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First Aid for Medicinal Chemists: Bioprospecting Cytochrome P450 Enzymes to Diversify Natural Product

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PURPOSE OF THE ABSTRACT

Cytochrome P450 enzymes (P450s) can selectively oxidise highly functionalised molecules in a synthetic late-stage fashion via the activation of inert C-H bonds, making them ideal for medicinal chemists to diversify natural products in drug discovery processes (Figure 1) [1].

White-rot fungi are an attractive source for bioprospecting novel P450s because their extraordinary lifestyle of metabolising lignin and detoxifying xenobiotics is enabled by a diverse enzymatic portfolio [2]. We noticed that the P450ome of the white-rot fungus *Polyporus arcularius* revealed an unusual enrichment of the sparingly characterised family CYP5035. The efficient heterologous expression of a small CYP5035 library in *Pichia pastoris* allowed identifying multifunctional P450s with activities towards several different natural product classes [3] and up-scaling of the whole-cell biotransformations to analyse their catalytic potential in several follow-up studies [4-6].

Recently, we also showed that human P450 enzyme 3A4, a key player in any drug discovery process, is highly efficient at diversifying a wide range of different natural product classes to a similar extent as its model substrate testosterone [7]. Expressed in *P. pastoris*, P450 3A4 diversified six steroids, alkaloids and terpenes to an unprecedented degree at a preparative 100-mg scale, allowing the identification of a total of 31 authentic human metabolites, many for the first time [8].

Therefore, eukaryotic P450s can act as an efficient first aid kit for medicinal chemists to diversify natural products for drug discovery purposes [1,9].

FIGURES

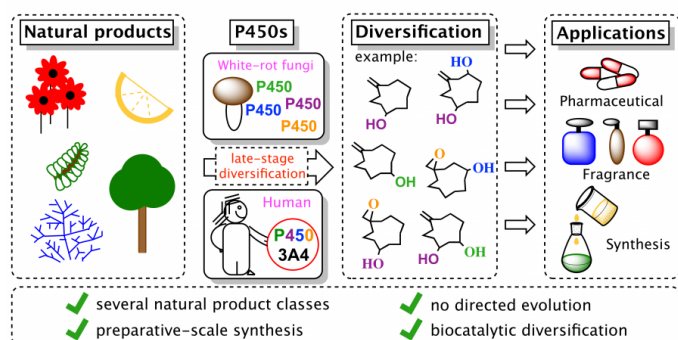


FIGURE 1

P450s - Synthetic First Aid for Chemists

P450s can serve as First Aid for Chemists for the synthesis and diversification of natural products in drug discovery. We used white-rot fungal and human P450s to demonstrate their efficiency for this task.

FIGURE 2

KEYWORDS

Cytochrome P450 Enzymes | Natural product diversification | White-rot fungi | Enzyme discovery

BIBLIOGRAPHY