Supplementary Material

Journal:

Drug Metabolism and Disposition

Title of Article:

Mechanistic pharmacokinetic modeling for the prediction of transporter-mediated disposition in human from sandwich culture human hepatocyte data

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Figure S1: Raw SCHH data for (A-B) pravastatin, (C-F) cerivastatin, (G) bosentan, (H-J) fluvastatin, (K-R) rosuvastatin, (S-U) valsartan and (V-X) repaglinide.

Solid diamonds represent HBSS only, open squares represent Ca2+/Mg2+ free, solid triangles represent HBSS + Rifamycin SV

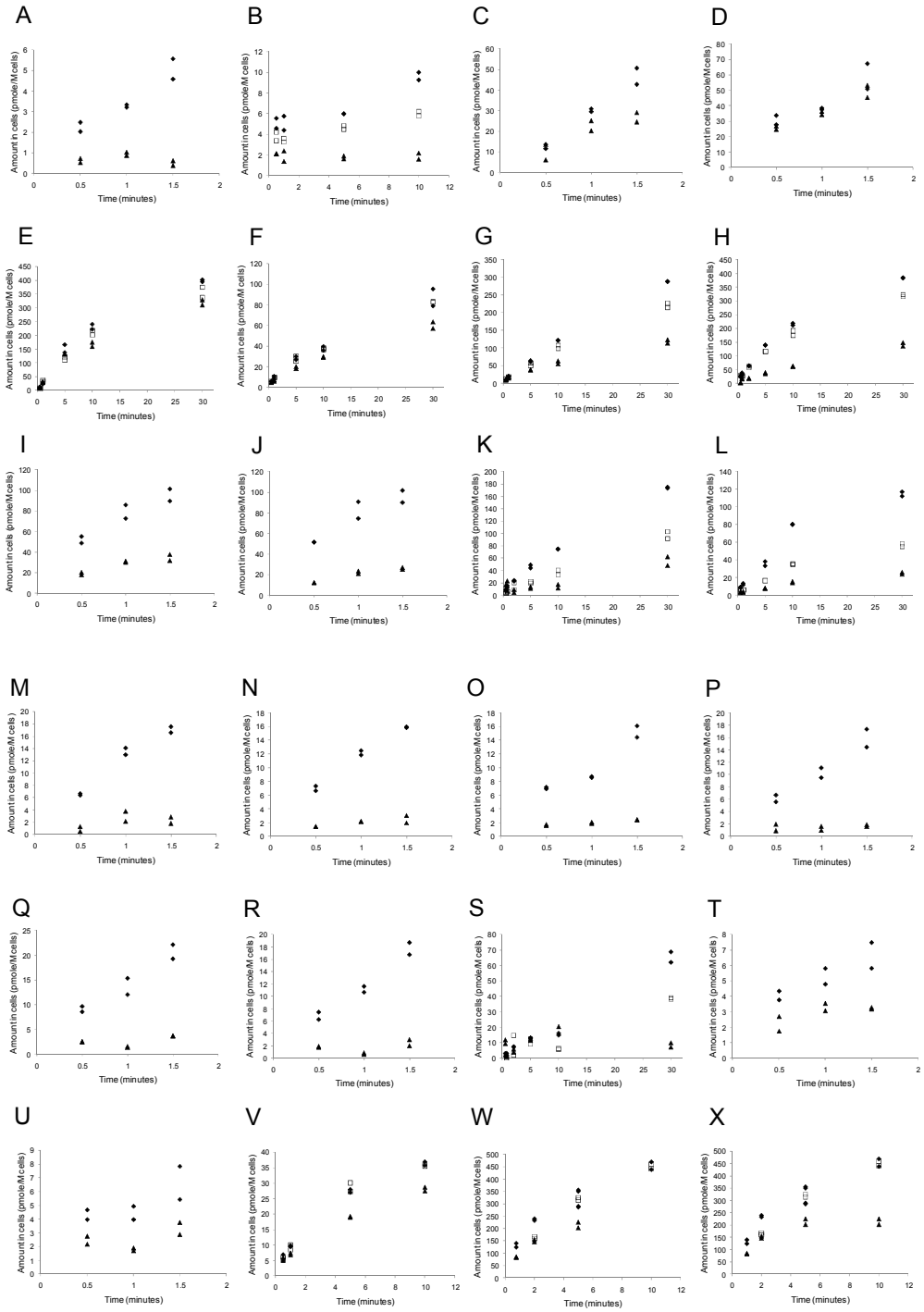

Figure S2: Fitted versus observed human plasma concentration time data for (A) pravastatin, (B) cerivastatin, (C) bosentan, (D) fluvastatin, (E) rosuvastatin, (F) valsartan, (G) repaglinide.

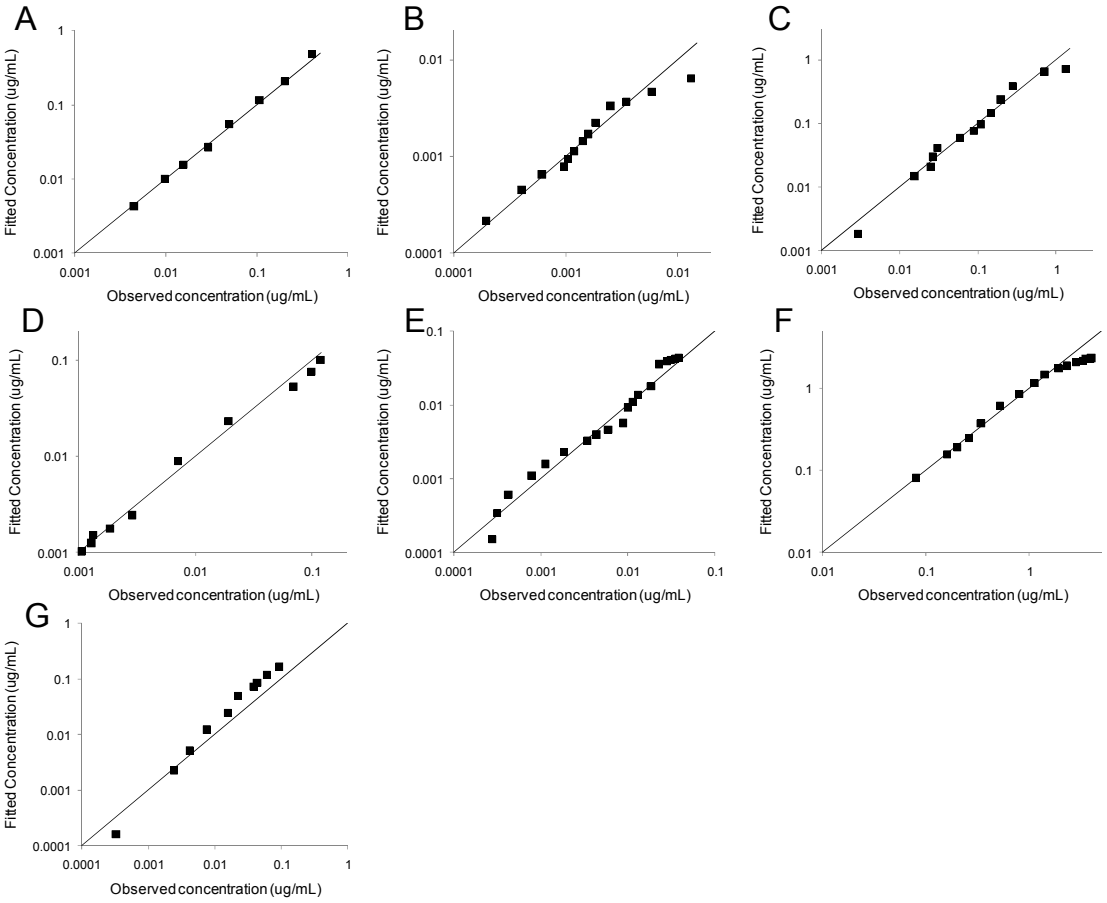

Figure S3: Contour plots for pairs of fitted parameters (A-C) pravastatin, (D-F) cerivastatin, (G-I) bosentan, (J-L) fluvastatin, (M-O) rosuvastatin, (P-R) valsartan and (S) repaglinide.

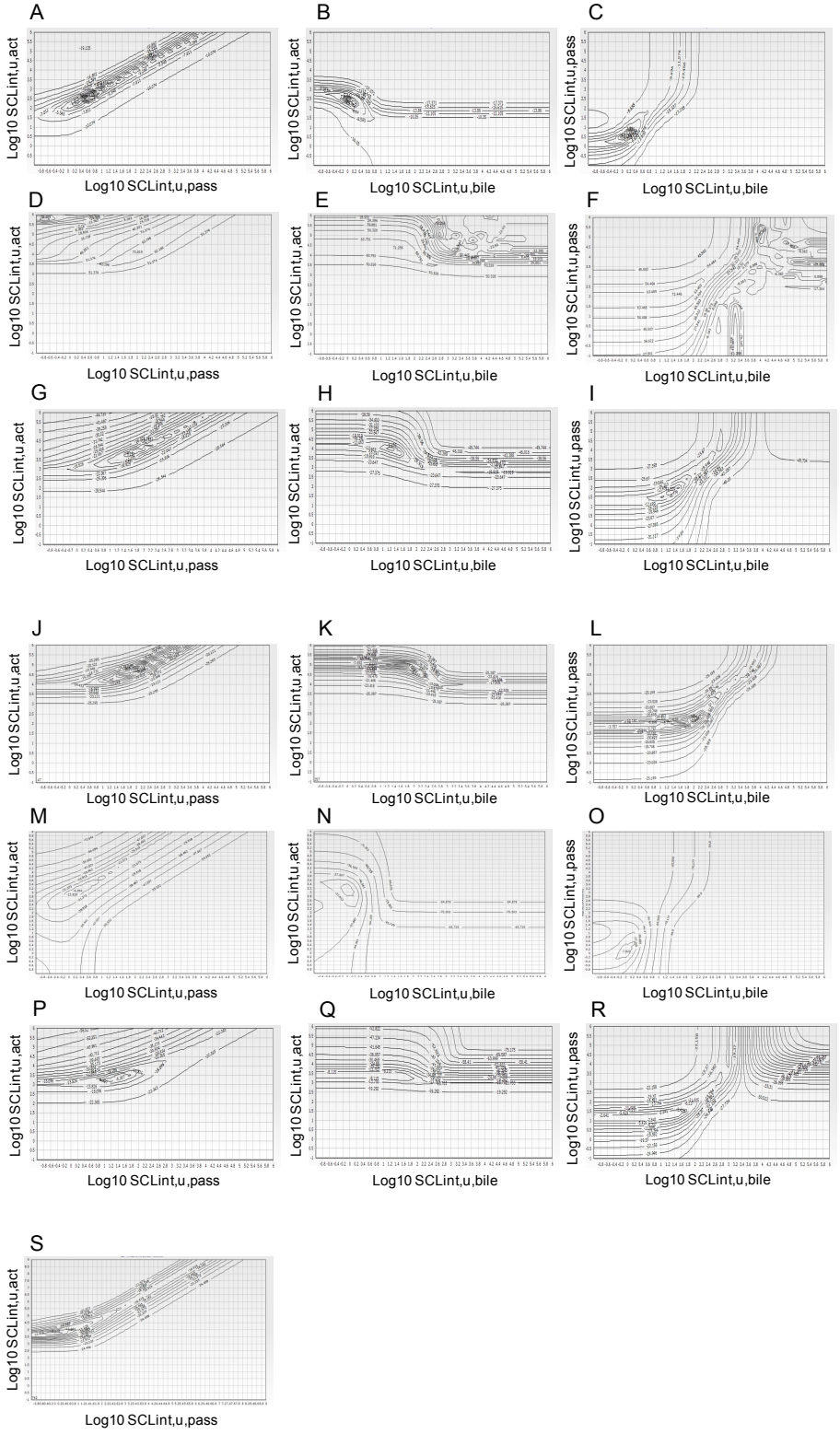

Table S1 – Clinical pharmacokinetic properties and substrate specificity for the compounds studied

Compound	CL,i.v. mL/min/kg	Vss,i.v. L/Kg	% renal CL	Substrate specificity
Pravastatin[1]	14	0.46	47	OATP1B1, MRP2
Cerivastatin[2]	2.9	0.33	0	OATP1B1, CYP3A4, 2C8
Bosentan[3]	2.3	0.67	0	OATP1B1, 1B3, 2B1, CYP3A4, 2C9
Fluvastatin[4]	8.7	0.16	0	OATP1B1, 2B1, 1B3, CYP2C9
Rosuvastatin[5]	11	1.7	30	OATP1B1, 1B3, 2B1, BCRP
Valsartan[6]	0.49	0.23	29	OATP1B1, 1B3
Repaglinide[7]	7.8	0.35	0	OATP1B1, CYP3A4, 2C8

[1] Singhvi et al., 1990; [2] Muck et al., 1997; [3] Weber et al., 1996; [4]Lindahl et al., 1996; [5]Martin et al., 2003; [6]Flesch et al., 1997; [7] Hatorp et al., 1998

Table S2 Quantification of OATP1B1, 1B3 and 2B1 in suspension hepatocytes and SCHH

	Suspension	SCHH at day 5	Change compared to suspension
	(fmol/ug protein)		%
OATP1B1	3.42±0.11	5.28±0.22	154[1]
OATP1B3	1.50±0.15	0.88±0.11	59[1]
OATP2B1	1.84±0.15	1.23±0.12	67*

[1] P<0.05, as compared to suspension.

Supplementary References

Flesch G, Muller P, and Lloyd P (1997) Absolute bioavailability and pharmacokinetics of valsartan, an angiotensin II receptor antagonist, in man. *Eur J Clin Pharmacol* 52:115-120.

Hatorp V, Oliver S, and Su CA (1998) Bioavailability of repaglinide, a novel antidiabetic agent, administered orally in tablet or solution form or intravenously in healthy male volunteers. *Int J Clin Pharmacol Ther* 36:636-641.

Lindahl A, Sandstrom R, Ungell AL, Abrahamsson B, Knutson TW, Knutson L, and Lennernas H (1996) Jejunal permeability and hepatic extraction of fluvastatin in humans. *Clin Pharmacol Ther* 60:493-503.

Martin PD, Warwick MJ, Dane AL, Brindley C, and Short T (2003) Absolute oral bioavailability of rosuvastatin in healthy white adult male volunteers. *Clin Ther* 25:2553-2563.

Muck W, Ritter W, Ochmann K, Unger S, Ahr G, Wingender W, and Kuhlmann J (1997) Absolute and relative bioavailability of the HMG-CoA reductase inhibitor cerivastatin. *Int J Clin Pharmacol Ther* 35:255-260.

Singhvi SM, Pan HY, Morrison RA, and Willard DA (1990) Disposition of pravastatin sodium, a tissue-selective HMG-CoA reductase inhibitor, in healthy subjects. *Br J Clin Pharmacol* 29:239-243.

Weber C, Schmitt R, Birnboeck H, Hopfgartner G, van Marle SP, Peeters PA, Jonkman JH, and Jones CR (1996) Pharmacokinetics and pharmacodynamics of the endothelin-receptor antagonist bosentan in healthy human subjects. *Clin Pharmacol Ther* 60:124-137.