Chemoenzymatic synthesis of NDP sugars to explore the GDP-mannose dehydrogenase from *p. Aeruginosa*

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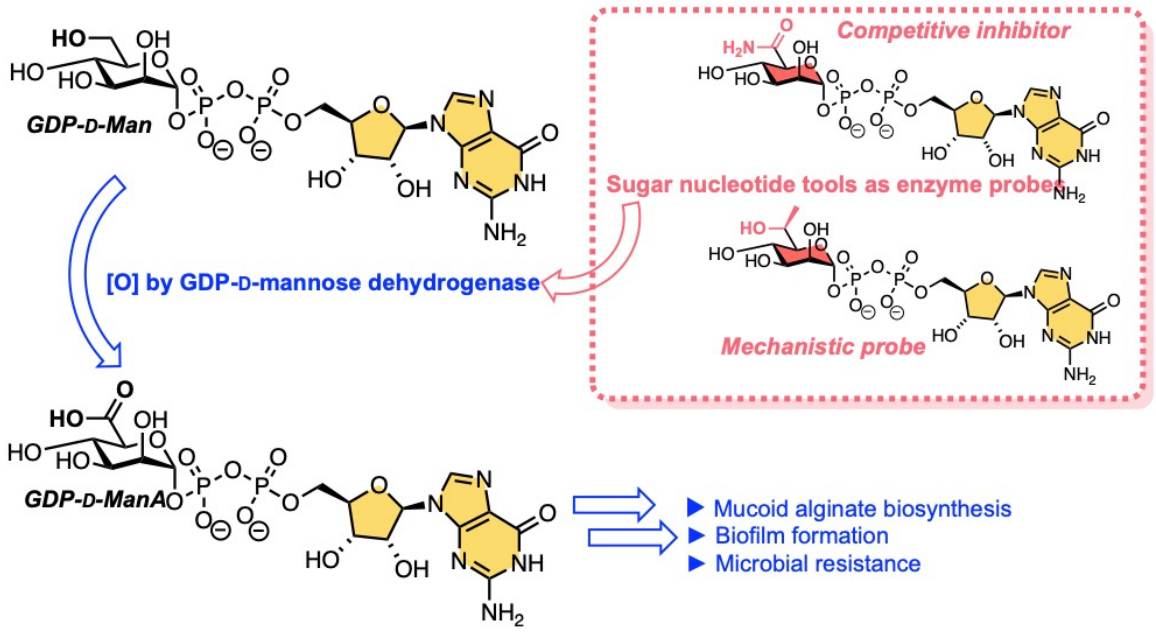
The opportunistic human pathogen *Pseudomonas aeruginosa* (PA) causes chronic bacterial infections in cystic fibrosis patients, contributing to a reduction in lung function and increased mortality rates. The lung environment induces a switch of *P. aeruginosa* to its mucoid phenotype, which is characterised by an overproduction of the exopolysaccharide alginate. Composed of β-D-mannuronic acid and its C5 epimer α-L-guluronic acid, alginate is a key component of the bacterial biofilm which increases persistence of the bacteria in the airways and retards antimicrobial treatments. Inspection of the PA biosynthetic pathway reveals a key enzyme involved in alginate production is GDP-mannose dehydrogenase (GMD), which catalyses an NAD^+-dependent oxidation of GDP-D-Man to GDP-D-ManA: the alginate feedstock monosaccharide. We have recently designed and synthesised a series of GDP-Man probes to interact with the GMD active site, providing mechanistic insight and identified a first sugar nucleotide inhibitor of GMD.



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