Compound lipophilicity for substrate binding to human P450s in drug metabolism

David F. V. Lewis[a], Miriam N. Jacobs[a] and Maurice Dickins[b]

[a] School of Biomedical and Molecular Sciences, University of Surrey, Guildford, Surrey, UK GU2 7XH
[b] Pfizer Central Research, Ramsgate Road, Sandwich, Kent, UK CT13 9NJ

"..lipophilicity calculated using the Pallas software (Compudrug)..."

Abstract

Compound lipophilicity is of key importance to P450 binding affinity and enzyme selectivity. Here, lipophilicity is discussed with reference to the human drug-metabolizing P450 enzymes of families CYP1, CYP2 and CYP3. From an extensive compilation of log P values for P450 substrates, and by analysis of relationships between partitioning energy and substrate-binding free energy, the relevance of lipophilicity and other factors pertaining to P450 binding affinity is explained, leading to the formulation of lipophilicity relationships within substrates of each human P450 enzyme involved in drug metabolism. Furthermore, log P values for P450 substrates appear to represent markers for enzyme selectivity. Together with the important roles of hydrogen bonding and – stacking interaction energies, the desolvation of the P450 active site makes a major contribution to the overall substrate-binding energy and, consequently, a good agreement with experimental information is reported based on this analysis.

Abstract

Lipophilicity appears to have a marked bearing on P450 substrate selectivity and metabolism. Substrate binding affinity is well correlated with log P data, and substrates of a given P450 exhibit well-defined ranges of log P values.

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