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
- For bioactivity testing
- For stability studies

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

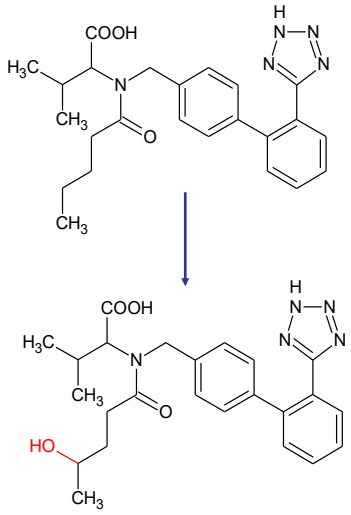
Off-target activity of drug metabolites

Differential pharmacological activities of valsartan and its main human metabolite 4-hydroxyvaleryl-valsartan

Many metabolites of drugs are wholly or partly responsible for both on-target or off-target *in vivo* activity. Metabolites of some drugs may initially be considered pharmacologically inactive, yet further investigation yields surprising alternative effects *via* different mechanisms. Off-target effects might synergize with the on-target effects or have other beneficial outcomes which could enhance or broaden the indication of the drug.[1]

One interesting example is the angiotensin receptor blocker (ARB) drug valsartan, used to treat a variety of cardiac conditions including hypertension. Valsartan is minimally metabolized by CYP2C9 in human liver microsomes with one main metabolite detected, 4-hydroxyvaleryl-valsartan, which accounts for 9% of the circulating dose[2]. This metabolite was found to have no significant ARB activity, however further investigation revealed unexpected potent inhibition of platelet aggregation[3]. This is significant given platelet aggregation plays a key role in the pathogenesis of coronary and cerebrovascular occlusions. The finding was considered of sufficient impact for Novartis to patent use of 4-hydroxyvaleryl-valsartan for treatment of coronary disease mediated by platelet aggregation (WO2003094915A1).

Screening of valsartan against 12 strains from Hypha's biotransformation panel, identified sp145 as the best actinomycete for scale-up. A total of 12.1mg of >95% pure 4-hydroxyvaleryl-valsartan was obtained from a 2L fermentation incubated with 200mg of valsartan. In addition, an unreported novel hydroxylated metabolite was purified and identified from this fermentation. Both these metabolites could also be produced by Poly-CYPs enzymes.



Biotransformation of valsartan to yield the main human circulating metabolite 4-hydroxyvaleryl-valsartan

Hypha's biotransformation systems provides chemists with a route for obtaining scalable amounts of human metabolites, some of which may have different, and potentially more desirable, activity profiles compared to the parent compound. Furthermore, there is the opportunity for capturing and testing novel hydroxylated metabolites.

[1] Urban *et al.*, 2012. Screening for safety-relevant off-target activities. In Polypharmacology in Drug Discovery. Ed. Jens-Uwe Peters.
[2] Nakashima *et al.*, 2005. Xenobiotica 35 (6), 589-602.
[3] Serebruany *et al.*, 2004. J. Cardiovasc Pharmacol. 43 (5), 677-684.

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 5 out of 6 of the top agrochemical companies worldwide.