On the recognition of mammalian microsomal cytochrome P450 substrates and their characteristics

Towards the prediction of human p450 substrate specificity and metabolism

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„...substrate specificity and **metabolism** David F.V. Lewis a Correspondence...isoforms associated with drug **metabolism** in humans. It is further reported...calculated via the Pallas system (**CompuDrug** Limited). Molecular and electronic...closely associated with its **metabolism**, using molecular models of..."

Abstract

The characteristics of mammalian microsomal P450 xenobiotic substrates are described, particularly with reference to the major P450 isoforms associated with drug metabolism in humans. It is further reported that a relatively small number of molecular, electronic, and physico-chemical properties are required to discriminate between chemicals that exhibit specificity for human P450 isoforms: CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Molecular templates of superimposed substrates are shown to be complementary with the putative active sites of the relevant enzymes, thus enabling a possible prediction of P450 specificity from structure. Factors contributing to metabolic clearance and binding affinity are also discussed, and methods for their calculation are described.

Author Keywords: cytochrome P450; substrate selectivity; human P450 isoforms; metabolic clearance; binding affinity

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