[Title] Substrate-Dependent Inhibition of Organic Anion Transporting Polypeptide 1B1: Comparative Analysis with Prototypical Probe Substrates, Estradiol-17β-Glucuronide, Estrone-3-Sulfate, and Sulfobromophthalein

[Authors] Saki Izumi, Yoshitane Nozaki, Takafumi Komori, Kazuya Maeda, Osamu Takenaka, Kazutomi Kusano, Tsutomu Yoshimura, Hiroyuki Kusuhara, and Yuichi Sugiyama

[Journal] Drug Metabolism and Disposition

Supplemental Table 1

Statistical analysis of stimulatory effect of tested compounds on OATP1B1-mediated uptake of [^{3}H]E_2G

Substrate	Inhibitors (μM)													
	E_1S	CsA	BSP	ritonavir	rifampin	tacrolimus	erythromycin	E_2G	TCA	ketoconazole	gemfibrozil	verapamil	probenecid	cimetidine
[^{3}H]E_2G	**0.01***	0.01	0.01	0.01	**0.01*****	**0.01*****	1	0.1	1	1	1	1	1	1
	0.03	0.03	0.03	0.03	**0.03*****	**0.03*****	3	0.3	3	3	3	3	3	3
	0.1	0.1	0.1	0.1	0.1	**0.1****	10	1	10	10	10	10	10	10
	0.3	0.3	0.3	0.3	0.3	0.3	30	3	30	30	30	30	30	30
	1	1	1	1	1	1	100	10	100	100	100	100	100	**100*****
	3	3	3	3	3	3	300	30	300		200	300	300	300
	10	10	10	10	10	10	1000	100	1000		500		1000	1000

Inhibitor concentrations, at which OATP1B1-mediated uptake of [^{3}H]E_2G (0.1 μM) was significantly stimulated in inhibition studies (Fig. 2), are highlighted in bold. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, significantly different from OATP1B1-mediated uptake of [^{3}H]E_2G without any inhibitors. E_1S, estrone-3-slufate; CsA, cyclosporin A; BSP, sulfobromophthalein; E_2G, estradiol-17β-glucuronide; TCA, taurocholate.

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Supplemental Table 2

Statistical analysis of stimulatory effect of tested compounds on OATP1B1-mediated uptake of [^{3}H]E_1S

Substrate	Inhibitors (μM)													
	E_1S	CsA	BSP	ritonavir	rifampin	tacrolimus	erythromycin	E_2G	TCA	ketoconazole	gemfibrozil	verapamil	probenecid	cimetidine
	0.01	**0.01***	0.01	0.01	0.01	0.01	1	0.1	1	1	1	1	1	1
	0.03	**0.03****	**0.03*****	0.03	0.1	**0.03*****	3	0.3	3	3	3	3	3	3
	0.1	**0.1*****	0.1	0.1	0.3	**0.1****	10	1	10	10	10	10	10	10
[^{3}H]E_1S	0.3	0.3	0.3	0.3	1	0.3	30	3	30	30	30	30	30	30
	1	1	1	1	3	1	100	10	100	100	100	100	100	100
	3	3	3	3	10	3	300	30	300		200	300	300	300
	10	10	10	10	30	10	1000	100	1000		500		1000	1000
				30,50,100	100									

Inhibitor concentrations, at which OATP1B1-mediated uptake of [^{3}H]E_1S (0.01 μM) was significantly stimulated in inhibition studies (Fig. 2), are highlighted in bold. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, significantly different from OATP1B1-mediated uptake of [^{3}H]E_1S without any inhibitors. E_1S, estrone-3-slufate; CsA, cyclosporin A; BSP, sulfobromophthalein; E_2G, estradiol-17β-glucuronide; TCA, taurocholate.

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Supplemental Table 3

Statistical analysis of stimulatory effect of tested compounds on OATP1B1-mediated uptake of [^{3}H]BSP

Substrate	Inhibitors (μM)													
	E_1S	CsA	BSP	ritonavir	rifampin	tacrolimus	erythromycin	E_2G	TCA	ketoconazole	gemfibrozil	verapamil	probenecid	cimetidine
[^{3}H]BSP	**0.01*****	**0.01*****	0.01	**0.01*****	**0.01*****	0.01	1	**0.1*****	**1*****	1	1	**1*****	**1***	1
	0.03***	**0.03*****	0.03	**0.03*****	**0.03*****	0.03	3	**0.3*****	**3***	**3****	3	**3*****	**3****	**3*****
	0.1	0.1	0.1	0.1	0.1	0.1	10	**1*****	**10*****	10	10	**10*****	10	**10*****
	0.3	0.3	0.3	0.3	0.3	0.3	30	**3*****	30	30	30	30	**30*****	**30*****
	1	1	1	1	1	1	100	10	100	100	100	100	100	**100*****
	3	3	3	3	3	3	300	30	300		200	300	300	**300*****
	10-10000	10	10	10	10	10	1000	100	1000		500		1000	**1000*****

Inhibitor concentrations, at which OATP1B1-mediated uptake of [^{3}H]BSP (0.01 μM) was significantly stimulated in inhibition studies (Fig. 2), are highlighted in bold. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, significantly different from OATP1B1-mediated uptake of [^{3}H]BSP without any inhibitors. E_1S, estrone-3-slufate; CsA, cyclosporin A; BSP, sulfobromophthalein; E_2G, estradiol-17β-glucuronide; TCA, taurocholate.