For more information contact:
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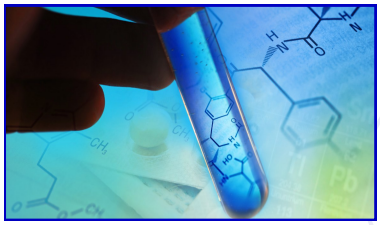


Custom production of glucuronide metabolites

Winter 2014

We provide a range of services for our clients using microbial chemistry, mammalian tissue and enzyme incubation expertise to produce:

- **Mammalian Phase I (CYP & non-CYP) and Phase II metabolites:**
  - *For Met ID*
  - *As quantitative standards*
  - *For bioactivity testing*
  - *For stability studies*
  - *For DMPK/ADME/TOX*
- **Analogues for lead diversification and optimization to:**
  - *Protect/widen IP coverage*
  - *Improve ligand lipophilicity efficiency*

Our track record

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

Hypha produces acyl, *N*- and *O*-glucuronides of investigational new drugs at >90% purity and in yields typically between 5 and 50mg. 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, see below), the production of which is subject to UGT1A9 polymorphism. MPAG has been reported to inhibit human transporter function, specifically OAT3 transporters, thereby increasing the risk of drug-drug interactions, such as the renal excretion of OAT3 drug substrates*.

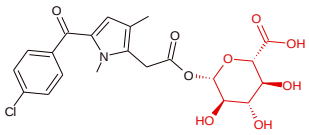
Acyl glucuronides are prepared for our clients for structural determination, for use as quantifiable standards and for the validation of extraction procedures, e.g. checking for reversion back to the de-conjugated parent drug during the processing and analysis of clinical samples. We have also custom-produced 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.

Hypha's glucuronidation production service permits acyl-glucuronide reactivity to be predicted, as well as the early detection of liabilities of *N*- and *O*- glucuronides such as drug-drug interactions, helping to better inform the decision to advance candidate compounds into development and the clinic.

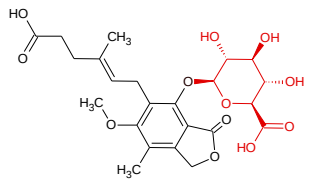
> *"We contacted Hypha Discovery to generate specific phase I and phase II metabolite standards in sufficient quantities and purity to allow structural confirmation and quantitation. Hypha exceeded expectations, providing 60mg of a phase I metabolite and over 100mg of a phase II metabolite at high purity. 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**
> **Snr Principal Investigator**
> **Incyte Corporation**
> **Wilmington, USA**

Zomepirac acyl glucuronide



Zomepirac acyl glucuronide formation led to the withdrawal of the drug due to irreversible protein binding. Hypha provides custom-made acyl glucuronides to enable toxicity studies and for use as analytical standards.

Mycophenolic acid 7-*O*-glucuronide



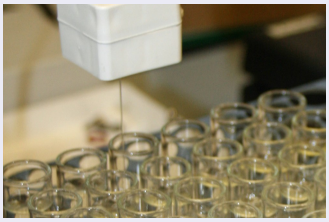
Mycophenolic acid is metabolised mainly to the *O*-glucuronide MPAG, which is known to inhibit hOAT3 transporters. An early warning of such liabilities is made possible by Hypha's glucuronide production service.

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.



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

Some of our partners and clients include:

DuPont, Gilead, Lundbeck, syngenta, selcia, European ScreeningPort, evotec, OSI, Incyte, ferrer

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.