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

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Table 1-1: Examples of in vitro marker reactions for P450-mediated metabolism (9/26/2016)

Enzyme	Marker reaction
CYP1A2	Phenacetin O-deethylation, 7-Ethoxyresorufin-O-deethylation
CYP2B6	Efavirenz hydroxylation, Bupropion hydroxylation
CYP2C8	Paclitaxel 6α-hydroxylation, Amodiaquine N-deethylation
CYP2C9	S-Warfarin 7-hydroxylation, Diclofenac 4'-hydroxylation
CYP2C19	S-Mephenytoin 4'-hydroxylation
CYP2D6	Bufuralol 1'-hydroxylation, Dextromethorphan O-demethylation
CYP3A4/5*	Midazolam 1'-hydroxylation, Testosterone 6β-hydroxylation

* Recommend the use of 2 structurally unrelated CYP3A4/5 substrates for evaluation of in vitro CYP3A4/5 inhibition.

Table 1-2: Examples of in vitro selective inhibitors for P450-mediated metabolism (9/26/2016)

Enzyme	Inhibitor
CYP1A2	α-Naphthoflavone, Furafylline*
CYP2B6**	Sertraline, Phencyclidine*, Thiotepa*, Ticlopidine*
CYP2C8	Montelukast, Quercetin, Phenelzine*
CYP2C9	Sulfaphenazole, Tienilic acid*
CYP2C19**	S-(+)-N-3-benzyl-nirvanol, Nootkatone, Ticlopidine*
CYP2D6	Quinidine, Paroxetine*
CYP3A4/5	Itraconazole, Ketoconazole, Azamulin*, Troleandomycin*, Verapamil*

Most chemical inhibitors are not specific for an individual CYP enzyme. The selectivity and potency of inhibitors should be verified in the same experimental conditions using probe substrates for each CYP enzyme.

* Time-dependent inhibitors. **No selective inhibitor is available in vitro for CYP2C19- and CYP2B6-mediated metabolisms. The inhibitors listed here can be used together with other information, such as metabolic profiles obtained from single enzyme expression systems.

Table 1-3. Examples of in vitro inducers for P450-mediated metabolism (9/26/2016)

Enzyme	Inducer*
CYP1A2	Omeprazole, Lansoprazole
CYP2B6	Phenobarbital
CYP2C8	Rifampicin
CYP2C9	Rifampicin
CYP2C19	Rifampicin
CYP3A4/5	Rifampicin

Table 2-1: Examples of clinical index substrates for P450-mediated metabolism (for use in index clinical DDI studies) (9/26/2016)

	Sensitive index substrates unless otherwise noted
CYP1A2	caffeine, tizanidine
CYP2B6[a]	-
CYP2C8	repaglinide[b]
CYP2C9	tolbutamide[c], S-warfarin[c]
CYP2C19	lansoprazole (c,d), omeprazole
CYP2D6	desipramine, dextromethorphan, nebivolol
CYP3A	midazolam, triazolam

* Note: Index substrates predictably exhibit exposure increase due to inhibition or induction of a given metabolic pathway and are commonly used in prospective clinical DDI studies. See section IV.A.2. of the main clinical DDI guidance document for details. Sensitive index substrates are index drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies. Moderate sensitive substrates are drug that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI studies.

This table is prepared to provide examples of clinical sensitive or moderate sensitive index substrates and is not intended to be an exhaustive list. Index substrates listed in this table were selected considering their sensitivity, specificity, safety profiles, and adequate number of reported clinical DDI studies with different in vivo inhibitors (≥ 3 for CYP3A or ≥ 2 for CYP1A2, 2C8, 2C9, 2C19, and 2D6). DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61], and the list of references is available here (/media/99924/download).

(a) We currently do not have sensitive index substrates for CYP2B6.
(b) Also OATP1B1 substrate.
(c) Moderate sensitive substrates.
(d) S-lansoprazole is a sensitive substrate in CYP2C19 EM subjects.

Abbreviations:
AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction; EM: extensive metabolizer; OATP1B1: organic anion transporting polypeptide 1B1.

Table 2-2: Examples of clinical index inhibitors for P450-mediated metabolisms (for use in index clinical DDI studies) (9/26/2016)

	Strong index inhibitors	Moderate index inhibitors
CYP1A2	fluvoxamine(a)	-
CYP2B6(b)	-	-
CYP2C8	clopidogrel(c), gemfibrozil(d)	-

CYP2C9	-	fluconazole[e]
CYP2C19	fluvoxamine[a]	-
CYP2D6	fluoxetine[f], paroxetine	mirabegron
CYP3A	clarithromycin[g], itraconazole[g]	erythromycin, fluconazole[e], verapamil[g]

Note: Index inhibitors predictably inhibit metabolism via a given pathway and are commonly used in prospective clinical DDI studies. See section IV.A.2. of the main guidance documents for details. Strong and moderate inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold and ≥2 to <5-fold, respectively.

This table is prepared to provide examples of clinical index inhibitors and is not intended to be an exhaustive list. Index inhibitors listed in this table were selected based on potency and selectivity of inhibition, safety profiles, and adequate number of reported clinical DDI studies with different in vivo substrates [≥ 3 for CYP3A, ≥ 2 for CYP1A2, 2C9, 2C19, and 2D6, or ≥ 1 for CYP2C8 (strong inhibitors)]. DDI data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61)], and the list of references is available here (Reference for examples of clinical index inhibitors for P450-mediated metabolisms).

[a] Strong inhibitor of CYP1A2 and CYP2C19, and moderate inhibitor of CYP2D6 and CYP3A.
[b] We currently do not have index inhibitors for CYP2B6.
[c] Strong inhibitor of CYP2C8, weak inhibitor of CYP2B6, and inhibitor of OATP1B1. The glucoronide metabolite is also an inhibitor for CYP2C8 and OATP1B1.
[d] Strong inhibitor of CYP2C8 and inhibitor of OATP1B1 and OAT3. The glucoronide metabolite is also an inhibitor for CYP2C8 and OATP1B1.
[e] Strong inhibitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A.
[f] Strong inhibitors of CYP2C19 and CYP2D6. (g) Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥1.25-fold).

Abbreviations:
AUC: area under the concentration-time curve; CYP: cytochrome P450; DDI: drug-drug interaction; OATP1B1: organic anion transporting polypeptide 1B1; OAT3: organic anion transporter 3; P-gp: P-glycoprotein.

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