In silico predictions of drug-drug interactions caused by CYP1A2, 2C9 and 3A4 inhibition – a comparative study of virtual screening performance

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Investigation of the clearance pathway is nowadays an integral part in early drug development, since alteration of metabolic enzymes can markedly influence the toxicological profile and efficacy of novel compounds. The cytochrome P450 (CYP) superfamily represents the major enzyme class responsible for the metabolism of exogenous compounds. Within this study, the three isoforms CYP1A2, 2C9 and 3A4, which account for approx. 70% of oxidative drug modifications [1,2], were investigated with several *in silico* methods including pharmacophore modeling [3,4], shape-based screening [5,6], docking [7], and 2D-similarity based comparison. [8,9] We generated multiple *in silico* models for the three isoforms using every method and investigated their ability to predict the inhibitory potential of compounds from our inhouse-database. After subsequent biological confirmation of the *in silico* predictions, we could analyze and compare the prospective performance of all methods, thereby defining the suitability of the applied techniques for CYP enzymes. While some software tools failed, others appeared to be of high relevance for the prediction of drug-drug interactions and may therefore be a valuable prioritization tool for planning experimental testing in drug development.

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