Synthesis and Biological Evaluation of Bile Acid Analogue Inhibitory to Clostridium difficile Spore Germination

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Clostridium difficile is an anaerobic, spore-forming, Gram-positive bacterium that causes a potentially fatal infection of the colon. C. difficile infection (CDI) is one of the most common hospital-acquired infections, and in recent years CDI has also become increasingly acquired in the community. Standard antibiotic-based strategies for the treatment of Clostridium difficile infections disrupt indigenous microbiota and commonly fail to eradicate bacterial spores, two key factors that allow recurrence of infection. As an alternative approach to controlling C. difficile infection, we have prepared a series of bile acid derivatives that inhibit taurocholate-promoted spore germination. These synthetic analogs were significantly more effective than naturally occurring bile acids at preventing C. difficile spore germination in a series of in vitro assays. Analogs designed to have limited intestinal absorption were prepared and found to be potent inhibitors of germination. Ongoing studies detailing the in vivo efficacy and pharmacokinetic properties of our analogs will be discussed.

Figure: UDCA analogues with improved potency towards C. difficile spore germination.