Glyceric Prodrug of Ursodeoxycholic Acid (UDCA): Novozym 435-Catalyzed Synthesis of UDCA-Monoglyceride

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ABSTRACT

Background: Bile acids (BAs) are a family of steroids synthesized from cholesterol in the liver. Among bile acids, ursodeoxycholic acid (UDCA) is the drug of choice for treating primary biliary cirrhosis and dissolving cholesterol gallstones. The clinical effectiveness of UDCA includes its choleretic activity, the capability to inhibit hydrophobic bile acid absorption by the intestine under cholestatic conditions, reducing cholangiocyte injury, stimulation of impaired biliary output, and inhibition of hepatocyte apoptosis. Despite its clinical effectiveness, UDCA is poorly soluble in the gastro-duo- deno-jejunal contents, and pharmacological doses of UDCA are not readily soluble in the stomach and intestine, resulting in incomplete absorption. Indeed, the solubility of 20 mg/L greatly limits the bioavailability of UDCA.

Objective: Since the bioavailability of drug products plays a critical role in the design of oral administration dosages, we investigated the enzymatic esterification of UDCA as a strategy of hydrophilization. This work proposes an enzymatic strategy for the covalent attack of highly hydrophilic molecules using acidic functions of commercially available bioactive compounds.

Methods: We decided to enzymatically synthesize a glyceric ester of UDCA bile acid to produce a more water-soluble molecule. The esterification reactions between UDCA and glycerol were performed with an immobilized lipase B from *Candida antarctica* (Novozym 435) in solvent-free and solvent-assisted systems.

Results: The optimization of the processes, such as lipase and compounds concentrations, solvents amount, temperatures, stirring speed, and times is reported.

Conclusion: N435 demonstrated itself to be a suitable enzyme for the effective production of UDCA-monoglyceride. The characterization of the UDCA-monoglyceride, enzymatically synthesized, has been performed by ^{1}H-NMR, ^{13}C-NMR, COSY, HSQC, HMBC, IR, and MS spectroscopy.

BIOGRAPHY

Dr. Federico Zappaterra is a Ph.D. in biomedical and biotechnological sciences; His work concerns the development of enzymatic modification protocols for poorly bioavailable active ingredients of pharmaceutical and agri-food interest. His expertise deals with free and immobilized enzymes for the esterification of active compounds using a green eco-sustainable approach. Federico's work focused on the study of the non-steroidal anti-inflammatory drug Ibuprofen, the third most prescribed drug in the world, and bile acids, such as UDCA. The innovative protocols he developed, some of them patented, allowed him to design several derivatives of pharma-industries active ingredients.

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