XENOTECH
A BioIVT Company

XenoTech UGT inhibition studies help evaluate the potential for drug candidates to cause DDIs with other drugs metabolized by UGTs.

During drug discovery or the early stages of drug development, drug candidates are usually screened for their metabolic stability in NADPH-fortified human liver microsomes (HLM) and for their ability to inhibit cytochrome P450 (CYP) enzymes. Those candidates that are substrates for, or inhibitors of, CYP enzymes are typically dropped from further development due to the high risk of drug-drug interactions (DDI). This process of attrition biases the selection of drug candidates away from CYP interactions and possibly towards drug candidates that are substrates for or inhibitors of other drug-metabolizing enzymes, such as UDP-glucuronosyltransferase (UGT) enzymes.

Guidance documents, review articles from regulatory agencies and consensus papers provide little advice regarding the conduct of UGT inhibition studies; however, they recognize that there are some DDIs related to non-CYP enzymes, such as UGTs. Investigation of a compound's ability to inhibit human UGT enzymes may be recommended by regulatory agencies.

XenoTech has examined a variety of conditions that can impact these types of studies, including system-dependent inhibition, cofactor concentration and the use of activators on the results of UGT inhibition studies.

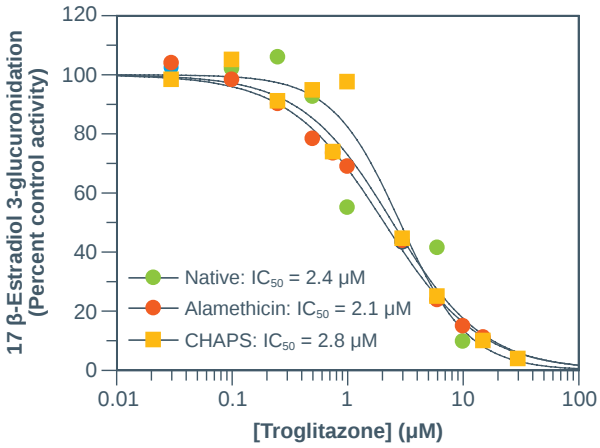
Features of XenoTech UGT Inhibition Studies

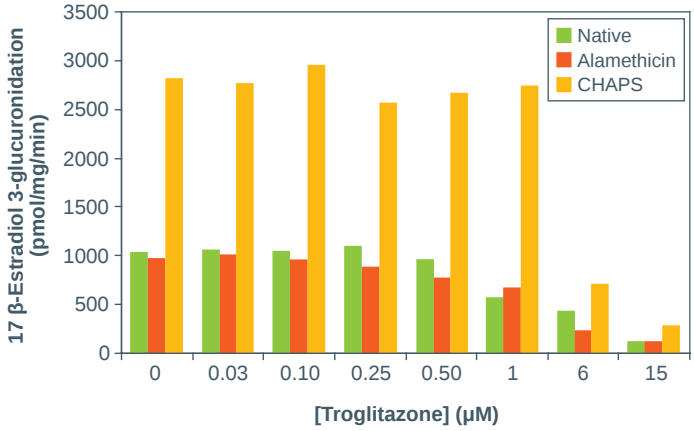
- Validated LC/MS/MS methods
- Deuterated internal standards in most cases
- Designed to minimize inhibitor depletion
- Positive control inhibitor for all UGT's
- Pooled, extensively-characterized, glycerol-free[1] HLM
- Comprehensive report

XenoTech's study design evaluates drug candidates as direct-acting inhibitors of UGT enzymes using an extensively characterized pool of human liver microsomes. Low protein concentrations and short incubation times are used to minimize artifacts caused by protein binding, metabolic instability or excessive metabolism of the marker substrate.

Contact us to learn more
at **www.xenotech.com**
or call **913.438.7450**.

Impact of the UGT activators CHAPS and alamethicin on the ability of troglitazone to inhibit microsomal UGT1A1 activity





Validated LC/MS/MS Methods

Enzyme	*Reaction*
UGT1A1	17β-Estradiol 3-glucuronidation
UGT1A3	Chenodeoxycholic acid 24-*O*-glucuronidation
UGT1A4	Trifluoperazine glucuronidation
UGT1A6	1-Naphthol glucuronidation
UGT1A9	Propofol glucuronidation
UGT2B7	Morphine 3-glucuronidation
UGT2B15	*S*-Oxazepam glucuronidation
UGT2B17	Testosterone 17β-O-glucuronidation

*deuterated internal standard not available
Additional unvalidated UGT methods available upon request.

1 Obach, S: Glycerolysis of Acyl Glucuronides as an Artifact of In Vitro Drug Metabolism Incubations. *DMD* August 2009 vol. 37 no. 8 1581-1586