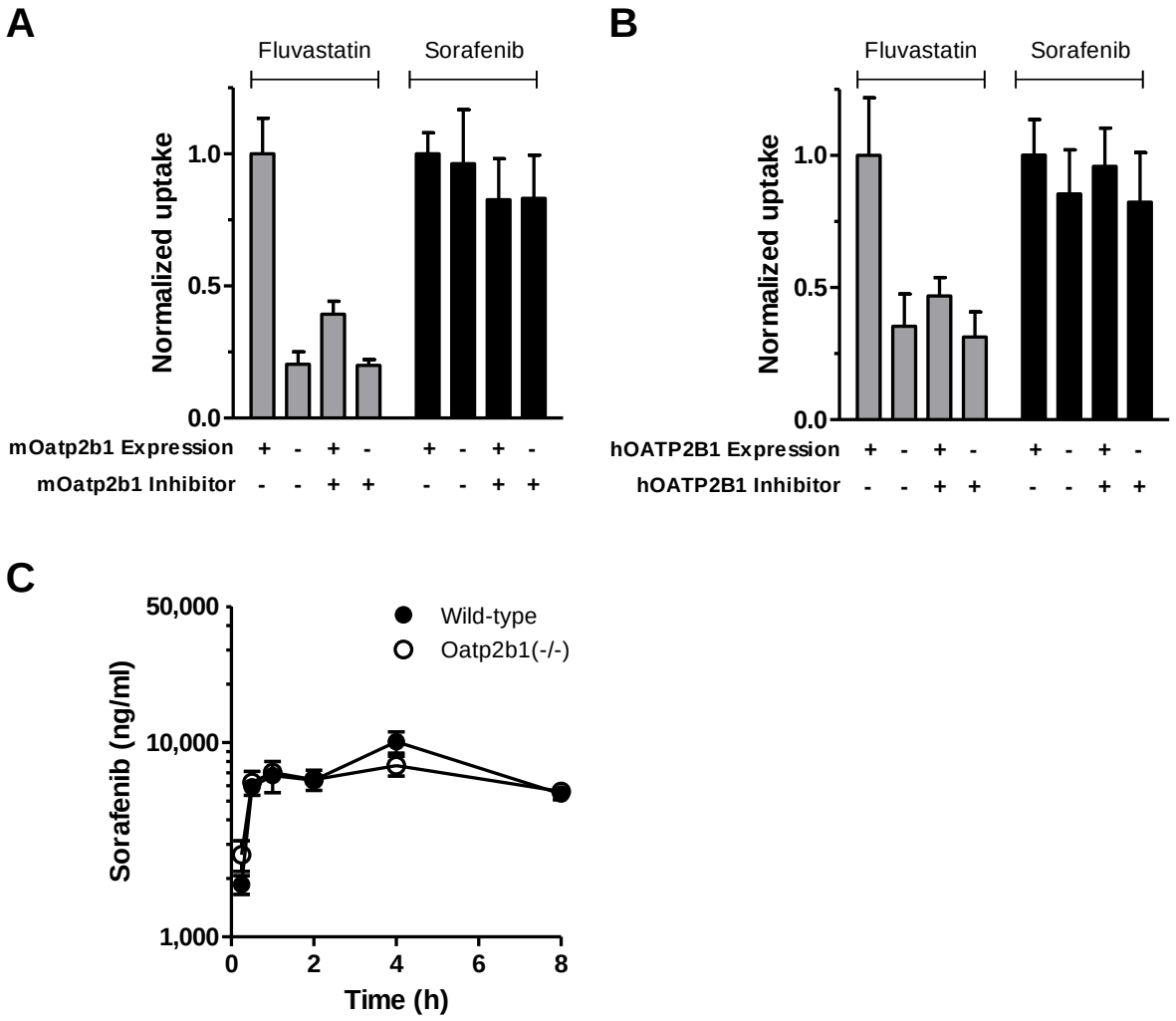
Figure S4: Evaluation of mouse Oatp2b1 (mOatp2b1) and human OATP2B1 (hOATP2B1) as transporters of sorafenib.



(A, B) Comparison between uptake of the OATP2B1 probe substrate fluvastatin (0.2 µM; [3H(G)]fluvastatin, 740 GBq/mmol, American Radiolabeled Chemicals Inc.) and sorafenib (1 µM) into HEK293T-mOatp2b1 or HEK293T-hOATP2B1 or vector-transfected HEK293T in absence or presence of the OATP2B1 inhibitor erlotinib (10 µM) after 15 min pre-incubation and 15 min co-incubation. HEK293T cells were transfected with pCMV6-AC-IRES-GFP plasmid (Origene) containing either mOatp2b1 or hOATP2B1 cDNA or with empty vector 24h before uptake assay. Data are means (bars) and SE (error bars) of 6 observations. (C) Plasma concentration-time profiles of sorafenib in wildtype (WT) and Oatp2b1-deficient female mice. Sorafenib (10mg/kg) was administered orally by gavage and serial plasma samples were obtained in individual mice (n=5/group). Sorafenib was measured in plasma by LC-MS/MS. Oatp2b1-deficient mice (Oatp2b1-/-) were established from embryos purchased from KOMP Repository. Rederived mice with Slco2b1$^{tm1a(KOMP)Wtsi}$ allele were crossed with transgenic mice expressing Flp and then Cre recombinase. The deletion of Slco2b1 was validated through qPCR.