DESIGN AND SYNTHESIS OF BIVALENT AND TETRAVALENT THIOGLYCOSIDES AS POTENTIAL INHIBITORS OF *PSEUDOMONAS AERUGINOSA* LECTINS LECA (PA-IL) AND LECB (PA-IIL)

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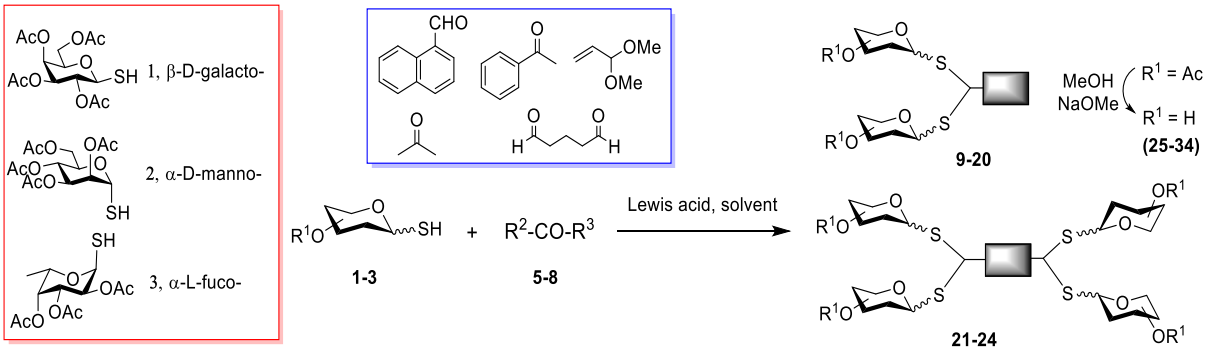
Pseudomonas aeruginosa is a Gram-negative bacterium currently recognized as the most critical bacterial pathogen on the WHO's priority pathogen list. Its ability to form abundant biofilms significantly contributes to its antimicrobial resistance. As a result, various strategies are being explored to identify and develop new antibacterial agents that can effectively inhibit biofilm formation. Two soluble lectins, LecA (PA-IL) and LecB (PA-IIL), play crucial roles in the initial adhesion to host tissues and biofilm formation, and act as key virulence factors [1]. LecA specifically binds to D-galactose (Gal), while LecB shows a strong preference for L-fucose (Fuc) but can also attach to other sugars like D-mannose. In pursuit of effective antibacterial agents, we report the synthesis of novel hydrolytically stable bivalent and tetravalent thioglycosides.

The construction of these analogs involved the formation of the 1-thiomonosaccharides derivatives **1-3**. 1,2-*trans*-glycosyl thiols such as **1** and **2** were prepared from the corresponding bromo sugar through reaction with thiocarbamide, followed by the cleavage with sodium bisulfite, whereas 1,2-*cis*-α-configured L-fucose **3** was produced through the thiol-ene coupling reaction of glycals and thioacetic acid (HSAc), using our recently published optimized conditions, followed by selective *S*-deacetylation [1]. The 1-thiomonosaccharides obtained were then reacted with aliphatic/aromatic oxo-compounds or their dialkyl acetals in the presence of a Lewis acid catalyst to produce the bivalent **9-20** or tetravalent **21-24** thiosugars [2]. This reaction was initially investigated using various solvents, including DMF, MeCN, and DCM, as well as several acidic catalysts such as pTSA, CSA, $BF_3.Et_2O$, TMSOTf, and TfOH. Finally, Zemplén deacetylations were performed to yield the free thioglycosides **25-34** (**Scheme 1**).



Scheme 1. Synthesis of bivalent and tetravalent thioglycosides

References:

1. L Faltinek, F Melicher, V Kelemen, E Mező, A Borbás , M Wimmerová . *Chem. - Eur. J.* **2024,** e202403546.
2. A Rana, S Halder, R Chakraborty, U Debnath, K Jana, AK Misra. *Bioorg. Chem.* **2025**, *154*, 108030.