

## In vitro ADME & PK

# UGT Inhibition (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7)

## Background Information



'Inhibitory interactions can occur when glucuronidation is a predominant metabolic elimination pathway, when the glucuronidation is catalysed by a single enzyme and when the therapeutic concentrations of the inhibitor are close to the  $K_i$  of the target UGT.'

<sup>1</sup>Rommel R *et al.*, (2007) Conjugative Metabolism of Drugs, in *Drug Metabolism in Drug Design and Development*, (Zhang D *et al.*, eds); pp 37-88, John Wiley & Sons, Inc.

- Uridine glucuronyl transferases (UGT) are a family of enzymes which play a major role in the Phase II metabolism of drugs.
- One in ten of the top two hundred prescribed drugs have glucuronidation as a clearance mechanism illustrating the importance of UGTs in drug metabolism.
- Functionally relevant polymorphisms have been demonstrated for the UGT genes. For example, the polymorphism in UGT1A1 can lead to toxicity associated with Gilbert's syndrome or the more severe Criglar-Najjar syndrome where levels of bilirubin are elevated.
- The regulatory authorities are now recommending that UGT inhibition is evaluated as part of *in vitro* drug-drug interaction (DDI) packages to determine if clinical DDI studies are required.
- In Cyprotex's UGT inhibition assay, a decrease in the formation of the UGT-specific metabolite compared to the vehicle control is used to calculate an  $IC_{50}$  value (test compound which produces 50% inhibition). Follow-up  $K_i$  determination is also available if required.
- Cyprotex can offer either early stage UGT inhibition screening or regulatory UGT inhibition assessments as part of a DDI package for IND or NDA submissions.

### Protocol

#### Substrates

Estradiol (UGT1A1), sulindac sulfone (UGT1A3), trifluoperazine (UGT1A4), naphthol (UGT1A6), propofol (UGT1A9), naloxone (UGT2B7)

#### Enzyme Source

Human UGT Supersomes™

#### Cofactors

UDPGA

#### Positive Controls

Silybin or atazanavir (UGT1A1), quinidine (UGT1A3), diclofenac (UGT1A4, UGT1A6, UGT1A9 and UGT2B7)

#### Analysis Method

LC-MS/MS

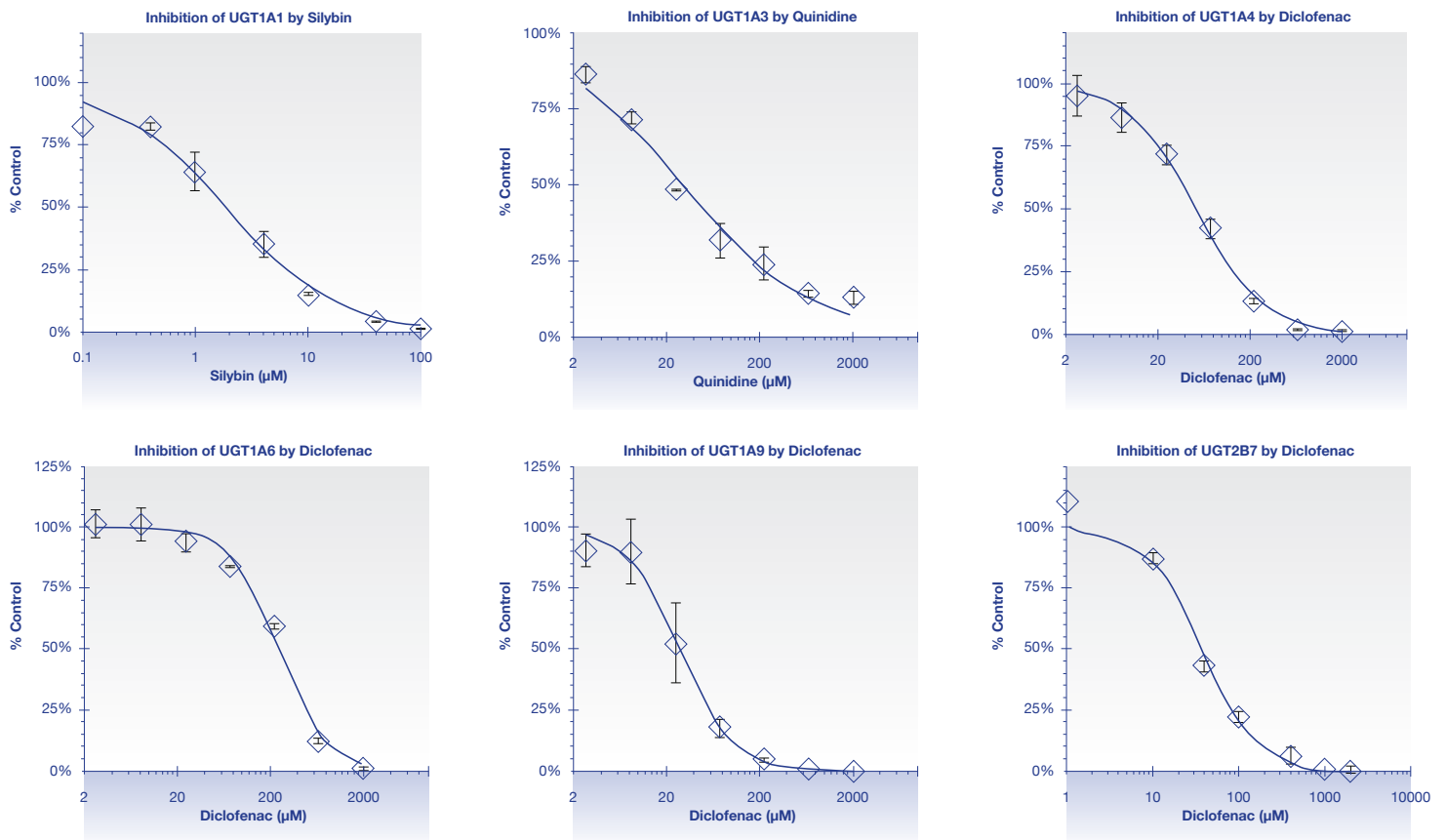
#### Data Delivery

$IC_{50}$   
Standard error of  $IC_{50}$

# Glucuronidation is a listed clearance mechanism for 1 in 10 of the top 200 prescribed drugs<sup>2</sup>

**Figure 1**

Graphs showing the inhibition of UGT isoforms by the positive control inhibitors in Cypotex's UGT inhibition assay. Data show the mean  $\pm$  standard deviation of 3 replicates.



**Table 1**

Summary of  $IC_{50}$  data (n=3) for known UGT inhibitors in Cypotex's UGT inhibition assay.

UGT Isoform	Substrate	Inhibitor	Mean $IC_{50} \pm$ standard deviation (n=3) (µM)
UGT1A1	Estradiol	Silybin	4.7 $\pm$ 3.5
UGT1A3	Sulindac sulfone	Ritonavir Quinidine	0.5 $\pm$ 0.1 35 $\pm$ 9.3
UGT1A4	Trifluoperazine	Diclofenac	61 $\pm$ 7.8
UGT1A6	Naphthol	Diclofenac	221 $\pm$ 32
UGT1A9	Propofol	Diclofenac Mycophenolic acid	29 $\pm$ 3.8 66 $\pm$ 22
UGT2B7	Naloxone	Diclofenac Quinidine	24 $\pm$ 11 139 $\pm$ 33

## References

- Remmel R *et al.*, (2007) Conjugative Metabolism of Drugs in *Drug Metabolism in Drug Design and Development*, (Zhang D *et al.*, eds); pp 37-88, John Wiley & Sons, Inc.
- Williams JA *et al.*, (2004) Drug-drug interactions for UDP-glucuronosyltransferase substrates: A pharmacokinetic explanation for typically observed low exposure (AUC<sub>i</sub>/AUC) ratios *Drug Metab Dispos* **32**(11); 1201-1208.