Alignment-Based Method for the Prediction of Sites of Metabolism of Xenobiotics

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Biotransformation of small organic molecules can produce metabolites with biological and physicochemical properties that differ substantially from those of the parent compound [1]. For example, an estimated 7% of all metabolites of drugs and drug-like molecules are toxic, while only about 3% of all metabolites maintain the desired target activity [2]. The ability to predict the atom positions in a molecule at which metabolic reactions are initiated (i.e. sites of metabolism) is of utmost importance to drug discovery, as the predictions can be used to guide lead optimization and avoid the formation of reactive products.

In 2008, Sykes et al. [3] published a pilot study in which they derived sites of metabolism (SoMs) based on molecular shape- and chemical feature-based alignment to molecules whose SoMs had been determined by experiment. This study suggested that alignment-based methods could have great potential for SoM prediction. We have therefore analyzed the breadth of applicability of alignment-based SoM prediction in detail. We transferred this approach from a structure-based to a ligand-based method and extended the applicability of the models from cytochrome P450 2C9 to all cytochrome P450 isozymes involved in drug metabolism. This approach results in good early enrichment comparable to that of reactivity models, which are generally considered to be the most accurate models for SoM prediction. However, the predictive capability of the alignment-based approach depends on the degree of molecular similarity to known ligands, yielding better predictions for more structurally similar molecules. As chemical reactivity is an important aspect of SoM determination that is not considered by the alignment-based approach, we additionally combined the alignment-focused method with a chemical reactivity model, leading to a further boost in accuracy.

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[3] M.J. Sykes, R.A. McKinnon, J.O. Miners, *J Med Chem,* **2008**, *51*, 780-791.