Homology modelling of CYP2A6 based on the CYP2C5 crystallographic template: enzyme–substrate interactions and QSARs for binding affinity and inhibition

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„...CYP2A6-mediated **metabolism** (see Table 1 for...Pallas System, **CompuDrug**, Budapest...for substrate **metabolism**. n =number of observations...Pallas Software, **CompuDrug** Limited, Budapest...inhibit CYP2A6 **metabolism** competitively...Pallas Software, **CompuDrug** Ltd., Budapest..."

Abstract

The results of homology modelling of the human P450 enzyme CYP2A6, based on the CYP2C5 crystallographic template structure are reported. A substantial number of selective substrates of the CYP2A6 enzyme fit the putative active site in a manner that is consistent with their known metabolites. Moreover, the evidence from site-directed mutagenesis experiments is in accordance with the current model, particularly in relation to complementary amino acid contacts within the haem environment. The binding of substrates is rationalized in terms of QSAR analyses and from a consideration of the contributory factors affecting the binding affinity. The latter approach appears to represent a highly correlated (R=0.99) method for estimating the relative strength of enzyme–substrate binding within CYP2A6-selective compounds, albeit within a fairly limited dataset of substrates.

Author Keywords: Cytochromes P450; CYP2A6; Homology modelling; QSARs
Abbreviations: QSARs, quantitative structure–activity relationships

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