www.hyphadiscovery.co.uk

HYPHA DISCOVERY

Metabolites and molecules for tomorrow's drugs

We 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**
***O*-dealkylation**
Carbonyl reduction
Heterocycle oxidation (AO)
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)
Sequential reactions e.g. hydroxylation & glucuronidation
***N*-acetylation**
Transamination

Accessing structurally-unknown metabolites for MIST compliance - a case study

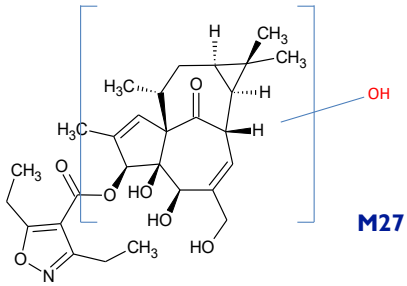
Ingenol disoxate is a chemically-stable topical dermal drug developed by one of Hypha's clients, effective at treating actinic keratosis and currently in Phase 3 clinical trials.

Profiling of ingenol disoxate against multiple species of hepatocytes, revealed M27 as a predominant metabolite, particularly in human hepatocytes.

Although accurate mass spectroscopy indicated the metabolite was mono-hydroxylated in the ingenol moiety, the precise location of the hydroxyl group could not be identified. Consequently, chemical synthesis was not feasible, nor bioanalytical quantification and further biological testing possible.

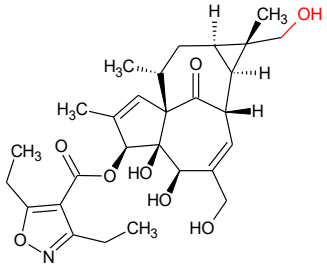
Hypha's scalable microbial screen highlighted 14 strains that produced oxidized metabolites of ingenol disoxate. After precise chromatographic matching by the client, the best-yielding strain was scaled up to produce a target amount of 10-50 mg of the human metabolite M27.

Following scale-up, 86 mg of M27 was supplied to the client at >99% purity, who identified the metabolite as 16-hydroxyingenol disoxate. In addition to this material, 5 mg of a dihydroxylated derivative was supplied for evaluation. A subsequent request for more M27 for further studies needed a minimum of 200 mg, with Hypha supplying 415 mg of M27 to the client at 99% purity.



M27

Accurate mass spectroscopy revealed mono-hydroxylation of the ingenol moiety



Resolution of the structure of the human metabolite M27 as 16-hydroxyingenol disoxate through provision of material generated via microbial biotransformation.

Having plentiful supply of this material, meant that scientists were able to confirm the structure of the major metabolite *via* NMR spectroscopy and undertake PK profiling assays, as well as respond immediately to a later request by the FDA for drug-drug interaction studies to be undertaken with the metabolite.

Ref: Carlsen *et al*., 2016. Biosynthesis, structural identification and quantification of low pg/ml levels of a major human metabolite of a dermal drug candidate. European Bioanalysis Forum, Barcelona, Nov. 2016.

For more information about our services, contact us at
mail@hyphadiscovery.co.uk

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, Selcia, Glactone Pharma, Phenex Pharmaceuticals, 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.