MODELLING HUMAN CYTOCHROMES P450 FOR EVALUATING DRUG METABOLISM: AN UPDATE

David F.V. Lewis*

School of Biomedical and Life Sciences, University of Surrey, Guildford, Surrey, GU2 7XH, UK

SUMMARY

Cytochrome P450 (CYP) enzymes represent the major catalysts for the Phase 1 metabolism of drugs and other xenobiotics in Mammalia, including *Homo sapiens*. There is considerable current interest in evaluating and, consequently, predicting the metabolic fate of new chemical entities (NCEs) via modelling molecular interactions with P450 constructs, such that sites of metabolism, particular CYP involvement and binding affinities, can be estimated. This paper focuses on the principles for homology modelling of typical enzyme-substrate interactions within the putative active sites of major P450s associated with drug metabolism in man. It also represents an update on previously published work in this journal /1/.

KEY WORDS

cytochromes P450, homology modelling, drug metabolism, substrate selectivity

INTRODUCTION

Enzymes of the cytochrome P450 (CYP) superfamily are responsible for catalyzing over 90% of drug oxidations in man and other animal species /2/. These haem-thiolate enzymes, of which over 750 distinct members are currently known /3/, utilise molecular oxygen and a reductant (NADPH or NADH) to mediate in mixed function oxidase activity for a large number of substrates (>1000) with a single oxygen insertion being a common feature of the Phase 1 metabolic

*e-mail: d.lewis@surrey.ac.uk

conversion /4/. The monooxygenase reaction can be summarised as follows:

$$RH + O_2 \xrightarrow[2e^-]{2H^+} ROH + H_2O$$

for a hydrocarbon substrate (RH) undergoing hydroxylation to form a metabolite (ROH) via a two-stage reduction process carried out by the P450 enzyme, with electron transfer being mediated by a flavoprotein reductase in the microsomal system /5/.

Due to the importance of these drug metabolising enzymes (DMEs) for the pharmaceutical industry in the development of new chemical entities (NCEs), there is current interest in modelling their substrate interactions leading to the possibility of making predictions about the likely metabolic fate in human subjects /6/. Fortunately, much is known about the P450 system, as it has been extensively studied over the past 40 years since its discovery in the late 1950s (reviewed in /7/). In particular, the crystal structures of four bacterial forms of the enzymes are currently available for investigation, and these represent potential templates for molecular modelling of the relevant mammalian forms via amino acid sequence homology /8,9/. Furthermore, the first X-ray crystal structure of a mammalian P450 was reported recently /10/ although the coordinates are not available until April 2001.

However, there are essentially two classes of P450 which have been delineated from protein sequence comparisons /11/ and it appears that most bacterial forms belong to Class I, whereas the mammalian microsomal enzymes are in the Class II category. It is fortunate though to have one paradigm for the second type of P450 in a bacterial form of known structure: this is known as CYP102 which is from *Bacillus megaterium* and catalyzes ω-2 oxidation of long chain fatty acids, such as palmitoleic and pentadecanoic acids /12/. The CYP102 haemoprotein domain, which has recently been resolved crystallographically /13/ with a bound substrate, exhibits a satisfactory sequence homology (~20% or more) with many Class II mammalian P450s, including those associated with drug metabolism in man /9/. To assist in

Abbreviations: CYP - cytochromes P450; NCEs - new chemical entities; QSAR - Quantitative Structure-Activity Relationship; AhR - aryl hydrocarbon receptor; ER - oestrogen receptor; GR - glucocorticoid receptor; PPAR - peroxisome proliferator-activated receptor.

sequence alignment, one can make use of an ever-increasing body of information from site-directed mutagenesis and residue modification (reviewed in /8/), whereas experimental evidence from the known metabolism of selective P450 substrates and inhibitors helps to define the docking orientation of these molecules within the putative active sites of the relevant P450 isoforms /1/.

Most drugs are oxidised via one or more of a relatively small number of human liver P450s and, therefore, modelling these enzymes (DMEs) with selective substrates constitutes the priority for further employment of the models in the prediction of NCE metabolism. In particular, CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2, CYP2A6 and CYP2B6 are the main catalysts for the Phase 1 oxidations of xenobiotics in human liver /2/. In addition, it is important to recognise that CYP2D6 and CYP2C19 are associated with genetic polymorphism in human ethnogeographical populations such that individuals possessing allelic variants of these genes will experience impaired metabolic function towards certain drug substrates /14/. Consequently, an evaluation of likely P450 enzyme selectivity at an early stage in the development of an NCE may be essential to the future use of the candidate drug to industry /15/. This paper explores a number of these aspects in relation to the rationalisation of P450 substrate selectivity via molecular structural techniques including protein homology modelling.

METHODS

The protein sequences of the human P450s were aligned with that of the CYP102 haemoprotein domain using the GCG package (Genetics Computer Group, Madison, Wisconsin) and then manually edited somewhat to conform with site-directed mutagenesis information. A typical alignment is shown in Lewis /8/ which provides an example for several CYP2 family proteins, whereas others have been reported previously /16/. Following the generation of a satisfactory alignment, the relevant P450 enzyme in each case was constructed from the palmitoleate-bound CYP102 crystal structure template using direct amino acid replacement, followed by loop-searching of the Protein Databank for the insertion of short stretches of peptide as required by the target sequence /16/. The Sybyl molecular modelling package (Tripos Associates, St. Louis, Missouri) was employed for all

of the enzyme building and subsequent refinement The raw structure was then energy minimised using the Tripos force field, including consideration of the haem iron atom, to achieve a satisfactory minimum energy geometry following several hundred interactive cycles of optimisation. Substrate or inhibitor molecules were then docked interactively using the location of the original bound substrate (palmitoleic acid) as a guide, although it is known that reduction of the enzyme brings about a significant movement of the substrate molecule towards the haem iron, with 3-4Å representing a typical distance between the iron and oxygenation position on the substrate /17/. Consequently, the majority of substrates and inhibitors were fitted relatively close to the haem, within the above distance range, such that particularly favourable interactions with active site residues could take place. The enzyme-substrate complexes were then energy minimised using molecular mechanics via the same procedure as that of the enzymes themselves. Molecular templates of individual human P450 substrates were also constructed by superimposing several docked substrates in the different P450 models /18/. The basis for this procedure was structural commonality and reinforcement of binding interactions with key amino acid residues, although it was found that the positions of metabolism in each case were found to lie relatively close to the haem iron, i.e. around 3-4Å distance. All molecular modelling studies were carried out on a Silicon Graphics Indigo^2 IMPACT 10000 graphics workstation operating under UNIX.

RESULTS AND DISCUSSION

The specific binding interactions between selected substrates of the human P450 enzymes, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, are shown in Figures 1-6, respectively. These indicate that there is a different pattern of hydrogen-bonding and π-π stacking residues depending on the P450 active site, and this reflects the particular substrate selectivity of the individual enzymes concerned. These are now be discussed for each human P450 isoform listed above, as follows:-

1. The CYP1A2 active site

From a consideration of Figure 1, it can be appreciated that the relatively planar heterocyclic substrate, caffeine, is 'sandwiched' between two complementary aromatic amino acid residues, namely, phenylalanine and tyrosine. Of these, the former has been probed using site-directed mutagenesis and is known to affect the metabolism of typical human CYP1A2 substrates (reviewed in /19/). In addition, the substrate is held in a specific orientation by three threonine residues, one of which has been shown to lie in the enzyme's catalytic centre from protein-adduct formation studies. The threonines form hydrogen bonds with two carbonyl oxygens, and a ring nitrogen atom, such that the substrate's N_3-methyl group is positioned directly above the haem iron. Consequently, this orientation is entirely consistent with the experimentally observed metabolism specifically catalyzed by CYP1A2 /19/.

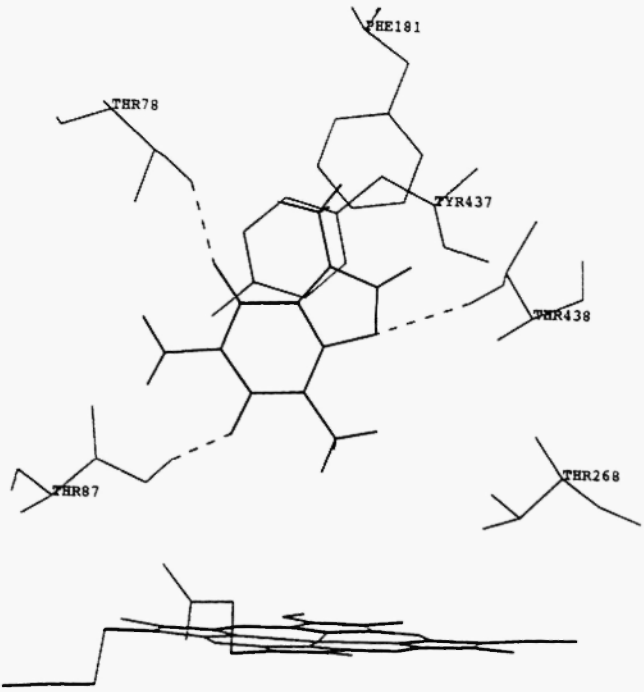

Fig. 1: Putative active site of human CYP1A2 showing the substrate caffeine and important amino acid residues.

2. The CYP2A6 active site

A view of the CYP2A6 active site is shown in Figure 2, from which it can be seen that the marker substrate coumarin becomes orientated with respect to the haem iron for oxygenation at the 7-position due to π-π stacking interactions and hydrogen bond contacts with nearby amino acid residues. These include a phenylalanine similar to that encountered in the CYP1A2 model, together with two hydrogen-bonded interactions from a histidine and a glutamine residue, which 'anchor' the substrate via its two oxygen atoms. The phenylalanine has been shown via site-directed mutagenesis of the mouse orthologues to be associated with substrate selectivity (reviewed in /8/) and this is also the case for the active site glutamine residue. Therefore, the putative reactive centre of CYP2A6 is consistent with experimental observations for coumarin 7-hydroxylase activity /20/.

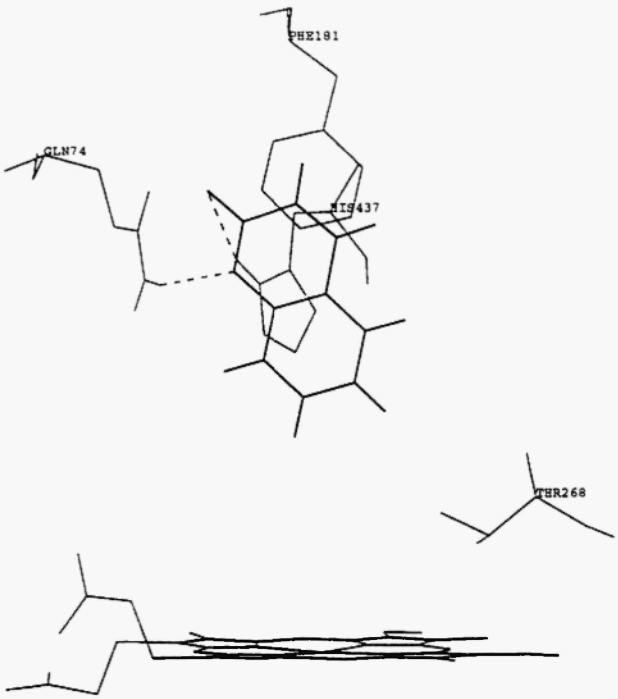

Fig. 2: Putative active site of CYP2A6 showing the selective substrate coumarin together with important amino acid residues.

3. The CYP2C9 active site

Figure 3 shows the putative active site for CYP2C9 in which the specific marker substrate, tolbutamide, is orientated for p-methyl hydroxylation via a number of reinforcing contacts with complementary amino acid residues, including a phenylalanine residue, an asparagine side-chain and a serine. These latter two amino acids participate in hydrogen-bonded interactions with the substrate and have also been the subject of site-specific mutagenesis experiments (reviewed in /8/). Together with a number of favourable hydrophobic contacts, these residues position tolbutamide such that its p-methyl group will lie directly above the haem iron for hydroxylation to occur, which is consistent with known findings /21/.

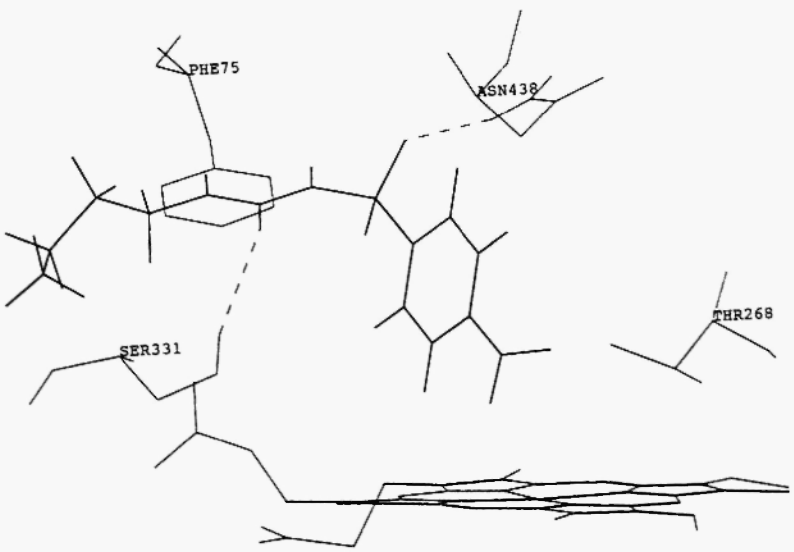

Fig. 3: Putative active site of CYP2C9 showing the marker substrate tolbutamide which contacts a number of important amino acid side-chains.

4. The CYP2C19 active site

Figure 4 shows the reactive centre of CYP2C19 in which the selective substrate omeprazole is orientated for 5′-methyl hydroxylation via a number of contacts with complementary amino acid residues /21/. In particular, hydrogen bonds from a histidine and an asparagine serve to position the omeprazole molecule relative to the haem such that the 5-methyl group is directly above the central iron atom. Additional contacts include a phenylalanine adjacent to the aforementioned histidine and an isoleucine residue which forms a hydrophobic interaction with one of the substrate's methyl groups. The histidine residue in CYP2C19 has been changed to isoleucine in mutagenesis studies (reviewed in /8/) and this appears to have a marked effect on omeprazole hydroxylase activity, thus indicating that this histidine side-chain could be involved in substrate binding.

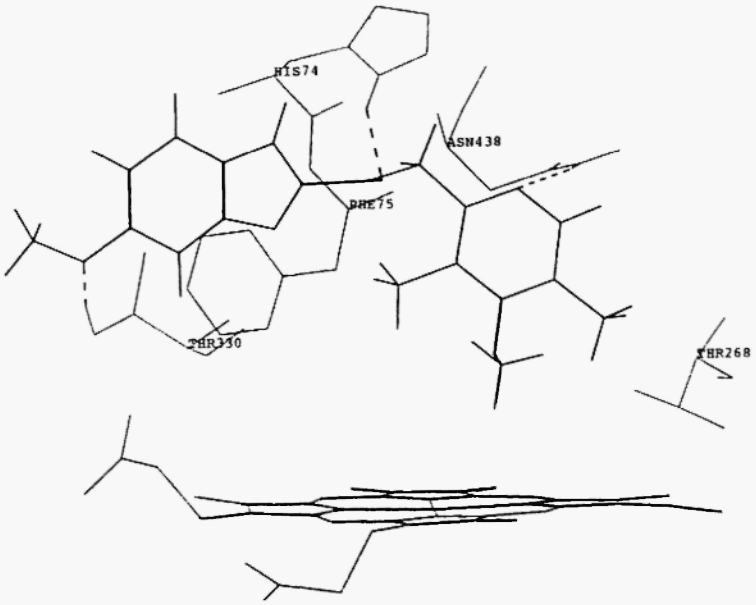

Fig. 4: Putative active site of CYP2C19 showing the substrate omeprazole interacting with a number of complementary amino acids.

5. The CYP2D6 active site

The selective substrate metoprolol is shown docked within the active site of CYP2D6 in Figure 5, in which orientation for metabolism (O-demethylation) is achieved by a combination of ion-pairing between an aspartate residue and the protonated basic nitrogen of metoprolol, together with π-π stacking with a nearby phenylalanine, and hydrogen bonding from threonine and glutamate residues to the phenoxypropanol grouping on the substrate. There are also hydrophobic interactions between two valine side-chains and complementary groups on metoprolol, with the majority of the aforementioned amino acids being the subject of site-directed mutagenesis experiments on CYP2D6, some involving either metoprolol itself or other selective substrates of the enzyme (reviewed in /8/). The model proposed appears to be in good agreement, therefore, with known observations regarding CYP2D6 activity /22/.

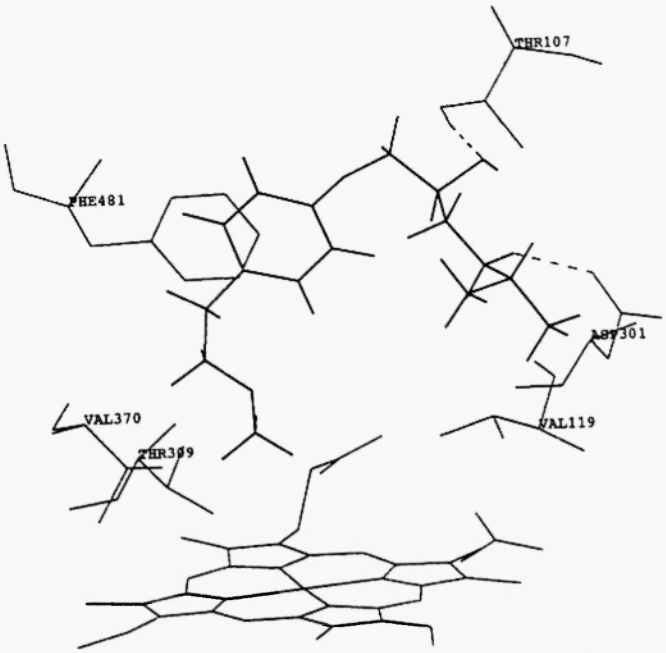

Fig. 5: Putative active site of CYP2D6 showing the selective substrate metoprolol which is in contact with several amino acid positions that have been probed using site-directed mutagenesis.

6. The CYP3A4 active site

Figure 6 displays the putative active site of CYP3A4 from which it can be appreciated that the selective substrate, nifedipine, is positioned for N-oxidation relative to the haem by a small number of favourable interactions with the enzyme. In particular, there is a π-π stacking contact with a phenylalanine close to the haem, together with a hydrogen bond from a nearby asparagine residue, which interacts with the substrate's nitro group. Although there are additional hydrophobic contacts between the CYP3A4 site and nifedipine, the two residues mentioned previously are sufficient to orientate the substrate for metabolism by bringing the N-H group close to the haem iron. Similar contacts are found in many other CYP3A4 substrates despite their considerable structural diversity and, consequently, one can rationalise metabolism mediated by this enzyme /23/ on the structural grounds outlined above. In fact, all of the drug oxidations shown by selective substrates of human hepatic P450s are consistent with the models described herein /1/.

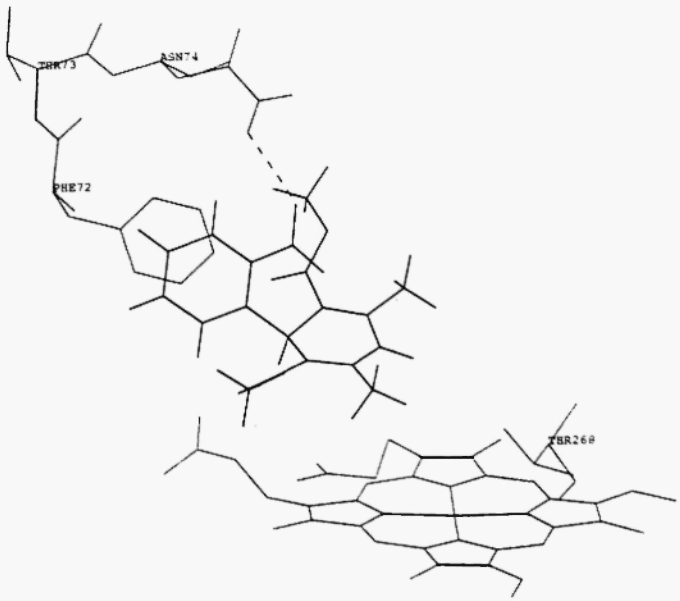

Fig. 6: Putative active site of CYP3A4 showing the marker substrate nifedipine in contact with amino acid side-chains.

7. Quantitative Structure-Activity Relationships (QSARs)

Tables 1 and 2 summarise the results of several QSAR studies on selective substrates and inhibitors of human P450s /24/, together with those carried out on inducers of various P450s (Table 2) which act as ligands to the nuclear receptors, AhR, hER, hGR and PPAR. The structural descriptors presented in Table 1 which correlate with activity tend to be largely consistent with the models of individual human P450s in terms of the particular contributions to binding affinities /29/. Consequently, these complementary findings support the proposed enzyme models, particularly with respect to active-site interactions.

CONCLUSIONS

The specific interactions between selective P450 substrates and the relevant enzymes which catalyze their metabolism both rationalise the experimental findings and are consistent with available evidence from site-specific mutagenesis data. Not only do these enzyme models agree closely with the results of site-directed mutagenesis, but there is also supporting evidence from structure-activity relationship studies using specific P450 substrates and inhibitors /24,25/. Table 3 provides details of the energetics of binding, together with haem-substrate distances in some cases. Furthermore, superimposed substrate templates are found to occupy the putative active sites of individual human P450s /18/ in which the spatial arrangement of reinforced hydrogen bonded contacts assists in defining enzyme selectivity. It is thus possible to explain the structural aspects of P450 substrate selectivity in terms of particular active site contacts, especially hydrogen-bonded and π-π stacking interactions; these provide a means for calculating binding affinity, and the results presented in Table 4 indicate a close fit with experimental data. In addition, it is possible to rationalise the kinetics of P450-mediated metabolism and the binding affinities of substrates in terms of electronic structural factors /29/. Consequently, one can now have a reasonable degree of confidence in using such models of human P450 enzymes to predict the likely metabolic fate of novel development compounds in a relatively short time-frame.

TABLE 1

QSARs for substrates of human P450s

	n	s	R	F	Ref.
1. CYP1A2 (substrates)					
a) ΔG_{bind} = 0.63μ - 1.55 I/w + 2.32 E_{LUMO} - 5.50 (±0.16) (±0.41) (±0.31)	11	0.47	0.95	22.5	/24/
b) ΔG_{bind} = 0.30μ - 0.90 I/w + 2.11 ΔE - 0.50 N_{HB}^{Site} - 22.41 (±0.12) (±0.36) (±0.25) (±0.17)	11	0.42	0.97	22.3	/24/
2. CYP2B6 (substrates)					
a) ΔG_{bind} = 3.99 N_{HB}^{Site} - 5.41 HB_{donors} - 1.92 $HB_{acceptors}$ - 4.19 (±0.76) (±0.86) (±0.23)	10	0.55	0.97	27.0	/24/
3. CYP2C9 (substrates)					
a) ΔG_{bind} = 9.59 log $D_{7.4}$ - 9.00 log P - 7.05 pK_a + 0.58 HB_{donors} + 49.08 (±0.83) (±0.82) (±0.65) (±0.15)	7	0.17	0.99	44.0	/9/
4. CYP2D6 (inhibitors)					
a) pK_i = 0.01 M_r - 0.48 log P - 0.57 $HB_{acceptors}$ + 1.79 $N_{basic}^{nitrogens}$ - 3.56 (±0.002) (±0.13) (±0.15) (±0.21)	11	0.19	0.98	35.2	/24/

5. CYP2E1 (inhibitors)							
a) pK_i = 0.98 log P - 0.20 log P^2 - 1.79 (±0.11) (±0.03)	[alcohols]	10	0.22	0.96	89.4		/25/
b) pK = 1.05 log $D_{7.4}$ - 0.24 log $D^2_{7.4}$ - 2.66 (±0.10) (±0.02)	[carboxylic acids]	11	0.17	0.97	119.0		/25/
6. CYP3A4 (substrates)							
a) ΔG_{ind} = 1.98 E_{LUMO} - 2.99 E_{HOMO} - 0.52 N^{Site}_{HB} + 3.55 $N^{site}_{\pi-\pi}$ - 35.10 (±0.45) (±0.61) (±0.14) (±0.71)		10	0.39	0.96	13.0		/21/

n = no. of compounds; s = standard error; R = correlation coefficient; F = variance ratio; log P = logarithm of the octanol/water partition coefficient; log $D_{7.4}$ = logarithm of the distribution coefficient at pH 7.4; ΔG_{ind} = free energy of binding, pK_i = negative logarithm of the inhibition constant, K_i; pEC_{50} = negative logarithm of the effective concentration required for 50% displacement of TCDD; $HB_{A,D}$ = no. of hydrogen bond acceptors, donors; N^{Site}_{HB} = no. of active site hydrogen bonds; μ = dipole moment; l/w = length to width ratio; $E_{LUMO, HOMO}$ = energy of the LUMO, HOMO frontier orbitals; $\Delta E = E_{LUMO} - E_{HOMO}$; M_r = relative molecular mass; IP = ionization potential; MFE = minimum free energy; Vol = volume of the Connolly solvent-accessible surface; $D^{O_1}_{Glu353}$ = distance between ligand hydroxyl group and key binding site residue Glu353; $D^{CO_2}_{A_r}$ = distance between carboxylate group and aromatic ring centre in ligand molecules.

TABLE 2

QSARs for nuclear hormone receptor binding

	n	s	R	F	Ref.
1. **AhR (CYP1 induction)**					
a) log Induction = log P - 0.40 l/w - 0.15 CR + 2.67	12	0.209	0.99	98.6	/26/
b) pEC_{50}^{PCBs} = 0.33 a/d² - 3.22 E_{HOMO} + 0.84 length - 36.44 (±0.04) (±0.50) (±0.26)	14	0.308	0.95	31.5	/26/
2. **hER (ligand binding affinity)**					
a) log Affinity = 0.765 E_{LUMO} + 0.066 MFE - 2.207 IP - 1.782 D_{Gu353}^{OH} 23.629 (±0.023) (±0.704) (±0.1842)	9	0.624	0.95	8.88	/27/
b) log Affinity = 0.064 MFE - 2.773 IP - 0.636 ΔE + 19.565 (±0.027) (±0.782) (±0.439)	9	0.620	0.94	11.67	/27/
3. **hGR (CYP3A4 induction)**					
a) Fold Induction = 10.61 l/w - 0.016 M.. - 0.88μ - 5.01 E_{LUMO} - 4.58 (±1.33) (±0.002) (±0.21) (±0.74)	8	0.47	0.98	17.5	*
4. **PPAR (peroxisome proliferation)**					
a) log Potency = 0.008 Vol - 0.22μ + 0.38 $D_{Ar}^{CO_2^-}$ - 2.95 (±0.002) (±0.06) (±0.19)	12	0.339	0.91	12.4	/28/

For legend, see Table 1.

* Lewis DFV and Ogg M, unpublished results, 2000.

TABLE 3

Energies and substrate-haem distances in P450 models

Enzyme - Substrate	Energy of Complex	Energy of Enzyme	PFE Term	Site of Metabolism - Iron (Å)
CYP2A6 - coumarin	-1670.104	-1647.540	-22.564	3.040 (7-hydrogen)
CYP2C9 - tolbutamide	-1614.591	-1586.116	-28.475	2.720 (4-methyl)
CYPC19 - omeprazole	-1723.886	-1712.300	-11.586	4.694 (5-methyl)
CYP2D6 - metoprolol	-1318.726	-1291.911	-26.815	3.350 (O-methyl)
CYP2E1 - nitrophenol	-1488.084	-1466.006	-22.078	4.591 (2-hydrogen)

PFE = perturbation free energy

where PFE = $E_{complex}$ - E_{enzyme}

All energies are in kcal.mole^{-1}.

TABLE 4

Comparison between calculated and experimental binding affinities for some P450 substrates and the enzymes concerned

No.	Substrate	CYP	$\Delta G_{Calc.}$	$\Delta G_{Expt.}$	Substrate Binding Affinity
1	Camphor	101	-7.687	-7.700	High
2	Lauric acid	102	-5.504	-5.394	Low
3	Caffeine	1A2	-5.384	-5.312	Low
4	Coumarin	2A6	-7.981	-8.054	High
5	Mephenytoin	2B6	-4.543	-4.608	Very Low
6	Tienilic acid	2C9	-8.167	-8.036	High
7	Metoprolol	2D6	-6.505	-6.451	Medium
8	Nitrophenol	2E1	-6.291	-6.378	Medium
9	Aflatoxin	3A4	-6.513	-6.208	Medium
10	Methoxyresorufin	1A2	-9.078	-9.458	Very High

Note: The agreement between calculated and experimental values is very good ($r^2 = 0.987$). References: Lewis *et al.* /1,29/.

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