SUPPLEMENTAL INFORMATION

Catalytic vs. Inhibitory Promiscuity and the Evolution of New Enzymatic Function

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The probes substrates used were: CYP19A1, testosterone; CYP26A1, all trans retinoic acid; CYP4F12, terfenadine; CYP1A2, phenacetin; CYP2C9, diclofenac, CYP2C19, (s)-mephenytoin; CYP2D6, dextromethorphan; CYP3A4, midazolam. For CYP26A1, the kcat/KM values were determined by HPLC using authentic product as standard, rather than by substrate depletion methods. In table 1, kcat and KM have their standard definitions and $k \rightarrow 0$ is the initial rate extrapolated from substrate depletion.

	CYP1A2				CYP2C8				CYP2C9				CYP2C19				CYP2D6			
	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax
Amiodarone	DNC*	DNC	---	---	DNC	DNC	---	---	DNC	DNC	---	---	DNC	DNC	---	---	DNC	DNC	---	---
Amitriptyline	---**	---	---	---	---	---	---	---	---	---	---	---	DNC	DNC	---	---	7.08	0.05	4.60	32.6
Artemisinin	0.03	0.04	3.90	0.1	0.05	0.05	4.90	0.2	---	---	---	---	---	---	---	---	---	---	---	---
Astemizole	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	6.02	0.05	4.60	27.7
Atenolol	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Bepridil	---	---	---	---	---	---	---	---	0.99	0.01	1.20	1.2	11.13	0.03	2.90	32.3	---	---	---	---
Budesonide	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Carbamazepine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
chloroquine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	4.24	0.02	1.90	8.1
Chlorpheniramine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1.15	0.02	2.40	2.8
Cimetidine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cisapride	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Clotrimazole	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cyclosporin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Danazol	---	---	---	---	0.14	0.04	4.20	0.6	---	---	---	---	---	---	---	---	---	---	---	---
Dexamethasone	---	---	---	---	---	---	---	---	DNC	DNC	---	---	---	---	---	---	---	---	---	---
Digoxin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Diltiazem	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Diphenhydramine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1.65	0.05	4.50	7.4
Diphenylhydantoin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Erythromycin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Fluconazole	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Flurbiprofen	---	---	---	---	---	---	---	---	---	---	---	---	0.12	0.03	2.50	0.3	---	---	---	---
Fluvoxamine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0.84	0.04	4.40	3.7
Haloperidol	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Isradipine	---	---	---	---	1.76	0.02	1.90	3.3	---	---	---	---	5.35	0.02	1.50	8.0	---	---	---	---
Ivermectin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Ketoconazole	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Lansoprazole	---	---	---	---	---	---	---	---	DNC	DNC	---	---	---	---	---	---	---	---	---	---
Loratadine	---	---	---	---	---	---	---	---	---	---	---	---	0.42	0.05	4.70	2.0	3.27	0.05	4.90	16.0
Lovastatin	---	---	---	---	0.40	0.04	3.70	1.5	---	---	---	---	---	---	---	---	---	---	---	---
Mefloquine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Methoxypsoralen	0.18	0.04	4.30	0.8	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Naproxen	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Nicardipine	---	---	---	---	0.01	0.09	9.10	0.1	---	---	---	---	1.73	0.03	3.20	5.5	3.49	0.03	2.70	9.4
Nifedipine	---	---	---	---	---	---	---	---	---	---	---	---	DNC	DNC	---	---	DNC	DNC	---	---
Norfloxacin	---	---	---	---	---	---	---	---	---	---	---	---	0.56	0.01	1.20	0.7	---	---	---	---
Orphenadrine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Paclitaxel	---	---	---	---	1.22	0.01	1.40	1.7	DNC	DNC	---	---	---	---	---	---	---	---	---	---
Paroxetine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0.29	0.21	21.20	6.2
Perphenazine	0.60	0.03	2.60	1.6	---	---	---	---	---	---	---	---	---	---	---	---	0.13	0.18	18.40	2.4
Pimozide	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0.33	0.05	4.60	1.5

Pravastatin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Promethazine	2.05	0.01	1.20	2.5	---	---	---	---	---	---	---	---	---	---	---	---	0.19	0.09	8.80	1.7
Propranolol	1.44	0.02	1.60	2.3	---	---	---	---	---	---	---	---	---	---	---	---	3.79	0.10	10.00	37.9
Quinapril	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Quinidine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Ranolazine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

	CYP1A2				CYP2C8				CYP2C9				CYP2C19				CYP2D6			
	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax
Sertraline	---	---	---	---	---	---	---	---	---	---	---	---	1.58	0.03	3.10	4.9	1.89	0.05	4.50	8.5
Simvastatin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Tamoxifen	---	---	---	---	0.04	0.06	6.20	0.2	---	---	---	---	---	---	---	---	---	---	---	---
Terfenadine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Ticlopidine	DNC	DNC	---	---	DNC	DNC	---	---	30.88	0.04	4.00	123.5	13.86	0.05	4.50	62.4	2.36	0.04	3.80	9.0
Verapamil	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Warfarin	---	---	---	---	---	---	---	---	1.75	0.08	8.11	14.20	---	---	---	---	---	---	---	---

	CYP2E1				CYP3A4				CYP3A5				CYP26A1				CYP4F12			
	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax
Amiodarone	DNC	DNC	---	---	57.80	0.04	4.40	254.3	14.80	0.03	2.90	42.9	---	---	---	---	---	---	---	---
Amitriptyline	---	---	---	---	---	---	---	---	6.03	0.02	1.90	11.5	---	---	---	---	---	---	---	---
Artemisinin	---	---	---	---	DNC	DNC	---	---	1.33	0.03	2.80	3.7	---	---	---	---	---	---	---	---
Astemizole	---	---	---	---	0.89	0.03	2.90	2.6	6.39	0.03	2.60	16.6	---	---	---	---	1.73	0.112	11.2	19.38
Atenolol	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Bepridil	3.18	0.02	2.40	7.6	3.58	0.03	3.40	12.2	6.33	0.03	3.10	19.6	---	---	---	---	---	---	---	---
Budesonide	0.50	0.02	1.50	0.8	0.97	0.05	4.90	4.8	9.91	0.02	1.90	18.8	---	---	---	---	---	---	---	---
Carbamazepine	---	---	---	---	---	---	---	---	7.09	0.04	4.10	29.1	---	---	---	---	---	---	---	---
chloroquine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Chlorpheniramine	---	---	---	---	---	---	---	---	0.65	0.02	2.30	1.5	---	---	---	---	---	---	---	---
Cimetidine	---	---	---	---	DNC	DNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cisapride	---	---	---	---	0.68	0.04	4.20	2.9	---	---	---	---	---	---	---	---	---	---	---	---
Clotrimazole	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Cyclosporin	DNC	DNC	---	---	0.00	0.03	3.40	0.0	---	---	---	---	---	---	---	---	---	---	---	---
Danazol	---	---	---	---	9.66	0.04	4.20	40.6	1.41	0.02	1.70	2.4	---	---	---	---	---	---	---	---
Dexamethasone	---	---	---	---	DNC	DNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Digoxin	---	---	---	---	DNC	DNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Diltiazem	---	---	---	---	0.77	0.02	1.90	1.5	---	---	---	---	---	---	---	---	---	---	---	---
Diphenhydramine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Diphenylhydantoin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Erythromycin	---	---	---	---	40.10	0.01	0.80	32.1	---	---	---	---	---	---	---	---	---	---	---	---
Fluconazole	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Flurbiprofen	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Fluvoxamine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Haloperidol	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Isradipine	DNC	DNC	---	---	5.54	0.10	9.90	54.8	0.11	0.04	3.70	0.4	---	---	---	---	---	---	---	---
Ivermectin	DNC	DNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Ketoconazole	---	---	---	---	0.04	0.04	4.10	0.1	---	---	---	---	---	---	---	---	---	---	---	---
Lansoprazole	---	---	---	---	DNC	DNC	---	---	0.02	0.09	8.80	0.2	---	---	---	---	---	---	---	---
Loratadine	---	---	---	---	0.36	0.04	3.60	1.3	---	---	---	---	---	---	---	---	---	---	---	---
Lovastatin	DNC	DNC	---	---	4.26	0.20	20.20	86.1	2.02	0.03	2.90	5.9	---	---	---	---	---	---	---	---
Mefloquine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Methoxypsoralen	0.43	0.01	1.10	0.5	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Naproxen	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Nicardipine	DNC	DNC	---	---	0.53	0.19	19.30	10.1	0.62	0.09	9.40	5.9	---	---	---	---	---	---	---	---
Nifedipine	DNC	DNC	---	---	65.10	0.04	4.30	279.9	0.45	0.02	1.80	0.8	---	---	---	---	---	---	---	---
Norfloxacin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Orphenadrine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Paclitaxel	DNC	DNC	---	---	0.32	0.04	3.70	1.2	---	---	---	---	---	---	---	---	---	---	---	---

Paroxetine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Perphenazine	---	---	---	---	2.87	0.03	3.40	9.8	0.01	0.03	2.80	0.0	---	---	---	---	---	---	---	---
Pimozide	---	---	---	---	DNC	DNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Pravastatin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Promethazine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Propranolol	---	---	---	---	---	---	---	---	0.01	0.01	0.90	0.0	---	---	---	---	---	---	---	---
Quinapril	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Quinidine	DNC	DNC	---	---	DNC	DNC	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Ranolazine	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

	CYP2E1				CYP3A4				CYP3A5				CYP26A1				CYP4F12			
	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax	Km	k->0	Clint	Vmax
Sertraline	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
Simvastatin	---	---	---	---	2.86	0.18	17.70	50.6	1.45	0.10	9.90	14.4	---	---	---	---	---	---	---	---
Tamoxifen	---	---	---	---	0.64	0.04	4.00	2.6	0.09	0.03	3.10	0.3	---	---	---	---	---	---	---	---
Terfenadine	---	---	---	---	0.12	0.03	2.50	0.3	DNC	DNC	---	---	---	---	---	---	0.58****	---	9.72	5.64
Ticlopidine	DNC	DNC	---	---	DNC	DNC	---	---	46.90	0.03	3.40	159.5	---	---	---	---	---	---	---	---
Verapamil	---	---	---	---	1.71	0.04	4.30	7.4	4.66	0.01	1.30	6.1	---	---	---	---	---	---	---	---
Warfarin	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

* Does not converge

** No turnover detected

*** Retinoic acid used as a positive control

**** Calculated from Metabolite formation data