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Microfluidic reactor for lipase-catalyzed regioselective synthesis of neohesperidin ester derivatives and their antimicrobial activity research

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ABSTRACT

Lipase-catalyzed regioselective synthesis of neohesperidin ester derivatives was performed by Lipase TL IM from *Thermomyces lanuginosus* in a continuous-flow microreactor and then their antimicrobial activity was studied. It appears that neohesperidin, neohesperidin dihydrochalcone with primary OH on the sugar part is the most reactive substrate. Various reaction parameters were investigated including substrate molar ratio, reaction time and temperature. Maximum conversion (92%) was obtained under the optimal condition of substrate molar ratio of 8:1 (vinyl esters: neohesperidin) at 52 °C for about 35 min. Then, the antibacterial activity of modified neohesperidin ester derivatives was examined and showed great improvement against gram negative and gram positive bacteria.

1. Introduction

Recently, microreactor technology has received a great deal of attention [1–3]. A key feature of such devices is their increased surface area-to-volume ratio which is a direct result of their decrease in physical size. Specific surfaces of microstructured devices can be as high as 50 000 m^2 m^{-3} whereas conventional laboratory apparatus does not usually exceed 1000 m^2 m^{-3}. A consequence of this increase in specific surface is the enhancement of mass and heat transport in the system. The advantages of microreactors have been substantiated by a growing number of examples over the past decade [4–11]. In recent years, there is an increasing interest for the enzymatic synthesis in microreactors [12–22].

Neohesperidin are natural polyhydroxylated diphenylpyrane derivatives that are widely distributed among various plants. In recent years, many studies have been published describing their properties. In particular, flavonoids exhibit strong antioxidant [23,24], anti-inflammatory [25], anti-tumoral [26,27] and antiviral activities [28,29]. The use of flavonoids in numerous cosmetic and pharmaceutic formulations seems very attractive. Unfortunately, the development of such products is seriously limited due to their poor solubility in apolar media like oils. Therefore, the acylation or the glycosylation of these molecules can be used as a tool to improve their properties. These reactions can be performed either chemically or enzymatically. However, due to the polyhydroxylated nature of these molecules, the enzymatic approach is more selective [30]. Both lipase and protease have been used to the enzymatic acylation of flavonoids. However, some of these methods always need longer reation time and the conversion yields were not ideal for some specific substrates [31–33].

So we report here, for the first time, microfluidic reactor for lipase-catalyzed regioselective synthesis of neohesperidin ester derivatives (Scheme 1) and then their antimicrobial activity were studied too. The aim of this paper is to investigate, under a continuous-flow microreactor, the effect of the flavonoid structure (hesperidin, neohesperidin, neohesperidin dihydrochalcone) and the carbon-chain length of the fatty acids (C2, C12 and C16) on the flavonoid acylation performance. Then we further studied the antimicrobial activity of neohesperidin ester derivatives with different chain lengths compared with the neohesperidin.

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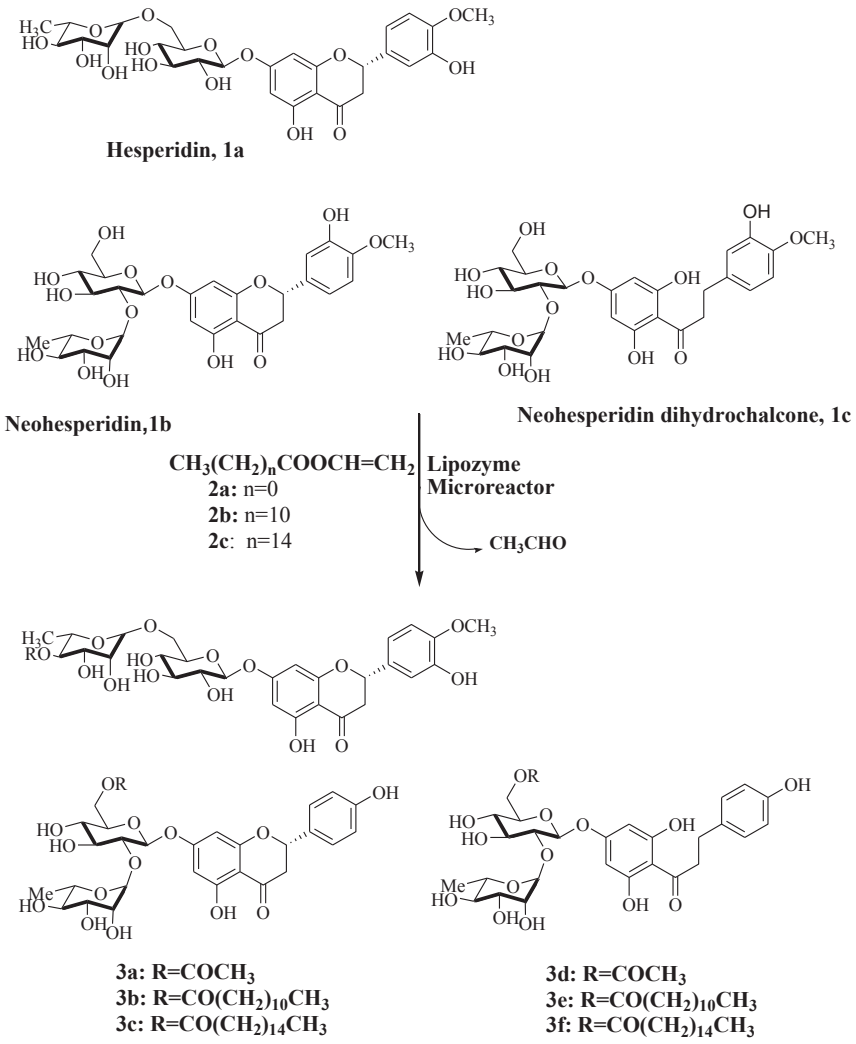

Scheme 1. Lipase-catalyzed regioselective acylation of hesperidin, neohesperidin and neohesperidin dihydrochalcone in microreactors.

2. Results and discussion

2.1. Experimental setup

The enzymatic synthesis of flavonoid esters was performed in microreactor. The equipment configuration that was used for the enzymatic synthesis of flavonoid esters reactions starting from neohesperidin and vinyl carboxylate is described in Fig. 1. Harvard Apparatus PHD 2000 syringe pumps were used to deliver reagents from syringes to the reactor. On the syringe pump, a 10 mL syringe with the neohesperidin solution and a 10 mL syringe with vinyl carboxylate in 2-methyl-2-butanol were mounted. Lipozyme TL IM were filled in silica gel tubing (inner diameter ID = 2.0 mm, length = 1 m). The reaction temperature was controlled by water

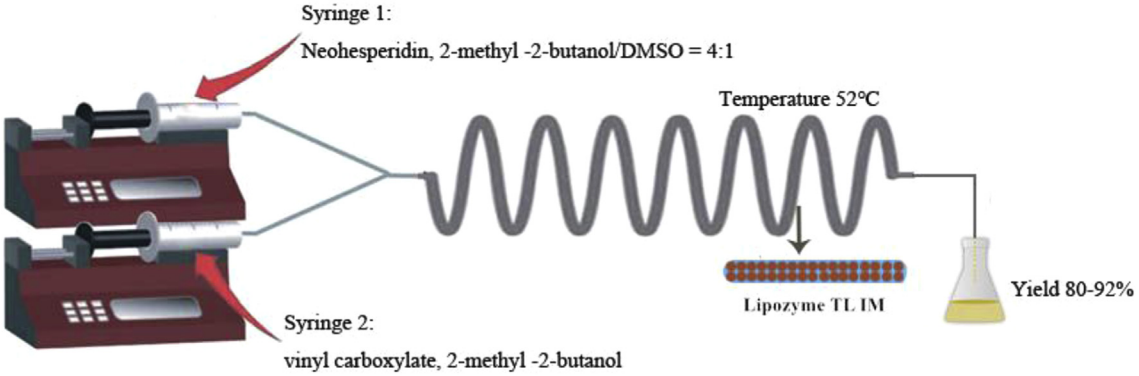

Fig. 1. Microreactor setup for the continuous-flow synthesis of neohesperidin ester catalyzed by Lipozyme TL IM.