Inhibition of Human Organic Anion Transporting Polypeptide (OATP) -1B1 and -1B3 by Tyrosine Kinase Inhibitors
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Purpose
The aim of this study is to assess the interaction of various tyrosine kinase inhibitors (TKIs) with the human OATPs expressed in the basolateral membrane of hepatocytes by conducting experiments in transfected Chinese Hamster Ovary (CHO) cells.

Methods
Human OATP-1B1 and -1B3 transfected CHO cells were employed as an in vitro model. We studied the interaction of pazopanib, erlotinib, canertinib, nilotinib and vandetanib with OATP-1B1 and -1B3 cells. The effect of increasing concentration of TKIs (0.1-100 μM) on the intracellular accumulation of prototypical OATP-1B1 and OATP-1B3 substrates [3H] estrone-3-sulfate and [3H] cholecystokinin-8 respectively was analyzed in the transfected variants. Rifampicin was included as the reference control.

Results
Out of the 5 TKIs tested, 2 TKIs, namely, pazopanib and nilotinib confirms their inhibitory potency towards OATP-1B1 transporter whereas vandetanib only inhibits OATP-1B3 transporter. Rifampicin (reference control) inhibited both OATP-1B1 and OATP-1B3 transporter proteins. The effect of increasing concentration of TKIs and rifampicin was done for the estimation of IC50 values for OATP-1B1 and OATP-1B3 transporter. The IC50 values of OATP-1B1 for pazopanib, nilotinib and rifampicin are 3.89 ± 1.21, 2.78 ± 1.13 and 10.46 ± 1.15μM respectively. Vandetanib, canertinib and erlotinib did not show any inhibitory activity towards OATP-1B1 transporter. Similarly, IC50 values of OATP-1B3 for rifampicin and vandetanib are 3.67 ± 1.20 and 18.13 ± 1.21μM respectively. No inhibitory activity of pazopanib, nilotinib, canertinib and erlotinib was observed with OATP-1B3 transporter.

Conclusion
Our findings indicate that some of the TKIs are inhibitor for OATP-1B1 & -1B3. This transporter mediated drug-drug interactions leading to altered drug concentration could potentially result in elevated plasma levels, unexpected toxicity or decreased efficacy for a drug that targets liver. Therefore, co-administration of these TKIs with an OATP substrate drug should be handled with caution. Inhibition of OATP-1B1 & -1B3 not only interfere with hepatic uptake of drugs but also with many endogenous substrates, including bilirubin. Thus their inhibition may also be proposed as an important mechanism for TKIs induced hyperbilirubinemia.