

Novel UDP-Galp and Galf-disaccharide Mimics: Inhibitors of the Biosynthesis of Mycobacterial Cell-wall Galactan?

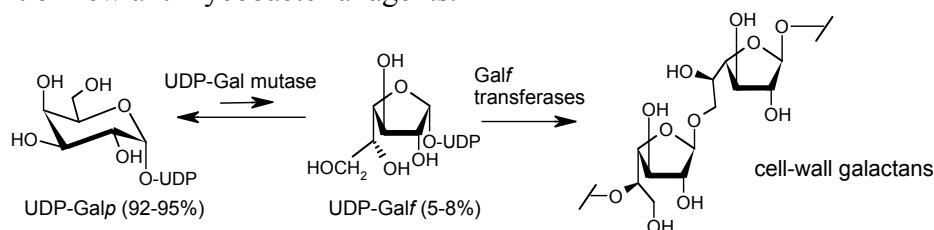
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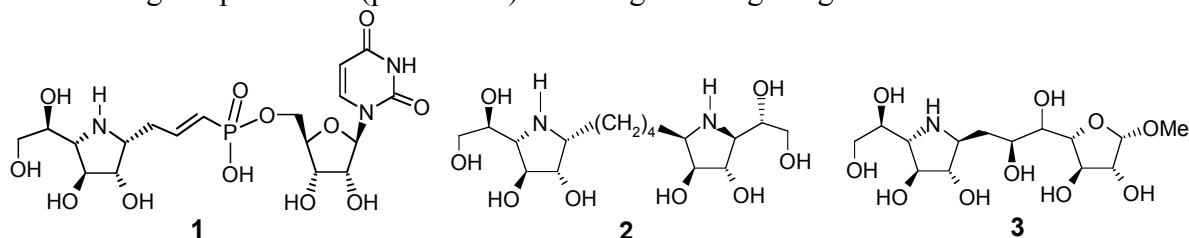
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The cell-wall of mycobacteria is an impenetrable barrier consisting of three layers of biomolecules (mycolic acids, arabinogalactans, and peptidoglycans) which provides the microorganism with efficient protection towards its environment. The central glycan section comprises a unique *galactofuran* core, made of alternating β -(1 \rightarrow 5) and β -(1 \rightarrow 6)-Galf linkages. As the furanose form of galactose is found only in prokaryotes and some lower eukaryotes, the biosynthesis of Galf-containing glycans has become a promising target for the development of new antimycobacterial agents.



The repeating Galf unit arises by way of an unprecedented ring-contraction process mediated by UDP-Gal mutase (UGM) which creates an equilibrium between UDP-Galp and UDP-Galf. The furanosyl sugar nucleotide is then substrate of Galf-transferases for the formation of the growing galactan chain. Remarkably, two bifunctional transferases appear to be sufficient to account for the assembly of the entire Galf-containing glycan.¹

As part of a program designed to identify inhibitors of the enzymes involved in this biosynthetic pathway, we have conceived and prepared² a series of novel analogs of UDP-Galf incorporating a pyrrolidine-iminosugar (e.g. **1**) as mimic of the furanosyl unit. Such analogs could be inhibitors of both UGM and the glycosyl transferases which use UDP-Galf as glycosyl donor: both reactions involve substantial cationic character in the TS of the C₁-O₁ bond-cleavage step and thus (protonated) iminosugar analogs might be efficient inhibitors.



Furthermore, we have prepared a series of novel Galf-disaccharide mimics incorporating two iminogalactitol units, as in **2**, or one iminogalactitol and one galactofuranose unit, as in compound **3**. Such compounds are mimics of the acceptors of the glycosyl transfer process and might act as inhibitors of these reactions. The synthetic strategies and the results of the ongoing biological studies on these compounds will be reported.

1. Beláňová, M. ; Danišková, P.; Brennan, P.J. ; Completo, G.C. ; Rose, N.L. et al. *J. Bacteriol.* 190 (2008) 1141.
2. Liautard, V. ; Desvergnès, V. ; Martin, O.R. *J. Org. Chem.* 73 (2008) 3103-3115.