Novel β-*C* and β-*N* fucosides as first synthetic ligands for BC2L-C N-term lectin from *B. cenocepacia*

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Burkholderia cenocepacia is an opportunistic Gram-negative bacterium, which causes infections in immuno-compromised individuals, mainly in cystic fibrosis patients. Several *B. cenocepacia* strains were found to be insensitive to many classes of antibiotics, making the treatment of related diseases very difficult.[1] The establishment of an infection by *B. cenocepacia* requires adhesion to host cells through carbohydrate/protein interactions. The BC2L lectins mediate this process and represent potential targets for antiadhesion antimicrobial therapy. Among the group of BC2L, BC2L-C presents an *N*-terminal trimeric domain with fucose-binding activity (BC2L-C-Nt) and a *C*-terminal domain, which recognises mannose (BC2L-C-Ct).[2]

This work aims at developing novel fucose-based glycomimetics able to interfere with the carbohydrate–lectin recognition of BC2L-C-Nt. A modular fragment-based library of *C*- and *N*-fucosides was designed and synthesized, starting from virtual screening of a fragment library.[3,4]The synthesized compounds were tested for their affinity towards BC2L-C-Nt through different biophysical techniques, including saturation transfer difference NMR spectroscopy (STD-NMR), isothermal titration calorimetry (ITC) and crystallographic studies. This study allowed to identify hit compounds with increased affinity compared to the monosaccharide parent structure, up to one order of magnitude.[4,5] These initial structure-activity relationships data will be used to develop high affinity ligands to be tested in the disruption of *B. cenocepacia* biofilm.

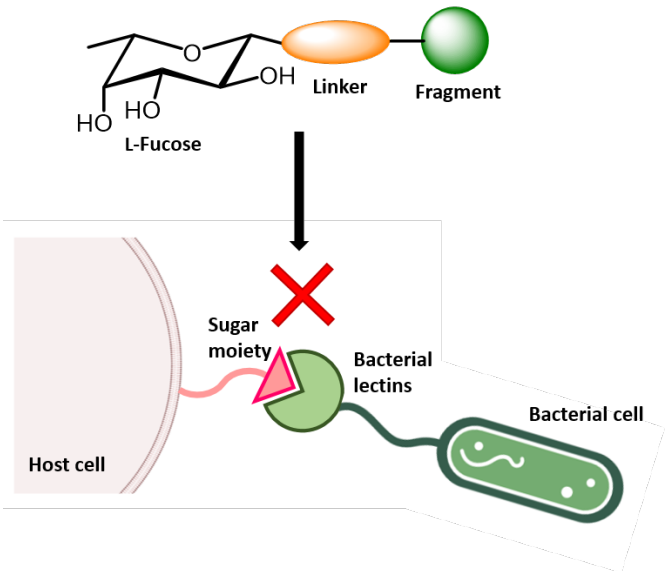

Figure 1. General structure of new BC2L-C ligands.

Bibliographic references:

(1) M. Serra-Burriel, C. Campillo-Artero, M. Keys et al. (2020), PLoS One (15) e0227139.
(2) O. Šulák, G. Cioci, M. Delia et al. (2010), Structure (18) 59–72.
(3) K. Lal, R. Bermeo, J. Cramer et al. (2021), Chemistry European Journal (27), 10341–10348.
(4) R. Bermeo, K. Lal, D. Ruggeri et al. (2022), ACS Chemical Biology (17) 2899–2910.
(5) S. Mazzotta, G. Antonini, F. Vasile et al. (2023), Molecules (28) 1494.