Abstract:

Many computational methods have been developed that predict the regioselectivity of metabolism by drug metabolising isoforms of the Cytochrome P450 class of enzymes (P450) [1-5]. Here we describe recent developments to a method for predicting 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.

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 quantum mechanical 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, as calculated by StarDrop™ [6], which is a measure of the efficiency of the product formation step. This is an important factor influencing the rate of metabolism and we will illustrate how this provides valuable guidance regarding the potential to redesign compounds to overcome issues due to rapid P450 metabolism.

[6] StarDrop

A copy of this poster as available as a PDF.
Psychological research has demonstrated that reproducible biases affecting human 
decision-making, known as cognitive biases, threaten objectivity and balance in individual and 
team decision-making. Drug discovery leaders receive much conflicting advice on possible 
ways to improve productivity and restore the rate of successful drug launches; however with 
help to overcome these psychological barriers, better decision-making can enhance R&D 
performance [1].

We will discuss four of the common biases that have serious implications for decision-making in 
drug discovery (summarised below). We will suggest approaches for overcoming these, such as 
strategies adapted from evidence-based medicine and computational tools that seek to guide 
the decision-making process, encouraging objective consideration of all of the available 
information and explicit consideration of the impact of uncertainty in drug discovery.