ADME: Cytochrome P450 inhibition using recombinant enzymes

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 assessed in early drug discovery is the potential of the test compound to inhibit a specific CYP450 isoform. This data is useful for further investigations of clinical drug-drug interactions (DDI).

CYP450 inhibition can be evaluated using recombinant enzymes, a high-throughput *in vitro* screening approach that includes the use of:

i. modified microsomes that contain only one specific CYP450 isoform , and

ii. specific substrates whose metabolism is monitored by fluorescence.

Assay description

CYP450 isoforms

CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4

Compound concentration

10µM (single point) or 0-100µM (IC50)

Compound requirements

50µl of 10mM stock solution or
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

Fluorescence

Table 1. CYP450 isoform specific substrates and positive controls

Isoform	Substrate	Positive control
CYP1A2	CEC	Furafylline
CYP2C9	MFC	Sulfaphenazole
CYP2C19	CEC	Tranylcypromine
CYP2D6	AMMC	Quinidine
CYP3A4	7-BQ/DBF/BFC	Ketoconazole

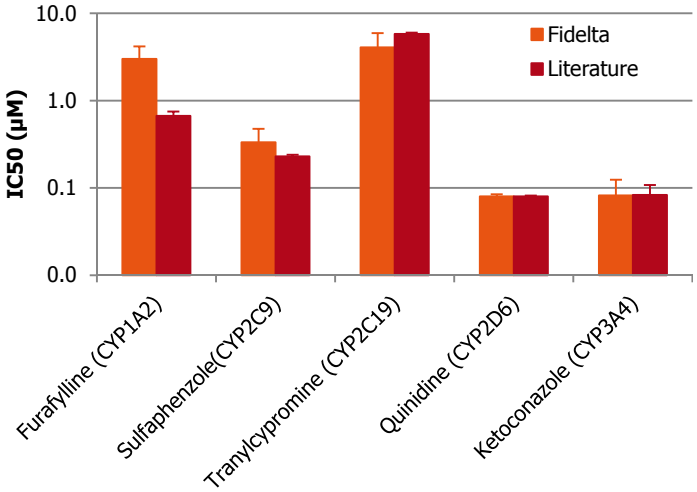

Figure 1. Comparison of IC_{50} values for CYP450 isoform specific positive control with literature values[1]

[1] Crespi et al. 1997, Anal Biochem 248, 188

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

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