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HYPHA DISCOVERY

Metabolites and molecules for tomorrow's drugs

www.hyphadiscovery.co.uk

Production of drug metabolites

We produce mammalian Phase I and II metabolites using microbial chemistry, S9 fractions and pure 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*-demethylation**
***O*-demethylation**
Carbonyl reduction
Heterocycle oxidation (AO)
Aromatic *O*-glucuronidation
Aromatic *N*-glucuronidation
Non-aromatic *O*-glucuronidation
Non-aromatic *N*-glucuronidation
Acyl-glucuronidation
***N*-sulfation**
***O*-sulfation**
Glycosidation
Thiol conjugation (GSH/NAC)
Sequential reactions e.g. hydroxylation & glucuronidation

Accessing non-CYP derived phase I metabolites

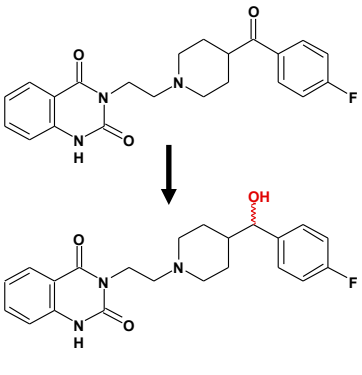
A consequence of the development of drugs that are less susceptible to clearance by CYP metabolism is the increased number of drugs that undergo metabolism *via* non-CYP mechanisms (Nishimuta *et al.* 2013. Drug Metab. Dispos. 41:1101-11).

It is thus important to be able to access metabolites resulting from these routes to inform the design and optimisation of such drugs, or to comply with the FDA Metabolites In Safety Testing (MIST) guidelines.

Microbes are known for their ability to produce mammalian metabolites of small molecules, in particular the products of cytochrome P450 metabolism and glucuronide conjugates.

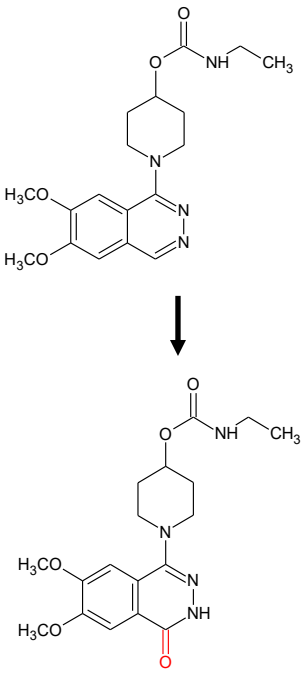
Microbial non-CYP phase I mechanisms involving monoamine oxidases, flavin-containing monooxygenases, xanthine oxidases, carboxylesterases and *N*-acetyltransferases are also well-known.
We have recently demonstrated the potential of our microbial panel to access products of non-CYP phase I reactions, specifically the human phthalazinone metabolite of carbazeran through the action of aldehyde oxidase and the carbonyl reductase metabolites of ketanserin (illustrated below) and loxoprofen. These metabolites were homologous to those derived from respective human liver cytosol reactions.

Formation of hydroxylated metabolites of ketanserin via the action of carbonyl reductase



The Hypha system provides a scalable method to produce material for structural and biological assessment.

Oxidation of carbazeran by aldehyde oxidase to form the phthalazinone metabolite



Why work with us?

We can provide a solution when chemical synthesis fails, often the case with hydroxylations and glucuronidation.

Our microorganisms achieve chemo-, regio- and enantio-specific synthesis and the process is applicable for even complex substrates, such as steroids, macrocycles and natural products.

Defined timelines and costs, using a single step transformation of the parent compound to capture multiple metabolites in a single screen. Metabolites are produced on a simple fee-for-service basis, i.e. no downstream terms.

Our process is scalable. Large quantities of a target molecule can be produced for further work.

We work with 8 out of 10 of the top pharma companies and 4 out of 6 of the top agrochemical companies worldwide. Some of our clients include:

DuPont, Gilead, Lundbeck, Leo, Selcia, Glactone Pharma, Phenex Pharmaceuticals AG, Incyte, Syngenta, UCB, Scynexis, Ferrer

About Hypha Discovery

Hypha Discovery Ltd is a UK-based microbial biotechnology company providing solutions to pharmaceutical and agrochemical R&D partners worldwide through the production of mammalian and microbial metabolites, as well as specialising in microbially-derived chemicals.