Quantitative structure–activity relationships (QSARs) for substrates of human cytochromes P450 CYP2 family enzymes

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"...52. a Calculated value (Pallas System, CompuDrug). b SM-12502=(+)- cis...12. a Calculated value (Pallas). Table 2B Baseline...a Calculated value (Pallas System, CompuDrug Limited). , where it can be..."

Abstract

The results of quantitative structure–activity relationship (QSAR) studies on substrates of human CYP2 family enzymes are reported, together with those of a small number of CYP2A6, CYP2C19 and CYP2D6 inhibitors. In general, there are good correlations (R=0.90–0.99) between binding affinity (based on K_m or K_D values) and various parameters relating to active site interactions such as hydrogen bonding and – stacking. There is also evidence for the role of compound lipophilicity (as determined by either log P or log $D_{7.4}$ values) in overall substrate binding affinity, and this could reflect the desolvation energy involved in substrate interaction within the enzyme active site. It is possible to estimate the substrate binding energy for a given P450 from a combination of energy terms relating to hydrogen bonding, – stacking, desolvation and loss in rotatable bond energy, which agree closely (R=0.98) with experimental data based on either K_m or K_D values. Consequently, it is likely that active site interactions represent the major contributory factors to the overall binding affinities for human CYP2 family substrates and, therefore, their estimation is of potential importance for the development of new chemical entities (NCEs) as this can facilitate an assessment of likely metabolic clearance.

Author Keywords: Human cytochromes P450 (CYP2); Substrates; Quantitive structure–activity relationships

Abbreviations: log P, logarithm of the octanol–water partition coefficient; M_r, relative molecular mass; N_{HB}, number of active site hydrogen bonds with substrate; N_{-}, number of active site -; stacking interactions with substrate; ΔG_{bind}, substrate binding affinity calculated using $RT\ln K_m$ where R is the gas constant T is the absolute temperature and K_m is the Michaelis Constant (M); ΔG_{part}, free energy of partitioning between octanol and water based on the expression; ΔG_{part}, -RTlnP where P is the partition coefficient; log $D_{7.4}$, ionization-corrected log P value, also termed the distribution coefficient; $N_{HB}^{A/D}$, number of hydrogen bond donors and acceptors in the molecule; pK_i, negative logarithm of K_i; the inhibition constant for P450-mediated metabolism; N_{HB}^{A}, number of hydrogen bond acceptors in the molecule; N_{HB}^{D}, number of hydrogen bond donors in the molecule; K_m, Michaelis constant for P450-mediated metabolism; pK_a, negative logarithm of the acid/base dissociation constant;

N_B, number of basic nitrogen atoms in the molecule; n, number of observations (i.e. compounds in the dataset); s, standard error; R, correlation coefficient; F, variance ratio (F-test)

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