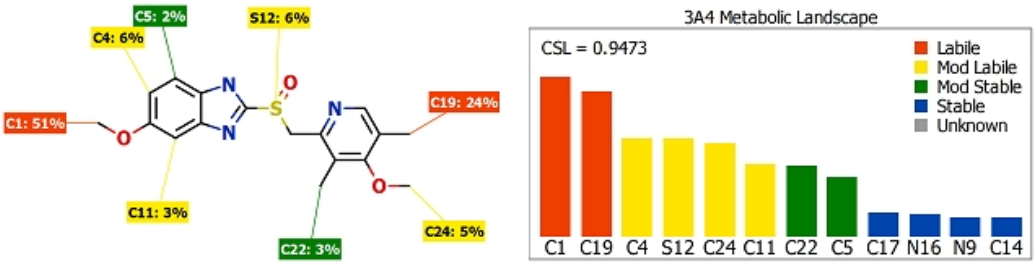
This recently submitted preprint describes the underlying methods, validation and example applications of the most recent models of Cytochrome P450 metabolism in StarDrop's P450 module .



Abstract

We describe methods for predicting Cytochrome P450 (CYP) metabolism incorporating both pathway-specific reactivity and isoform-specific accessibility considerations. Semi-empirical quantum mechanical (QM) simulations, parameterized using experimental data and ab initio calculations, estimate the reactivity of each potential site of metabolism in the context of the whole molecule. Ligand-based models, trained using high quality regioselectivity data, correct for orientation and steric effects of the different CYP isoform binding pockets. The resulting models identify a site of metabolism in the top 2 predictions for between 82% and 91% of compounds in independent test sets across seven CYP isoforms. In addition to predicting the relative proportion of metabolite formation at each site, these methods estimate the activation energy at each site, from which additional information can be derived regarding their lability in absolute terms. We illustrate how this can guide the design of compounds to overcome issues with rapid CYP metabolism.

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