Multidisciplinary Insights into the Structure-Function Relationship of the CYP2B6 Active Site

(Supplemental Tables)

Drug Metabolism and Disposition

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Supplemental Table 1. Historical *in silico* insights of predicted active site amino acids and their topological locations around various ligands within P450 homology modeled CYP2B6.

Homology Model of CYP2B6	PDB ID	Ligand Bound/Docked	Predicted Active Site Amino Acids[a,b]	Topological Location in CYP2B6	Reference
CYP102	Not Reported	Tamoxifen	**F206,** **S210,** **F297,** Q473	Helix F, F-F' loop, Helix I, C-terminal coil	(Lewis and Lake, 1997)
	1FAG	4-trifluoromethyl-7-ethoxycoumarin	T205, **F206,** **S294,** **T302,** **L363,** Q473, **C475**	Helix F, Helix F, Helix I, Helix I, K-K' loop, C-terminal coil, β4-1 strand	(Lewis et al., 1999)
	1FAG	*(S)*-mephenytoin	R109, **I114,** **F206,** **T302,** Q473, E474, **C475**	B'-C loop, B'-C loop, Helix F, Helix I, C-terminal coil, β4-1 strand, β4-1 strand	(Lewis et al., 1999)
	1FAG	Bupropion	**I114**, T205, **F206,** **L363,** Q473, E474	B'-C loop, Helix F, Helix F, K-K' loop, C-terminal coil, β4-1 strand	(Lewis et al., 1999)
	1FAG	Testosterone	**I101,** **I114,** T205, **F206,** **I209,** **T302,** **L363,** E474, **C475**	B-B' loop, B'-C loop, Helix F, Helix F, Helix F, Helix I, K-K' loop, β4-1 strand, β4-1 strand	(Lewis et al., 1999)
	1FAG	Antipyrine	**I114,** **F206,** **T302,** **C475**	B'-C loop, Helix F, Helix I, β4-1 strand	(Lewis et al., 1999)
	1FAG	Diazepam	**I114,** **F206,** **T302,** **L363,** Q473, E474, **C475**	B'-C loop, Helix F, Helix I, K-K' loop, C-terminal coil, β4-1 strand, β4-1 strand	(Lewis et al., 1999)
	1FAG	Methoxychlor	**I114,** T205, **F206,** **T302,** Q473,	B'-C loop, Helix F, Helix F, Helix I, C-terminal coil,	(Lewis et al., 1999)

			C475	β4-1 strand	
	1FAG	Cyclophosphamide	**I114,** **S294,** **T302,** **L363,** Q473, **C475**	B'-C loop, Helix I, Helix I, K-K' loop, C-terminal coil, β4-1 strand	(Lewis et al., 1999)
	1FAG	Ifosfamide	**S294,** **A298,** **T302,** **L363,** E474 **C475**	Helix I, Helix I, Helix I, K-K' loop, β4-1 strand, β4-1 strand	(Lewis et al., 1999)
	1FAG	7-pentoxyresorufin	**I114,** T205, **F206,** **T302,** **L363,** M365, **C475**	B'-C loop, Helix F, Helix F, Helix I, K-K' loop, K-K' loop, β4-1 strand	(Lewis et al., 1999)
	1FAG	7-benzyloxyresorufin	**I101,** **I114,** T205, **F206,** **T302,** **L363,** M365, **C475**	B-B' loop, B'-C loop, Helix F, Helix F, Helix I, K-K' loop, K-K' loop, β4-1 strand	(Lewis et al., 1999)
	1FAG	Orphenadrine	**I114,** **F115,** **F297,** **T302,** **L363,** E474	B'-C loop, B'-C loop, Helix I, K-K' loop, Helix I, β4-1 strand	(Lewis et al., 1999)
	1FAG	Selegiline	**I114,** **F115,** **F206,** **A298,** **T302,** **L363**	B'-C loop, B'-C loop, Helix F, Helix I, K-K' loop, Helix I	(Salonen et al., 2003)
CYP2C5	1DT6	4-trifluoromethyl-7-ethoxycoumarin	**I114,** **F115,** T205, **F206,** **S294,** **F297,** **T302,** **L363,** **V477**	B'-C loop, B'-C loop, Helix F, Helix F, Helix I, Helix I, Helix I, K-K' loop, C-terminal coil	(Lewis et al., 2002)
	1DT6	4-trifluoromethyl-7-ethoxycoumarin (orientation 1)	**F206,** **A298,** **E301,** **T302,** T305, T306,	Helix F, Helix I, Helix I, Helix I, Helix I, Helix I,	(Wang and Halpert, 2002)

			L362, **L363,** **V367,** **V477,** **G478,** **K479**	K-K' loop, K-K' loop, K-K' loop, C-terminal coil, C-terminal coil, β4-2 strand	
	1DT6	4-trifluoromethyl-7-ethoxycoumarin (orientation 2)	**K100,** M103, **I114,** **F115,** **F206,** **F297,** **A298,** **T302,** **V367,** **V477**	B-B' loop, B-B' loop, B'-C loop, B'-C loop, Helix F, Helix I, Helix I, Helix I, K-K' loop, C-terminal coil	(Wang and Halpert, 2002)
	1DT6	7-benzyloxyresorufin	**I114,** **F115,** **F206,** **F297,** **A298,** **E301,** **T302,** **L363,** **V367,** **V477,** **G478**	B'-C loop, B'-C loop, Helix F, Helix I, Helix I, Helix I, Helix I, K-K' loop, K-K' loop, C-terminal coil, C-terminal coil	(Wang and Halpert, 2002)
	1DT6	Cyclophosphamide	**I114,** **F115,** **F206,** **I209,** L216, **S294,** **F297,** **A298,** **T302,** **L363,** **V367,** **V477**	B'-C loop, B'-C loop, Helix F, Helix F, Helix F', Helix I, Helix I, Helix I, Helix I, K-K' loop, K-K' loop, C-terminal coil	(Bathelt et al., 2002)
	1DT6	Ifosfamide	**I114,** **F115,** **F206,** **I209,** L216, **S294,** **F297,** **A298,** **T302,** **L363,** **V367,** **V477**	B'-C loop, B'-C loop, Helix F, Helix F, Helix F', Helix I, Helix I, Helix I, Helix I, K-K' loop, K-K' loop, C-terminal coil	(Bathelt et al., 2002)
	1DT6	7-ethoxycoumarin	M103, **I209,** **L363,** **V367,** **V477**	B-B' loop, Helix F, K-K' loop, K-K' loop, C-terminal coil	(Spatzenegger et al., 2003)

	1DT6	4-trifluoromethyl-7-ethoxycoumarin	**S294,** **L363,** **V367,** **V477**	Helix I, K-K' loop, K-K' loop, C-terminal coil	(Spatzenegger et al., 2003)
	1DT6	7-pentoxyresorufin	**I114,** **F206,** S207, **T302,** **V367**	B'-C loop, Helix F, Helix F, Helix I, K-K' loop	(Lewis et al., 2004)
	1N6B	4-trifluoromethyl-7-ethoxycoumarin	**K100,** **I114,** **F115,** T205, **F206,** **T302,** **L363**	B-B' loop, B'-C loop, B'-C loop, Helix F, Helix F, Helix I, K-K' loop,	(Lewis et al., 2006)
CYP2B1[c]	N/A	3-cyclopentyloxy-*N*-(3,5-dichloro-4-pyridyl)-4-methoxybenzamide (RP 73401)	M103, R109, **L363,** M365, **V477**	B-B' loop, B'-C loop, K-K' loop, K-K' loop, C-terminal coil	(Domanski et al., 1999)
CYP2B4	Not Reported	Bergamottin	**A298,** **T302,** **L363**	Helix I, Helix I, K-K' loop	(Kent et al., 2006)
	1SUO	4-trifluoromethyl-7-ethoxycoumarin	**K100,** **I114,** **F115,** T205, **F206,** **T302,** **L363**	B-B' loop, B'-C loop, B'-C loop, Helix F, Helix F, Helix I, K-K' loop,	(Lewis et al., 2006)
	1SUO	Cyclophosphamide	**V104,** I110, **I114,** **F115,** **F206,** F208, **I209,** **F297,** **A298,** **E301,** **T302,** S320, **L363,** **V367,** **V477,** **G478**	B-B' loop, B'-C loop, B'-C loop, B'-C loop, Helix F, Helix F, Helix F, Helix I, Helix I, Helix I, Helix I, Helix J, K-K' loop, K-K' loop, C-terminal coil, C-terminal coil	(Nguyen et al., 2008)
	1SUO	4-(4-chlorophenyl) imidazole	**S210,** **F297,** **T302**	F-F' loop, Helix I, Helix I	(Lewis et al., 2010)

[a] Amino acids are numbered according to full-length refseq CYP2B6 (NX_P20813-1).
[b] Bolded and underlined amino acids indicate those found in the CYP2B6 active site according to the CYP2B6 crystal structures that have been solved and molecular docking results that have been yielded to date (Table 1).
[c] The CYP2B1 crystal structure utilized within Domanski et al., 1999 was homology modeled from a consensus of P450 BM-3, P450cam, and P450terp (Szklarz et al., 1995) and then used as a homology model for CYP2B6.

Supplemental Table 2. Kinetic parameters for the CYP2B6.1-mediated metabolism of substrates for which there are no reported catalytic constants of CYP2B6 mutants.

Substrate	Metabolic Method	Expression System[a]	K_m (μM)[a]	k_{cat} (min^{-1})[a]	Reference
Amitriptyline	*N*-demethylation	Human B-lymphoblastoid cell microsomes	144.4	NR	(Ekins and Wrighton, 1999)
Antipyrine	4-hydroxylation	Human B-lymphoblastoid cell microsomes	17,700	NR	(Ekins and Wrighton, 1999)
Arteether	*O*-deethylation	Human B-lymphoblastoid cell microsomes	28	NR	(Ekins and Wrighton, 1999)
Azinphos-methyl	*S*-oxidation	Supersomes	2.2	2.8	(Buratti et al., 2002)
2,2',4,4'-tetrabromodiphenyl ether (BDE-47)	3-hydroxylation	Supersomes	6.4	0.0106	(Feo et al., 2013)
	4-hydroxylation		2.7	0.150	(Erratico et al., 2013)
	4'-hydroxylation		1.2	0.270	(Erratico et al., 2013)
	5-hydroxylation		3.8	0.948	(Feo et al., 2013)
			5.8	0.300	(Erratico et al., 2013)
	6-hydroxylation		4.2	0.202	(Feo et al., 2013)
			2.8	0.260	(Erratico et al., 2013)
2,2',4,4',5-pentabromodiphenyl ether (BDE-99)	1'-hydroxylation	Supersomes	0.1	0.2116	(Erratico et al., 2012)
	2-hydroxylation		0.3	0.0068	(Erratico et al., 2012)
	4-hydroxylation		0.3	0.0276	(Erratico et al., 2012)
	4'-hydroxylation		0.9	0.2467	(Erratico et al., 2012)
	5'-hydroxylation		2.4	0.4573	(Erratico et al., 2012)
	6'-hydroxylation		0.3	0.0141	(Erratico et al., 2012)
2,2',4,4',6-pentabromodiphenyl ether (BDE-100)	3-hydroxylation	Supersomes	5.2	0.0099	(Gross et al., 2015)
	4'-hydroxylation		5.5	0.066	(Gross et al., 2015)
	5'-hydroxylation		4.9	0.166	(Gross et al., 2015)
	6'-hydroxylation		7.0	0.043	(Gross et al., 2015)
(R)-1,3-Benzodioxolyl-*N*-methylbutanamine (MBDB)	*N*-demethylation	Supersomes	138	2.5	(Niwa et al., 2011)
(S)-1,3-Benzodioxolyl-*N*-methylbutanamine (MBDB)			119	0.7	(Niwa et al., 2011)
(R)-1,3-Benzodioxolyl-*N*-methylbutanamine (MBDB)	Demethylenation		83	3.3	(Niwa et al., 2011)

(S)-1,3-Benzodioxolyl-*N*-methylbutanamine (MBDB)			56	0.2	(Niwa et al., 2011)
7-benzyloxyresorufin	*N*-demethylation	Human B-lymphoblastoid cell microsomes	1.28	NR	(Ekins and Wrighton, 1999)
7-benzyloxyquinoline	*O*-debenzylation	Baculovirus-infected insect cell microsomes	NR	0.55	(Renwick et al., 2001)
Bromoketamine	*N*-demethylation	Baculovirus-infected insect cell microsomes	10	94	(Wang et al., 2019)
4-chloromethyl-7-ethoxycoumarin	*O*-deethylation	Human B-lymphoblastoid cell microsomes	33.7	NR	(Ekins and Wrighton, 1999)
Carbaryl	Methyl hydroxylation	Supersomes	45	15.54	(Tang et al., 2002)
	4-hydroxylation		11	0.80	(Tang et al., 2002)
	5-hydroxylation		110	0.29	(Tang et al., 2002)
Cinnarizine	*p*-hydroxylation	Human B-lymphoblastoid cell microsomes	17.2	NR	(Ekins and Wrighton, 1999)
Clobazam	*N*-demethylation	Supersomes	289	5.70	(Giraud et al., 2004)
3-cyano-7-ethoxycoumarin	*O*-deethylation	Human B-lymphoblastoid cell microsomes	71.3	NR	(Ekins and Wrighton, 1999)
Deschloroketamine	*N*-demethylation	Baculovirus-infected insect cell microsomes	184	83	(Wang et al., 2019)
Dextromethorphan	*N*-demethylation	Human B-lymphoblastoid cell microsomes	350	NR	(Ekins and Wrighton, 1999)
Diazepam	*N*-demethylation	Human B-lymphoblastoid cell microsomes	181	NR	(Ekins and Wrighton, 1999)
Diazinon	*S*-oxidation	Supersomes	14.83	5.44	(Ellison et al., 2012)
	Dearylation		13.94	2.60	(Ellison et al., 2012)
1,2-dibromoethane	2-bromo acetaldehyde formation	Human B-lymphoblastoid cell microsomes	9,700	NR	(Ekins and Wrighton, 1999)
N,N-diethyl-m-toluamide (DEET)	Ring methyl hydroxylation	Supersomes	40.2	22.3	(Usmani et al., 2002)
			46.2	34.7	(Edwards et al., 2005)
Disulfoton	*S*-oxidation	Supersomes	11.2	62.2	(Usmani et al., 2004)
Efavirenz *trans*-alkene analog	7- or 8-hydroxylation	Supersomes	0.23	0.13	(Cox and Bumpus, 2014)

Efavirenz 13-propyl analog	5- or 7-hydroxylation and 8-hydroxylation		1.10	0.97	(Cox and Bumpus, 2014)
Efavirenz benzoxazine analog	7- or 8-hydroxylation		0.22	3.2	(Cox and Bumpus, 2014)
Efavirenz methyl benzoxazine analog	Methyl hydroxylation		1.4	NR	(Cox and Bumpus, 2016)
	5-, 7-, or 8-hydroxylation		1.0	NR	(Cox and Bumpus, 2016)
Efavirenz quinazolinone analog	Benzene ring hydroxylation		11	NR	(Cox and Bumpus, 2016)
Efavirenz *trans*-alkene quinazolinone analog	5-, 7-, or 8-hydroxylation		13	NR	(Cox and Bumpus, 2016)
Efavirenz quinolinone analog	Benzene ring hydroxylation		14	NR	(Cox and Bumpus, 2016)
Efavirenz benzo[d][1,3]dioxin-2-one analog	Unknown hydroxylation		5.5	NR	(Cox and Bumpus, 2016)
Endosulfan-α	*S*-oxidation	Supersomes	16.2	11.4	(Casabar et al., 2006)
			5.58	10.31	(Lee et al., 2006)
(-)-fenchone	6-exo-hydroxylation	Supersomes	150	12.9	(Miyazawa and Gyoubu, 2007)
	6-endo-hydroxylation		260	5.33	(Miyazawa and Gyoubu, 2007)
	10-hydroxylation		200	10.66	(Miyazawa and Gyoubu, 2007)
Fluoroketamine	*N*-demethylation	Baculovirus-infected insect cell microsomes	40	103	(Wang et al., 2019)
(R)-fluoxetine	*N*-demethylation	Supersomes	126	1.19	(Niwa et al., 2011)
(S)-fluoxetine			546	2.55	(Niwa et al., 2011)
7-hydroxyefavirenz	14-hydroxylation	Supersomes	62.4	1.3	(Ogburn et al., 2010)
8-hydroxyefavirenz	14-hydroxylation	Supersomes	2.12	8.5	(Ward et al., 2003)
			23.2	4.21	(Ogburn et al., 2010)
Ifosfamide	*N*-dechloro-ethylation	*Escherichia coli* C41 DE3	2,000	0.4	(Calinski et al., 2015)
	4-hydroxylation		4,600	3.8	(Calinski et al., 2015)
Deuterated ifosfamide[c]	*N*-dechloro-ethylation		2,000	0.2	(Calinski et al., 2015)
	4-hydroxylation		2,000	4.1	(Calinski et al., 2015)
(R)-ifosfamide	*N*-dechloro-ethylation	Supersomes	1,900	8.2	(Roy et al., 1999)
(S)-ifosfamide			900	11.8	(Roy et al., 1999)
(R)-ifosfamide	4-hydroxylation		NR	<0.4	(Roy et al., 1999)

			2,240	1.98	(Niwa et al., 2011)
(S)-ifosfamide			NR	2.08	(Roy et al., 1999)
			1,270	17.1	(Niwa et al., 2011)
Imipramine	*N*-demethylation	*Saccharomyces cerevisiae* microsomes	383	NR	(Ekins and Wrighton, 1999)
β-ionone	4-hydroxylation	Supersomes	5.6	572.8	(Marumoto et al., 2017)
Lidocaine	*N*-deethylation	Human B-lymphoblastoid cell microsomes	537.6	NR	(Ekins and Wrighton, 1999)
Loperamide	*N*-demethylation	Supersomes	65.6	0.008	(Kim et al., 2004)
Malathion	*S*-oxidation	Supersomes	3.09	3.6	(Buratti et al., 2005)
(S)-mephenytoin	*N*-demethylation	Human B-lymphoblastoid cell microsomes	564	NR	(Ekins and Wrighton, 1999)
(S)-mephobarbital	*N*-demethylation	Human B-lymphoblastoid cell microsomes	264	0.008	(Kobayashi et al., 1999a)
Methiocarb	*S*-oxidation	Supersomes	11.0	28.0	(Usmani et al., 2004)
Methyl parathion	*S*-oxidation	Supersomes	1.25	10.39	(Ellison et al., 2012)
	Dearylation		141	1.42	(Ellison et al., 2012)
Midazolam	1'-hydroxylation	Human B-lymphoblastoid cell microsomes	46.1	NR	(Ekins and Wrighton, 1999)
Naphthalene	1-hydroxylation	Supersomes	58.6	20.2	(Cho et al., 2006)
	2-hydroxylation		93.8	0.8	(Cho et al., 2006)
	1,2-dihydroxylation		49.5	2.2	(Cho et al., 2006)
Nevirapine	3-hydroxylation	Human B-lymphoblastoid cell microsomes	834	NR	(Erickson et al., 1999)
Nonane	2-hydroxylation	Supersomes	79.0	76.0	(Edwards et al., 2005)
2-nonanol	*C*-oxidation	Supersomes	35.0	72.8	(Edwards et al., 2005)
(R)-norketamine	5-hydroxylation	Supersomes	21.6[b]	16.72[b]	(Desta et al., 2012)
	C-oxidation		286.5	13.0	(Desta et al., 2012)
(S)-norketamine	5-hydroxylation		36.1[b]	16.3[b]	(Desta et al., 2012)
	C-oxidation		146.8	7.61	(Desta et al., 2012)

Parathion	*S*-oxidation	Supersomes	0.8	1.7	(Buratti et al., 2002)
		NR	0.61	4.827	(Foxenberg et al., 2007)
	Dearylation		0.74	1.804	(Foxenberg et al., 2007)
Pethidine	*N*-demethylation	Supersomes	262	82	(Murray et al., 2020)
Phorate	*S*-oxidation	Supersomes	32.1	70.8	(Usmani et al., 2004)
Propofol	4-hydroxylation	Human B-lymphoblastoid cell microsomes	10	21	(Court et al., 2001)
(-)-*cis*-rose oxide	9-hydroxylation	Supersomes	159.2	60.67	(Nakahashi et al., 2015)
(-)-*trans*-rose oxide			73.80	154.0	(Nakahashi et al., 2015)
Sertraline	*N*-demethylation	Human B-lymphoblastoid cell microsomes	30.7	2.04	(Kobayashi et al., 1999b)
(+)-*cis*-3,5-dimethyl-2-(3-pyridyl) thiazolidin-4-one hydrochloride (SM-12502)	*S*-oxidation	Human B-lymphoblastoid cell microsomes	1,767	NR	(Ekins and Wrighton, 1999)
Styrene	Glycol formation	Human B-lymphoblastoid cell microsomes	180	NR	(Ekins and Wrighton, 1999)
Verapamil	*O*-demethylation	Human B-lymphoblastoid cell microsomes	137.4	NR	(Ekins and Wrighton, 1999)

[a] NR indicates data/values that were not reported.
[b] These authors analyzed the diastereomeric metabolites formed by CYP2B6-mediated 5-hydroxylation of *(R;S)*-norketamine; CYP2B6 showed the highest intrinsic clearance with its production of *(2S,5S;2R,5R)*-hydroxynorketamine, the K_m and k_{cat} of which is reported.
[c] This ifosfamide was deuterated on its alpha and alpha' carbons.

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