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RESEARCH ARTICLE

Quantitative structure-activity relationships (QSARs) for inhibitors and substrates of CYP2B enzymes: importance of compound lipophilicity in explanation of potency differences

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Abstract

The results of quantitative structure-activity relationship (QSAR) studies on inhibitors and substrates of cytochrome P450 2B (CYP2B) subfamily enzymes are reported. It was found that lipophilicity (in the form of log P) is the most important property for explaining the variations in inhibitory activity, and there are similarities between QSARs for both substrates and inhibitors for CYP2B6 (human), and also between those of other CYP2B enzymes, such as CYP2B1 (rat) and CYP2B4 (rabbit). Both linear and quadratic lipophilicity relationships are evidenced in human and other mammalian species, and the particular type of expression found is probably due to the nature of the compounds under investigation, as it is usually the homologous series which tend to show quadratic relationships in log P. The findings from QSAR studies can be rationalized by molecular modelling of the active site interactions with both P450 crystal structures and homology models of CYP2B subfamily enzymes.

Keywords: *Cytochromes P450; QSARs; Lipophilicity; Enzyme Inhibition*

Abbreviations: CYP, cytochrome P450; QSAR, quantitative structure-activity relationship; log P, logarithm of the octanol/water partition coefficient; HOMO, highest occupied molecular orbital; AM1, Austin Model 1. For statistical results, n, number of observations; s, standard error; R, correlation coefficient; F, variance ratio.

Introduction

The cytochromes P450 (CYP) are a superfamily of haem-thiolate enzymes for which over 8500 individual members are currently known [1]. In mammalian species, P450s are generally associated with the Phase 1 oxidative metabolism of drugs and other xenobiotics, although various endogenous functionalities are known, including biosynthesis of the steroid hormones and long chain fatty acid metabolism [2]. Enzymes of the CYP2B subfamily, which are inducible by phenobarbital, catalyse the metabolism of many foreign compounds in mammals, including: 7-benzyloxyresorufin, 7-pentoxyresorufin, 7-ethoxycoumarin, benzphetamine, aminopyrine and testosterone [3,4] many of which have been employed as diagnostic probe substrates for CYP2B isoforms in mouse, rat, rabbit, hamster, monkey and man.

Substrates of CYP2B are characterised by generally non-planar molecules which usually possess the capability for hydrogen bond formation, and most inhibitors of these enzymes are substrate analogues such as: secobarbital, orphenadrine and proadifen (SKF-525A) although chloramphenicol probably inhibits CYP2B via covalent binding to an active site lysine [5]. CYP2B6, the human orthologue, accounts for some 4% involvement in the Phase 1 metabolism of drugs and other foreign compounds [6,7] although CYP2B isoforms play somewhat greater roles in exogenous

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metabolism for other mammalian species such as the rat and rabbit [3].

There have been several recent QSAR studies on inhibitors of CYP1 and CYP2 family P450s [8–10]. We have previously reported QSARs in selected substrates of CYP2B subfamily enzymes [11–13] and the current work presents the results of related investigations on CYP2B inhibitors and some additional substrates, including those of the human orthologue, CYP2B6. As with the previous studies, we have utilised compound lipophilicity in the form of log P values, where P is the octanol/water partition coefficient, to aid in an understanding of the likely structure-activity relationships for inhibition, which also includes molecular modelling with the enzymes themselves, where crystal structures of related forms such as CYP2B4 and CYP2C5 with and without bound substrates or inhibitors are now available. However, it is thought that the inhibitor-bound CYP2B4 crystal structure [14] represents the most satisfactory template for homology modelling of CYP2B6, and Figure 1 shows the active site of CYP2B6, modelled from CYP2B4, which contains a bound inhibitor. This inhibitor molecule (CBP) docked into the CYP2B6 haem pocket (Figure 1) displays the "butterfly wing" conformation which is common to many CYP2B substrates and inhibitors such as phenobarbital, proadifen (SKF525A) and DDT.

Methods

The inhibition data was collated from the literature for several series of structurally related compounds, including: primary aliphatic amines [15] and 2-alkyl-benzimidazoles [16], together with a range of diverse compounds [17]. In addition, CYP2B-related activities for a series of 7-alkoxycoumarins [18] and of barbiturates [19] were retrieved from previously reported studies. Compound lipophilicities in the form of log P values were obtained from tabulations of experimental data [20, 21] or calculated via the ClogP (BioByte, Pomona, CA) and Pallas (CompuDrug, Budapest, Hungary) software systems. These have both been shown to give good correlations with experimental values of the order of 0.95 for the correlation coefficients with significant dataset sizes [22]. However, for the homologous series of eight 7-alkoxycoumarins, it was necessary to employ calculated log P values for 50% of the compounds. Consequently, we have derived a calibration equation between the experimental log P values of 4 congeners and calculated log P produced by Clog P (BioByte). For these data, there is an excellent correlation between experimental log P and Clog P, according to Equation 1:

$$\log P_{expt} = 1.027\,\mathrm{ClogP} - 0.036 \quad (\pm 0.011) \qquad (1)$$
$$n = 4;\ s = 0.0175;\ R = 0.9999;\ F = 9998.5$$

Using this equation, the calculated log P values (based on Clog P) are very close to the experimentally determined log P data. Furthermore, one can also employ the above equation to extrapolate calculated log P values for the four congeners where experimental log P data are unavailable. These new calculated log P values (calibrated log P) are all slightly higher than those calculated directly from ClogP. The relevant data are shown below in Table 1.

Table 1. Data set of log P values for 7-alkoxycoumarins.

Congener	$\log P_{expt}$	Clog P	Calibrated log P
Methoxy	1.74	1.74	1.75
Ethoxy	2.3	2.27	2.3
Propoxy	2.86	2.8	2.84
Butoxy	N/A	3.33	3.38
Pentoxy	3.92	3.86	3.93
Hexoxy	N/A	4.38	4.46
Heptoxy	N/A	4.91	5.01
Octoxy	N/A	5.44	5.55

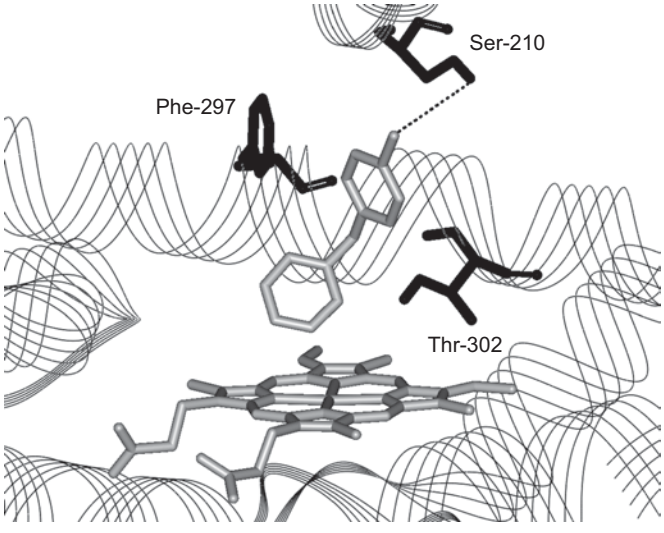

Figure 1. The selective CYP2B6 inhibitor, 4-(4-chlorobenzyl)pyridine (CBP), is shown docked into the active site of this enzyme. The mode of binding and its calculated energy are consistent with the experimental findings for this compound [25].

where N/A signifies that the data were not available. The calibrated log P values can be utilised to see if there is any significant difference in the correlation with biological activity. In fact, the results demonstrate that there is a good agreement between QSAR equations produced from the calibrated log P values and the dataset of experimental and Clog P values.

$$\log \mathrm{Rate} = 1.134 - 0.571 \log P_{calib} \quad (\pm 0.065) \qquad (2)$$
$$n = 8;\ s = 0.2269;\ R = 0.964;\ F = 78.17$$

$$\log \mathrm{Rate} = 1.175 - 0.589 \log P \quad (\pm 0.068) \qquad (3)$$
$$n = 8;\ s = 0.2310;\ R = 0.962;\ F = 75.32$$

These equations are also presented in the summary of QSARs in Table 9, 3a)i) Equation (6) and 3a)ii) Equation (7).

Table 2. Inhibition and log P data for primary aliphatic amines inhibiting CYP2B4 in rabbit. Reference [15].

Compound	Log P	-Log K_i	K_i (μM)	log P (pH 7)
Propanamine	0.48	-1.255	18	-1.81
Butanamine	0.86	-0.602	4	-1.22
Pentanamine	1.49	-0.255	1.8	-0.86
Hexanamine	2.06	0.347	0.45	-0.42
Heptanamine	2.57	0.886	0.13	0.15
Octanamine	3.09	1.824	0.015	0.76
Decanamine	4.1	2	0.01	1.92
Dodecanamine	5.11	1.886	0.013	2.8

Log P, logarithm of the octanol/water partition coefficient; K_i, inhibition constant (μM),

Table 3. Inhibition and log P data for diverse inhibitors of the human enzyme CYP2B6. Reference [17].

Compound	Log P	ΔG_{part} (kcalmol^{-1})	ΔG^{inh}_{bind} (kcalmol^{-1})	IC_{50} (μM)
Ticlopidine	4.39[d]	-6.227	-9.213	0.32
ThioTEPA	0.53	-0.752	-8.166	1.75
Tranylcypromine	1.49	-2.113	-7.814	3.1
Ketoconazole	3.72	-5.277	-7.739	3.5
Metyrapone	1.76[c]	-2.496	-7.636	4.14
Xanthate C8	3.78[d]	-5.362	-7.318	6.93
Benzylisothiocyanate	3.16	-4.482	-7.186	8.59
Retinol	5.68	-8.057	-6.765	17.0
Deramciclane	4.00[c]	-5.674	-5.954	63.5
Troglitazone	4.16[d]	-5.901	-5.751	88.2
Ethynylestradiol	3.67	-5.206	-5.574	100
MBA	3.39[c]	-4.809	-9.994	0.09

TEPA, triethylene-amino-phosphoramide
MBA, (N-α-methylbenzyl)-1-aminobenzotriazole
log P, logarithm of the octanol/water partition coefficient
[c] value calculated via the Pallas software (CompuDrug)
[d] value calculated via the ClogP software (BioByte)
ΔG_{part}, -RTlnP where P is the partition coefficient
$IC_{50,}$ concentration required for 50% inhibition of bupropion metabolism

ΔG^{inh}_{bind} ,RTlnIC_{50}

Table 4. O-dealkylation rates of 7-alkoxycoumarins mediated by CYP2B4 in the rabbit: HOMO energies and log P data. Reference [18].

Compound	Log P	E(HOMO)	Rate	Log rate	ΔG_{part} (kcalmol^{-1})
Methoxy	1.74	-9.331	0.917	-0.038	-2.468
Ethoxy	2.30	-9.295	0.977	-0.010	-3.262
Propoxy	2.86	-9.289	0.691	-0.160	-4.057
Butoxy	3.33[d]	-9.287	0.134	-0.873	-4.723
Pentoxy	3.92	-9.286	0.044	-1.356	-5.560
Hexoxy	4.38[d]	-9.289	0.024	-1.620	-6.213
Heptoxy	4.91[d]	-9.287	0.020	-1.699	-6.965
Octoxy	5.44[d]	-9.288	0.014	-1.854	-7.716

log P,logarithm of the octanol/water partition coefficient
[d], value calculated via the ClogP software (BioByte)
E(HOMO), energy of the highest occupied molecular orbital (eV) calculated via the AM1 method
Rate, nmol product/min/nmol P450

Results and discussion

Table 2 shows the dataset for a homologous series of primary aliphatic amines which act as inhibitors towards the PB-inducible P450 isoform in the rabbit, which is assumed to be primarily composed of CYP2B4 [3]. Tables 3 to 8 provide the relevant dataset information for the other CYP2B inhibitors of relevance to this study. Analysis of the data in Table 2 reveals that there is a clear parabolic relationship between -log K_i and logP, in accordance with the quadratic expression presented as equation 1 in Table 9. This latter table summarises all of the lipophilicity relationships investigated in this work, and thus facilitates comparison between the various series of compounds and the different types of relationship for governing variations in inhibitory potency or substrate binding affinity. Table 3 provides information for a diverse group of 12 CYP2B6 inhibitors and there appears to be a clear linear relationship between inhibition and lipophilicity, as given in Table 9.

For the homologous series of 8 alkoxycoumarins shown in Table 4, there is a linear relationship between rate of dealkylation mediated by CYP2B4 and log P itself, and also when combined with HOMO energy, which is equivalent to the compound ionization potential. However a quadratic relation exists between logP and the logarithm of the dealkylation activity in phenobarbital-induced animals for substituted alkoxycoumarins (Table 5). Careful analysis of the expression involving a combination of log P and E (HOMO) indicates that this relationship is not as significant statistically as that which only involved log P and, consequently, this correlation should be viewed with caution. The relevant expressions are shown in Table 9, as equations 3a, 3b and 3c, respectively. In a set of 16 diverse substrates (Table 6) of CYP2B6, the human orthologue, there is a clear linear relationship between log P and -logKm, as shown in equation 4a (Table 9) and a plot of this is shown in Figure 2. This expression can also be formulated as a lipophilicity relationship by conversation of log P and log Km to their

Table 5. Induction of O-dealkylation activity of 7-alkoxycoumarins (CYP2B1-related) by phenobarbital in rat. Reference [26].

Compound	Log P	Log PB	PB
7-Ethoxycoumarin (EC)	2.27	0.778	6
4-Methyl EC	2.77	0.903	8
4-Methyl-6-ethyl EC	3.80	1.623	42
3,4-Dimethyl-6-ethyl EC	4.24	1.491	31
4-Methyl-7-methoxy EC	2.24	0.778	6
4-Methyl-6-ethyl MC	3.27	1.763	58
4-Methyl-6-ethyl PC	5.38	0.699	5
3-Acetyl EC	1.75	1.114	13
4-Acetyl MC	1.23	1.146	14

log P, logarithm of the octanol/water partition coefficient calculated via the Pallas Software (CompuDrug)
EC, 7-ethoxycoumarin
MC, 7-methoxycoumarin
PC, 7-pentoxycoumarin
PB, fold induction of O-dealkylase activity relative to control for phenobarbital-treated rats

Table 6. Binding and log P data for diverse substrates of the human enzyme CYP2B6. Reference [27].

Compound	Log P	ΔG_{part} (kcalmol^{-1})	ΔG_{bind} (kcalmol^{-1})	-Log K_m	K_m (μM)
7-Benzyloxyresorufin	4.75[c]	-6.738	-8.359	5.893	1.28
Testosterone	3.32	-4.709	-6.095	4.297	50.5
Benzphetamine	2.27[e]	-3.22	-5.716	4.03	93.4
7-Ethoxycoumarin (EC)	2.3	-3.262	-5.588	3.939	115
Diazepam	2.86	-4.057	-5.6	3.947	113
Bupropion	2.54	-3.603	-5.629	3.969	107.5
(S) Mephenytoin	1.9	-2.695	-4.608	3.249	564
SM-12502	1.06	-1.504	-3.905	2.753	1767
Antipyrine	0.23	-0.326	-2.485	1.752	17700
4-Chloromethyl EC	2.94[c]	-4.17	-6.344	4.472	33.7
(R) Deprenyl	2.9	-4.114	-6.357	4.481	33
Propofol	3.7	-5.248	-7.092	5	10
Lidocaine	1.62	-2.298	-4.638	3.269	537.6
Carbamazepine	1.98	-2.809	-4.475	3.155	700
Imipramine	2.48	-3.518	-4.847	3.417	383
Arteether	3.29	-4.667	-6.458	4.553	28

EC, 7-ethoxycoumarin
K_m, Michaelis constant for substrate metabolism (μM)
log P, logarithm of the octanol/water partition coefficient
[c] value calculated via the Pallas software system (CompuDrug)
[e] value estimated from data reported in another solvent system

Table 7. Inhibition and log P data for 2-n-alkyl-benzimidazoles inhibiting CYP2B1 in rat. Reference [16].

Alkyl group	Log P	-Log K_i	K_i (μM)
Pentyl	3.96	0.602	0.25
Hexyl	4.48	0.770	0.17
Heptyl	4.96	1.523	0.03
Octyl	5.48	1.222	0.06
Nonyl	5.92	0.921	0.12

log P, logarithm of the octanol/water partition coefficient
K_i, inhibition constant (μM)

Table 8. Spectroscopic binding and log P data for barbiturates metabolised by CYP2B1. Reference [19].

Alkyl group	Log P	K_S (μM)	-Log K_S
Propyl	0.87	0.235	0.629
Butyl	1.7	0.089	1.051
Pentyl	2.23	0.032	1.495
iso-Pentyl	2.11	0.038	1.42
sec-Pentyl	2.13	0.045	1.347
Me_2-Butyl	2.39	0.025	1.602
Hexyl	3.08	0.019	1.721
Heptyl	3.64	0.02	1.699
Octyl	3.85	0.024	1.62
Nonyl	4.13	0.056	1.252

log P, logarithm of the octanol/water partition coefficient
K_S, spectroscopic binding constant (μM)

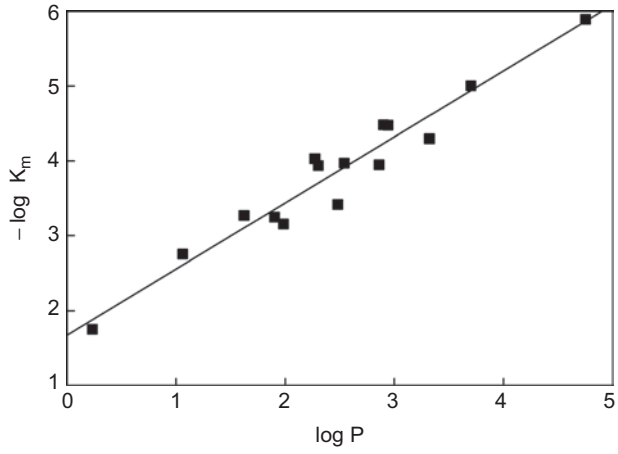

Figure 2. Lipophilicity relationship for 16 diverse CYP2B6 substrates showing the clustering of points about the line, based on the data presented in Tables 6 and 8.

respective free energies, as presented in equation 4b in Table 9. The intercept of this relation indicates that the most common type of interaction within the CYP2B6 active site is likely to be hydrogen bonding [11,12,23,24], and molecular modelling supports this viewpoint. For a series of n-alkyl-benzimidazoles, inhibition of CYP2B1 (Table 7) exhibits a parabolic relationship with log P, as shown in Table 9, equation 5. In this case, the negative logarithm of the K_i value has been used as a measure of the inhibitory activity of the n-alkyl-benzimidazoles.

Finally, for a series of barbiturate derivatives binding to CYP2B1 (Table 8), there is also a parabolic relationship between log P and, in this case, -log K_S, where K_S, is the spectroscopic binding constant. The data used to generate equation 6 in Table 9 are shown in Table 8. The relevant equation in Table 9 (equation 6) can be compared with that of the 7-alkoxycoumarins (equation 3a, Table 9) where it can be appreciated that the terms are of similar value. This tends to suggest that the optimal characteristics of the CYP2B active site are translated into providing similar quadratic expressions relating compound lipophilicity to binding in homologous series, and equation 1 in Table 9 governing the inhibition of primary aliphatic amines also displays similar characteristics to the other quadratic expressions mentioned previously. However, it is noted that the optimal log P values for certain series of compounds which show quadratic relationships between activity and this lipophilicity parameter tend to vary somewhat, as listed in Table 9. To some extent, the optimal log P for a homologous series depends upon the way in which the various congeners become orientated within the enzyme active site. There is also some degree of chain folding that is likely to occur as the series is ascended, together with the actual length of the substrate access channel in the CYP2B enzyme which have to be taken into account when considering the implications of the optimal log P for a series of related compounds.

Conclusions

In general, there is a trend of binding and inhibition being dependent on compound lipophilicity, although it is also important to emphasise the role of active site interactions

Table 9. Summary of QSARs in CYP2B inhibitors and substrates.

Inhibitor or substrate		n	s	R	F	Log P_{opt}
1.Aliphatic primary amines (CYP2B4)						
$-\log Ki = 0.934\,\log P - 0.193\,\log P2 + 0.880$ (± 0.065) (± 0.039)	(4)	8	0.2156	0.989	114.53	2.42
2.Diverse inhibitors (CYP2B6)						
$\Delta G^{inh}_{bind} = 0.761\,\Delta G_{part} - 1.060$ (± 0.093)	(5)	11	0.4832	0.939	67.46	N/A
3.7-Alkoxycoumarins (CYP2B4 and CYP2B1)						
a) i) $\text{Log rate} = 1.175 - 0.589\,\log P$ (± 0.068)	(6)	8	0.231	0.962	75.32	N/A
ii) $\text{Log rate} = 1.134 - 0.571\,\log P_{calib}$ (± 0.065)	(7)	8	0.2269	0.964	78.17	N/A
b) $\log \text{rate} = 71.69 - 0.650\,\log P + 7.562\,E(H)$ (± 0.092) (± 7.800)	(8)	8	0.2303	0.969	38.38	N/A
c) $\log PB = 1.209\,\log P - 0.193\,\log P^2 - 0.195$ (± 0.238) (± 0.036)	(9)	9	0.1577	0.951	28.26	3.13
4.Diverse substrates (CYP2B6)						
a) $-\log K_m = 0.881\,\log P + 1.676$ (± 0.058)	(10)	16	0.2378	0.971	233.45	N/A
b) $\Delta G_{bind} = 0.881\,\Delta G_{part} - 2.377$ (± 0.058)	(11)	16	0.3373	0.971	233.45	N/A
5.n-Alkyl-benzimidazoles (CYP2B1)						
$-\log K_i = 4.759\,\log P - 0.508\,\log P^2 - 9.828$ (± 2.252) (± 0.251)	(12)	5	0.2627	0.863	5.84	4.68
6.Barbiturates (CYP2B1)						
$-\log K_S = 1.386\,\log P - 0.223\,\log P^2 - 0.502$ (± 0.207) (± 0.039)	(13)	10	0.1197	0.950	65.22	3.11

$\log P_{opt}$, optimal log P calculated as the maximum of the quadratic equation;
N/A, not applicable
References to biological data for the above series:
1. [13,15,28]
2. [17]
3. [18,26]
4. [23]
5. [16]
6. [19]

(hydrogen bonding and π-π stacking) plus the relevance of specific parameters in certain species of compounds, which have a particular significance in terms of the essential structural features in the compounds concerned. Therefore formulating the lipophilicity relationship in terms of free energies of binding and partitioning represents a very simple and straightforward method for estimating the contributions to the overall binding affinity between substrates or inhibitors and the relevant CYP2B active site. Hydrophobicity (or lipophilicity) is, therefore, a key feature of CYP2B-substrate (or inhibitor) interactions and there is also a hydrogen bond formed in many cases, as shown for the docked CBP inhibitor in the active site of CYP2B6 (Figure 1). For homologous series, where alkyl chain length varies over a significant range, the normally linear relationship of bioactivity with log P becomes quadratic in nature due to the fact that the size of the pocket will be exceeded after a certain point in the series, and/or that the lengthy hydrocarbon chain will start to adopt a more folded conformation within the active site environment. Consequently, one can regard the overall lipophilicity of a compound as being a combination of hydrophobicity and polarity, such that the optimal log P within a series of structurally related compounds binding to, for example, a P450 enzyme active site may not necessarily take the same value when compared between different series of homologues, because the log P of the parent group will be different in each case and this clearly represents a component of the overall log P value.

Declaration of interest

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