Preprint Paper.

Abstract

We present a study based on density functional theory calculations to explore the rate limiting steps of product formation for oxidation by Flavin-containing Monooxygenase (FMO) and glucuronidation by the UDP-glucuronosyltransferase (UGT) family of enzymes. FMOs are responsible for the modification phase of metabolism of a wide diversity of drugs, working in conjunction with Cytochrome P450 (CYP) family of enzymes, and UGTs are the most important class of drug conjugation enzymes. Reactivity calculations are important for prediction of metabolism by CYPs and reactivity alone explains around 70 – 85 per cent of the experimentally observed sites of metabolism within CYP substrates. In the current work we extend this approach to propose model systems which can be used to calculate the activation energies, i.e. reactivity, for the rate-limiting steps for both FMO oxidation and glucuronidation of potential sites of metabolism. These results are validated by comparison with the experimentally observed reaction rates and sites of metabolism, indicating that the presented models are suitable to provide the basis of a reactivity component within generalizable models to predict either FMO or UGT metabolism.

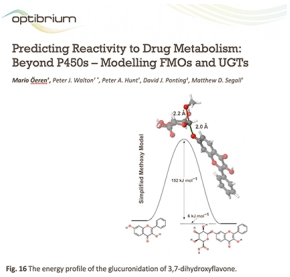

Fig. 16 The energy profile of the glucuronidation of 3,7-dihydroxyflavone.

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