Factors influencing rates and clearance in P450-mediated reactions: QSARs for substrates of the xenobiotic-metabolizing hepatic microsomal P450s

D. F. V. Lewis[a] **and M. Dickins**[b]

[a] School of Biomedical and Life Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK
[b] GlaxoWellcome Research and Development Limited, Park Road, Ware, Hertfordshire SG12 0DP, UK

„...5000 min -1 (or more) for arachidonate **metabolism** (omega -2 hydroxylation) by CYP102...maximum velocity of the reaction involving **metabolism** of the substrate. The intrinsic clearance...calculated using the Pallas system (**CompuDrug** Limited, Budapest). Electronic structural..."

Abstract

Various contributory factors associated with the kinetics of cytochrome P450-mediated catalytic activity and the metabolic clearance of drug substrates are discussed and evaluated, based on literature data and physicochemical parameters. Quantitative relationships between molecular structure and biological activity for several series of P450 substrates are presented which point to certain commonalities in P450-catalyzed reactions. In particular, it appears that frontier orbital energies are especially important for the estimation of reaction rates and clearance for many P450 substrates, although occasionally these have to be combined with other descriptors, such as compound lipophilicity (in the form of log *P* or log D_{74}).
Author Keywords: Cytochromes; P450; Metabolic rates
Abbreviations: CYP, cytochromes P450; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; QSAR, quantitative structure–activity relationship

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