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Abstract

Cytochrome P450 (P450) enzymes are responsible for almost 80% of drug metabolism in humans, and metabolism by P450s may lead to several issues for potential new drugs including: low bioavailability, rapid clearance, drug-drug interactions leading to toxicity or lack of efficacy, bioactivation to form reactive or toxic metabolites and variable metabolism in the patient population due to genetic polymorphisms.

In this article, we will discuss some of the questions that a drug discovery team may wish to ask in order to address or, ideally, avoid these issues. For example: Is a compound a substrate for a P450 enzyme and, if so, which isoform? For a compound that is metabolized by a P450, what sites are vulnerable to metabolism, what metabolites will be formed and what strategies could be explored to reduce the rate of metabolism?

In vitro experiments using liver microsomes or hepatocytes can be used address these questions, although more detailed studies are time consuming and expensive. Therefore, computational, or *in silico*, predictions can be used to supplement experimental data or prioritise compounds for more detailed studies. Furthermore, *in silico* methods can help to guide the design of new compounds to overcome issues, exploring many optimisation strategies before the medicinal chemist chooses which compounds to synthesise and test. We will describe the state of the art of computational approaches for predicting P450 metabolism and identify areas for future development.

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