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Hydroxysteroid dehydrogenases: promiscuous enzymes for diverse synthetic applications

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PURPOSE OF THE ABSTRACT

Hydroxysteroid dehydrogenases (HSDHs) are NAD(P)H-dependent enzymes belonging to the superfamily of short-chain dehydrogenases/reductases (SDRs). In Nature, these enzymes catalyze the reversible oxidoreduction of the hydroxyl/keto groups of neutral steroids, bile acids and other steroid derivatives with exquisite selectivity. Specifically, HSDHs have been shown to display very high regioselectivity for the hydroxyl groups at different positions, e.g., at C-3, C-7, and C-12 of bile acids. For each one of these positions, HSDHs usually show high stereoselectivity for either the hydroxyl group above (β configuration) or below (α configuration) the plane of the steroid molecule. [1,2]

The use of HSDHs on substrates not showing the core structure of steroid molecules, i.e. the investigation of their potential substrate promiscuity, represent an enabling tool for synthetic organic chemists seeking for novel, biocatalyzed and selective processes. For instance, some years ago a study reported the stereoselective reductions of α-ketoesters catalyzed by HSDHs, [3] but, after a careful literature check, very few reports can be found on this topic.

Therefore, the presented work aims at describing the efforts made by us to fill this gap by exploring the substrate promiscuity on different non-steroid molecules of a library of microbial HSDHs, showing either 7α, 7β, or 12α activity, and originated by already reported sources, as well as from newly identified (meta)genomic sequences.

Accordingly, the selected enzymes were tested as biocatalysts for the stereoselective reduction of a panel of different substrates (Figure 1).

Figure 1. Examples of the substrate promiscuity of HSDHs.

At first, simple ketones and aldehydes were tested, then α-keto esters were studied as synthons of pharmaceutical interest along with selected cyclic ketones. [4,5] After this, the HSDHs-mediated biotransformation of racemic “Wieland-Miescher ketone”, an important intermediate widely used in the total synthesis of complex natural terpenoid products, [6] was implemented in multi-enzymatic entry to isolate its enantiomers and alcohol derivatives. [7] Moreover, HSDHs performances were tested on complex natural, bioactive products, like gingerol and gingerdiols, as well as towards “bulky-bulky” ketones like aryl decorated γ-keto esters, synthetic precursors of valuable bioactive metabolites. [8]

FIGURES

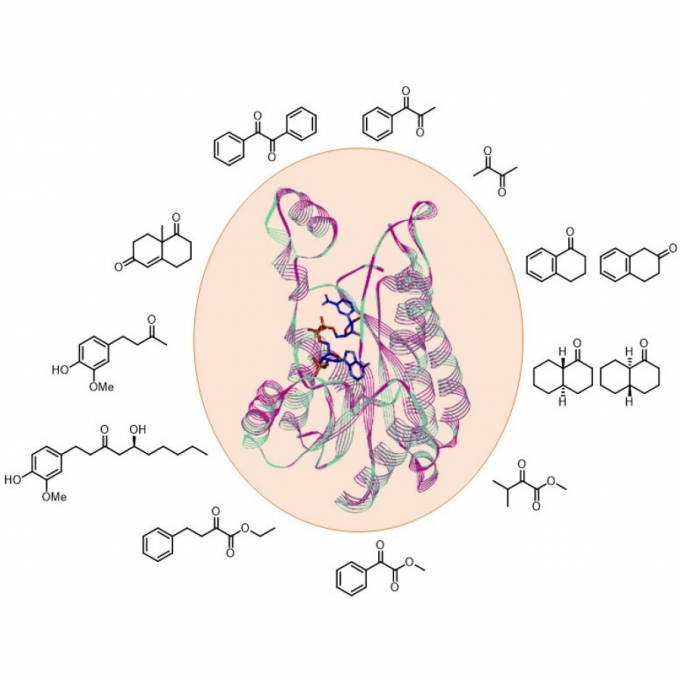

FIGURE 1

FIGURE 2

Figure 1

Examples of the substrate promiscuity of HSDHs.

KEYWORDS

Hydroxysteroid dehydrogenases | Enzyme promiscuity | Oxidoreductases | Chiral Synthons

BIBLIOGRAPHY

[1] E. E. Ferrandi, S. Bertuletti, D. Monti, S. Riva, European Journal of Organic Chemistry 2020, 2020, 4463-4473.

[2] S. Bertuletti, E. E. Ferrandi, D. Monti, G. Fronza, I. Bassanini, S. Riva, ChemCatChem 2021, 13, 4948-4953.

[3] D. Zhu, J. E. Stearns, M. Ramirez, L. Hua, Tetrahedron 2006, 62, 4535-4539.

[4] E. E. Ferrandi, I. Bassanini, S. Bertuletti, S. Riva, C. Tognoli, M. Vanoni, D. Monti, International Journal of Molecular Sciences 2022, 23, 12153.

[5] S. Bertuletti, E. E. Ferrandi, S. Marzorati, M. Vanoni, S. Riva, D. Monti, Advanced Synthesis and Catalysis 2020, 362, 2474-2485.

[6] H. Hagiwara, Natural Product Communications 2020, 15, 1934578X2092534.

[7] S. Bertuletti, I. Bayout, I. Bassanini, E. E. Ferrandi, N. Bouzemi, D. Monti, S. Riva, European Journal of Organic Chemistry 2021, 2021, 3992-3998.

[8] R. Nasti, I. Bassanini, E. E. Ferrandi, F. Linguardo, S. Bertuletti, M. Vanoni, S. Riva, L. Verotta, D. Monti, ChemBioChem 2022, 23, e202200105.