Cytochrome P450 Drug Interaction Table "Flockhart Table"

The table contains lists of drugs in columns under the designation of specific cytochrome P450 isoforms.

CYTOCHROME P450 DRUG INTERACTION TABLE

A drug appears in a column if there is published evidence that it is metabolised, at least in part, via that isoform. It does not necessarily follow that the isoform is the principal metabolic pathway in vivo, or that alterations in the rate of the metabolic reaction catalysed by that isoform will have large effects on the pharmacokinetics of the drug.

An abbreviated clinical table designed for practical use during prescribing is also available.

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/"

Cytochrome P450-Based Drug Interactions

- Drug-drug interactions involving induction or inhibition of metabolism of one drug by co-administration of another
  - nb also applies to OTC medications, herbal remedies, nutraceuticals and some foods
- CYP3A4 is involved in biotransformation of ~60% of drugs undergoing oxidative metabolism (CYP2D6 is involved in ~20%)
  - activity may differ between individuals
- Some metabolic variation is genetic
  - knowledge of pharmacogenetics can mitigate genetic polymorphism
  - 8% Caucasians, 4% African-Americans, 1% Asians are poor metabolisers through CYP2D6
  - some ultra-rapid metabolisers have duplicate genes for CYP2D6
- Inducer
  - activity of CYP is increased and rate of metabolism increases
- Inhibitor
  - activity of CYP is decreased and rate of metabolism decreases

Inducers of CYP Enzymes

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
broccoli brussel sprouts char-grilled meat insulin methylcholanthrene[1] modafinil nafcillin beta-naphthoflavone[1] omeprazole[1] tobacco	phenobarbital phenytoin rifampin	rifampin[1]	rifampin secobarbital	carbamazepine norethindrone NOT pentobarbital prednisone rifampicin[1]	dexamethasone rifampin	ethanol isoniazid	HIV Antivirals: efavirenz nevirapine barbiturates carbamazepine glucocorticoids modafinil oxcarbazepine phenobarbital[2] phenytoin[2] pioglitazone rifabutin rifampin[1] St. John's wort troglitazone[1]

Inhibitors of CYP Enzymes

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
fluvoxamine ciprofloxacin cimetidine amiodarone fluoroquinolones furafylline[1] interferon methoxsalen mibefradil ticlopidine	thiotepa ticlopidine[2]	gemfibrozil[2] trimethoprim[2] glitazones montelukast[1] quercetin[1]	fluconazole[2] amiodarone fenofibrate fluvastatin fluvoxamine[2] isoniazid lovastatin phenylbutazone probenicid sertraline sulfamethoxazole sulfaphenazole[1] teniposide voriconazole zafirlukast	PPIs: lansoprazole omeprazole2 pantoprazole rabeprazole chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oxcarbazepine probenicid ticlopidine2 topiramate	bupropion cinacalcet fluoxetine paroxetine quinidine[1] duloxetine sertraline terbinafine amiodarone cimetidine celecoxib chlorpheniramine chlorpromazine citalopram clemastine clomipramine cocaine diphenhydramine doxepin doxorubicin escitalopram halofantrine histamine H1 receptor antagonists hydroxyzine levomepromazine methadone metoclopramide mibefradil midodrine moclobemide perphenazine ranitidine reduced-haloperidol ritonavir ticlopidine	diethyl-dithiocarbamate[2] disulfiram	HIV Antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole[1] ketoconazole[1] nefazodone saquinavir telithromycin aprepitant erythromycin fluconazole grapefruit juice verapamil[2] diltiazem cimetidine amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine starfruit telaprevir voriconazole

A **Strong inhibitor** is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
A **Moderate inhibitor** is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
A **Weak inhibitor** is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.
All other inhibitors.

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
amitriptyline	bupropion[1]	amodiaquine[2]	**NSAIDs:**	**PPIs:**	tamoxifen:	**Anesthetics:**	**Macrolide antibiotics:**
caffeine[2]	cyclophosphamide	cerivastatin	diclofenac[1]	lansoprazole	**TAMOXIFEN GUIDE**	enflurane	clarithromycin
clomipramine	efavirenz[1]	paclitaxel	ibuprofen	omeprazole2		halothane	erythromycin[2] (not 3A5)
clozapine	ifosphamide	repaglinide	lornoxicam	pantoprazole	**Beta Blockers:**	isoflurane	NOT azithromycin
cyclobenzaprine	methadone	sorafenib	meloxicam	rabeprazole	carvedilol	methoxyflurane	telithromycin
estradiol	sorafenib	torsemide	S-naproxen→Nor		S-metoprolol	sevoflurane	
fluvoxamine			piroxicam	**Anti-epileptics:**	propafenone		**Anti-arrhythmics:**
haloperidol			suprofen	diazepam→Nor	timolol	acetaminophen→NAPQI	quinidine→3-OH (not 3A5)
imipramine N-DeMe				phenytoin(O)		aniline2	
mexiletine			**Oral Hypoglycemic Agents:**	S-mephenytoin[1]	**Antidepressants:**	benzene	**Benzodiazepines:**
naproxen			tolbutamide[1]	phenobarbitone	amitriptyline	chlorzoxazone1	alprazolam
olanzapine			glipizide		clomipramine	ethanol	diazepam→3OH
ondansetron				amitriptyline	desipramine	N,N-dimethylformamide	midazolam[1]
phenacetin[1]→ acetaminophen→NAPQI			**Angiotensin II Blockers:**	carisoprodol	fluoxetine	theophylline→8-OH	triazolam[2]
propranolol			losartan	citalopram	imipramine		**Immune Modulators:**
riluzole			irbesartan	chloramphenicol	paroxetine		cyclosporine
ropivacaine				clomipramine	venlafaxine		tacrolimus (FK506)
tacrine[2]			**Sulfonylureas:**	clopidogrel			
theophylline[2]			glyburide	cyclophosphamide	**Antipsychotics:**		**HIV Antivirals:**
tizanidine			glibenclamide	hexobarbital	haloperidol		indinavir
verapamil			glipizide	imipramine N-DeME	perphenazine		nelfinavir
(R)warfarin			glimepiride	indomethacin	risperidone→9-OH		ritonavir
zileuton			tolbutamide	R-mephobarbital	thioridazine		saquinavir
zolmitriptan				moclobemide	zuclopenthixol		
			amitriptyline	nelfinavir			**Prokinetic:**
			celecoxib	nilutamide	alprenolol		cisapride
			fluoxetine	primidone	amphetamine		
			fluvastatin	progesterone	aripiprazole		**Antihistamines:**
			glyburide	proguanil	atomoxetine		astemizole
			nateglinide	propranolol	bufuralol[1]		chlorpheniramine
			phenytoin-4-OH2	teniposide	chlorpheniramine		terfenadine[2]
			rosiglitazone	R-warfarin→8-OH	chlorpromazine		
			tamoxifen		clonidine		
			torsemide		codeine (→O-desMe)		
			S-warfarin[1]		debrisoquine[2]		
					dexfenfluramine		
					dextromethorphan[1]		
					donepezil		

CYP450 Substrates

2D6	2E1	3A4,5,7
duloxetine encainide flecainide fluvoxamine lidocaine metoclopramide methoxyamphetamine mexiletine minaprine nebivolol nortriptyline ondansetron oxycodone perhexiline phenacetin phenformin promethazine propranolol sparteine tramadol		**Calcium Channel Blockers:** amlodipine diltiazem felodipine lercanidipine nifedipine[2] nisoldipine nitrendipine verapamil **HMG CoA Reductase Inhibitors:** atorvastatin cerivastatin lovastatin NOT pravastatin NOT rosuvastatin simvastatin **Steroid 6beta-OH:** estradiol hydrocortisone progesterone testosterone[1] **Miscellaneous:** alfentanil aprepitant aripiprazole boceprevir buspirone cafergot caffeine→TMU cilostazol cocaine codeine-N-demethylation dapsone dexamethasone dextromethorphan[2]

docetaxel
domperidone
eplerenone
fentanyl
finasteride
gleevec
haloperidol
irinotecan
LAAM
lidocaine
methadone
nateglinide
ondansetron
pimozide
propranolol
quetiapine
quinine
risperidone
salmeterol
sildenafil
sirolimus
sorafenib
sunitinib
tamoxifen
taxol
telaprevir
terfenadine
torisel
trazodone
vincristine
zaleplon
ziprasidone
zolpidem

There is a similar list of drugs that can induce/inhibit P-glycoprotein

P-glycoprotein:
- Efflux transporter in the brain (neuroprotective)
- Cause efflux of drugs from liver by biliary excretion (reduces absorption)

Some Examples

- Grapefruit juice (flavonoid constituent naringin, ~ 10% of dry weight) inhibits CYP3A4, increasing half-life and reducing clearance of lovastatin and limvastatin
  - Inhibition of intestinal CYP3A4 means that some drugs can exhibit a significantly increased (up to x3) mean oral bioavailability when co-administered with grapefruit juice
- Verapamil and diltiazem (calcium channel blockers) inhibit CYP3A4 and P-glycoprotein and can cause significant increases of concentration in statins (prolonged efficacy)
- Rifampin and St. John's wort induce CYP3A4 and P-glycoprotein and can cause significant decreases of concentration in statins (loss of efficacy)
- Metabolism of metoprolol and timolol (beta-blockers) decreases with co-administration of CYP2D6 inhibitor cimetidine (H_2 receptor antagonist)
- Metabolism of diazepam (antidepressant) is reduced (increased half-life, reduced clearance) with co-administration of CYP2C19 inhibitor omeprazole (proton pump inhibitor)

Eli Lilly markets fluoxetine (as the hydrochloride) in 20 mg yellow/green capsules, along with a 20 mg/5 mL oral syrup. There are a number of generic manufacturers of bioequivalent fluoxetine.

Fluoxetine (log P = 4.2) is almost completely absorbed following oral administration (%F = 70–90), is highly CNS-penetrant (brain/plasma ratio in humans of 2.6:1) and possesses the largest volume of distribution of any SSRI (14-100 L/kg). Whilst the enantiomers of fluoxetine are nearly equipotent at blocking serotonin reuptake [(*S*) is *ca.* 1.5-times more potent than (*R*)], they are metabolised differently and at different rates. Fluoxetine displays low plasma protein binding (*~5%)* and a long half-life ($t_{1/2}$ = 1-3 days for acute dosing and 4–6 days upon chronic dosing). Upon administration, fluoxetine displays nonlinear pharmacokinetics and is subjected to significant hepatic metabolism by cytochrome P_{450} enzymes (primarily 3A4, 2C9, 2C19, 2D6) forming one active metabolite and a number of inactive metabolites. Norfluoxetine, the active metabolite, possesses comparable receptor pharmacology to fluoxetine, but possesses a significantly longer half-life ($t_{1/2}$ = 4-16 days) with plasma concentrations of norfluoxetine typically being 100–130% of fluoxetine. The (*S*)-norfluoxetine metabolite is 5-20 times more potent than (*R*)-norfluoxetine. Plasma levels of both fluoxetine and norfluoxetine can persist for more than 3 weeks after discontinuation of treatment.

From pharmacokinetic data, the (*R)*-enantiomer could be expected to result in less variable plasma levels of fluoxetine and its active metabolites and reduced prevalence of drug-drug interactions than observed with racemic fluoxetine. Although racemic fluoxetine has been shown to be a safe and effective antidepressant for many years, the (*R*)-enantiomer was shown not to be viable due to safety concerns (statistically significant prolongation of cardiac repolarisation).