Supplementary Figure Legends

Supplementary Figure S1. Estradiol-17β-D-glucuronide transport in HEK293 OATP1B1 and OATP1B3 cells. [^{3}H]Estradiol-17β-D-glucuronide (0.1 μM) was incubated with HEK293 cells expressing OATP1B1, OATP1B3, or vector control (VC) for 15 minutes. Intracellular concentrations were determined by liquid scintillation counting. Data represent the mean ± SE of triplicate samples (representative data; n=3).

Supplementary Figure S2. Drug diffusion in PAMPA assay. The indicated compounds were added to the donor side of an artificial lipid membrane and allowed to diffuse overnight at room temperature. Concentration of drug on the acceptor side was measured by liquid scintillation counting and percentage diffusion relative to drug added to the donor side was determined. Data represent the mean ± SE of 4 to 20 replicates.

Supplementary Figure S3. Influence of Oatp-deficiency on sorafenib, sorafenib N-oxide, and total active compound (sorafenib + N-oxide) pharmacokinetics. Female (**A**, **B**) wildtype (WT) and Oatp1b2(-/-) mice (n =4/group) and (**C**, **D**) WT, Oatp1a/b(-/-), OATP1B1^{tg}, and OATP1B3^{tg} mice (n = 4/group) were given 10 mg/kg sorafenib via oral gavage. (**A**, **C**) Sorafenib N-oxide (S-N-oxide) and (**B**, **D**) total active compound (sorafenib + sorafenib N-oxide) plasma concentrations were determined by LC-MS/MS. Data represent the mean ± SE (*, P<0.05; **, P<0.01); mean AUC ± SE is shown in parentheses.

Supplementary Figure S4. Influence of Oatp1b2-deficiency on the metabolic ratio of sorafenib-glucuronide and sorafenib N-oxide *in vivo*. Female wildtype (WT) and Oatp1b2(-/-) mice (n =4/group) were given 10 mg/kg sorafenib via oral gavage. Sorafenib, sorafenib N-oxide (S-N-oxide) and sorafenib-glucuronide (S-glu) concentrations in plasma were determined

by LC-MS/MS. Data represent AUC ratios of metabolites to parent drug, and are expressed as the mean ± SE (*, P<0.05).

Supplementary Figure S5. Influence of Oatp1b2-deficiency on the liver-to-plasma ratio of sorafenib, sorafenib N-oxide, and sorafenib-glucuronide *in vivo*. Female wildtype (WT) and Oatp1b2(-/-) mice (n =3/group) were given 60 mg/kg sorafenib via oral gavage. Sorafenib, sorafenib N-oxide (S-N-oxide) and sorafenib-glucuronide concentrations in liver and plasma at 0.5 and 1.5 hours after sorafenib administration were determined by LC-MS/MS. Data represent the mean ± SE (*, P<0.05).

Supplementary Figure S6. Influence of Oatp1b2-deficiency on sorafenib N-oxide formation *ex vivo*. Liver and intestinal microsomes (1 mg/mL) from wildtype (WT) and Oatp1b2(-/-) mice were incubated with sorafenib 10 μM for 60 min and sorafenib N-oxide formation velocity was determined. Data represent the mean ± SE from 2 experiments performed with triplicate samples (n = 6) (*, P<0.05).

Supplementary Figure S7. Estradiol-17β-D-glucuronide transport in HEK293 OATP1B1 variant cells. [^{3}H]Estradiol-17β-D-glucuronide (0.1 μM) was incubated with T-Rex293 cells expressing OATP1B1*1A, *5, or *15 for 15 min. Intracellular concentrations were determined by liquid scintillation counting. Data represent the mean ± SE of triplicate samples (representative data; n=3) (***, P<0.001).

Supplementary Figure S8. Influence of Oatp1a/b-deficiency on sorafenib metabolism *ex vivo*. Intestinal and liver microsomes (1 mg/mL) from wildtype (WT) and Oatp1a/b (-/-) mice were incubated with sorafenib 10 μM for 60 min and sorafenib-glucuronide (**A**) and sorafenib N-

oxide (**B**) formation velocity was determined. Data represent the mean ± SE from triplicate samples (n = 3) (*, $P<0.05$).