Beta-fucosylamides as antiadhesives glycodrugs targeting bacterial lectins

Résumé

Bacterial infections have a great impact on public health, that is rising following the spread of multi-drug resistant (MDR) bacteria. Those emerged to be associated with severe nosocomial infections and represent a major hazard to hospitalized patients immunocompromised. New or alternative anti-infective strategies have become an urgent concern. Many bacteria produce carbohydrate binding proteins called lectins that recognize glycoconjugates at the surface of the host cells and mediate adhesion which is one of the initial and essential stages for host colonization and infection. The inhibition of glycoconjugates-lectin interactions is being explored as an efficient approach to anti adhesion therapy and biofilm destabilization in order. Here, our targets are fucose binding lectins from the opportunistic Gram-negative bacteria *Pseudomonas aeruginosa* and *Burklholderia cenocepacia* named LecB and Bc2LC-Nter, respectively. Based on structure or fragment-based design studies (1-3), we developed independently for each lectin, N-β-L-fucosyl amides as glycomimetic antagonists (4-6). We investigated their potential by different biophysical methods such as inhibition of fluorescence polarization for indirect assays, and Saturation Transfer Difference NMR and Isothermal Titration Calorimetry for direct binding assays. This resulted in a new hit compound with good solubility and an order of magnitude gain over α-methyl fucoside for Bc2LC-Nter (6) and in unprecedented high-affinity ligands in the two-digit nanomolar range for LecB (5). Crystallographic studies permitted to identified the interactions responsible for the high affinity. Those compounds are now being tested on the other lectin to determine if they can have a bigger spectrum of action.

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Mots-Clés: Glycodrugs, lectins, antiadhesive therapy