U.S. Food and Drug Administration

Drugs

Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

CYP Enzymes

In vitro

Table 1: Chemical inhibitors for in vitro experiments* (9/25/2006)

CYP	Inhibitor (1) Preferred	Ki (μM)	Inhibitor (1) Acceptable	Ki (μM)
1A2	furafylline (2)	0.6-0.73	a -naphthoflavone	0.01
2A6	tranylcypromine	0.02-0.2	pilocarpine	4
	methoxsalen (2)	0.01-0.2	tryptamine	1.7 (3)
2B6			3-isopropenyl-3-methyl diamantane (4)	2.2
			2-isopropenyl-2-methyl adamantane (4)	5.3
			sertraline	3.2 (5)
			phencyclidine	10
			triethylenethiophosphoramide (thiotepa)	4.8
			clopidogrel	0.5
			ticlopidine	0.2
2C8	montelukast		trimethoprim	32
	quercetin	1.1	gemfibrozil	69-75
			rosiglitazone	5.6
			pioglitazone	1.7
2C9	sulfaphenazole	0.3	fluconazole	7
			fluvoxamine	6.4-19
			fluoxetine	18-41
2C19			ticlopidine	1.2
			nootkatone	0.5
2D6	quinidine	0.027-0.4		
2E1			diethyldithiocarbamate	9.8-34
			clomethiazole	12
			diallyldisulfide	150
3A4/5	ketoconazole	0.0037- 0.18	azamulin	(6)
	itraconazole	0.27, 2.3	troleandomycin	17
			verapamil	10, 24

* Note that this is not an exhaustive list which was created May 1, 2006.

1. Substrates used for inhibition studies include: **CYP1A2**, phenacetin-o-deethylation, theophylline-N-demethylation; **CYP2A6**, coumarin-7-hydroxylation; **CYP2B6**, 7-pentoxyresorufin-O-dependentylation,

bupropion hydroxylation, 7-ethoxy-4-(trifluoromethyl)-coumarin O-deethylation, S-mephenytoin-N-demethylation; Bupropion-hydroxylation; **CYP2C8**, taxol 6-alpha-hydroxylation; **CYP2C9**, tolbutamide 4-methylhydroxylation, S-warfarin-7-hydroxylation, phenytoin 4-hydroxylation; **2CYP2C19**, (S)-mephenytoin 4-hydroxylation **CYP2D6**, dextramethorphan O-demethylation, desbrisoquine hyddroxylase; **CYP2E1**, chlorzoxazone 6-hydroxylation, aniline 4-hydroxylase; **CYP3A4/5**, testosterone-6ß-hydroxylation, midazolam-1-hydroxylation; cyclosporine hydroxylase; nefedipine dehydrogenation.

2. Furafylline and methoxsalen are mechanism-based inhibitors and should be pre-incubated before adding substrate.
3. cDNA expressing microsomes from human lymphoblast cells.
4. Supersomes, microsomal isolated from insect cells transfected with baculovirus containing CYP2B6.
5. IC50 values.
6. Specific time-dependent inhibitor.

Table 2. Preferred and acceptable chemical substrates for in vitro experiments* (9/25/2006)

CYP	Substrate Preferred	Km (µM)	Substrate Acceptable	Km (µM)
1A2	phenacetin-O-deethylation	1.7-152	7-ethoxyresorufin-O-deethylation	0.18-0.21
			theophylline-N-demethylation	280-1230
			caffeine-3-N-demethylation	220-1565
			tacrine 1-hydroxylation	2.8, 16
2A6	coumarin-7-hydroxylation	0.30-2.3		
	nicotine C-oxidation	13-162		
2B6	efavirenz hydroxylase	17-23	propofol hydroxylati on	3.7-94
	bupropion-hydroxylation	67-168	S-mephenytoin-N-demethylation	1910
2C8	Taxol 6-hydroxylation	5.4-19	amodiaquine N-deethylation	2.4,
			rosiglitazone para-hydroxylation	4.3-7.7
2C9	tolbutamide methyl-hydroxylation	67-838	flurbiprofen 4'-hydroxylation	6-42
	S-warfarin 7-hydroxylation	1.5-4.5	phenytoin-4-hydroxylation	11.5-117
	diclofenac 4'-hydroxylation	3.4-52		
2C19	S-mephenytoin 4'-hydroxylation	13-35	omeprazole 5-hydroxylation	17-26
			fluoxetine O-dealkylation	3.7-104
2D6	(±)-bufuralol 1'-hydroxylation	9-15	debrisoquine 4-hydroxylation	5.6
	dextromethorphan O-demethylation	0.44-8.5		
2E1	chlorzoxazone 6-hydroxylation	39-157	p-nitrophenol 3-hydroxylation	3.3
			lauric acid 11-hydroxylation	130
			aniline 4-hydroxylation	6.3-24
3A4/5**	midazolam 1-hydroxylation	1-14	erythromycin N-demethylation	33 – 88
			dextromethorphan N-demethylation	133-710
			triazolam 4-hydroxylation	234
	testosterone 6 b -hydroxylation	52-94	terfenadine C-hydroxylation	15
			nifedipine oxidation	5.1- 47

* Note that this is not an exhaustive list (created May 1, 2006).

** Recommend use of 2 structurally unrelated CYP3A4/5 substrates for evaluation of in vitro CYP3A inhibition. I the drug inhibits at least one CYP3A substrate in vitro, then in vivo evaluation is warranted.

Table 3. Chemical Inducers for In Vitro Experiments* (5/1/2006)

CYP	Inducer [1] -Preferred	Inducer Concentrations (µM)	Fold Induction	Inducer [1] -Acceptable	Inducer Concentrations (µM)	Fold Induction
1A2	omeprazole	25-100	14-24	lansoprazole	10	10
	ß-naphthoflavone[2]	33-50	4-23			
	3-methylcholanthrene	1,2	6-26			
2A6	dexamethasone	50	9.4	pyrazole	1000	7.7
2B6	phenobarbital	500-1000	5-10	phenytoin	50	5-10
2C8	rifampin	10	2-4	phenobarbital	500	2-3
2C9	rifampin	10	3.7	phenobarbital	100	2.6
2C19	rifampin	10	20			
2D6	none identified					
2E1	none identified					

3A4	rifampin[3]	10-50	4-31	phenobarbital[3]	100-2000	3-31
				phenytoin	50	12.5
				rifapentine	50	9.3
				troglitazone	10-75	7
				taxol	4	5.2
				dexamethasone[4]	33-250	2.9- 6.9

* Note that this is not an exhaustive list (created May 1, 2006).

1. Except for the cases noted below, the following test substrates were used: CYP1A2, 7-ethoxyresorufin; CY 2A6, coumarin; CYP2C9, tolbutamide, CYP2C19, S-mephenytoin; CYP3A4, testosterone.
2. CYP1A2: 1 of 4 references for b -naphthoflavone used phenacetin.
3. CYP3A4: 2 of 13 references for rifampin and 1 of 3 references for phenobarbital used midazolam.
4. CYP3A4: 1 of the 4 references for dexamethasone used nifedipine.

In vivo

Table 4. Examples of in vivo substrate, inhibitor, and inducer for specific CYP enzymes for study (oral administration) [1] * (5/1/2006)

CYP	Substrate	Inhibitor	Inducer
1A2	theophylline, caffeine	fluvoxamine	smokers versus non-smokers [2]
2B6	efavirenz		rifampin
2C8	repaglinide, rosiglitazone	gemfibrozil	rifampin
2C9	warfarin, tolbutamide	fluconazole, amiodarone	rifampin
		(use of PM versus EM subjects) [3]	
2C19	omeprazole, esoprazole, lansoprazole, pantoprazole	omeprazole, fluvoxamine, moclobemide	rifampin
		(use of PM versus EM subjects) [3]	
2D6	desipramine, dextromethorphan, atomoxetine	paroxetine, quinidine, fluoxetine	none identified
		(use of PM versus EM subjects) [3]	
2E1	chlorzoxazone	disulfirum	ethanol
3A4/ 3A5	midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam	atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	rifampin, carbamazepine

* Note that this is not an exhaustive list (created May 1, 2006).

1. Substrates for any particular CYP enzyme listed in this table are those with plasma AUC values increased by **2-fold or higher** when co-administered with inhibitors of that CYP enzyme; for CYP3A, only those with plasma AUC increased by **5-fold or higher** are listed. Inhibitors listed are those that increase plasma AUC values of substrates for that CYP enzyme by 2-fold or higher. For CYP3A inhibitors, only those that increase AUC of CYP3A substrates by 5-fold or higher are listed. Inducers listed are those that decrease plasma AUC values of substrates for that CYP enzyme by **30% or higher**.
2. A clinical study can be conducted in smokers as compared to non-smokers (in lieu of an interaction study with an inducer), when appropriate.
3. A clinical study can be conducted in poor metabolizers (PM) as compared to extensive metabolizers (EM) for the specific CYP enzyme (in lieu of an interaction study with an inhibitor), when appropriate.

Classification of Inhibitors

Table 5. Classification of CYP3A inhibitors *[1] (5/1/2006)

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Weak CYP3A inhibitors
≥ 5-fold increase in AUC	≥ 2 but <5-fold increase in AUC	≥ 1.25 but <2-fold increase in AUC
atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice(a), verapami	cimetidine

* Note that this is not an exhaustive list (created May 1, 2006).

(1) Please note the following:

- A *strong inhibitor* is one that caused a ≥ 5-fold increase in the plasma AUC values or more than 80% decrease in clearance of *CYP3A substrates (not limited to midazolam, a sensitive CYP3A substrate)* in clinical evaluations
- A *moderate inhibitor* is one that caused a ≥ 2- but < 5-fold increase in the AUC values or 50-80% decrease in clearance of *sensitive CYP3A substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval* in clinical evaluations.
- A *weak inhibitor* is one that caused a ≥ 1.25 - but < 2-fold increase in the AUC values or 20-50% decreas in clearance of *sensitive CYP3A substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval* in clinical evaluations

(a) The effect of grapefruit juice varies widely.

Table 6. Classification of inhibitors of other CYP enzymes * (1) (5/1/2006)

Strong	Moderate	Weak
CYP1A2 inhibitors	CYP1A2 inhibitors	CYP1A2 inhibitors
fluvoxamine	ciprofloxacin mexiletine propafenone zileuton	acyclovir cimetidine famotidine norfloxacin verapamil
CYP2C8 inhibitors	CYP2C8 inhibitors	CYP2C8 inhibitors
gemfibrozil		trimethoprim
CYP2C9 inhibitors	CYP2C9 inhibitors	CYP2C9 inhibitors
	amiodarone, fluconazole, oxandrolone	sulfinpyrazone
CYP2C19 inhibitors	CYP2C19 inhibitors	CYP2C19 inhibitors
omeprazole		
CYP2D6 inhibitors	CYP2D6 inhibitors	CYP2D6 inhibitors
fluoxetine, paroxetine, quinidine	duloxetine, terbinafine	amiodarone, sertraline

* Note that this is not an exhaustive list (created May 1, 2006).

(1) Please note the following:

- A *strong inhibitor* is one that caused a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance of *CYP substrates (not limited to sensitive CYP substrate)* in clinical evaluations
- A *moderate inhibitor* is one that caused a > 2- but < 5-fold increase in the AUC values or 50-80% decrease in clearance of *sensitive CYP substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval* in clinical evaluations.
- A *weak inhibitor* is one that caused a > 1.25 - but < 2-fold increase in the AUC values or 20-50% decreas in clearance of *sensitive CYP substrates when the inhibitor was given at the highest approved dose and th shortest dosing interval* in clinical evaluations

Classification of Substrates

Table 7. Examples (1) of sensitive CYP3A substrates or CYP3A substrates with narrow therapeutic range * (5/1/2006)

Sensitive CYP3A substrates (1)	CYP3A Substrates with Narrow therapeutic range (2)
budesonide, buspirone, eplerenone , eletriptan, felodipine, fluticasone, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam, vardenafil	alfentanil, astemizole(a), cisapride(a), cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(a)

* Note that this is not an exhaustive list (created May 1, 2006).

1. *Sensitive CYP3A substrates* refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP3A inhibitor.

2. CYP3A *substrates with narrow therapeutic range* refers to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of CYP3A inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

(a) Not available in the United States.

Table 8. Examples sensitive CYP substrates or CYP substrates with narrow therapeutic range * (5/1/2006)

Sensitive CYP1A2 substrates [1]	CYP1A2 substrates with narrow therapeutic range [2]
duloxetine, alosetron	theophylline, tizanidine
Sensitive CYP2C8 substrates [1]	CYP2C8 substrates with narrow therapeutic range [2]
repaglinide	paclitaxel
Sensitive CYP2C9 substrates [1]	CYP2C9 substrates with narrow therapeutic range [2]
	warfarin, phenytoin
Sensitive CYP2C19 substrates [1]	CYP2C19 substrates with narrow therapeutic range [2]
omeprazole	s-mephenytoin
Sensitive CYP2D6 substrates [1]	CYP2D6 substrates with narrow therapeutic range [2]
desipramine	thioridazine

* Note that this is not an exhaustive list (created May 1, 2006).

1. *Sensitive CYP substrates* refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.
2. CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

P-gp Transporters

Table 9. Acceptable In Vitro P-gp Substrates * (5/1/2006)

Drug	Conc. Used (µM)	Caco-2 Ratio**	MDR1-MDCK*** Ratio**	MDR1-LLCPK*** Ratio**
Digoxin	0.01-10	4-14	4	4
Loperamide	1-10	2-5		3.4
Quinidine	0.05	3		5
Vinblastine [a]	0.004-10	2-18	> 9 [b]	3
Talinolol	30	26		

* Note that this is not an exhaustive list (created May 1, 2006).

** $P_{app, B-A} / P_{app, A-B}$; P_{app} = apparent permeability

*** Data for MDR1-MDCK and MDR1-LLCPK are the ratio observed in transfected cells relative to the ratio observed in respective wild-type cells.

[a] Vinblastine is also a substrate for MRP2 that is constitutively expressed in Caco-2, and wild type MDCK and LL-CPK1 cells.

[b] Data are derived from net B to A flux in the absence of GF120918, a potent P-gp inhibitor, relative to that observed in the presence of GF120918.

Table 10. In Vitro P-gp Inhibitors * (5/1/2006)

Inhibitor	IC50 (µM) Caco-2*	Ki (µM) Caco-2*	MDCK-MDR1*	LLC-PK1 MDR1**
Cyclosporine A [a]	1.3	0.5	2.2	1.3
Ketoconazole [a]	1.2			5.3

LY335979	0.024			
Nelfinavir [a]	1.4			
Quinidine [b]	2.2	3.2	8.6	
Ritonavir [a]	3.8			
Saquinavir [a]	6.5			
Tacrolimus	0.74			
Valspodar (PSC833)	0.11			
Verapamil	2.1	8	15	23
Elacridar (GF120918) (GG 918)		0.4	0.4	
Reserpine		1.4	11.5	

* Note that this is not an exhaustive list (created May 1, 2006).

* Digoxin as a P-gp substrate

** Vinblastine as a P-gp substrate

[a] also CYP3A inhibitor

[b] also CYP2D6 inhibitor

Major Human Transporters

Table 11. Major human transporters * [(1)] (5/1/2006)

Gene	Aliases	Tissue	Substrate	Inhibitor	Inducer
ABCB1	P-gp, MDR1	intestine, liver, kidney, brain, placenta, adrenal, testes	digoxin, fexofenadine, indinavir, vincristine, colchicine. topotecan, paclitaxel	ritonavir, cyclosporine, verapamil, erythromycin, ketocoanzole, itraconazole, quinidine, elacridar (GF120918) LY335979, valspodar (PSC 833)	rifampin, St John's Wort
ABCB4	MDR3	liver	digoxin, paclitaxel, vinblastine		
ABCB11	BSEP	liver	vinblastine		
ABCC1	MRP1	intestine, liver, kidney, brain	adefovir, indinavir		
ABCC2	MRP2, CMOAT	intestine, liver, kidney, brain	indinavir, cisplatin,	cyclosporine	
ABCC3	MRP3, CMOAT2	intestine, liver, kidney, placenta, adrenal	etoposide, methotrexate, tenoposide		
ABCC4	MRP4				
ABCC5	MRP5				
ABCC6	MRP6	liver, kidney	cisplatin, daunorubicin		
ABCG2	BCRP	intestine, liver, breast, placenta	daunorubicin, doxorubicin, topotecan, rosuvastatin, sulfasalazine	elacridar (GF120918)	
SLCO1B1	OATP1B1, OATP-C OATP2	liver	rifampin, rosuvastatin, methotrexate, pravastatin, thyroxine	cyclosporine rifampin	
SLCO1B3	OATP1B3, OATP8,	liver	digoxin, methotrexate, rifampin,		
SLCO2B1	SLC21A9, OATP-B	intestine, liver, kidney, brain	pravastatin		
SLC10A1	NTCP	liver, pancreas	rosuvastatin		
SLC10A2	ASBT	ileum, kidney, biliary tract			
SLC15A1	PEPT1	intestine, kidney	ampicillin, amoxicillin, captopril, valacyclovir		
SLC15A2	PEPT2	kidney	ampicillin, amoxicillin, captopril, valacyclovir		

SLC22A1	OCT-1	liver	acyclovir, amantadine, desipramine, ganciclovir metformin	disopyramide, midazolam, phenformin, phenoxy-benzamine quinidine, quinine, ritonavir, verapamil
SLC22A2	OCT2	kidney, brain	amantadine, cimetidine, memantine	desipramine, phenoxy-benzamine quinine
SLC22A3	OCT3	skeletal muscle, liver, placenta, kidney, heart	cimetidine	desipramine, prazosin, phenoxy-benzamine
SLC22A4	OCTN1	kidney, skeletal muscle, placenta, prostate, heart	quinidine, verapamil	
SLC22A5	OCTN2	kidney, skeletal muscle, prostate, lung, pancreas, heart, small intestine, liver	quinidien, verapamil	
SLC22A6	OAT1	kidney, brain	acyclovir, adefovir, methotrexate, zidovudine	probenecid, cefadroxil, cefamandole, cefazolin,
SLC22A7	OAT2	liver, kidney	zidovudine	
SLC22A8	OAT3	kidney, brain	cimetidine, methotrexate, zidovudine	probenecid, cefadroxil, cefamandole, cefazolin,

* Note that this is not an exhaustive list (created May 1, 2006).

1. ABC:ATP-binding cassette transporter superfamily; SLC: solute-linked carrier transporter family; SLCO: solute-linked carrier organic anion transporter family; MDR1: multi-drug resistance; MRP: multi-drug resistance related protein; BSEP:bile salt export pump; BCRP: breast cancer resistance protein; OAT: organic anion transporter; OCT: organic cation transporter; NTCP: sodium taurocholate co-transporting polypeptide; ASBT: apical sodium-dependent bile salt transporter.

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