ADME: Cytochrome P450 inhibition in human liver microsomes

Background:
Co-administration of drugs can result in drug-drug interaction, as drugs compete for the same enzymes. Inhibition of CYP450 enzymes is a principal mechanism of metabolism-based drug-drug interactions and a common cause of adverse drug events. Therefore, one of the crucial properties in early drug discovery is the assessment of the potential of test compounds to inhibit a specific CYP450 isoform. This data is useful for further investigations of clinical drug-drug interactions (DDI).
The human liver microsomal assay is accepted as the 'gold standard' for *in vitro* DDI assessment as it is closest to the native enzyme environment. This assay is therefore used to characterise development compounds where data will be submitted to regulatory authorities.

Assay description

CYP450 isoforms

CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4

Compound concentration

10µM (single point) or 0-100µM (IC50)

Compound requirements

1-2 mg of dry matter

Incubation details

isoform specific substrate (see Table 1)
isoform specific time of incubation

Assay controls

known isoform specific positive control
(see Table 1 and Figure 1)

Detection method

LC-MS/MS with internal standard

Table 1. CYP450 isoform specific substrates and positive controls

Isoform	Substrate	Positive control
CYP1A2	Phenacetin	Fluvoxamine
CYP2C9	Diclofenac	Sulfaphenazole
CYP2C19	S-mephenytoin	Ticlopidine
CYP2D6	Bufuralol	Quinidine
CYP3A4	Midazolam*	Ketoconazole

* Testosterone also used as substrate

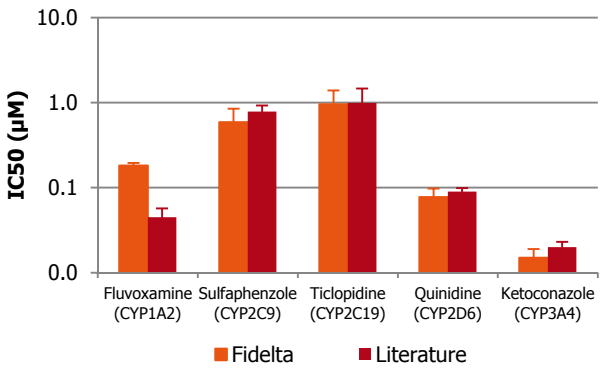

Figure 1. Comparison of IC_{50} values for CYP450 isoform specific positive control with literature values[1,2,3]

[1] Obach 2006, J Pharmacol Exp Ther 316, 336
[1] Zientek et al. 2008, J Pharmacol Toxicol Method 58, 206
[1] Zambon et al. 2010, Drug Metabol Lett 4, 120

Assay details adjustable to client's and/or project specific requests

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