Synthesis of Fluorescent Bile Salt Derivatives and Their Utility as Tracers of the Canalicular Lipid Transporter System

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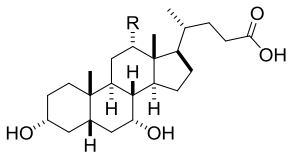
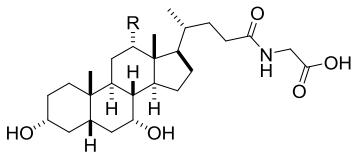
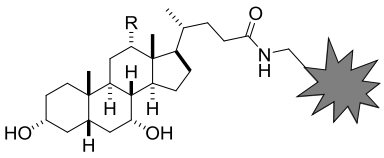
Canalicular bile salt secretion implicates the concomitant interplay of a series of ABC-transporters, i.e. BSEP (Bile salts export pump), MDR3 (or ABCB4) and ABCG5/G8. This process regulates the quantity of all constituents and ensures the formation of a healthy bile. The disruption of the equilibrium between cholesterol, phospholipids and bile salts can lead to cholestatic liver injury. Very little is known about the influence of drugs and xenobiotics on this equilibrium. The development of an analytical system to investigate the impact of exogenous compounds on bile formation would be very beneficial. The goal of our research is the synthesis of novel bile salt derivatives as probes to investigate the mechanism of bile salt secretion into the canaliculus and its disruption caused by drugs and other substances.



R = OH; **Cholic acid** (**CA**)
R = H; **Chenodeoxycholic acid** (**CDCA**)



R = OH; **Glycocholic acid** (**GC**)
R = H; **Glycochenodeoxycholic acid** (**CDCA**)



Fluorescent bile salt

Three fluorescent dyes were coupled to the side chains of cholic acid (CA) and chenodeoxycholic acid (CDCA) to mimic the known transport substrate glycocholate (GC). Nitrobenzofurazan (NBD), dansyl and a coumarin dye (Pacific Blue) were selected to investigate the impact of these different dyes on transport behaviour. Transport of the synthetic fluorescent bile salts was assessed in CHO cells expressing NTCP (Na^+-taurocholate cotransporting polypeptide), organic anion-transporting polypeptides OATP1B1, OATP1B3 or OATP2B1, as well as in Sf9 cell vesicles expressing BSEP. Our data suggest that the fluorescent bile acids are still recognised as substrates and that subtle structural changes in the bile acid structure can have a significant impact on transporter selectivity.