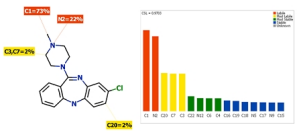
Matt gave this presentation at "Drug Discovery USA 2015 - Advances in Drug Discovery and Design"

Abstract

In this presentation we will describe recent developments to a method for predicting Cytochrome P450 metabolism that combines quantum mechanical (QM) simulations to estimate the reactivity of potential sites of metabolism on a compound with a ligand-based approach to account for the effects of orientation and steric constraints due to the binding pockets of different P450 isoforms. The resulting models achieve accuracies of 85-90% on independent test sets across multiple P450 isoforms. While valuable, predicting the relative proportion of metabolite formation at different sites on a compound is only a partial solution to designing more stable compounds. The advantage of a QM approach is that it provides a quantitative estimate of the reactivity of each site, from which additional information can be derived regarding the vulnerability of each site to metabolism in absolute terms. One such measurement is the site lability, which is a measure of the efficiency of the product formation step and an important factor influencing the rate of metabolism. We will illustrate how this provides valuable guidance to redesign compounds and overcome issues due to rapid P450 metabolism, using practical examples from lead optimisation projects.



A copy of Matt's slides is available as a PDF file.

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