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HYPHA DISCOVERY

Metabolites and molecules for tomorrow's drugs

Scalable synthesis of glucuronides

Acyl, *O*-, *N*- and *N*-carbamoyl glucuronides of drugs

We produce and scale-up mammalian phase I and II metabolites for a variety of applications:

- **Structure elucidation**
- **Standards for quantitation**
- **DDI & TOX studies**
- **Bioactivity testing**
- **Stability studies**

One-stop metabolite shop techniques

Multiple techniques for making metabolites have been developed as part of Hypha's one-stop metabolite shop

- **Late-stage chemical synthesis**
- **Microbial biotransformation**
- **Recombinant enzymes (CYPs/AO/FMOs/UGTs)**
- **Mammalian biotransformation (Microsomes/S9 fractions)**
- **Gut metabolism (faecal incubations)**

Glucuronides are common Phase II metabolites of drugs which are often needed as standards for bioanalysis and for DDI testing. For acyl glucuronides, additional safety assessments may be needed due to their potential ability to directly acylate proteins and undergo intramolecular rearrangement producing reactive aldehydes leading to protein glycation. However, not all acyl glucuronides cause problems, and chemical reactivity assays, *in vitro* assessments, and evaluation of exposure in toxicology species is recommended in early clinical development to assess any risk.[1]

Glucuronides can be responsible for clinically relevant DDIs, such as those attributed to the acyl glucuronides of clopidogrel[2] and gemfibrozil[3], which selectively inhibit CYP2C8. Further issues can arise due to β-glucuronidase-mediated hydrolysis to the parent drug, the propensity for which differs due to marked species differences in expression of β-glucuronidases.[4]

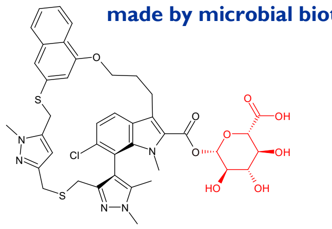
We use both late-stage chemical synthesis and biotransformation methods to make glucuronides for clients. In addition, we have designed our methods to minimise instability resulting from the formation of acyl migration isomers. Synthesised glucuronides are purified with the option of structure confirmation by cryoprobe NMR spectroscopy and the provision of Certificates of Analysis.

References

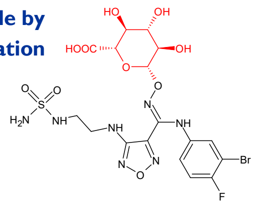
[1]Walles *et al.*, 2020. Chem Res Toxicol 33:1551-1560.
[2]Tornio *et al.*, 2014. Clin Pharmacol Ther 96(4):498-507.
[3]Ogilvie *et al.*, 2006. Drug Metab Dispos 34(1):191-197.
[4]Smith *et al.*, 2018. Drug Metab Dispos 46(6):980-912.

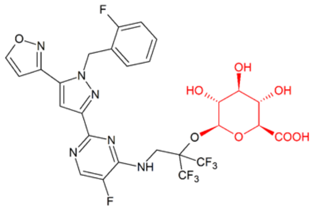
Published examples of glucuronides of drugs made for clients

109 mg AZD5991 acyl glucuronide made by microbial biotransformation

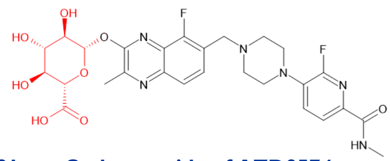


112 mg *O*-glucuronide of epacadostat made by microbial biotransformation



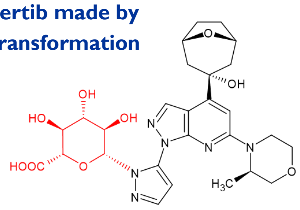


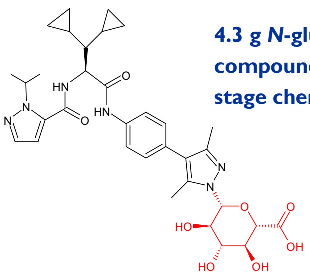
184 mg *O*-glucuronide of praliciguat made by microbial biotransformation



481 mg *O*-glucuronide of AZD9574 made by late-stage chemical synthesis

25 mg *N*-glucuronide of camonsertib made by microbial biotransformation





4.3 g *N*-glucuronide of LEO compound 1 made by late-stage chemical synthesis

For more information contact us at enquiries@hyphadiscovery.com

About Hypha Discovery

Hypha Discovery Ltd is a UK-based CRO providing solutions to pharmaceutical and agrochemical R&D partners through the synthesis, purification and identification of metabolites, purification of drug manufacturing impurities and production of natural products. We have an extensive client base and work with many pharma and agrochemical companies worldwide.