Cytochrome P450 Inhibition

**Background Information**

- Cytochrome P450 are a family of enzymes which play a major role in the metabolism of drugs.
- Assessment of the potential of a compound to inhibit a specific cytochrome P450 enzyme is important as co-administration of compounds may result in one or both inhibiting the other’s metabolism. This may affect plasma levels in vivo and potentially lead to adverse drug reactions or toxicity.
- In vitro cytochrome P450 inhibition data are useful in designing strategies for investigating clinical DDI Studies.
- Cyprotex’s Cytochrome P450 Inhibition assays use industry accepted probe substrates and human liver microsomes.
- In Cyprotex’s Cytochrome P450 Inhibition assay, a decrease in the formation of the metabolites compared to the vehicle control is used to calculate an IC\textsubscript{50} value (test compound concentration which produces 50% inhibition).

**Protocol**

**Typical Test Article Concentrations**
0, 0.1, 0.25, 1, 2.5, 10, 25 µM (different concentrations available)

**CYP Isoforms**
CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (other isoforms are available)

**Test Article Requirements**
Dependent on number of isoforms assessed

**Controls**
Known isoform specific inhibitors

**Analysis Method**
LC-MS/MS (with the exception of ethoxyresorufin for CYP1A)

**Data Delivery**
IC\textsubscript{50}, Standard error of IC\textsubscript{50}
In vitro P450 inhibition data are valuable in the design of clinical DDI study strategies and can be used to predict the magnitudes of DDI\(^1\).

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Known cytochrome P450 inhibitors were screened in Cyprotex’s Cytochrome P450 Inhibition assay in quadruplicate over 4 separate assays.

The effect of 5 known CYP3A4 inhibitors (clotrimazole, ketoconazole, mibefradil, nicardipine and verapamil) on the 1-hydroxylation of midazolam was investigated on 4 separate occasions. Error bars represent the standard deviation of 4 replicates on each experiment. The data show good consistency for inhibitors with a range of inhibition potential.

Figure 1
Cyprotex’s Cytochrome P450 Inhibition data for CYP3A4.

Figure 2
Comparison of Cyprotex’s IC\(_{50}\) values (mean± standard deviation) for the control inhibitors with literature\(^2,3,4,5,6,7,8\) values.

References