

Note

Synthesis of 2-deoxy-2-fluoro and 1,2-ene derivatives of the naturally occurring glycosidase inhibitor, salacinol, and their inhibitory activities against recombinant human maltase glucoamylase

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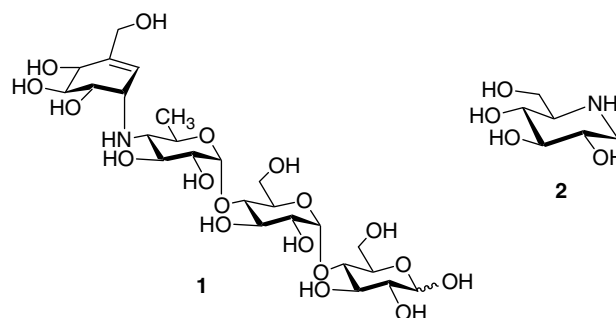
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Abstract—2-Deoxy-2-fluorosalicinol and a 1,2-ene derivative of the naturally occurring glycosidase inhibitor salacinol were synthesized for structure activity studies with human maltase glucoamylase (MGA). 2-Deoxy-2-fluorosalicinol was synthesized through the coupling reaction of 2-deoxy-2-fluoro-3,5-di-*O*-*p*-methoxybenzyl-1,4-anhydro-4-thio-*D*-arabinitol with 2,4-*O*-benzylidene-*L*-erythritol-1,3-cyclic sulfate in hexafluoroisopropanol (HFIP) containing 0.3 equiv of K₂CO₃. Excess of K₂CO₃ resulted in the elimination of HF from the coupled product, and the formation of an alkene derivative of salacinol. Nucleophilic attack of the 1,4-anhydro-4-thio-*D*-arabinitol moiety on the cyclic sulfate did not proceed in the absence of K₂CO₃. No reaction was observed in acetonitrile containing K₂CO₃. The target compounds were obtained by deprotection with TFA. The 2-deoxy-1-ene derivative of salacinol and 2-deoxy-2-fluorosalicinol inhibited recombinant human maltase glucoamylase, one of the key intestinal enzymes involved in the breakdown of glucose, with an IC₅₀ value of 150 μM and a K_i value of 6 ± 1 μM, respectively.

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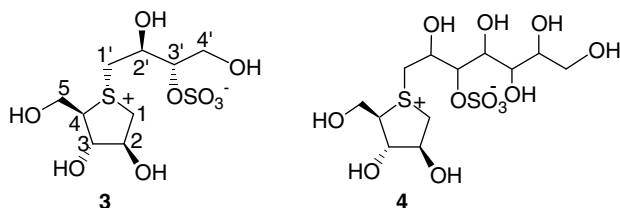
Glycosidase enzymes are fundamental in the biochemical processing of carbohydrates.^{1–5} For example, pancreatic α-amylase converts starch to maltooligosaccharides, and membrane-bound glucosidases convert these oligosaccharides to glucose in the small intestine. Inhibition of these enzymes in patients suffering from type II diabetes (noninsulin dependent diabetes) could be one strategy for controlling blood glucose levels by delaying the breakdown of carbohydrates.^{6–8} One example of this class of inhibitors is acarbose **1**, a naturally occurring glycosidase inhibitor, which has been used for the oral treatment of type II diabetes.^{7,9–11} Deoxynojirimycin **2** is another glucosidase inhibitor whose derivatives have been used in the treatment of diabetes, Gaucher's disease, and viral infections.^{12–17}



Salacinol **3** and kotalanol **4** are two naturally occurring glycosidase inhibitors that have been isolated from roots and stems of a Sri Lankan plant, *Salacia reticulata*.^{18,19} We and others have synthesized salacinol and compounds related to salacinol including heteroanalogues, stereoanalogues, chain-extended homologues, C-2 substituted analogues, and counterion variants.²⁰

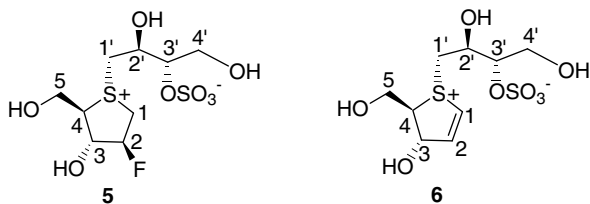
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These inhibitors contain ammonium, selenonium, or sulfonium ion as putative mimics of the oxacarbenium-ion like transition states in glycosidase-mediated hydrolysis reactions.^{21–25}



Theoretical and experimental studies on nucleotides containing 1,2,4-trideoxy-2-fluoro-1,4-anhydro-4-thio-D-arabinose sugar ring had indicated an unusual conformational preference due to steric and stereoelectronic effects.²⁶ In addition, the substitution of a fluorine atom for a hydroxyl group has proven advantageous in the design of carbohydrate-based enzyme inhibitors. Thus, a kinetic study with UDP-Galf and its C3- fluorinated analogue, UDP-[3-F]Galf showed that the catalytic efficiency (k_{cat}/K_m) of UDP-galactopyranose mutase for UDP-[3-F]Galf decreased by approximately three orders of magnitude in comparison to that of UDP-Galf.²⁷ This difference has been attributed, by STD-NMR and molecular dynamics, to the partial population of a binding mode of UDP-[3-F]Galf that is non-productive with respect to reaction.²⁸ Therefore, it was of interest to synthesize a salacinol analogue with a fluorine atom at the C-2 position (5) to probe its glycosidase inhibitory activity.

We report herein the synthesis of 5 and its elimination product 6, together with their inhibitory activities against human maltase glucoamylase (MGA), a key intestinal enzyme involved in the breakdown of malto-oligosaccharides into glucose.



Retrosynthetic analysis indicated that the target compound 5 could be synthesized by removal of the benzylidene and *p*-methoxybenzyl (PMB) protecting groups in compound 7, which could be synthesized, in turn, by nucleophilic attack of compound 8 at the less hindered carbon of 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate 9. Compound 8 could be synthesized from 1,4-anhydro-2-deoxy-2-fluoro-3,5-*O*-(1,1,3,3-tetraisopropylidisiloxane-1,3-diyl)-4-thio-D-arabinitol 10 (Scheme 1).^{26,29}

Compound 10 was synthesized from 1,4-anhydro-4-thio-D-arabinitol according to literature procedures.^{26,29} The silyl protecting group in 10 was removed using tetrabutylammonium fluoride (TBAF), and the resulting

diol was protected with the acid labile protecting group, *p*-methoxybenzyl (PMB), to afford compound 8 in 58% yield (Scheme 2).

The alkylation reaction of 8 with 2,4-*O*-benzylidene-L-erythritol-1,3-cyclic sulfate 9^{30,31} in hexafluoroisopropanol (HFIP) as the solvent containing an excess of K_2CO_3 in a sealed tube did not yield the desired compound 7, but yielded the elimination product 11. Presumably elimination follows alkylation owing to the increased acidity of the protons adjacent to the sulfonium-ion center. Compound 11 was deprotected using trifluoroacetic acid (TFA, 90%) to afford compound 6 for testing as a potential glycosidase inhibitor (Scheme 3).

The alkylation reaction of 8 with the cyclic sulfate 9 in HFIP did not proceed in the absence of K_2CO_3 at 50–70 °C, and at higher temperatures, the starting materials started to decompose. The alkylation reaction of 8 with the cyclic sulfate 9 in acetonitrile containing K_2CO_3 was attempted but the reaction did not proceed and starting compounds were recovered. This result suggested that HFIP might be the best choice of solvent for this type of reaction.

Interestingly, the alkylation reaction of 8 with the cyclic sulfate 9 in HFIP containing 0.3 M equiv of K_2CO_3 in a sealed tube at 68 °C proceeded smoothly to give the desired coupled product 7. The benzylidene and *p*-methoxybenzyl protecting groups were then removed using trifluoroacetic acid (90%) to afford the desired product 5 (Scheme 3).

Finally, we comment on the inhibitory activities of compounds 5 and 6 against recombinant human maltase glucoamylase (MGA). Compound 6 inhibited MGA with an $IC_{50} = 150 \mu M$, whereas compound 5 showed greater inhibition with $K_i = 6 \pm 1 \mu M$. Because salacinol itself shows a $K_i = 0.2 \pm 0.02 \mu M$,³² it would appear that the OH group on C-2 of salacinol is critical as a hydrogen-bond donor with functional groups in the active site of MGA.

1. Experimental

1.1. General methods

Optical rotations were measured at 21 °C. 1H and ^{13}C NMR were recorded with frequencies of 500 and 125 MHz, respectively. All assignments were confirmed with the aid of two-dimensional 1H , 1H (gCOSY) and 1H , ^{13}C (gHMQC) experiments using standard Varian pulse programs. Processing of the data was performed with MestRec software. Analytical thin-layer chromatography (TLC) was performed on aluminum plates pre-coated with silica gel 60F-254 as the adsorbent. The developed plates were air-dried, exposed to UV light and/or sprayed with a solution containing 1% $Ce(SO_4)_2$.

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