

We can produce and scale-up mammalian phase I and II metabolites using microbial catalysts, mammalian tissue fractions and recombinant enzymes:

- For DMPK / ADME / TOX
- For Met ID
- As standards for quantitation

Proven Reactions

- Methyl hydroxylation
- Methylene hydroxylation
- Methine hydroxylation
- Aromatic hydroxylation
- N-oxidation
- N-methylation
- N-dealkylation
- N-acetylation
- O-dealkylation
- Carbonyl reduction
- Heterocycle oxidation via aldehyde oxidase
- Aromatic O-glucuronidation
- Aromatic N-glucuronidation
- Non-aromatic O-glucuronidation
- Non-aromatic N-glucuronidation
- Acyl-glucuronidation
- Other glycosidations (AgChem)
- N-sulfation
- O-sulfation
- Thiol conjugation (GSH/NAC)
- Transamination
- Amino acid conjugations
- Sequential reactions e.g. hydroxylation & glucuronidation

For more information contact us at mail@hyphadiscovery.com

ABOUT HYPHA DISCOVERY

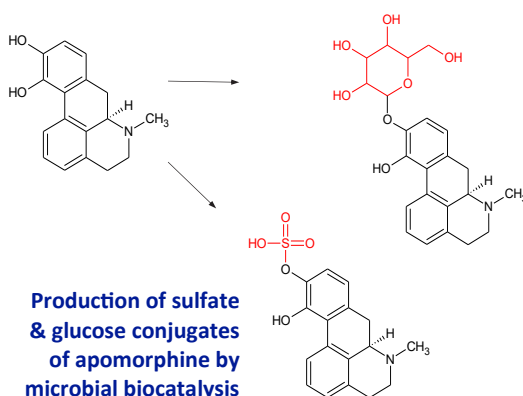
Hypha Discovery Ltd is a UK-based microbial biotechnology company providing solutions to pharmaceutical and agrochemical R&D partners through the production of mammalian and microbial metabolites, as well as specialising in microbially-derived chemicals. As part of our extensive client base, we work with 8 out of 10 of the top pharma companies and 4 out of 6 of the top agrochemical companies worldwide.

Sulfated drug metabolites

Scaled up supply of O- and N- sulfate conjugates

Phase 2 conjugated metabolites such as sulfates can be screened for and scaled-up using a variety of methods including microbial biotransformation, mammalian biotransformation and chemical synthesis. Metabolites can be supplied at microgram to multi mg scale, and at gram scale via the microbial and chemical synthesis routes.

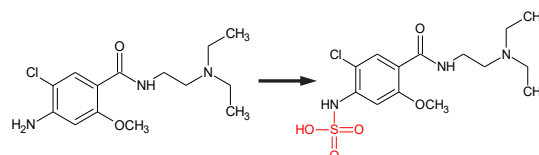
Sulfated metabolites of several drugs have been produced by microbes in Hypha's panel, such as O-sulfated metabolites of apomorphine and genistein, Scale-up of the apomorphine biotransformation generated 3.2 mg of the sulfate conjugate for definitive MetID. A glucose conjugate was produced in parallel, demonstrating broader conjugative capabilities of microbial biotransformation.



Production of sulfate & glucose conjugates of apomorphine by microbial biocatalysis

To demonstrate N-sulfation, the dopamine receptor antagonist metoclopramide was screened against Hypha's microbial and S9 panels. Metoclopramide has significant individual variation in metabolism, featuring multiple metabolites

generated via both oxidative and conjugative pathways. Argikar *et al.* reported ten principal metabolites comprising five oxidation products, four glucuronides and one sulfate conjugate. Sulfate conjugation occurs at the primary amine *in vivo* with marked variability in levels due to polymorphism of human sulfotransferases.



The sulfated metabolite of metoclopramide was produced by two fungal species but not detected in *in vitro* liver S9 incubations, despite being a known circulating metabolite. Glucuronides were produced by both microbial and S9 systems, with several microbes also generating oxidative metabolites and other sugar conjugates.

Case Study

A recent project for a large pharma client involved supply of two sulfated metabolites in mg amounts. Following a dual system screening approach, more than 50mg of an O-sulfate was produced from porcine S9 fractions and more than 10mg of a N-sulfate via a microbial biocatalytic route. Employing the best yielding path for creating each sulfated metabolite meant that requirements were successfully met for supply of both metabolites at high purity.