Accessing major human drug metabolites from mixed conjugative pathways

Major circulatory and excretory metabolites of lorcaserin

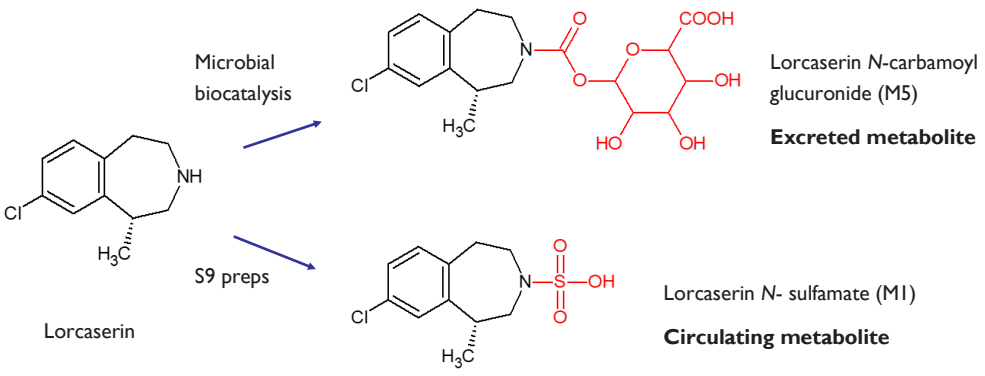
Lorcaserin (Belviq®) is a selective 5-HT_{2C} receptor agonist acting on the hypothalamus to reduce appetite and treat obesity. It has also been found to reduce the use and craving for opioid drugs in pre-clinical studies.[1] Lorcaserin *N*-sulfamate (M1) is the major circulating metabolite in plasma with lorcaserin *N*-carbomoyl glucuronide (M5) being the major excretory metabolite in urine. Screening of lorcaserin against Hypha's panels of microbes and liver S9 preps gave scalable routes to accessing both metabolites.

N-carbamoyl glucuronidation is not a common disposition mechanism, however it has been observed for drugs containing primary and secondary amino functionalities and is becoming more commonly reported.[2] In humans, lorcaserin glucuronidation is predominantly catalyzed by three UDP-glucuronyltransferases (UGT2B7, UGT2B15 and UGT2B17)[3]. Hypha's microbes were able to replicate the action of these human UGTs to produce the same metabolite. In total, four microbes in Hypha's Phase II screening panel of 23 strains were able to produce the *N*-carbamoyl glucuronide. One strain was scaled up to 0.5L to generate 10 mg of purified material from 50 mg of parent compound for structure confirmation by NMR spectroscopy. Various hydroxylated metabolites of lorcaserin were also formed by at least 4 other strains.

In humans, sulfotransferases (SULTS) catalyze formation of the lorcaserin *N*-sulfamate metabolite (M1) *via* multiple SULT isoforms with SULT1A1 reported as the most efficient.[4] Seven species in Hypha's mammalian liver S9 panel were able to produce the target metabolite with canine and primate species being the best producers of M1.

Employing multiple biocatalytic screening routes to access human drug metabolites, as exemplified here for lorcaserin, offers an excellent scalable system for obtaining key metabolites needed for clinical development programs.

[1]Neelakantan *et al.*, ACS Chemical Neuroscience 2017. DOI: 10.1021/ACSHEMNEURO.6B00413
[2]Gundez *et al.*, 2010.DMD 38(3), 361-7
[3]Sadeque *et al.*, 2012. DMD 40(4), 772-8
[4]Sadeque *et al.*, 2016. DMD 4494), 570-5



Major human metabolites of lorcaserin produced using microbial biocatalysis (lorcaserin *N*-carbamoyl glucuronide) and mammalian liver S9 preps (lorcaserin *N*-sulfamate)

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

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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 4 out of 6 of the top agrochemical companies worldwide.