.2				366				-11.2	-11.9	
Mirtazapine			1.2				1.2				259				-9.1	-11.4	
Mitoxantrone		3.38					3.38			1.91							# rot.b. >= 11
Moclobemide			1.1				1.1				352				-11.2	-10.5	
Monensin		2.88					2.9			102					-14.5	-16.2	
Morphine					1.7		1.7						18		-14.4	-14.7	
Nalbuphine	2.17			1.15			1.7	0.7	140			130			-13.9	-13.4	
Nalmefene			1.1				1.1								-14.0	-13.2	
Naloxone	1.29			0.41			0.9	0.6	495			410			-14.6	-10.8	ER < 1
Naltrexone	1.04		1.1	0.75			1.0	0.2	402		204	369			-15.5	-13.0	
Nelfinavir	22.3	8.86					15.6	9.5	35.3	38.1					-15.3	-15.5	
Nemonapride			1.6				1.6				206				-15.0	-14.4	
Neostigmine	2.23	1.81					2.0		6.92	7.58							quaternary ammonium
Nicardipine		1.08					1.1			614					-11.6	-15.3	
Nicotrol			1.3				1.3				281				-9.1	-8.2	
Nifedipine		1.26					1.3			610					-10.5	-10.7	
Nimodipine			1.5				1.5				154				-9.0	-11.0	
Nitrazepam	1.17						1.2		389						-10.4	-11.5	
Nitrendipine		0.8					0.8			604					-9.8	-10.8	ER < 1
Nordazepam	0.93						0.9		647						-10.0	-13.6	ER < 1
Nortriptylene	1.39				0.6		1.0	0.6	337				91		-9.6	-14.4	
Noscapine	1.03						1.0		642						-12.9	-12.5	
Olanzapine			2				2.0				188				-14.6	-10.7	
Oxcarbazepine			1.4				1.4								-10.8	-11.3	
Oxprenolol	1.37						1.4		308						-8.7	-10.0	
Oxycodone			1.1				1.1				283				-12.5	-11.4	
Paliperidone (9-Hydroxyrisperidone)			4.1		2.1		3.1	1.4			215		168		-15.4	-14.7	
Paroxetine			5.5		0.7		3.1	3.4			10		61		-11.5	-13.2	
Pergolide			1.6				1.6				97				-10.2	-13.1	
Perospirone			7.8				7.8								-13.6	-13.7	
Perphenazine	1.47						1.5		305						-11.0	-13.4	
Pheniramine	1.41						1.4		308						-9.8	-10.5	
Phenytoin			1.1		0.9		1.0	0.1			286		240		-13.3	-11.7	
Pirenzapine	3.63						3.6		1.76						-15.2	-12	
Practolol		1.32					1.3			12.4					-13.0	-10.4	
Pramipexole			1				1.0				128				-13.0	-8.6	
Prazosin		4.63			3.2		3.9	1.0		143			106		-19.7	-12.7	
Prednisolone					3.8		3.8						123		-13.1	-14.6	
Procyclidine	0.95						1.0		703						-7.8	-12.3	
Progabide	0.88						0.9		684						-10.7	-13.6	ER < 1
Promazine	1.15						1.2		336						-10.8	-11.3	
Promethazine	1.27						1.3		430						-10.1	-10.5	
Propoxyphene					0.7		0.7						219		-5.3	-11.9	ER < 1
Propranolol	1.04	1.04		0.51			0.9	0.3	403	496		379			-9.7	-11.9	ER < 1
Protriptylene	2.37						2.4		259						-9.4	-13.9	
Puromycin		3.1					3.1			11.5					-20.2	-12.9	
Pyridostigmine		1.24					1.24			10.2							quaternary ammonium
Quetiapine			1.8				1.8				218				-8.1	-13.5	
Quinidine		27.2		11.4	16.1		18.2	8.1		36.4		31	80		-14.1	-12.6	
Ramelteon			1				1.0				334				-8.7	-11.8	
Ranitidine		1.35					1.35			14.4							quaternary ammonium

Rasagiline			1				1.0								-7.3	-9.1	
Reboxetine			1.4				1.4			122					-10.0	-12.8	
Reserpine		3.71					3.7		68.1						-14.3	-11.2	
Riluzole			1.5				1.5			304					-9.8	-9.1	
Rimonabant			2.5				2.5			35					-10.1	-12.1	
Risperidone	1.61		2.6		1.2		1.8	0.7	389			198			-12.8	-12.6	
Ritonavir		54.4			49.5		54.4			15.8			56				# rot.b. >= 11
Rivastigmine			1				1.0								-9.4	-9.6	
Ropinirole			1.3				1.3								-9.6	-12.4	
Ropivacaine			1				1.0								-10.7	-10.7	
Saquinavir	261	165					213.0	67.9	1.51	3.01					-20.8	-16.8	
Scopolamine	1.14			0.97			1.1	0.1	171			156			-7.8	-12.1	
Selegiline	0.76				0.8		0.8	0.0	703			232			-5.5	-9.3	ER < 1
Sertindole			10.4				10.4								-12.8	-14.1	
Sertraline			11.2		3.6		7.4	5.4				22	19		-9.0	-13.1	
Sulfasalazine	1.65			0.5			1.1	0.8	6.23			6			-26.5	-12.9	
Sulpiride					0.9		0.9					3	9		-17.0	-12.9	ER < 1
Sumatriptan	1.48	1.37					1.4	0.1	3.99	9.53					-16.5	-11.8	
Tacrine	0.93		1.3				1.1	0.3	438						-14.5	-11.8	
Talipexole			1.2				2.2								-10.5	-8.6	
Taxol		>108					>108			<1.25							MW > 800
Terfenadine	2.88	4.66					3.8	1.3	146	65.6					-8.2	-16.6	
Testosterone		0.73					0.7			916					-5.9	-12.4	ER < 1
Thiopental					0.9		0.9						252		-11.4	-10.4	ER < 1
Tiagabine			1.5				1.5					207			-14.8	-13.1	
Tianeptine			1.5				1.5					227			-14.7	-12.9	
Topiramate			1.1				1.1								-13.1	-11.1	
Toxindole	1.15						1.2		519						-7.8	-8.9	
Trazodone	0.94				0.8		0.9	0.1	747				197		-12.6	-12.0	ER < 1
Triamterene		0.99					1.0			185					-21.3	-10.2	
Trimethoprim	1.94	3.61					2.8	1.2	97.8	73.9					-19.2	-10.7	
Trimipramine	0.92						0.9		405						-9.7	-12.8	ER < 1
Tripolidine					0.9		0.9								-8.6	-10.4	ER < 1
Tropisetron			1.2				1.2								-12.6	-12.8	
Varenicline			1.2				1.2					246			-12.7	-8.9	
Venlafaxine			1.3		0.6		1.0	0.5				207	221		-8.3	-11.3	
Verapamil	1.73	1.16	2.3	0.96	1.8		1.6	0.5	415	591		335	126		-8.0	-16.8	
Vinblastine		> 23		17.63			20.3			< 10		16					MW > 800
Vincristine		6.31					6.3			2.36							MW > 800
Vinorelbine		69.8					69.8			2.52					-24.5	-12.5	
Vinpocetine			2.1				2.1					47			-7.2	-10.7	
Warfarin	0.83						0.8		781						-9.4	-10.7	ER < 1
Yohimbine		1.17					1.2				429				-12.7	-15	
Zaleplon			1.4				1.4					371			-11.9	-13.7	
Zimeldine	1.01						1.0		676						-8.5	-11.5	
Ziprasidone			2.3				2.3					103			-13.9	-13.7	
Zolmitriptan	2.48						2.5		2.52						-16.0	-12.6	
Zolpidem	1.14		1.2		0.7		1.0	0.3	694			803	234		-10.7	-11.6	
Zonisamide			1				1.0					291			-13.8	-9.4	
Zotepine			5.1				5.1								-10.5	-13.3	

Table S2.

Compound	CNS+ /CNS-	Average ER	logPm	GlideXP (kcal/mol)	Excluded
Amitriptyline	CNS+	1.3	-7.8	-13.0	
Anitpyrine	CNS+	0.8	-8.3	-9.4	
Caffeine	CNS+	0.6	-11.5	-9.7	
Carbamazepine	CNS+	0.9	-10.7	-11.4	
Chlopromazine	CNS+	2.4	-10.8	-11.8	
Clonidine	CNS+	1.0	-13.2	-9.6	
Desipramine	CNS+	0.8	-11.6	-12.3	
Doxylamine	CNS+	0.8	-12.0	-11.8	
Fluoxetine	CNS+	1.9	-7.4	-12.7	
Guanfacine	CNS+	1.2	-13.1	-11.8	
Indomethacin	CNS+	0.7	-15.4	-12.5	
Atenolol	CNS-	1.0	-13.0	-10.0	
Bretylium tosylate	CNS-		-	-	quaternary ammonium
Cefuroxime	CNS-		-26.1	-11.4	
Chlorothiazide	CNS-		-20.9	-10	
Furosemide	CNS-		-21.0	-12.2	
Lincomycin	CNS-		-15.7	-11	
Methotrexate	CNS-	0.7	-34.6	-9.8	
Ranitidine	CNS-		-	-	quaternary ammonium
Sulfasalazine	CNS-	1.1	-26.5	-12.9	
Digoxin	CNS-		-	-	11 rotatable bonds
Dipyridamole	CNS-	22.7	-20.9	-13.6	
Etoposide	CNS-	2.8	-19.3	-17.7	
Labetalol	CNS-	8.9	-15.0	-14.9	
Loperamide	CNS-	9.0	-10.3	-15.6	
Quinidine	CNS-	18.2	-14.1	-12.6	
Rhodamine 123	CNS-		-21.0	-12.0	
Vinblastine	CNS-		-	-	MW > 800

Table S3.

Compound	Mean P _{app} (10 ⁻⁶ cm/s)		Average ER	logP _m	Glide XP (kcal/mol)	ER _{calc}
	A to B	B to A				
1	24.4	29.6	1.2	-10.68	-10.9	1.2
2	10.6	16.7	1.6	-14.4	-9.9	2.9
3	21.8	30.9	1.4	-12.36	-12.7	4.8
4	19.6	31.8	1.6	-13.78	-12.9	15.2
5	20.3	36.4	1.8	-14	-13	19.2
6	4.75	42.8	9	-16.19	-14.6	235.8
7	10.3	45.5	4.4	-13.02	-13.2	10.2
8	14.5	34.2	2.4	-13.32	-14.2	20.1
9	0.51	2.9	5.8	-15.97	-12.3	58.1
10	8.41	25.8	3.1	-12.76	-11	2.3

Table S4.

Series #	Compound Number	ER	logER	Exp Rank	P _{app} (10 ⁻⁶ cm/s)	ER _{calc}	logER _{calc}	Calc Rank
1	1	22.6	1.35	1	NR	145	2.16	1
	2	8.6	0.93	2	21	11	1.06	2
	3	3.2	0.51	3	31	5	0.71	6
	4	2.3	0.36	4	28	6	0.77	5
	5	8.6	0.93	2	25	7	0.86	3
	6	1.9	0.28	5	34	7	0.85	4
2	7	10	1.00	1	<1	3214	3.51	1
	8	1.3	0.11	2	3	1282	3.11	2
3	9	17	1.23	3	20	31	1.50	5
	10	11	1.04	4	33	45	1.65	4
	11	5	0.70	5	27	31	1.49	5
	12	1.6	0.20	6	38	133	2.12	3
	13	50	1.70	1	19	233	2.37	1
	14	20	1.30	2	31	185	2.27	2
4	15	5.8	0.76	1	60	434	2.64	1
	16	3.2	0.51	2	69	52	1.72	2
	17	1.1	0.04	3	68	7	0.81	3
5	18	4.1	0.61	1	28.8	146	2.16	1
	19	2.6	0.41	2	54	26	1.42	2
6	20	4.3	0.63	2	-	2	0.36	1
	21	2.7	0.43	3	-	1	0.12	3
	22	20	1.30	1	-	2	0.31	2
7	23	6.8	0.83	2	-	171	2.23	1
	24	13	1.11	1	-	162	2.21	2
	25	2	0.30	3	-	11	1.03	6
	26	2	0.30	3	-	21	1.33	4
	27	1.4	0.15	4	-	28	1.44	3
	28	2	0.30	3	-	18	1.26	5
8	29	74	1.87	1	-	1867	3.27	1
	30	2.9	0.46	2	-	88	1.94	2
	31	2.6	0.41	3	-	53	1.72	2

9	32	14.0	1.15	1	-	124	2.09	1
	33	4.7	0.67	2	-	25	1.39	3
	34	2.0	0.29	4	-	15	1.19	4
10	35	2.5	0.40	5	27	316	2.50	4
	36	14	1.15	1	34	8317	3.92	1
	37	4.8	0.68	2	21	1519	3.18	2
	38	2.3	0.36	6	26	206	2.31	5
	39	2.6	0.41	4	31	543	2.74	3
	40	3.1	0.49	3	26	150	2.18	6
11	41	23	1.36	1	1	2709	3.43	1
	42	3	0.48	2	7	43	1.64	2
12	43	1.9	0.28	2	-	2	0.22	2
	44	9.1	0.96	1	-	3	0.49	1
13	45	-	-		-	3	0.41	
	46	2.4	0.38	4	-	5	0.72	2
	47	11.4	1.06	1	-	7	0.86	1
	48	3	0.48	3	-	5	0.69	3
	49	3.9	0.59	2	-	2	0.39	4
14	50	yes			-	43	1.63	
	51	yes			-	14	1.14	
	52	yes			-	27	1.44	
	53	no			-	2	0.25	
	54	no			-	10	1.00	
15	55	no			-	2	0.33	
	56	NR	-		-			
16	57	5.8	0.76		-			
	58	2.9	0.46	2	28.5	2	0.27	2
17	59	6.8	0.83	1	6.6	119	2.07	1
	60	-	-			14	1.15	
	61	-	-			9	0.96	
	62	10	1.00	1	NR	75.9	1.88	2
	63	0.9	-0.05		19	177.1	2.25	
	64	1.5	0.18	2	0.4	255.9	2.41	1
	65	0.6	-0.22		18	53.8	1.73	