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Synthesis and antimicrobial activity of 6-sulfo-6-deoxy-D-glucosamine and its derivatives

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ABSTRACT

6-Sulfo-6-deoxy-D-glucosamine (GlcN6S), 6-sulfo-6-deoxy-D-glucosaminitol (ADGS) and their *N*-acetyl and methyl ester derivatives have been synthesized and tested as inhibitors of enzymes catalyzing reactions of the UDP-GlcNAc pathway in bacteria and yeasts. GlcN6S and ADGS at micromolar concentrations inhibited glucosamine-6-phosphate (GlcN6P) synthase of microbial origin. The former was also inhibitory towards fungal GlcN6P N-acetyl transferase, but at millimolar concentrations. Both compounds and their *N*-acetyl derivatives exhibited antimicrobial *in vitro* activity, with MICs in the 0.125–2.0 mg mL^{-1} range. Antibacterial but not antifungal activity of GlcN6S was potentiated by D-glucosamine and a synergistic antibacterial effect was observed for combination of ADGP and a dipeptide Nva-FMDP.

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1. Introduction

Enzymes participating in biosynthesis of polysaccharides constituting microbial cell walls are considered promising targets for antimicrobial chemotherapy [1,2]. These include four enzymes of the cytosolic pathway leading to the ultimate formation of UDP-GlcNAc, a sugar-nucleotide precursor of chitin in fungi and peptidoglycan in bacteria. Interestingly, the fungal and bacterial versions of the pathway are somewhat different. In fungi, the four successive reactions are as follows: (a) conversion of fructose-6-P (Fru6P) into glucosamine-6-phosphate (GlcN6P); (b) acetylation of GlcN6P to GlcNAc6P; (c) isomerization of GlcNAc6P to GlcNAc1P; and (d) uridinylation of GlcNAc1P to give UDP-GlcNAc [1]. In prokaryotic cells, the first and the last step are essentially the same, but GlcN6P is first isomerized to give GlcN1P, which is subsequently N-acetylated [2]. In both versions, the first committed step is catalyzed by the enzyme known under a trivial name of GlcN6P synthase. The target potential of this enzyme has been already demonstrated [3]. Inhibitors of GlcN6P synthase known to date are structural analogs of L-glutamine, including N^3-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP), analogs of the *cis*-enolamine transition state intermediate, including 2-amino-2-deoxy-D-glucitol-6-phosphate (ADGP) and of the reaction product, *i.e.* GlcN6P. ADGP and GlcN6P inhibit the enzyme *in vitro* but demonstrate low antimicrobial activity, due to the poor uptake by microbial cells and intracellular metabolism, including possible phosphatase-assisted dephosphorylation of both and degradation by NagB or conversion to GlcN1P by GlcN6P isomerase (GlmM) of the latter, obviously preventing access to the target enzyme [4,5]. In search for the cell penetrating and non-metabolizable inhibitors of enzymes of the UDP-GlcNAc pathway, we have synthesized 2-amino-6-sulfo-2,6-dideoxy-D-glucose (GlcN6S), its *N*-acetyl and methyl ester derivatives, 2-amino-2,6-dideoxy-D-glucitol-6-sulfonic acid (ADGS) and NAcADGS. One of these compounds, namely GlcN6S, was previously shown to exhibit growth inhibitory activity against some bacteria [6], other compounds are entirely novel.

2. Results

2.1. Chemistry

The synthetic strategy leading to compounds **3–8** is outlined in Scheme 1. An initial substrate was the commercially available *N*-

Abbreviations: cfu, colony forming units; GlcN, D-glucosamine; IPTG, isopropyl β-thiogalactoside; ISOM, isomerase domain of GlcN6P synthase; LB, Luria-Bertani; MIC, minimal inhibitory concentration; UDP-GlcNAc, uridine 5′-diphospho-*N*-acetyl-D-glucosamine.

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