Custom production of glucuronide metabolites

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 The drug was ultimately withdrawn from the market in 1983.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 better informing the decision to advance candidate compounds into development.

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.

**Our track record**

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

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**Why work with us?**

**High success rates.** A high % of compounds have been derivateised 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.

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For more information contact:

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Myth of mammalian phase I and II metabolism standards for use as quantitation standards or larger amounts for DMPK/ADME/TOX.

- Probe improvements in drugability through the generation of metabolites for ID, use as quantitation standards or larger amounts for DMPK/ADME/TOX.
- Lipophilic rescue through creation of more polar metabolites.
- Creation of analogues for lead diversification and optimisation studies, and to protect/widen IP.

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**Zomepirac acyl glucuronide**

**Mycophenolic acid 7-O- glucuronide**

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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.