Towards New Fidaxomicin Antibiotics: Combining Metabolic Engineering and Semisynthesis

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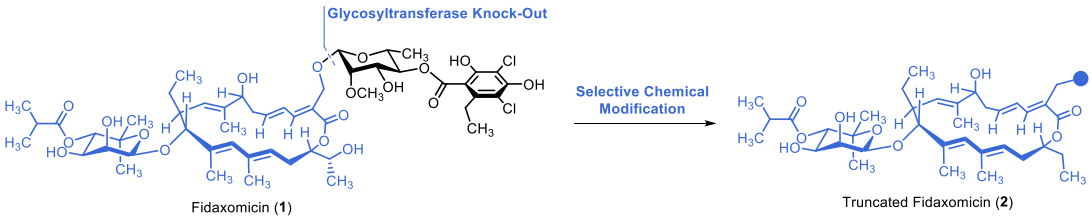
Fidaxomicin (**1**, tiacumicin B, lipiarmycin A3)[1] constitutes a macrocyclic antibiotic which demonstrates potent activity against various Gram-positive bacteria through inhibition of RNA-polymerase (RNAP).[2] Fidaxomicin is marketed to treat *Clostridium difficile* infections in the gut. Moreover, its antibacterial activity against resistant strains of *Mycobacterium tuberculosis* and *Staphylococcus aureus* is of great interest, as these strains still pose a global problem.[3,4] In 2015 our research group accomplished the first total synthesis of this complex natural product.[5–9]



In order to address some of the disadvantages of fidaxomicin such as low bioavailability due to its low water solubility, we set out to construct truncated derivatives that maintain antibiotic activity. The biosynthetic pathway[10] of fidaxomicin-producing bacteria was disrupted to yield the mono-glycosylated macrolide **2**. Herein we present the optimization of growth conditions and subsequent chemical modification of the isolated secondary metabolites.

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