ENGINEERING OF PENICILLIN G ACYLASES FOR THE PRODUCTION OF B-LACTAM ANTIBIOTICS ON AN INDUSTRIAL SCALE

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β-lactam antibiotics are the most important class of antibacterial compounds in clinical applications, which have been industrially produced by conventional chemical methods. The chemical synthesis of β-lactam antibiotics is carried out under stringent conditions which results in high downstream process costs and the environmentally-damaging processes. For those reasons, the efforts have been made to replace traditional chemical processes with enzymatic conversion processes for more sustainable production of β-lactam antibiotics. Penicillin G acylase (PenG acylase) has been found to be useful in the synthesis of β-lactam antibiotics. In order to adopt a process advantageous to industrial and economic angles, it is preferred that the enzyme activity, synthesis/hydrolysis ratio, and operational stability are sufficiently high. Using directed evolution in combination with high-throughput screening system, PenG acylase from Achromobacter sp. CCM 4824 was engineered and then immobilized in epoxy or amide type acrylate resin. In the synthesis of cephalexin, cefprozil, cefaclor, cephradine, cefadroxil, or amoxicillin, specific activity was highly increased by 165, 121, 154, 153, 36, 853-fold, respectively, by using 7-ADCA, 7-ACCA, or 6-APA as a β-lactam nucleus, and PGM, HPGM, or DHME as an acyl donor, which also exhibited high synthesis/hydrolysis ratio up to 68-folds, compared with the wild type. All enzymes could be recycled over 200 cycles without any inactivation, making sure the repetitive use for the industrial application. These data indicate that the engineered PenG acylase from Achromobacter can be used to direct the synthesis of various β-lactam antibiotics by the combination of β-lactam nuclei with various acyl groups.