Sulfated drug metabolites

Scaled up supply of O- and N-sulfate conjugates

Phase II conjugated metabolites such as sulfates can be screened for and scaled-up using either microbial biocatalysis and/or liver S9 fractions. Metabolites can be supplied at microgram to multi mg scale, and at gram scale via the microbial route.

Sulfated metabolites of several drugs have been produced by microbes in Hypha’s panel, such as O-sulfated metabolites of apomorphine and genistein. Scale-up of the apomorphine biotransformation generated 3.2 mg of the sulfate conjugate for definitive MetID. A glucose conjugate was produced in parallel, demonstrating broader conjugative capabilities of microbial biotransformation.

The sulfated metabolite of metoclopramide was produced by two fungal species but not detected in in vitro liver S9 incubations, despite being a known circulating metabolite. Glucuronides were produced by both microbial and S9 systems, with several microbes also generating oxidative metabolites and other sugar conjugates.

Production of sulfate and glucose conjugates of apomorphine by microbial biocatalysis

To demonstrate N-sulfation, the dopamine receptor antagonist metoclopramide was screened against Hypha’s microbial and S9 panels. Metoclopramide has significant individual variation in metabolism, featuring multiple metabolites generated via both oxidative and conjugative pathways. Argikar et al. reported ten principal metabolites comprising five oxidation products, four glucuronides and one sulfate conjugate. Sulfate conjugation occurs at the primary amine in vivo with marked variability in levels due to polymorphism of human sulfotransferases.

Case Study

A recent project for a large pharma client involved supply of two sulfated metabolites in mg amounts. Following a dual system screening approach, more than 50 mg of an O-sulfate was produced from porcine S9 fractions and more than 10 mg of a N-sulfate via a microbial biocatalytic route. Employing the best yielding path for creating each sulfated metabolite meant that requirements were successfully met for supply of both metabolites at high purity.

Argikar et al., 2010. Identification of novel metoclopramide metabolites in humans; in vitro and in vivo studies. DMD 38(8), 1295-1307.

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.