Molecular modelling of human CYP1B1 substrate interactions and investigation of allelic variant effects on metabolism

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„...investigation of allelic variant effects on **metabolism** David F.V. Lewis a * * Corresponding...effects of allelic variants of CYP1B1 on **metabolism**. In general, it appears that the CYP1B1...selectivity for the enzyme, and the sites of **metabolism** can be rationalized in terms of specific..."

Abstract

Molecular modelling of human CYP1B1 based on homology with the mammalian P450, CYP2C5, of known three-dimensional structure is reported. The enzyme model has been used to investigate the likely mode of binding for selected CYP1B1 substrates, particularly with regard to the possible effects of allelic variants of CYP1B1 on metabolism. In general, it appears that the CYP1B1 model is consistent with known substrate selectivity for the enzyme, and the sites of metabolism can be rationalized in terms of specific contacts with key amino acid residues within the CYP1B1 heme locus. Furthermore, a mode of binding interaction for the inhibitor, -naphthoflavone, is presented which accords with currently available information. The current paper shows that a combination of molecular modelling and experimental determinations on the substrate metabolism for CYP1B1 allelic variants can aid in the understanding of structure–function relationships within P450 enzymes.
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