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HYPHA DISCOVERY

Metabolites and molecules for tomorrow's drugs

Phase 1 drug metabolites

Production of human and novel non-mammalian metabolites of cyclosporin A

It is well known that metabolites of drug compounds may have different efficacy and side effects to that of the parent compound. Investigation and production of these metabolites is critical for exploration and understanding of SAR, and to ensure thorough patent coverage. Metabolites can also be sourced to create antibodies used in development of assays for therapeutic drug monitoring.

Hypha's has the ability to create both mammalian and microbial metabolites of drug candidates at scale, in order to permit characterization and assessment towards full SAR and patent coverage. This is possible with both synthetic and natural product derived drugs.

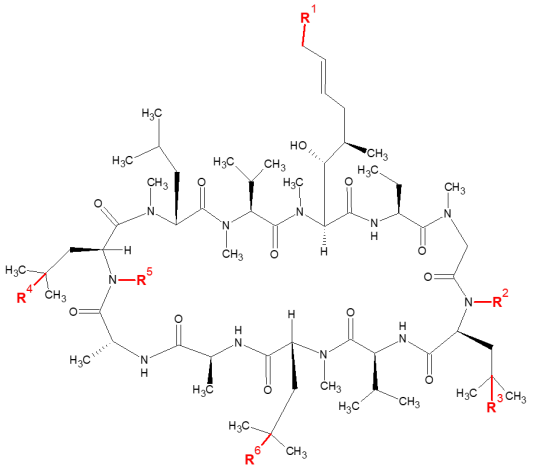
In this case study, all of the main human metabolites of cyclosporin A were produced using microbes in Hypha's biotransformation panels, and by using PolyCYPs® enzymes. Additionally we are able to form novel microbial-derived metabolites.

"Hypha Discovery has been a valuable metabolite ID partner. Hypha have provided biotransformation, metabolite purification and structure elucidation answers to some of our most challenging metabolism and metabolite ID problems. We really appreciate the breadth of expertise available at Hypha Discovery and will definitely reach out for future work."

Director of DMPK, US Pharma Company

Production of mammalian metabolites of cyclosporin A by PolyCYPs enzymes and strains in Hypha's microbial panel

Compound	R^1	R^2	R^3	R^4	R^5	R^6
Cyclosporin A	H	CH_3	H	H	CH_3	H
AM1	OH	CH_3	H	H	CH_3	H
AM19	OH	CH_3	H	OH	CH_3	H
AM19N	OH	CH_3	H	H	H	H
AM4	H	CH_3	OH	H	CH_3	H
AM4N	H	H	H	H	CH_3	H
AM49	H	CH_3	OH	OH	CH_3	H
AM6	H	CH_3	H	H	CH_3	OH
AM9	H	CH_3	H	OH	CH_3	H
AM9N	H	CH_3	H	OH	H	H



Why work with us?

High success rates. We have a high success rate in making even the most difficult-to-synthesize metabolites using our one-stop metabolite shop techniques. Our processes are applicable to broad structural types and provide a method for capturing multiple metabolites in a single screen. We also have expertise in purification and structure elucidation by NMR.

Scalable and reproducible process. We have an excellent reproducibility rate where target molecules can be scaled up to produce mg to gram 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.

We produce and scale-up mammalian phase 1 and 2 metabolites using chemical synthesis, microbial catalysts, mammalian tissue fractions and recombinant enzymes:

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

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
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About Hypha Discovery

We are a UK-based CRO providing solutions to pharmaceutical and agrochemical clients globally through the production, purification and characterization of metabolites of drugs and agrochemicals. We have delivered projects for 8 of the top 10 pharma companies and 5 out of 6 of the top agrochemical companies in provision of metabolites.