Improving drug metabolism outcomes with mechanistic *in silico* modelling

Matthew D. Segall, Daniel Barr, Mario Öeren
R&D, Optibrium Limited, Cambridgeshire, United Kingdom, info@optibrium.com

Introduction

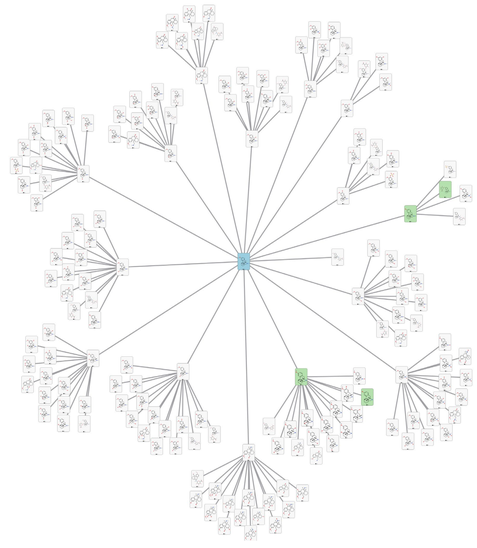
Unexpected metabolism can lead to the failure of many late-stage drug candidates or even the withdrawal of approved drugs. Therefore, during early research, it is important to predict the routes, sites, and products of metabolism of potential drug-like molecules, helping to alleviate these risks and to aid in the identification of metabolites from *in vitro/in vivo* experiments.

Optibrium's mechanistic metabolism models cover metabolism by cytochrome P450 (CYP), aldehyde oxidase (AOX), flavin-containing monooxygenase (FMO), UDP-glucuronosyltransferase (UGT), and sulfotransferase (SULT) enzymes [1-5]. By combining these models, metabolic pathway analysis proposes the most likely metabolites with greater precision than other methods, assisting in metabolite identification studies and enabling potentially active, reactive, or toxic metabolites to be identified [6].

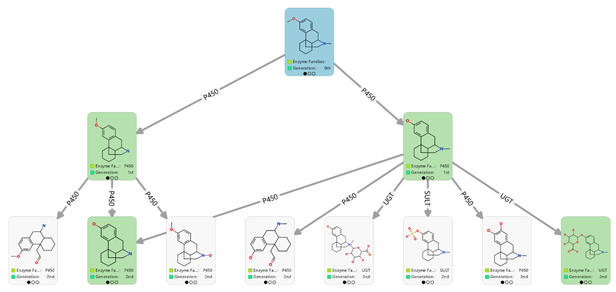
Predict metabolite profiles

The number of potential metabolites of a compound is enormous, making it challenging to predict the most likely metabolites with precision. Optibrium's mechanistic approach to predicting metabolism results in greater precision, while retaining high sensitivity to the experimentally observed metabolites, as illustrated for Dextromethorphan (cyan card) and its observed metabolites (green cards).

Possible metabolites (Precision 4%)

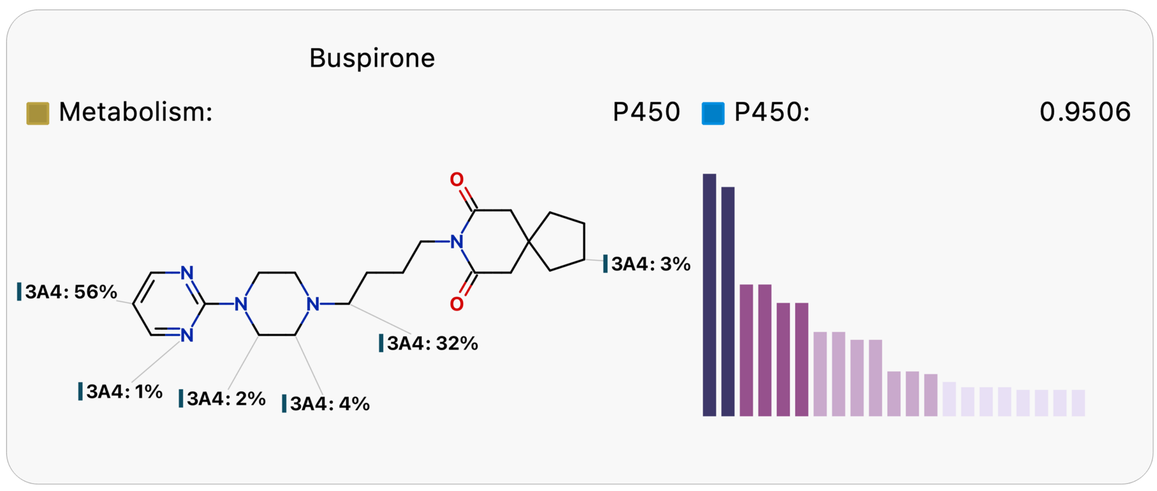


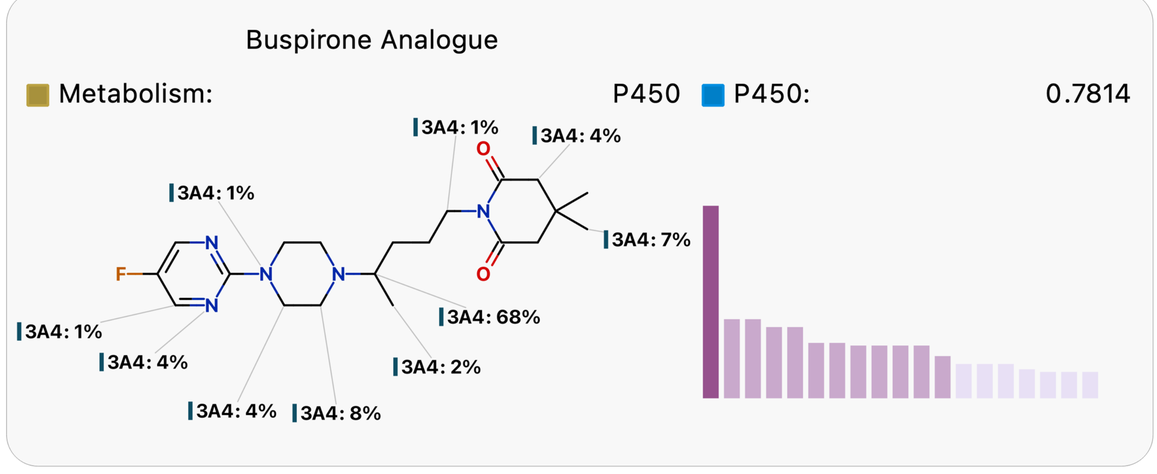
Predicted metabolites (Precision 40%)



Design out metabolic instability

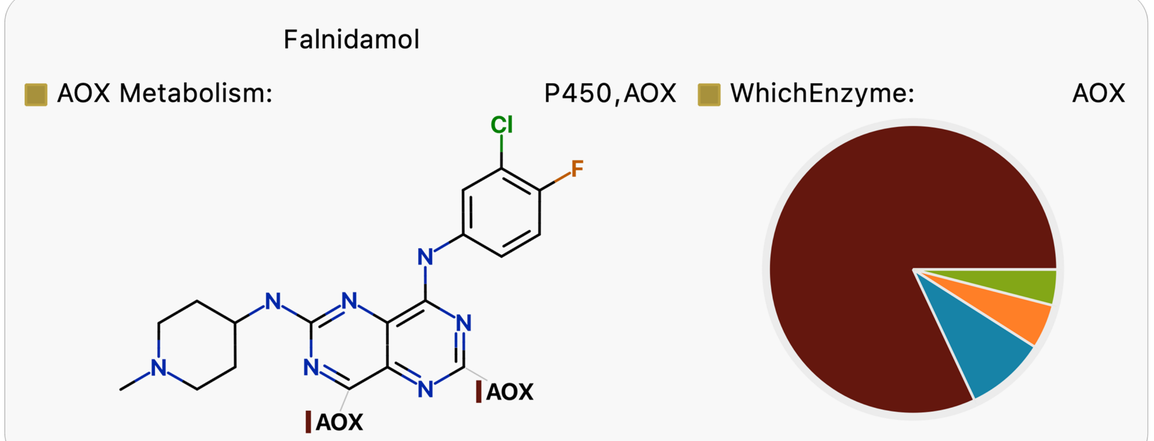
Predicting sites of metabolism and their lability guides the design of more stable compounds. For example, blocking the most labile predicted sites of Buspirone results in reduced lability to metabolism by CYP3A4 and an increase in experimental *in vitro* half-life from 4.6 minutes to 40 minutes.





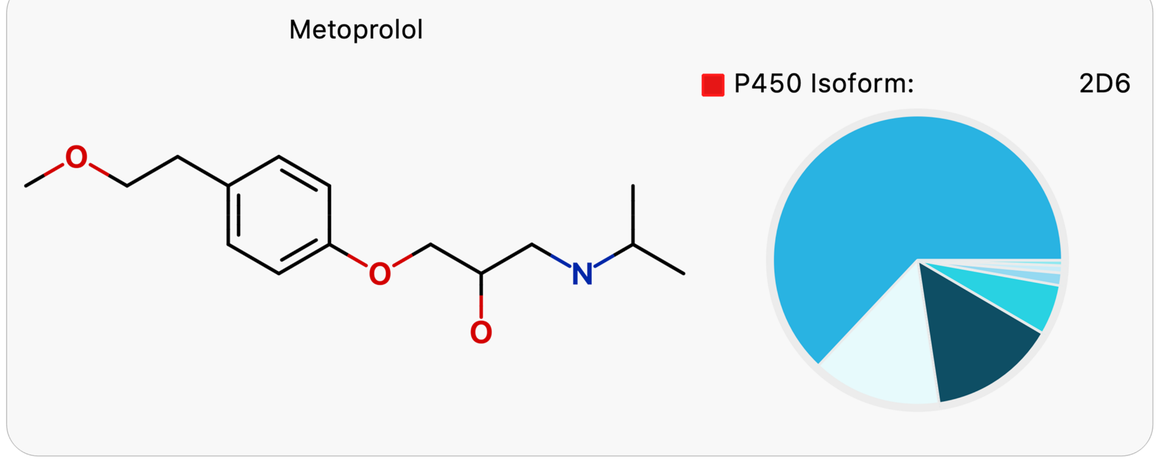
Avoid expensive clinical failures

A focus on microsomal stability can lead to unexpected metabolism by other enzymes in late-stage studies. Falnidamol failed in the clinic due to poor oral bioavailability caused by AOX, which was missed in preclinical studies using rats and dogs [9]. The WhichEnzyme™ model [6] identifies AOX as the most likely isoform responsible for Falnidamol's metabolism. This would have enabled prioritisation of appropriate *in vitro* and PK studies; e.g., using guinea pigs or rhesus monkeys in preclinical studies would have revealed the risk of AOX-mediated metabolism.



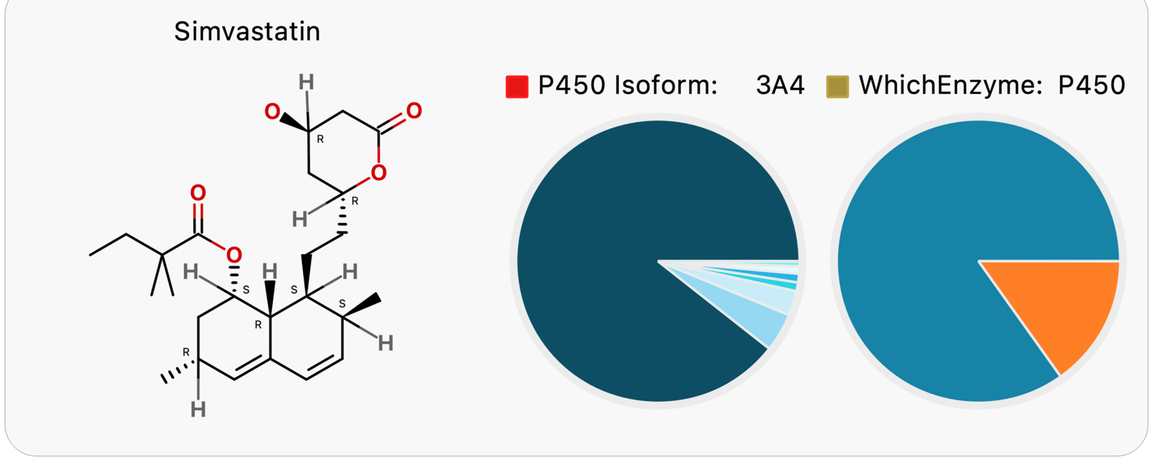
Identify risks from genetic polymorphisms

Genetic polymorphisms in some P450 isoforms, e.g. CYP2D6, CYP2C9 and CYP2C19 lead to significant increases in drug exposure in substantial subpopulations. The WhichP450™ model can identify compounds that are likely to be metabolised predominantly by a single polymorphic isoform, indicating an increased risk, e.g. Metoprolol [8]. Prioritising metabolism phenotyping experiments can confirm the risk and avoid late-stage issues.



Avoid drug-drug interactions

Compounds metabolised by only a single isoform of a single enzyme pose a significant risk of drug-drug interactions (DDIs). Inhibition or induction of that isoform by a co-administered drug can lead to significant changes in exposure. For example, Optibrium's WhichEnzyme™ and WhichP450™ models reveal that Simvastatin is primarily metabolised by CYP3A4, so coadministration with potent CYP3A4 inhibitors such as Ketoconazole is contraindicated. Prioritising phenotyping experiments can confirm these risks early in a project and guide compound design.



References

[1] Öeren et al. J. Med. Chem. 2022, 65, 14066-14081
[2] Öeren et al. J. Chem. Inf. Model 2023, 63, 3340-3349
[3] Öeren et al. J. Comput.-Aided Mol. Des. 2020, 35, 541-555
[4] Tyzack et al. J. Chem. Inf. Model. 2016, 56, 2180–2193
[5] Hunt et al. J. Comput.-Aided Mol. Des. 2018, 56, 2180-2193
[6] Öeren et al. Xenobiotica 2023, 63, 1-49
[7] Tandon et al. Bioorg. Med. Chem. Lett. 2004, 14, 1709–1712
[8] Meloche et al. BJCP 2020, 86, 1015-1033
[9] Hutzler et al. Drug Metab. and Dispos. 2014, 42, 1751-1760
[10] Akram et al. Int. J. Cardiology 2007, 118, e19-20

Learn More

...about our metabolism models and peer-reviewed publications via the QR code or by visiting https://optibrium.com/metabolism.