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Synthesis of new analogues of salacinol containing a pendant hydroxymethyl group as potential glycosidase inhibitors

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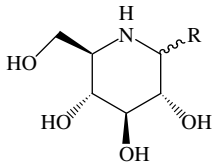
Abstract—The synthesis of new analogues of the naturally occurring glycosidase inhibitor, salacinol, and its ammonium analogue, ghavamiol is described. These analogues contain an additional hydroxymethyl group at C-1, which was intended to form additional polar contacts within the active site of glycosidase enzymes. The target zwitterionic compounds were synthesized by means of nucleophilic attack at the least hindered carbon atom of 2,4-*O*-benzylidene-L (or D)-erythritol 1,3-cyclic sulfate by 2,5-anhydro-1,3:4,6-di-*O*-benzylidene-2,5-dideoxy-5-thio (or 1,5-imino)-L-iditol.

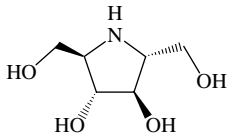
Keywords: Glycosidase inhibitors; Analogues of salacinol and ghavamiol; Ammonium salt; Sulfonium salt; Cyclic sulfate

1. Introduction

Glycosidases are responsible for the hydrolysis of poly- and oligosaccharides into monomers or cleavage of bonds between sugars and a noncarbohydrate aglycon. These enzymes are involved in several metabolic pathways and an alteration of glycosidase activity by inhibitors in vivo has the potential for the control of certain cellular functions. Thus, glycosidase inhibitors have shown promising chemotherapeutic applications against diabetes,[1] cancer,[2] and viral infections including AIDS.[3]



1. R = OH
2. R = H



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The glycosidase-mediated reaction can occur with one of the two possible stereochemical outcomes—inversion or retention of configuration at the anomeric center. The currently accepted mechanisms of glycosidic bond cleavage involve general acid catalysis with protonation of the exocyclic oxygen atom at the anomeric center by a carboxylic acid group in the active site of the enzyme that results in the formation of an oxacarbenium ion transition state,[4] which then reacts with a molecule of water to form the products. An attractive approach to potent inhibitors is to create compounds that mimic the transition state of an enzyme-catalyzed reaction.[5] Many natural and synthetic polyhydroxylated pyrrolidines and polyhydroxylated pyrrolizidines alkaloids, such as nojirimycin **1**, 1-deoxynojirimycin (DNJ) **2**, and 2,5-dihydroxymethyl-3,4-dihydroxy-pyrrolidine (DMDP) **3** are carbohydrate mimics, commonly referred to as azasugars, act as glycosidase inhibitors. It has been postulated that their activity is due to their resemblance to the oxacarbenium-ion-like transition state that arises from the protonation of the ring nitrogen at physiological pH.[5a] DMDP (**3**), a common secondary metabolite, has been reported to be a good glucosidase inhibitor, with mild inhibition of some other glycosidases.

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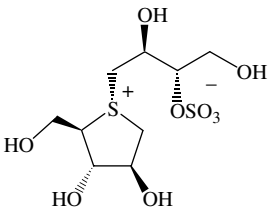

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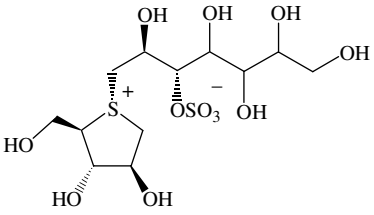

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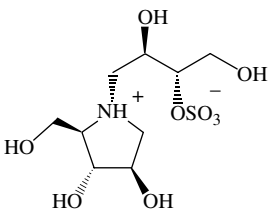

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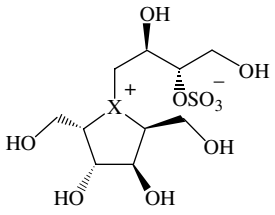
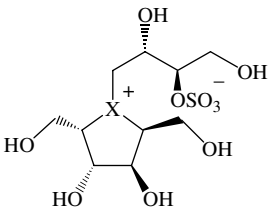
Recently, a new class of naturally occurring glycosidase inhibitor with an intriguing inner salt, sulfonium sulfate was isolated from *Salacia reticulata*[6] a plant from India and Sri Lanka known for its anti-diabetic properties. The bioassay-guided separation using intestinal α-glucosidase inhibitory activity resulted in the isolation of two potent α-glucosidase inhibitors, namely, salacinol (**4**) and kotalanol (**5**). The unique structure of salacinol is a sulfonium ion (1,4-anhydro-4-thio-D-pentitol cation) stabilized by an internal sulfate counter ion (1-deoxy-L-erythritol-3-sulfate anion). These glucosidase inhibitors are also presumably mimics of the oxacarbenium-ion transition state in glucosidase-mediated hydrolysis reactions, but could function simply by providing stabilizing electrostatic interactions with active site carboxylate residues.

In the search for new glycosidase inhibitors, we have reported the synthesis and glucosidase inhibitory properties of the different stereoisomers and heteroatom congeners of salacinol[7] in which the ring sulfur atom has been substituted by the cognate atoms nitrogen and selenium. Enzyme inhibition assays with a panel of glycosidase enzymes have indicated that the stereochemistry at the different stereogenic centers, the nature of the heteroatom, the size of the heterocyclic ring, and the length and nature of the side chain play a significant role in discrimination between different glycosidase enzymes.[8] Our recent investigation by X-ray crystallography[9] of the interaction of salacinol and its analogues with Golgi α-mannosidase II (GMII) indicated that, as speculated, in all of these derivatives, the positively charged sulfonium center was in close proximity to an aspartate residue in the enzyme active site. In addition, a comparison of the interactions with those of the naturally occurring inhibitor, swainsonine demonstrated that the coordination of salacinol **4** with the Zn atom in the enzyme active site is pentacoordinate (T5) whereas that of swainsonine is hexacoordinate (T6). We speculated that octahedral coordination was important to generate a good inhibitor. We report herein the synthesis of new analogues **7**–**10** of salacinol (**4**) and the corresponding ammonium analogue, ghavamiol **6** that incorporate an additional hydroxymethyl group at C-1 that might facilitate T6 coordination in the active site of GMII but might also provide favorable polar contacts in the active site of other glycosidase enzymes.



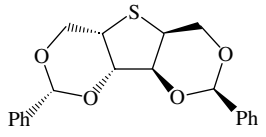
7. X = S
9. X = NH



8. X = S
10. X = NH

2. Results and discussion

The general synthetic strategy involved alkylation of the anhydroalditol at the heteroatom by a cyclic sulfate derivative, whereby selective attack of the heteroatom at the least hindered primary center would afford the desired target molecules.



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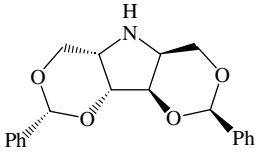

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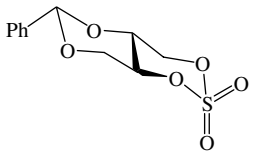

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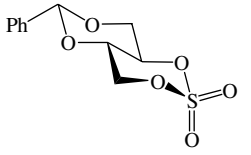

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Thioether (**11**) was synthesized according to a reported method[10] by the radical-mediated cyclization of the corresponding 1,5-bis-dithiocarbonate derivative using tributyltin hydride with α,α-diazoisobutyronitrile (AIBN) as a radical initiator (Scheme 1). The corresponding dithiocarbonate was synthesized, in turn, from 1,3:4,6-di-*O*-benzylidene-D-mannitol by the sequential addition of sodium hydride, carbon disulfide, and methyl iodide in THF (Scheme 1).