www.hyphadiscovery.co.uk

HYPHA DISCOVERY

Metabolites and molecules for tomorrow's drugs

Newsletter Spring 2015

Lead diversification through biological C-H bond activation

We provide a range of services for our clients using microbial chemistry, mammalian tissue and enzymology expertise to produce:

- **Mammalian Phase I (CYP & non-CYP) and Phase II metabolites:**
  - *For Met ID*
  - *As standards for quantitation*
  - *For bioactivity testing*
  - *For stability studies*
  - *For DMPK / ADME / TOX*
- **Analogues for lead diversification and optimization:**
  - *Obtain novel derivatives*
  - *Improve activity / selectivity*
  - *Improve ligand lipophilicity efficiency*
  - *Protect / widen IP coverage*

Reactions

Aliphatic and aromatic hydroxylation Selective *N*-oxidation	✓
N- + *O*-dealkylation/ hydrogenation/ dehydrogenation	✓
N-, *O*– and acyl glucuronidation (+ other glycosidation)	✓
Sulfation	✓

Lead compounds of diverse structural types can be biotransformed by Hypha's microbial panel to produce arrays of analogues. These products can be generated at small scale for testing or further derivatisation.

The cleavage of unactivated C-H bonds is one of the most challenging reactions in chemical biology (Stone, 2009). However, nature is highly effective at selecting and oxidizing C-H bonds, and Hypha's biological process activates C-H bonds resulting in both aliphatic and aromatic hydroxylation.

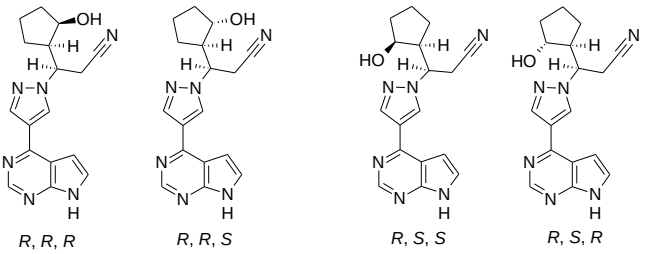
Projects for our clients worldwide have resulted in the identification of novel active derivatives, including molecules with different biological selectivities. These metabolites can be those previously seen in mammalian species, or new derivatives specifically produced by microbes.

Stone, 2009. Curr Opin Chem Biol. 13(1): 114

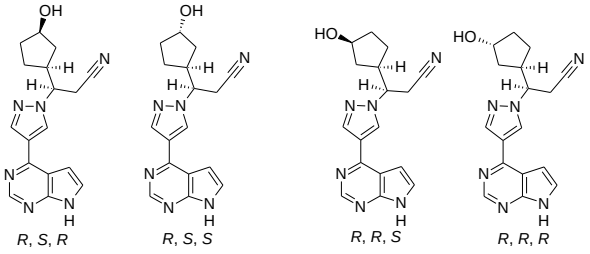
One project conducted for Incyte with the JAK inhibitor ruxolitinib, resulted in the production of an array of hydroxylated and further oxidized keto metabolites from a variety of microbial species in our panel. Metabolites of interest were then scaled up for further characterization.

Selected derivatives produced via aliphatic methylene hydroxylation by microbial species in Hypha's biotransformation panel. Keto derivatives of metabolites were also produced and identified.

2-hydroxylation of cyclopentane moiety



3-hydroxylation of cyclopentane moiety

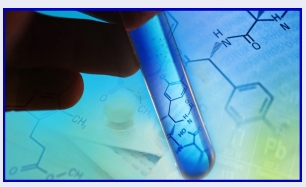


Why work with us?

High success rates. A high % of compounds have been derivatised by our strains. The process is applicable to broad structural types and provides a method for capturing multiple metabolites in a single screen.

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



For more information contact:

mail@hyphadiscovery.co.uk

Some of our partners and clients include:

DuPont, Gilead, Lundbeck, syngenta, selcia, European ScreeningPort, evotec, OSI, Incyte, ferrer

About Hypha Discovery

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