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Quantitative Structure–Activity Relationships (QSARs) Within Series of Inhibitors for Mammalian Cytochromes P450 (CYPs)

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The results of quantitative structure–activity relationship (QSAR) studies on series of P450 inhibitors are reported. Cytochrome P450 families CYP1, CYP2 and CYP51 have been investigated for QSAR analysis, including those of CYP2 subfamilies: CYP2A, CYP2B, CYP2C, CYP2D and CYP2E. The accumulated evidence indicates different structural descriptors being involved, depending on the P450 enzyme concerned, although compound lipophilicity in the form of either $\log P$ or $\log D_{7.4}$ appears to represent a common factor in some cases. This is thought to represent desolvation of the P450 active site, although quadratic expressions in lipophilicity tend to suggest that membrane transport is important, especially for CYP2B and CYP2E isoforms. In general, there is close agreement ($R = 0.95–0.99$) between experimental pK_i values and those calculated via QSAR analysis.

Keywords: QSAR; P450s; Inhibitors; CYPIA; CYP2A6; CYP2B1; CYP2C19; CYP2D6; CYP2E1; CYP51

INTRODUCTION

The cytochromes P450 (CYP) constitute a superfamily of heme-thiolate enzymes in which there is current interest, particularly for the human and other mammalian forms, due to their importance in the Phase 1 metabolism of a vast number and variety of chemicals, including pharmaceutical agents [1]. Inhibitors of individual human P450s, for example, are of importance in the assessment of enzyme activity and substrate selectivity [2], where a number of diagnostic agents have been identified for various P450 enzymes, as shown in Table I. Some selective inhibitors of human P450s are clearly substrate analogues [3]. For example, furafylline is analogous to caffeine which is a marker substrate for CYP1A2 [1], whereas the selective CYP2A6 inhibitor, 8-methoxypsoralen, is structurally related to the typical marker

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substrate coumarin [3]. Moreover, sulfaphenazole is a close analogue to tolbutamide which is a selective substrate of CYP2C9, whereas the selective CYP2D6 inhibitor, quinidine, is analogous to propranolol [4] which is a typical substrate of this enzyme. Some of these examples are listed in Table I, which contains information on selective substrates and inhibitors of the major human P450s involved in the metabolism of drugs and other xenobiotics, using data compiled from the literature [1–3]. Where available, values for the K_m and K_i of substrates and inhibitors, respectively, have been included in Table I which also presents information on the relative importance of specific P450 isoforms in drug oxidations together with their average percentage of human hepatic P450 complement.

METHODS

In order to gain further understanding of the likely structural criteria governing the inhibition of human P450s, we have collated data from the literature on selective inhibitors of CYP1A and those which can act as inhibitors for other mammalian P450s, namely: CYP2A, CYP2B, 2C, 2D, 2E and CYP51. This compilation of inhibitory data in the form of either K_i or IC_{50} values (in μM) has been employed for the generation of quantitative structure–activity relationships (QSARs) based on multiple linear regression analysis of the relevant datasets, which include physicochemical characteristics and molecular structural information on the various inhibitors concerned. In some cases, the $\log P$ and $\log D_{7.4}$ data were calculated using the Pallas system (CompuDrug Limited, Budapest).

RESULTS AND DISCUSSION

Inhibitors of CYP1A Enzymes

Table II presents information on substituted benzimidazoles which can act as inhibitors for CYP1A enzymes via nitrogen atom ligation of the heme iron (reviewed in reference [5]). It is found that the variation in inhibitory activity for the 8 compounds can be explained ($R = 0.98$) by a combination of molecular planarity (area/depth) and square of the dipole moment (μ^2) as shown in Eq. (1), Table II [6]. Planarity in the molecule is important for occupancy of the CYP1A active site, whereas the polarity of the molecule (μ^2 term) probably relates to orientation of the inhibitor within the enzyme active site [6]. For a series of substituted acyl hydroxycoumarins, however, inhibitory potency in the form of $-\log IC_{50}$ values appears to be related ($R = 0.98$) to the magnitude of the highest occupied molecular orbital (HOMO) energy. Table III

TABLE I Substrates and inhibitors of human cytochromes P450 (references to data: [1,2,15,19,20])

CYP	Involvement in drug oxidations (%)	Typical marker substrate	K_m (μM)	Selective inhibitor	K_i or K_m (μM)
1A2	8.2	Caffeine	180	Furafylline	0.7
2A6	2.5	Coumarin	2.1	8-Methoxypsoralen	0.5
2B6	3.4	4-Trifluoromethyl 7-ethoxycoumarin	2.9	Orphenadrine	30
2C8 } 2C9 }	15.8	Rosiglitazone	10	Sulfinpyrazone	17
		Tolbutamide	132	Sulfaphenazole	0.2
2C19	8.3	Omeprazole	8.6	Fluconazole	2
2D6	18.8	Propranolol	2.73 (K_D)	Quinidine	0.06
2E1	4.1	Benzene	25	Pyridine*	0.4
3A4	34.1	Erythromycin	1.8 (K_D)	Ketoconazole	0.1

* It has been reported [18] that 3-amino-1,2,4-triazole is selective for CYP2E1 but its K_i value of 10 mM suggests that it does not exhibit high binding affinity towards this enzyme.

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TABLE II Benzimidazole inhibitors of CYP1A activity (reference to data: [6])

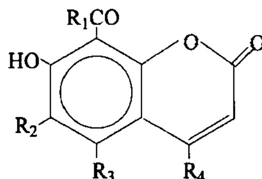
Compound	$-\log IC_{50}$	Area/depth	μ^2	
1. 4-Benzamido-6-chlorobenzimidazole	4.585	24.77	56.596	
2. 2-Phenylethylbenzimidazole	4	22.48	16.112	
3. 2-(2-chlorophenoxymethyl)benzimidazole	4.284	22.19	42.237	
4. Benzo(1,2-d)benzimidazole	4.2676	26.66	16.467	
5. Naphtho(1,8-de)benzimidazole	4.1427	27.91	17.481	
6. Dibenzo(9,10-d)benzimidazole	5	37.29	13.498	
7. 2-Methyl-6-ethoxybenzoxazole	3.3665	17.25	0.4238	
8. 2-Methyl-6-methoxybenzothiazole	3.6778	18.17	1.4019	
QSAR equation	*n*	*s*	*R*	*F*
1. $-\log IC_{50} = 0.07(\pm 0.01)\,\text{Area/depth} + 0.01(\pm 0.0003)\,\mu^2 + 2.33$	8	0.127	0.98	53.0

provides the relevant data for these compounds, and it is possible that the frontier orbital energy value could relate to the charge-transfer interaction energy between inhibitor and enzyme, although hydrogen bond donor properties may be an alternative explanation of the findings. The inhibitory activity of an homologous series of alkoxymethylene dioxybenzenes is directly related to compound planarity as it can be shown that the area/depth^2 parameter gives a 0.96 correlation with experimental pIC_{50} values [6]. Consequently, CYP1A inhibition appears to be largely determined by the overall molecular planarity of the inhibitor, although other factors such as polarity and frontier orbital energies are also important in the cases of the benzimidazoles and acyl coumarins series, respectively.

Inhibitors of CYP2A6

Table IV presents structural and inhibition data

TABLE III Acyl hydroxy coumarins and inhibition of CYP1A activity (reference to data: [14])



	R_1	R_2	R_3	R_4	E(HOMO)	pIC_{50}
1	Me	H	H	Me	−8.887	−1.929
2	Me	H	H	Pr^n	−8.877	−1.845
3	Me	H	H	4-Me Ph	−8.065	−0.903
4	Me	H	H	3-Me Ph	−8.645	−1.079
5	Me	H	H	2-Me Ph	−8.653	−0.978
6	Ph	H	H	Me	−8.811	−1.556
7	Ph	H	H	Ph	−8.767	−1.267
8	H	Me	H	Me	−8.905	−1.763
9	H	Me	H	Et	−8.891	−1.681
10	H	Me	H	Ph	−8.676	−1.161
11	Me	H	Et	Ph	−8.64	−0.969
12	Pr^n	H	H	4-Me Ph	−8.585	−0.778
QSAR Expression			*n*	*S*	*R*	*F*
1 $pIC_{50} = 3.214(\pm 0.217)\,E_H + 26.777$			12	0.0890	0.98	197.8

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TABLE IV CYP2A6 inhibitors (reference to K_i data: [15])

Compound	K_i (μM)	pK_I	log P	pK_a	M_r	log M_r	HB_A	HB_D	log $D_{7.4}$
1. 8-Methoxypsoralen	0.05	1.301	2.37*	Neutral	216.2	2.3349	4	0	2.37
2. Pilocarpine	1	0	1.14	7.05†	351.4	2.5458	3	0	0.98
3. R-Menthofuran	2.5	−0.398	3.43*	Neutral	150.24	2.1767	1	0	3.43
4. Nicotine	15	−1.176	1.17	8.0†	162.2	2.2101	1	0	0.47
5. 4-Nitrophenol	28	−1.447	1.91	Neutral	139.12	2.1434	3	1	1.91
6. Menadione	12	−1.079	2.2	Neutral	172.19	2.236	2	0	2.2
7. Metyrapone	16	−1.204	1.78	Neutral	226.3	2.3547	3	0	1.78
8. Tranylcypromine	0.04	−1.398	1.52	8.2†	133.2	2.1245	1	2	0.66

QSAR Expressions	n	s	R	F
1. $pK_i = 7.31(\pm1.11)\log P - 7.26(\pm1.59)\log M_r - 5.17(\pm0.79)\log D_{7.4} + 0.80(\pm0.15)\,HB_A - 24.12$	8	0.4154	0.97	12.36

*Calculated value.
†Basic value.

TABLE V CYP2B1 inhibitors (reference to data: [9])

Compound	log $P_{7.0}$*	log P	pK_a	E_H	E_L	ΔE	pK_1	pK_2
1. Propanamine	−1.81	0.48	10.68	−9.822	3.6989	13.521	−1.255	–
2. Butanamine	−1.22	0.86	10.64	−9.826	3.6342	13.461	−0.602	−1.301
3. Pentanamine	−0.86	1.49	10.61	−9.822	3.5952	13.418	−2.553	−0.6990
4. Hexanamine	−0.42	2.06	10.60	−9.821	3.5498	13.371	0.3468	−0.3010
5. Heptanamine	0.15	2.57	10.66	−9.821	3.5167	13.3740	0.8861	0.2218
6. Octanamine	0.76	3.09	10.61	−9.821	3.4921	13.313	0.8239	0.6990
7. Decanamine	1.92	4.10	10.64	−9.821	3.4592	13.28	2.0000	1.1549
8. Dodecanamine	2.80	5.10	10.60	−9.822	3.4398	13.262	1.8861	1.2218

QSAR expressions	n	s	R	F
1. $pK_1 = 0.934(\pm0.065)\log P_{7.0} - 0.193(\pm0.039)\log P_{7.0}^2 + 0.880$	8	0.2156	0.989	114.53
2. $pK_1 = 48.98(\pm1.15) - 13.63\,E_L$	8	0.2717	0.979	141.35
3. $pK_1 = 182.8 - 13.62(\pm1.20)\,\Delta E$	8	0.2845	0.977	128.36
4. $pK_2 = 13.31(\pm1.29)\,E_L - 176.9(\pm44.86)\,E_H - 1690.1$	7	0.1638	0.984	62.14

*log P value at neutral pH.

on 8 structurally diverse inhibitors of CYP2A6, together with a QSAR showing a good correlation ($R = 0.97$) between the total number of hydrogen bond acceptors and donors, compound lipophilicity in the form of log P, relative molecular mass and distribution coefficient (log $D_{7.4}$) at pH 7.4 (Eq. (1), Table IV). These findings indicate that hydrogen bonding characteristics are likely to be of importance for inhibition of CYP2A6, together with ability of molecules to fit the CYP2A6 active site and desolvate the haem pocket (log M_r value). The findings exhibit a close agreement with the results of homology modelling studies of CYP2A6 [7] where hydrogen-bonded interactions appear to be a recurrent feature of substrate binding to this enzyme.

Inhibitors of CYP2B1

The relevant data for a series of 8 primary aliphatic amines, acting as inhibitors of CYP2B1, is presented in Table V. The inhibition constants K_1 and K_2 represent high and low affinity binding constants, respectively, towards phenobarbital-induced rat hepatic microsomal P450. Several parameters are found to give good correlations ($R = 0.98$–0.99) with pK_1 (Eqs. (1)–(3), Table V) whereas a linear combination of the frontier orbital energies correlate ($R = 0.98$) with the low

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TABLE VI Data set for CYP2C19 inhibitors (K_i = inhibition constant; M_r=relative molecular mass; $HB_{A,D}$ = number of hydrogen bond donors, acceptors; $pK_i = -\log K_i$; reference to data: [16])

Compound	K_i (μM)	pK_i	M_r	$\log M_r$	HB_A	HB_D
1. S-Mephenytoin	60	4.2218	218.28	2.3390	2	1
2. Omeprazole	4.1	5.3872	345.45	2.5384	5	1
3. Propranolol	112	3.9508	259.35	2.4139	3	2
4. Diazepam	100	4.0000	284.75	2.4545	2	0
5. R-Warfarin	32	4.4949	308.33	2.4890	4	1
6. Phenytoin	280	3.5528	252.27	2.4019	2	2
7. LY307640	9.2	5.0362	359.48	2.5557	5	1
8. Fluconazole	2	5.6990	306.30	2.4861	7	1
9. Tranylcypromine	8	5.0969	133.20	2.1245	1	2
10. Desmethyldiazepam	115	3.9393	270.73	2.4325	2	1

QSAR Expression	n	s	R	F
1. $pK_i = 0.029(\pm 0.006) M_r - 19.13(\pm 2.93) \log M_r + 0.381(\pm 0.049) HB_A - 0.278(\pm 0.108) HB_D + 42.09$	10	0.1720	0.98	38.4

affinity binding data in the form of pK_2 values. Eq. (1) in Table V demonstrates the importance of a quadratic expression in $\log P$ to explaining the variation in pK_1 data. This finding indicates that there is an optimally preferred lipophilicity of $\log P = 2.42$ for these compounds, which probably relates to an ideal alkyl chain length of about 10 or 11 carbon atoms. However, Eqs. (2)–(4), Table V show that frontier orbital energies are also relevant to the binding of aliphatic amines to CYP2B1, and it is possible that this could represent a frontier-controlled interaction between the amino group and the haem iron atom in P450. It can be shown that the most potent inhibitor in this series is able to fit the putative active site of the relevant enzyme [8,9] as it is of an optimal size for binding within the heme pocket. Consequently, the QSAR analysis on these compounds is consistent with available experimental evidence, and with molecular modelling studies of likely active site interactions.

Inhibitors of CYP2C19

Table VI provides information on 10 competitive CYP2C19 inhibitors with K_i values ranging from 2 to 280 μM. Equation (1) in Table VI shows that the pK_i values of these 10 compounds can be explained in terms of a linear combination of their relative molecular masses (M_r) and the numbers of hydrogen bond donor/acceptors (HB_D and HB_A) in the molecule. The high correlation coefficient ($R = 0.98$) for this expression indicates that there is a very good agreement between experimental and calculated pK_i values for these 10 compounds. Moreover, the findings are consistent with molecular modelling of the CYP2C19 enzyme itself, where it has been shown that hydrogen bonding at several sites is of key importance to substrate binding and selectivity [10].

Inhibitors of CYP2D6

The relevant data for 11 inhibitors of CYP2D6 are shown in Table VII. For 7 of these compounds, there is a good correlation ($R = 0.977$) between pK_i and $\log D_{7.4}$, as presented in Eq. (1), Table VII. However, when all 11 compounds are included, the most significant correlation ($R = 0.979$) is provided by a combination of relative molecular mass (M_r), lipophilicity ($\log P$), number of hydrogen bond acceptors (HB_A) and number of basic nitrogens (N_B) in the molecule (Eq. (2), Table VII). As all of the inhibitors contain at least one nitrogen atom which is protonated at physiological pH, there is a degree of

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TABLE VII CYP2D6 Inhibitors (reference to data: [16])

Compound	$\log P$	pK_a	$\log D_{7.4}$	Mr	HB_A	N_B	pK_i
1. Oxprenolol	2	9.3	0.09	265.35	3	1	−1.0000
2. Propranolol	3.37	9.5	1.18	259.35	2	1	−0.8261
3. Bufuralol	3.50	9.0	1.89	261.36	2	1	−0.6812
4. Citalopram	3.68	9.36	1.87	324.43	3	1	−0.7076
5. Amitriptyline	5.04	9.4	2.50	263.38	0	1	−0.6021
6. Chlorpromazine	5.40	9.5	2.79	318.86	1	1	−0.5798
7. Desmethylimipramine	4.05	10.0	1.45	266.39	1	1	−0.3617
8. Clomipramine	5.19	9.4	3.32	314.86	1	1	−0.3424
9. Levopromazine	3.39	9.4	1.39	328.47	2	1	0.0000
10. Yohimbine	2.59	9.87	2.18	354.49	3	1	−0.3979
11. Quinidine	2.83	7.9	2.21	324.42	3	2	1.5229
QSAR Expressions*				N	s	R	F
1. $pK_i = 0.187(\pm0.028)\log D_{7.4} - 1.041$				7	0.0478	0.977	85.09
2. $pK_i = 0.014(\pm0.002)M_r - 0.477(\pm0.132)\log P - 0.567(0.150)\mathrm{HB_A} - 1.794(\pm0.212)N_B - 3.557$				11	0.1874	0.979	35.17

*Compounds 7, 9, 10 and 11 were excluded from QSAR Eq. (1).

commonality between the two expressions for pK_i, because $\log D_{7.4}$ is the ionization-corrected lipophilicity at pH7.4, although the simpler relationship (Eq. (1), Table VII) does not hold for all of the CYP2D6 inhibitors in the dataset. Nevertheless, active site modelling of CYP2D6-selective compounds shows that the protonated nitrogen forms an ion-pair with an aspartate residue close to the heme [11], a finding which has been supported by site-directed mutagenesis, and hydrogen bonding also features in many of the modelled substrate interactions with CYP2D6. Consequently, the QSAR results presented here show consistency with information obtained from molecular modelling of enzyme–substrate/inhibitor interactions for CYP2D6, together with experimental evidence from site-specific mutation of certain key active site residues, such as aspartate-301.

Inhibitors of CYP2E1

In Table VIII, there is information presented on the inhibition of CYP2E1 by primary alcohols and carboxylic acids. Inspection of the QSAR Eqs. (1) and (2), Table VIII shows that related properties feature in both cases. For the alcohols, a quadratic in $\log P$ gives a good correlation ($R = 0.963$) with inhibition whereas, in the case of carboxylic acids, an analogous expression in $\log D_{7.4}$ exhibits a parallelism ($R = 0.968$) with the inhibitory activity. The $\log D_{7.4}$ values represent ionization-corrected lipophilicities at pH 7.4 and are, therefore, more appropriate than $\log P$ values for the carboxylic acids which will be appreciably ionized at physiological pH. The inhibition of CYP2E1-mediated activity by diverse aliphatic alcohols (15 compounds) is presented in Table IX. In this case, the data is for the inhibition of aniline 4-hydroxylation by various primary and secondary alcohols. The QSAR expression provided in Table IX shows that a combination of molecular length and number of carbon atoms gives a good correlation ($R = 0.95$) with inhibitory activity in the form of pIC_{50} values. Molecular modelling of CYP2E1 indicates that alcohols of a certain chain length range are likely to occupy the putative active site and form hydrogen-bonded interactions with the distal threonine sidechain [12].

Inhibitors of CYP51

Table X provides the relevant information on 7 antifungal agents which exhibit inhibitory

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TABLE VIII Datasets for CYP2E1 inhibitors (N_C=number of carbon atoms; reference to data: [12])

(A) Primary alcohols

Compound	log P	N_C	K_i (μM)	pK_i
1. Methanol	−0.74	1	610	−2.7853
2. Ethanol	−0.30	2	102	−2.0086
3. Propan-l-ol	0.25	3	20	−1.3010
4. Butan-l-ol	0.84	4	13	−1.1139
5. Pentan-l-ol	1.51	5	9	−0.9542
6. Hexan-l-ol	2.03	6	6	−0.7782
7. Heptan-l-ol	2.62	7	3	−0.4771
8. Octan-l-ol	3.07	8	6	−0.7782
9. Nonan-l-ol	4.02	9	6	−0.7782
10. Decan-l-ol	4.56	10	53	−1.7243

QSAR equation	n	s	R	F
1. $pK_i = 0.983(\pm0.107)\log P - 0.203(\pm0.026)\log P^2 - 1.789$	10	0.2177	0.963	89.4

(B) Carboxylic acids

Compound	log P	pK_a	log $D_{7.4}$	K_i (μM)	pK_i
1. Hexanoic acid	1.92	4.87	−0.61	2610	−3.4166
2. Heptanoic acid	2.37	4.90	−0.12	328	−2.5159
3. Octanoic acid	3.05	4.89	0.54	162	−2.2095
4. Nonanoic acid	3.39	4.91	0.95	113	−2.0531
5. Decanoic acid	4.09	4.90	1.59	66	−1.8195
6. Undecanoic acid	4.41	4.91	1.95	23	−1.3617
7. Dodecanoic acid	4.6	5.3	2.5	22	−1.3424
8. Tridecanoic acid	5.43	4.91	2.95	45	−1.6532
9. Tetradecanoic acid	5.94	4.91	3.45	120	−2.0792
10. Pentadecanoic acid	6.45	4.91	3.97	296	−2.4713
11. Hexadecanoic acid	7.17	4.5	4.27	340	−2.5315

QSAR Equation	n	s	R	F
2. $pK_i = 1.047(\pm0.096)\log D_{7.4} - 0.244(\pm0.024)\log D_{7.4}^2 - 2.659$	11	0.1689	0.968	119.0

activity towards CYP51. These azole compounds are able to inhibit the fungal P450 involved in 14α-demethylase via haem iron ligation. In particular, the azole nitrogen atom binds directly to the haem group thus preventing access for dioxygen [13]. It would appear that the inhibitory activity can be described ($R = 0.95$) by a two-variable expression (Eq. (1), Table X) involving compound planarity (area/depth^2) and magnitude of the LUMO energy (E_L). The more potent inhibitors combine high molecular planarity with low E_L values, and it is possible that the latter indicates a potential for hydrogen bond acceptance [13]. Molecular modelling of these compounds within the putative active site of CYP51 shows that both hydrogen bonding and π-stacking interactions are relevant, so it is possible that the ability to fit the enzyme's active site relates to the inhibitors' overall planarity comprised of aromatic ring moieties in the molecule.

CONCLUSIONS

It appears from the results obtained in this study that QSAR methods are applicable to various P450 enzyme inhibitors, giving rise to good correlations with inhibitory activity in the form of K_i or IC_{50} values. It is possible to rationalize these findings in terms of structural interactions with the enzyme active site in each case. Table XI

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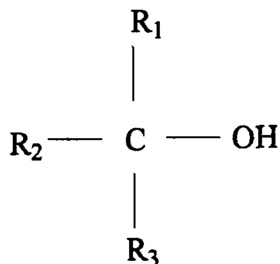
TABLE IX Alcohols and inhibition of CYP2E1 activity (N_C = number of carbon atoms in the molecule; length = overall length of molecule reference to data: [17])



	R_1	R_2	R_3	N_C	Length	pIC_{50}
1	Me	H	H	2	6.5	−1.10
2	Et	H	H	3	7.7	−0.48
3	Pr^n	H	H	4	9.0	−0.05
4	Bu^n	H	H	5	9.3	0.27
5	Pe^n	H	H	6	10.7	0.54
6	Hex^n	H	H	7	11.5	0.68
7	Pr^i	H	H	4	7.7	−0.39
8	Bu^i	H	H	5	8.8	−0.19
9	Ph	H	H	7	9.3	0.32
10	Me	Me	H	3	6.3	−0.47
11	Et	Me	H	4	6.3	−0.35
12	Pr^n	Me	H	5	7.4	−0.07
13	Bu^n	Me	H	6	8.3	0.15
14	Pe^n	Me	H	7	8.2	0.25
15	Et	Me	H	5	6.3	−0.37
QSAR Expression			n	s	R	F
1. $pIC_{50} = 0.177(\pm 0.035)N_C + 0.122(\pm 0.034)\,\text{length} - 2.034$			15	0.1501	0.95	61.2

TABLE X CYP51 inhibitors (a/d^2 = ratio of molecular area to the square of the depth; E_L = energy of the lowest unoccupied molecular orbital; reference to data: [13])

Compound	pIC_{50}	a/d^2	E_L	$\log D_{7.4}$	$\log P$
1. Itraconazole	1.6576	2.3	1.8939	5.13	5.14
2. Terconazole	1.4949	2.2	2.0572	3.79	4.56
3. Parconazole	1.4685	2.3	2.0572	3.19	3.21
4. Propiconazole	1.3979	2.1	1.9592	2.82	2.82
5. Ketoconazole	1.2596	2.0	1.9783	3.30	3.33
6. Miconazole	1.0969	2.0	1.8994	6.26	6.29
7. Imazalil	1.0555	1.8	2.1198	3.76	3.79
QSAR equation	n	s	R	F	
1. $pIC_{50} = 0.58(\pm 0.10)\,a/d^2 - 1.14(\pm 0.41)\,E_L + 2.45$	7	0.0841	0.95	18.6	

provides a summary of the QSAR studies described above, and it would appear that there are notable differences between factors involved in the inhibition of various P450s. However, some commonalities also exist, such as the appearance of the lipophilicity parameter, $\log P$, which features in several examples of the QSAR expressions listed.

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TABLE XI QSARs for P450 inhibition

	n	s	R	F
1. CYP1A				
(a) Methylenedioxybenzenes [6]				
$pIC_{50} = 1.22(\pm 0.14)\,a/d^2 - 5.68$	8	0.208	0.96	71.7
(b) Benzimidazoles [6]				
$pIC_{50} = 0.07(\pm 0.01)\,a/d^2 + 0.01(\pm 0.003)\,\mu^2 - 2.33$	8	0.127	0.98	53
(c) 7-Hydroxy-8-acylcoumarins [6]				
$pIC_{50} = 3.21(\pm 0.22)\,E_H + 26.78$	12	0.089	0.98	197.8
2. CYP2A6				
(a) Diverse compounds				
$pK_i = 7.31(\pm 1.11)\log P - 7.26(\pm 1.59)\log M_r - 5.17(\pm 0.79)\log D_{7.4} + 0.80(\pm 0.15)\,HB - 24.12$	8	0.415	0.97	12.4
3. CYP2B1				
(a) Aliphatic amines [10]				
$pK_1 = 0.934(\pm 0.065)\log P - 0.193(\pm 0.039)\log P^2 - 0.88$	8	0.216	0.99	114.5
4. CYP2C19				
(a) Diverse compounds [16]				
$pK_i = 0.03(\pm 0.01)\,M_r - 19.13(\pm 2.93)\log M_r + 0.38(\pm 0.05)\,HB_A - 0.28(\pm 0.11)\,HB_D + 42.09$	10	0.172	0.98	38.4
5. CYP2D6				
(a) Diverse compounds [16]				
$pK_i = 0.01(\pm 0.0002)\,M_r - 0.48(\pm 0.13)\log P - 0.57(\pm 0.15)\,HB_A + 1.79(\pm 0.21)\,N_B - 3.56$	11	0.187	0.98	35.2
6. CYP2E1				
(a) Diverse alcohols [17,12]				
$pIC_{50} = 0.18(\pm 0.04)\,N_C + 0.12(\pm 0.03)\,\text{length} - 2.03$	15	0.15	0.95	61.2
(b) Primary alcohols [12]				
$pK_i = 0.98(\pm 0.11)\log P - 0.20(\pm 0.03)\log P^2 - 1.79$	10	0.218	0.96	89.4
7. CYP51				
(a) Azoles [13]				
$pIC_{50} = 0.58(\pm 0.10)\,a/d^2 - 1.14(\pm 0.41)\,E_L + 2.45$	7	0.084	0.95	18.6

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