

# Custom production of glucuronide metabolites

## We provide a range of services for our clients using our expertise in microbial chemistry

- Mimic mammalian phase I & II metabolism to produce metabolites for ID, use as quantitation standards or larger amounts for DMPK/ADME/TOX.
- Probe improvements in drug-gability through the generation of derivatives.
- Lipophilic rescue through creation of more polar metabolites.
- Creation of analogues for lead diversification and optimisation studies, and to protect/widen IP.

## Our track record

- Alkyl and phenolic hydroxylation ✓
- N-oxidation ✓
- N- + O-dealkylation/ hydrogenation/ dehydrogenation ✓
- N-, O- and acyl glucuronidation (+ other glycosidation) ✓
- Sulfation ✓

\* Wolf et al., Nephrol Dial Transplant (2007) 22: 2497–2503

Some of our partners and clients include:



Hypha Discovery produces acyl glucuronides for structural determination, quantifiable standards and for the validation of extraction procedures, e.g. checking for reversion back to the de-conjugated parent drug during the processing and analysis of clinical samples. We have also custom-synthesized glucuronide standards for acyl migration kinetics measurement to assess potential reactivity towards proteins which can lead to toxicity and immune response.

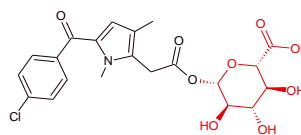
In the example below, Hypha created the acyl glucuronide of zomepirac, which is known to irreversibly react with proteins leading to anaphylaxis. The drug was ultimately withdrawn from the market in 1983.

Hypha produces acyl, N- and O-glucuronides of investigational new drugs at >90% purity (usually >95%) and in yields typically between 5 and 50mg, although larger (100's mg to low g) amounts are sometimes manufactured for more extensive studies. An example of O-glucuronide production is the selective glucuronidation of mycophenolic acid to its major

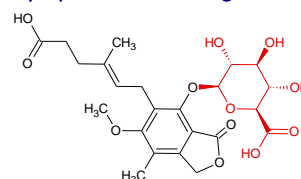
metabolite, 7-O-mycophenolic acid glucuronide (MPAG), the production of which is subject to UGT1A9 polymorphism in humans. MPAG has been reported to inhibit human transporter function, specifically OAT3 transporters, thereby increasing the risk of drug-drug interactions, particularly the renal excretion of OAT3 drug substrates\*.

Hypha's glucuronidation production service enables the early detection of liabilities of N- and O- glucuronides such as drug-drug interactions due to transporter inhibition, in addition to helping to assess the extent of reactivity of acyl-glucuronides and thereby bet-

### Zomepirac acyl glucuronide



### Mycophenolic acid 7-O- glucuronide



ter informing the decision to advance candidate compounds into development.

*"We contacted Hypha Discovery to generate specific phase I and phase II metabolite standards in sufficient quantities and purity to allow structural confirmation and quantitation. Hypha exceeded expectations, providing 60mg of a phase I metabolite and over 100mg of a phase II metabolite at high purity. Hypha's team was a pleasure to work with and communicative and responsive throughout the process. We will undoubtedly be working with Hypha Discovery in the future."*

**Jason Boer, Senior Principal Investigator, Incyte Corporation, Wilmington, USA**

Zomepirac acyl glucuronide formation has been the major factor in the withdrawal of Zomepirac from the market, due to the toxic protein binding of the metabolite. Hypha can provide custom made acyl glucuronides for toxicity studies or as analytical standards.

Mycophenolic acid is metabolised mainly to the O-glucuronide MPAG, which is known to inhibit hOAT3 transporters. Hypha can provide custom-made glucuronides for the early warning assessment of liabilities.

## Why work with us?

**High success rates.** A high % of compounds have been derivatised by our strains. The process is applicable to broad structural types and provides a method for capturing multiple metabolites in a single screen.

**Scalable and reproducible process.** We have an excellent

reproducibility rate where target molecules can be scaled up to produce mg to g quantities.

**Defined timelines and costs.** Metabolites are produced on a simple-fee-for-service basis, i.e. no downstream terms. The process is

stage-gated so the client has control throughout.



## ABOUT HYPHA DISCOVERY

Hypha Discovery Ltd is a UK-based microbial biotechnology company helping partners in pharmaceutical and agrochemical R&D worldwide succeed through the production of mammalian and microbial metabolites, as well as specialising in microbially-derived chemicals.