BIOTRANS
LA ROCHELLE 2023

N°113 / PC
TOPIC(s) : Industrial biocatalysis

POLYCYPS: BIOCATALYTIC TOOLS FOR THE OPTIMISATION OF DRUG LEADS

AUTHORS

Vincent POON / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Aksana KHAN / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Emily HOPKINS / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Tetsuo KOKUBUN / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Kinga NYTKO / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Richard PHIPPS / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Frank SCHEFFLER / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Julia SHANU-WILSON / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Liam EVANS / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Jonathan STEELE / HYPHA DISCOVERY LIMITED, 154B BROOK DRIVE, ABINGDON
Stephen WRIGLEY / HYPHA DISCOVERY LIMITIED, 154B BROOK DRIVE, ABINGDON

PURPOSE OF THE ABSTRACT

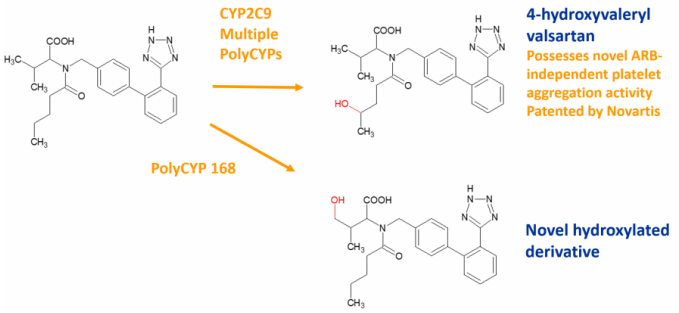
PolyCYPs® enzymes are bacterial Class I and Class III cytochrome P450s (P450s) successfully mined from actinomycete bacteria in Hypha's biotransformation panel. Eighteen of the best performing P450s as well as human aldehyde oxidase and flavin-containing monooxygenase 3 were developed into an easy-to-use lyophilised cell-free extract kit.

PolyCYPs enzymes are available in screening and scale-up format which enables the production of low milligram amounts of oxidised metabolites for purification and identification. Multi-gram quantities of metabolites and oxidised derivatives can be generated using a Streptomyces lividans whole cell biotransformations expressing the specific PolyCYP enzyme.

The poster features the application of PolyCYP enzymes to produce multiple oxidised metabolites and derivatives of drug compounds in parallel and provides opportunities to:

1. Boost DMPK properties, particularly metabolic stability
2. Empirically discover new polar interactions in binding sites, improving potency and selectivity
3. Establish if metabolites are active before deprioritising a scaffold due to metabolic instability
4. Utilise hydroxylated derivatives/metabolites as a handle for late-stage functionalisation e.g. fluorination
5. Rapidly expand polar SAR and broaden IP coverage, including the exemplification of active metabolites.

FIGURES



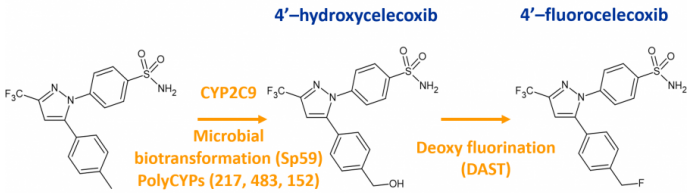


FIGURE 1

Valsartan case study

PolyCYPs used to quickly generate metabolites and oxidised derivatives with enhanced properties that could widen IP coverage.

FIGURE 2

Celecoxib case study

PolyCYPs providing handles for late-stage hydroxylation-fluorination strategy

KEYWORDS

Cytochrome P450 | Biocatalyst | Drug metabolism | Late-stage functionalisation

BIBLIOGRAPHY

J. Boström, D. Brown, R. Young, and G. M. Keserü, Nat. Rev. Drug. Discov., 2018 17, 709-727

J. Shanu-Wilson, L. Evans, S. Wrigley, J. Steele, J. Atherton, and J. Boer,
ACS Med. Chem. Lett., 2020, 11, 2087-2107