

## **Supplementary data:**

The role of BSEP gene repression in drug-induced cholestatic liver toxicity

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Drug Metabolism & Disposition

### **Supplemental Table 1**

BSEP expression changes as a percentage of DMSO, as depicted in Figure 1 are summarized, along with BSEP IC<sub>50</sub> values and reported DILI severity score. Drugs that did not meet the criteria set forth in Chen et al. (2011) and were determined not to have DILI concern are indicated by (--). Abbreviations used for DILI represent withdrawn drugs (W); DILI implicated in the box warning (BW), warnings and precautions (WP), or adverse reactions (AR) sections of label; and most DILI concern (MDC) or less DILI concern (LDC) classifications.

### **Supplemental Figure 1**

Effect of BSEP repressors on NRF2 and LRH-1 mRNA expression. Human primary hepatocytes from two donors were treated with vehicle control (0.1% DMSO) or multiple concentrations of lopinavir, troglitazone, benzbromarone, bosentan, and glimepiride as detailed in "Materials and Methods". NRF2 (A) and LRH-1 (B) mRNA expression was measured using real-time PCR.

**Table 1. Correlation between BSEP expression and DILI**

	Compounds	Average BSEP Expression (% DMSO)	Human BSEP IC <sub>50</sub> (uM)*	DILI Severity Score**
Represses BSEP ≥ 60%	Lopinavir	21.9 ± 9.5	17.3	8; WP, MDC
	Troglitazone	24.2 ± 8.9	5.9	-2; W, MDC
	Benzbromarone	32.4 ± 4.2	17.5	-2; W, MDC
	Bosentan	35.8 ± 5.9	22.0	7; BW, MDC
	Glimepiride	39.2 ± 9.0	15.7	7; AR, LDC
Represses BSEP 20-60%	Fenofibrate	42.0 ± 7.6	15.3	3; WP, LDC
	Glyburide	45.2 ± 3.5	6.1	--
	Nelfinavir	47.4 ± 6.5	11.8	--
	Erythromycin estolate	58.8 ± 5.6	13.0	5; WP, MDC
	Gefitinib	59.2 ± 2.2	10.9	--
	Saquinavir	59.6 ± 6.0	4.9	3; WP, LDC
	Ritonavir	60.8 ± 8.5	2.2	5; WP, MDC
	Rifampicin	68.1 ± 10.4	25.3	8; WP, MDC
	Cinnarizine	72.8 ± 12.1	15.7	--
	17-alpha ethinyl estradiol	79.1 ± 7.0	14.0	2; AR, LDC
Represses BSEP ≤ 20%	Itraconazole	81.9 ± 20.9	18.0	--
	Imatinib	86.2 ± 14.3	25.1	--
	Simvastatin	89.4 ± 8.5	24.7	3; WP, LDC
	Paclitaxel	95.9 ± 3.5	15.0	--
	Telmisartan	100.9 ± 15.1	16.2	--
	Pazopanib	106.3 ± 13.0	10.3	8; BW, MDC
	Lapatinib	106.3 ± 4.0	6.5	8; BW, MDC
	Indinivir	107.4 ± 14.7	21.2	8; WP, MDC
	Ketoconazole	114.6 ± 25.1	3.4	8; BW, MDC
	Nefazodone	118.2 ± 19.4	6.1	8; BW, MDC
	Sorafenib	134.4 ± 6.8	8.0	--
	Fusidic Acid	135.5 ± 6.7	10.1	--
	Pioglitazone	141.9 ± 13.4	0.4	3; WP, LDC
	Nicardipine	159.4 ± 8.4	7.9	--
	Cyclosporine-A	186.8 ± 19.4	0.9	2; WP, LDC

\*BSEP IC<sub>50</sub> values reported by Morgan et al. (2010)

\*\*DILI severity score determined by Chen et al. (2011) and the associated LTKB benchmark dataset (FDA)

Figure 1

