P450 substraten – inhibitors - inducers

- In this version you will find new literature references, which describe whether an inhibitor is strong, moderate or weak (see below for criteria specified by the FDA).
- You will also encounter new data about FDA preferred and acceptable substrates for in vitro experiments.

Below the list of drugs that are metabolized by a specific cytochrome P450 isoform are the published **inhibitors**, **inducers** and **genetic influences** on that isoform. Drug names are hyperlinks to specific literature references, most of which now include a link to the abstract of the article in the NLM's PubMed database. Also, you can click on the PubMed link after the drug name to perform a live MedLINE search of articles possibly related to that drug and Cytochrome P450. Enzymes denoted with a colored bullet or with either a superscript number 1 or 2 are taken from the FDA Drug Development and Drug Ineractions: Table of Substrates, Inhibitors and Inducers (May 2006).*

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SUBSTRATES

FDA preferred[1] and acceptable[2] **substrates** for in vitro experiments.*

1A2	2B6	2C8	2C19	2C9	2D6	2E1	3A4,5,7
amitriptyline caffeine[2] clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine N-DeMe mexiletine naproxen olanzapine ondansetron phenacetin[1] => acetaminophen=>NAPQI propranolol riluzole ropivacaine tacrine[2] theophylline[2] tizanidine verapamil (R)warfarin zileuton zolmitriptan	bupropion[1] cyclophosphamide efavirenz[1] ifosfamide methadone	paclitaxel torsemide amodiaquine[2] cerivastatin repaglinide	Proton Pump Inhibitors: lansoprazole omeprazole[2] pantoprazole rabeprazole E-3810 Anti-epileptics: diazepam=>Nor phenytoin(O) S-mephenytoin[1] phenobarbitone amitriptyline carisoprodol citalopram chloramphenicol clomipramine clopidogrel cyclophosphamide hexobarbital imipramine N-DeME indomethacin R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin=>8-OH	NSAIDs: diclofenac[1] ibuprofen lornoxicam meloxicam S-naproxen=>Nor piroxicam suprofen Oral Hypoglycemic Agents: tolbutamide[1] glipizide Angiotensin II Blockers: losartan irbesartan Sulfonylureas: glyburide/ glibenclamide glipizide glimepiride tolbutamide amitriptyline celecoxib fluoxetine fluvastatin glyburide nateglinide phenytoin-4-OH[2] rosiglitazone tamoxifen torsemide S-warfarin[1]	Beta Blockers: carvedilol S-metoprolol propafenone timolol Antidepressants: amitriptyline clomipramine desipramine imipramine paroxetine Antipsychotics: haloperidol perphenazine risperidone=>9OH thioridazine zuclopenthixol alprenolol amphetamine aripiprazole atomoxetine bufuralol[1] chlorpheniramine chlorpromazine codeine (=>O-desMe) debrisoquine[2] dexfenfluramine dextromethorphan[1] duloxetine encainide flecainide fluoxetine fluvoxamine lidocaine metoclopramide methoxyamphetamine mexilletine minaprine nebivolol nortriptyline ondansetron	Anesthetics: enflurane halothane isoflurane methoxyflurane sevoflurane acetaminophen =>NAPQI aniline[2] benzene chlorzoxazone[1] ethanol N,N-dimethyl formamide theophylline =>8-OH	Macrolide antibiotics: clarithromycin erythromycin[2] (not 3A5) NOT azithromycin telithromycin Anti-arrhythmics: quinidine=>3-OH (not 3A5) Benzodiazepines: alprazolam diazepam=>3OH midazolam[1] triazolam[2] Immune Modulators: cyclosporine tacrolimus (FK506) HIV Antivirals: indinavir nelfinavir ritonavir saquinavir Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine terfenadine[2] Calcium Channel Blockers: amlodipine diltiazem felodipine lercanidipine nifedipine[2]

					oxycodone perhexiline phenacetin phenformin promethazine propranolol sparteine tamoxifen tramadol venlafaxine		nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin NOT pravastatin simvastatin Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone[1] Miscellaneous: alfentanyl aprepitant aripiprazole buspirone cafergot caffeine=>TMU cilostazol cinacalcet cocaine codeine- N-demethylation dapsone dexamethasone dextromethorphan[2] docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan LAAM lapatinib lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone NOT rosuvastatin salmeterol sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

INHIBITORS

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's response to that particular medication, e.g. making it ineffective.

strong A **Strong inhibitor** is one that cause a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

moderate A **Moderate inhibitor** is one that cause a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.

weak A **Weak inhibitor** is one that cause a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

others All other inhibitors.

FDA preferred[1] and acceptable[2] **inhibitors** for in vitro experiments.*

1A2	2B6	2C8	2C19	2C9	2D6	2E1	3A4,5,7
fluvoxamine ciprofloxacin cimetidine amiodarone fluoroquinolones furafylline[1] interferon methoxsalen mibefradil	thiotepa ticlopidine[2]	gemfibrozil[2] trimethoprim[2] glitazones montelukast[1] quercetin[1]	PPIs: lansoprazole omeprazole[2] pantoprazole rabeprazole chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oxcarbazepine probenicid ticlopidine[2] topiramate	fluconazole[2] amiodarone fenofibrate fluvastatin fluvoxamine[2] isoniazid lovastatin phenylbutazone probenicid sertraline sulfamethoxazole sulfaphenazole[1] teniposide voriconazole zafirlukast	bupropion fluoxetine paroxetine quinidine[1] duloxetine terbinafine amiodarone cimetidine sertraline celecoxib chlorpheniramine chlorpromazine cinacalcet citalopram clemastine clomipramine cocaine diphenhydramine doxepin doxorubicin escitalopram goldenseal halofantrine histamine H1 receptor antagonists hydroxyzine levomepromazine methadone metoclopramide mibefradil midodrine moclobemide perphenazine ranitidine red-haloperidol ritonavir ticlopidine tripelennamine	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 delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit voriconazole

INDUCERS

Inducers stimulate the production of the enzyme thus increasing the rate of metabolism causing the substrate drug to clear out of the system faster. This will also affect the individual's response to the medication, i.e. making he drug ineffective because it has not been in the system long enough to have an effect.

FDA preferred[1] and acceptable[2] **inducers** for in vitro experiments.*

1A2	2B6	2C8	2C19	2C9	2D6	2E1	3A,4,5,7
broccoli brussel sprouts char-grilled meat insulin methylcholanthrene[1] modafinil nafcillin beta-naphthoflavone[1] omeprazole[1] tobacco	phenobarbital rifampin	rifampin[1]	carbamazepine norethindrone NOT pentobarbital prednisone rifampin[1]	rifampin secobarbital	dexamethasone rifampin	ethanol isoniazid	HIV Antivirals: efavirenz nevirapine barbiturates carbamazepine efavirenz glucocorticoids modafinil nevirapine oxcarbazepine phenobarbital[2] phenytoin[2] pioglitazone rifabutin rifampin[1] St. John's wort troglitazone[1]

GENETICS

1A2	2B6	2C8	2C19	2C9	2D6	2E1	3A4,5,7
Chr15	Chr19	Chr10	Chr10	Chr10	Chr22	Chr10	Chr7