The protein kinase inhibitors midostaurin and nintedanib are time-dependent inhibitors of cyp3a4

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Aims: Protein kinase inhibitors display a tendency to affect cytochrome P450 (CYP) 3A4 by time-dependent inhibition. As CYP2C8 and CYP3A4 share overlapping substrate specificity, we tested six novel kinase inhibitors for time-dependent inhibition of these enzymes.
Methods: The inhibitory effects of dovitinib, masitinib, midostaurin, nintedanib, trametinib and vatalanib on amodiaquine N-deethylation (CYP2C8) and midazolam 1'-hydroxylation (CYP3A4) were evaluated in human liver microsomes. Static predictions were used to estimate the clinical significance of the observed inhibition.
Results: Dovitinib, midostaurin and nintedanib exhibited time-dependent inhibition of CYP3A4 (IC_{50} shift >1.5), whereas masitinib, trametinib and vatalanib did not affect CYP2C8 or CYP3A4 by time-dependent inhibition (IC_{50} shift <1.5). Further experiments identified midostaurin and nintedanib as mechanism-based inhibitors of CYP3A4, with maximal inactivation rate (k_{inact}) and inhibitor concentration supporting half of k_{inact} (K_I) values of 0.052 1/min and 2.72 μM, and 0.025 1/min and 17.3 μM, respectively. Predictions indicated that standard doses of nintedanib are unlikely to cause drug interactions with CYP3A4-dependent substrates, whereas midostaurin could increase the plasma exposure to such substrates several-fold. Furthermore, based on reversible inhibition, masitinib and vatalanib were predicted to increase the plasma exposure to sensitive CYP2C8 and CYP3A4 substrates by ≥2-fold.
Conclusion: Our data identifies two additional kinase inhibitors as time-dependent inhibitors of CYP3A4, and detects a risk for drug interactions between several of the tested inhibitors and CYP2C8 and CYP3A4 substrates.