



Review

Industrial biotransformations in the synthesis of building blocks leading to enantiopure drugs

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ABSTRACT

Due to the growing demand of enantiomerically pure compounds, as well as the increasing strict safety, quality and environmental requirements of industrial synthetic processes, the development of more sustainable, healthy and economically attractive strategies for the synthesis of chiral biologically active molecules is still an open challenge in the pharmaceutical industry. In this context, the biotransformations field has emerged as a real alternative to traditional synthetic routes, because of the exquisite chemo-, regio- and enantioselectivities commonly displayed by enzymes; thus, biocatalysis is becoming a widespread methodology for the synthesis of chiral compounds, not only at laboratory scale, but also at industrial scale. As hydrolases and oxido-reductases are the most employed enzymes, this review is focused on describing several industrial processes based on the use of these enzymes for obtaining chiral compounds useful for the pharmaceutical industry.

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1. Introduction

The synthesis of optically pure compounds is increasingly in demand in the pharmaceutical, fine chemicals and agroalimentary industries, as it is well established the importance of the chirality on the activity and properties of many compounds. Thus, the development of new processes for the obtaining of chiral molecules is still an open challenge in organic synthesis, and the production of fine chemicals and drugs by biotechnological methodologies is an emerging research field (Nestl et al., 2011). Due to the high chemo-, regio- and enantioselectivities commonly displayed by enzymes, the biotransformations field has acquired more interest for the production of chiral building blocks, as well as biologically active compounds (de Carvalho, 2011), offering the development of more environmentally and economically attractive processes.

In addition, REACH regulation and the environmental restrictions approved by US, Japan and E.U. in the last decade, has opened a great debate in Fine Chemicals Industry about its immediate future. In this way, Green Chemistry philosophy (Anastas and Eghbali, 2010), promoting the industrial use of chemicals obtained from biomass, the use of green solvents and more sustainable industrial processes, is impacting R + D + i industrial research. The key success in developing "greener" industrial processes is the effective integration of catalytic technologies (chemical or enzymatic) into a general organic synthesis scheme.

In this sense, biocatalysis presents many appealing features in the context of Green Chemistry specially for the synthesis of chiral building blocks leading to enantiopure drugs or food additives (Nestl et al., 2011): gentle reaction conditions (physiological pH and temperature, water as the usual reaction medium, although many green solvents can also be used, as we mentioned before) and an environmentally friendly catalyst (an enzyme or a cell) displaying high activities and chemo-, regio- and stereoselectivities in multifunctional molecules. Additionally, the use of biocatalysts generally circumvents the need for functional group activation, therefore avoiding protection and deprotection steps usually required in traditional organic syntheses. These properties affords processes which are shorter, produce less waste and are, therefore, both environmentally and economically smarter than conventional routes.

Nevertheless, although enzymes are very active and selective biocatalysts, for industrial purposes, a very common reason to engineer them is to increase their stability under the reaction conditions (Tao and Kazlauskas, 2011). In fact, reaction conditions can differ dramatically from those present in a cell, demanding high temperatures, extremes of pH, high substrate and product concentrations, oxidants, and organic cosolvents. Sometimes an enzyme must tolerate these conditions for only a few minutes or hours, but in a continuous manufacturing process, an enzyme may need to tolerate them for months. There are many ways to increase robustness of biocatalysts, being their immobilization probably one of the most traditionally studied and used (Hanefeld et al., 2009). On the other hand, the use of molecular enzyme engineering techniques, such as directed

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