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Graphical Abstract

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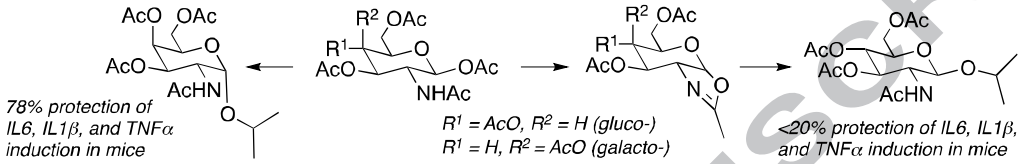

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Synthesis of *anti*-inflammatory α-and β-linked acetamidopyranosides as inhibitors of toll-like receptor 4 (TLR4)§

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ABSTRACT

The low-molecular weight isopropyl 2-acetamido-α-glucoside **16** (C34) inhibits toll-like receptor 4 (TLR4) in enterocytes and macrophages *in vitro*, and reduces systemic inflammation in mouse models of endotoxemia and necrotizing enterocolitis. We used a copper(II)-mediated solvolysis of anomeric oxazolines and an acid-mediated conversion of β-glucosamine and β-galactosamine pentaacetates to generate analogs of **16** at the anomeric carbon and at C-4 of the pyranose ring. These compounds were evaluated for their influence on TLR4-mediated inflammatory signaling in cultured enterocytes and monocytes. Their efficacy was confirmed using a NF-kB-luciferase reporter mouse, thus establishing the first structure-activity relationship (SAR) study in this series and identifying the more efficacious isopropyl 2-acetamido-α-galactoside **17**.

Carbohydrates are best known for their structural and energy storage functions in biological systems, but they demonstrate many other features, including the control of molecular and cellular recognition events (*1, 2*). Mono-, oligo- and polysaccharides can be found as conjugates of peptides, lipids, and secondary metabolites and modulate their physical and biological properties (*1, 3*). 2-Amino-2-deoxyglycosides, mainly glycosides of *N*-acetylglucosamine, are glycoconjugates present in human milk, blood, bacterial lipopolysaccharide antigens and plant root cells (*4, 5*). Glucosamine (Fig. 1) is a known treatment for pain maintenance in osteoarthritis and has no adverse side effects when compared to non-steroidal *anti*-inflammatory drugs (NSAIDs), nor does it affect glucose metabolism (*6*). Post-translational modification of nuclear and cytoplasmic proteins by *O*-glycosidic attachment of β-*N*-acetylglucosamine is essential for cell viability, and improves cell survival under stress (*7*). Glucosamine- and *N*-acetylglucosamine-derived glyco-conjugates have also shown promise as lead structures in drug development (*8*).

Peptidoglycan fragments are recognized and induce signaling by toll-like receptors (TLRs), activating a pathway in innate immune cells that mediates an antimicrobial and pro-inflammatory response. In addition to common immunodisorders, TLRs have also been linked to carcinogenesis, and therefore they have evolved into major targets for drug discovery (*9*).

Several toll-like receptor 4 (TLR4) antagonists are under development as targeted therapeutics, including Eritoran from Eisai Pharmaceuticals (suspended in human Phase III trials), AV411 from Avigen (Phase II), and NI0101 from NovImmune (Preclinical) (*9*). Lipid A mimetics similar to Eritoran have become popular synthetic targets (*10-12*) and have sparked our interest in the use of glucosamine as a central scaffold for SAR elaboration of immunomodulating TLR ligands. As glucosamine is a component of the disaccharide core of both Lipid A and Eritoran (Fig. 1), we sought to mimic key structural features of these large liposaccharides, while reducing molecular weight and lipophilicity to generate more drug-like analogs. Using *in silico* drug discovery followed by *in vivo* testing, we recently discovered novel small molecule TLR4 inhibitory mono- and

§ Dedicated to the memory of Prof. Harry Wasserman, in deep appreciation of his many insightful contributions to Organic Chemistry.

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oligosaccharides (*13*). In particular, isopropyl 2-acetamidopyranoside C34 was found to inhibit TLR4 in enterocytes and macrophages *in vitro* and to reduce systemic inflammation in mouse models of endotoxemia and necrotizing enterocolitis (*13*). Subsequently, our strategy examined three areas for further structure-activity relationship (SAR) studies of this lead compound for TLR4-mediated inflammatory diseases: an α- vs β-glycosidic linkage, the configuration at C-4 of the pyranose (glucosamine vs galactosamine), and the length, size and hydrophilicity of the glycosyl chain. The pyranose hydroxyl and amino groups were *O*- and *N*-acetylated to mimic the longer acyl chains in Lipid A and Eritoran (Fig. 1).

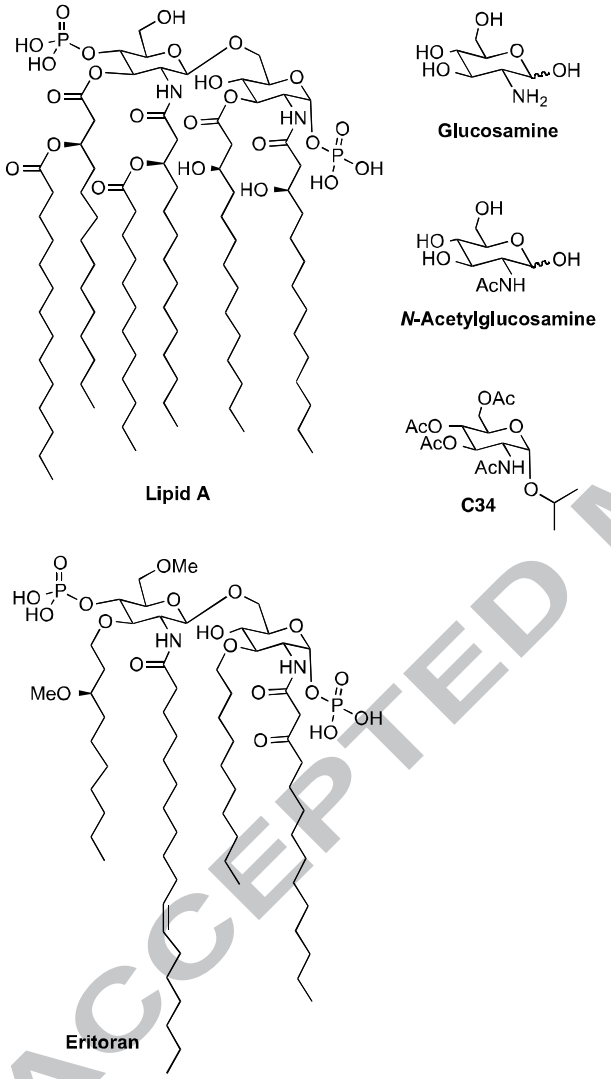
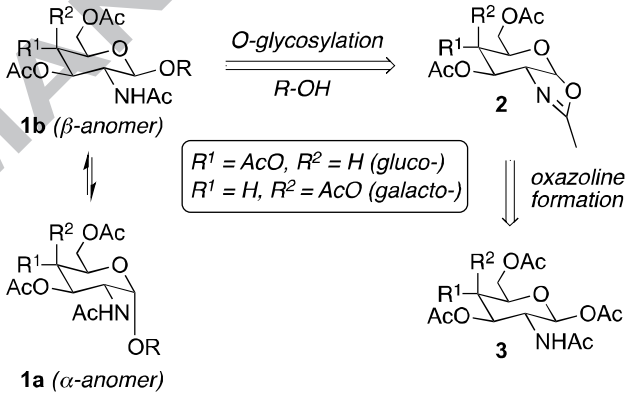


Figure 1. Glycoconjugates.

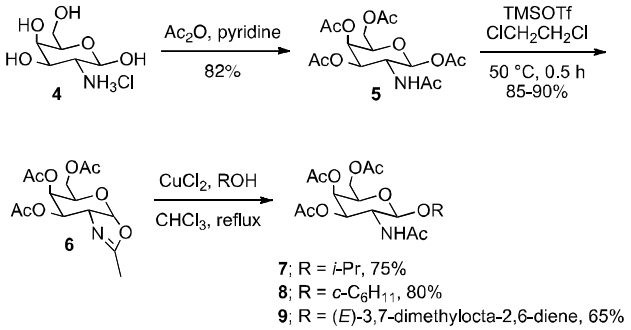
The exploration of glycosylation methods for 2-amino-2-deoxyglycopyranosides was based on traditional literature protocols for carbohydrates, with some distinct differences due to the presence of the C-2 nitrogen atom (*4*). Glycosylation of 2-acetamido-2-deoxy-D-glucosamine (*N*-acetylglucosamine, GlcNAc) under standard Koenigs-Knorr conditions proceeded in good diastereoselectivity for the 1,2-*trans*-glycoside, but resulted in a large amount of the oxazoline side product (*4*). Furthermore, these conditions were limited to reactive glycosyl acceptors with a primary hydroxyl group which are often used in a large excess (*4*). If the *N*-acetyl group cyclizes to the oxazolinium intermediate and looses a proton to give the oxazoline, the glycosylation frequently stalls (*4, 14*). Because of the tendency of GlcNAc glycosyl donors to form the oxazoline side product, various alternatives to the *N*-acetyl group have been examined in glycosylation reactions (*15*), including protection with phthaloyl (*16*), tetrachlorophthaloyl (*17, 18*), 4,5-dichlorophthaloyl (*19*), dithiasuccinoyl (*20, 21*), trichloro- (*22, 23*), and trifluoroacetyl (*22, 24*), trichloroethoxycarbonyl (*25-28*), diacetyl (*29*), dimethylmaleoyl (*30*), and thiodiglycoloyl (*31*) groups, or a 2-azido group (*5, 32-34*).

While these protective groups resolve the oxazoline issue, each requires additional steps for protection and subsequent substitution with the *N*-acetyl group in the desired analogs. Ring opening of aziridines such as those generated from iodosulfonamidation of glycals (*35*) or from the photolysis of triazolines (*36*) present an additional alternative for the formation of 2-amino-2-deoxyglycopyranosides, but these methods were unsuccessful in our hands. In contrast, the opening of oxazoline **2** with alcohols under mild, copper(II)-catalyzed conditions showed promise for formation of the β-glycosides 3,4,6-tri-acetyl-*N*-acetylglucosamine and 3,4,6-tri-acetyl-*N*-acetylgalactosamine **1b** in our preliminary studies (*13, 14, 37,* Scheme 1). Furthermore, an acid catalyzed isomerization of the β-anomers **1b** was envisioned to lead to the thermodynamically more stable α-anomers **1a**, thus allowing a convergent approach from readily available pentaacetates **3**.

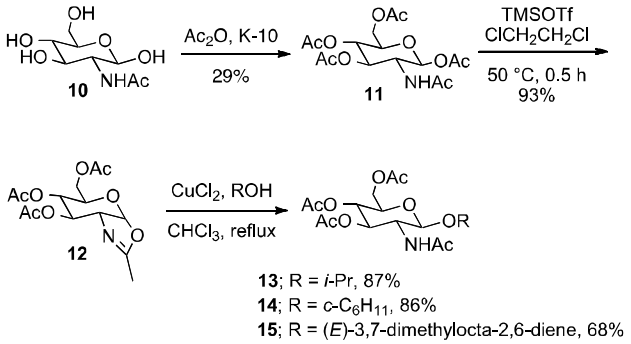


Scheme 1. Retrosynthetic analysis for α-and β-anomers **1** of 2-acetamido-2-deoxy-D-glucose and -galactose.

The fully protected galactosamine β-pentaacetate **5** (*38*) and glucosamine β-pentaacetate **11** (*39*) were prepared from tetrols **4** and **10**, respectively, using pertinent literature procedures (Schemes 2 and 3). The corresponding oxazolines **6** and **12** were subsequently obtained in high yields with TMSOTf in 1,2-dichloroethane (*14, 40-42*). Other literature methods to access glyco-oxazolines, including $SnCl_4$ in dichloromethane, did not lead to the desired products (*43, 44*). Oxazolines **6** and **12** were then heated at reflux in $CHCl_3$ in the presence of $CuCl_2$ and isopropanol, cyclohexanol, and geraniol as glycosyl acceptors to give the corresponding C-2 glycosides in good yields as pure β-anomers after recrystallization or chromatographic purification (*14*). Six different derivatives were prepared with the goal to vary lipophilicity, with 3 epimeric pairs differing only by their configuration at C-4. Glycosylation of isopropanol gave pyranosides **7** and **13** with a *c*logP of -0.5, whereas the cyclohexyl derivatives **8** and **14** were more lipophilic (*c*log P 0.6). The geraniol glycosides **9** and **15** (*c*logP 1.8) represented the most lipophilic small molecule analogs of Lipid A and Eritoran in this series (*45*).

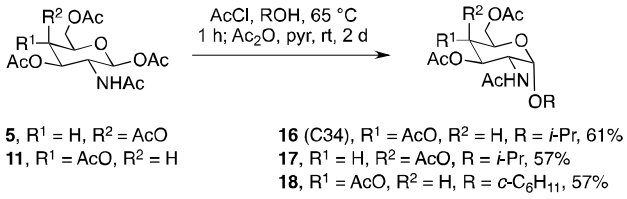


Scheme 2. Synthesis of three β-glycosides of 2-acetoamido-2-deoxy-D-galactose (**7**-**9**).



Scheme 3. Synthesis of three β-glycosides of 2-acetoamido-2-deoxy-D-glucose (**13**-**15**).

The corresponding α-glycosides in the galactosamine and glucosamine series proved more difficult to synthesize, and at first all previously envisioned acid catalyzed isomerization conditions starting with the corresponding β-glycosides were unsuccessful. Finally, heating the β-glucosamine and β-galactosamine pentaacetates **11** and **5**, respectively, in *in situ* prepared 5% HCl in *i*-propanol and cyclohexanol, in analogy to literature conditions used for the synthesis of methyl α-D-glucosamine from D-glucosamine pentaacetate,(*46*) provided a 3:1 mixture of partly deacylated α:β anomers (Scheme 4). After reacetylation with acetic anhydride in pyridine, the mixture of anomers was separated by chromatography on SiO_2 to give the desired α-anomeric glycosides **16**-**18** in moderate yields. Extensive NMR analyses were performed to assign the configurations of all glycoside products (*47*).



Scheme 4. Acid-mediated tandem glycosylation and β- to α-anomeric equilibration.

As discussed in the introduction, many chronic inflammatory diseases and certain cancers trace their origin to increased signaling from the innate immune receptor TLR4, and our preliminary studies had identified **16** (C34) as a potent anti-inflammatory agent in mouse models of endotoxemia and necrotizing enterocolitis (*13*). In order to investigate the SAR of **16** and determine potential therapeutic benefits of analog structures, we screened compounds **7**-**9**, **13**-**15**, and **17**-**18** for the response on TLR4-mediated inflammatory signaling in cultured enterocytes (non-transformed rat small intestinal IEC-6 cells) and monocytes (mouse RAW 264.7 cells). Efficacy was subsequently confirmed using the NF-kB-luciferase reporter mouse, followed by assessment of pro-inflammatory cytokines IL6, IL1β and TNFα via *qRT-PCR* (*48*).

As shown in Table 1, isopropyl-β-galactoside **7**, isopropyl-α-glucoside **16** and cyclohexyl-α-glucoside **18** produced the strongest *anti*-inflammatory suppression of LPS-induced cytokine mRNA levels in IEC6 cells, whereas geranyl-β-galactoside **9** and β-glucosides **13**-**15** were comparatively ineffective. These results, in combination with the intermediate level of activity of cyclohexyl-β-galactoside **8** and isopropyl-α-galactoside **17**, indicate that a *syn*-configuration of acetate groups at C-4 and anomeric substituents at C-1 are preferred with regard to suppression of the pro-inflammatory IL6, IL1β and TNFα. The larger, more lipophilic geranyl group at the anomeric carbon in **9** and **15** also appears detrimental to bioactivity. The analogous measurements in RAW cells are consistent with these data (Table 1).

Table 1. Biological evaluation of anti-inflammatory activities

Compound	Suppression of LPS-induced IL6, IL1β, and TNFα mRNA levels in IEC6 cells[a]	Suppression of LPS-induced IL6, IL1β, and TNFα induction in RAW cells[b]	Protection of IL6, IL1β, and TNFα induction in mice[c]
7	58.0% (p<0.01)	50% (p<0.01)	<64% (p<0.01)
8	44% (p<0.01)	50% (p<0.05)	<60% (p<0.01)
9	<20%	<20%	<20%
13	<20%	<20%	<20%
14	<20%	<20%	48%
15	30%	32%	<20%
16 (C34; *ref. 13*)	55% (p<0.01)	50% (p<0.01)	69% (p<0.01)
17	43% (p<0.01)	50% (p<0.01)	78% (p<0.01)
18	54% (p<0.05)	50% (p<0.01)	64% (p<0.01)

Treatment and dosages: [a]IEC6 cells (LPS 25 μg/mL, compounds 5 μg/mL, 30 min pretreatment). [b]Raw cells (LPS, 10 ng/mL, compounds 5 μg/mL, 30 min pre-treatment). [c]Mice (LPS 2.5 mg/kg, compounds 2.5 mg/kg, 30 min pre-pretreatment).

A more complex pattern emerges in the *in vivo* biological assessment. While acetamidopyranosides **9**, **13**, and **15** are still inactive, protection of cytokine expression in mice is most effective with 2.5 mg/kg of isopropyl-α-galactoside **17** (78%), slightly surpassing isopropyl-β-galactoside **7** (64%), isopropyl-α-glucoside **16** (69%) and cyclohexyl-α-glucoside **18** (64%). Furthermore, cyclohexyl-β-glucoside **14** picks up moderate protective activity. This slight discrepancy from the cell-based biological activities is likely due to different rates of *in vivo* absorption, metabolism and excretion of these compounds and illustrates the importance of a multi-tiered assay strategy.

In conclusion, we have established a viable synthetic strategy to access configurationally diverse 2-acetamidopyranoside derivatives and used a small set of analogs to establish a preliminary SAR for our previous lead structure, TLR4 inhibitor **16** (C34). Thus, we were able to identify analogs that were equipotent to **16** in cell-based models. Most significantly, we also discovered an analog **17** that showed a significantly higher efficacy in an *in vivo* rodent model of inflammatory disease. Further characterization of the biological and therapeutic potential of these inhibitors of cytokine release will be reported in due course.

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48. For a detailed description of assay conditions, see the Supplementary Material.

Supplementary Material

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Synthetic procedures, spectroscopic data, and assay conditions.