PREDICTION OF DRUG-DRUG INTERACTIONS BASED ON TIME-DEPENDENT INHIBITION FROM HTS OF CYP INHIBITION.

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We are performing an evaluation of CYP inhibition potentials in the discovery stage to screen candidates using fluorometric substrates. This method is applied also to evaluate time-dependent inhibition (TDI) that contains mechanism-based inhibition (MBI). We established the method for predicting a interaction caused by CYP3A4 inhibition using IC₅₀ values obtained from +/- preincubation (IC₅₀(+) and IC₅₀(-), respectively). The predicted increases of AUC of co-administrated drugs were calculated from the ratios of IC₅₀(-)/IC₅₀(+)(+) and IC₅₀(-)/plasma concentration of inhibitor at steady states. The values of the predicted increase of AUC had well correlated with reported drug interaction of MBI compounds. Furthermore, a false negative result was not obtained in our prediction. It was possible to predict risk of the drug interaction caused by TDI compounds using this method. In conclusion, it was possible to perform quantitative drug interaction prediction by the results of CYP inhibition screening data in the discovery stage of drug candidates. This method can predict and reduce risk of a drug interaction easily and efficiently in early stages of drug discovery where speedy and suitable decisions are required.