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Synthesis and Evaluation of Di- and Trimeric Hydroxylamine-Based β-(1→3)-Glucan Mimetics

Angélique Ferry,[†] Gaëlle Malik,[†] Xavier Guinchard,[†] Václav Větvička,[‡] and David Crich*[,§]

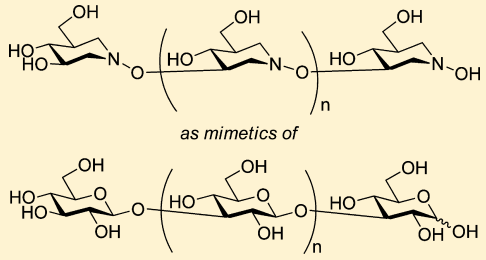
[†]Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France

[‡]Department of Pathology, University of Louisville, 323 East Chestnut Street, Louisville, Kentucky 40202, United States

[§]Department of Chemistry, Wayne State University, 5101 Cass Ave, Detroit, Michigan 48202, United States

Supporting Information

ABSTRACT: Di- and trimeric hydroxylamine-based mimetics of β-(1→3)-glucans have been accessed by an asymmetric synthesis route featuring an iterative double ring-closing reductive amination reaction. These oligomeric hydroxylamines are demonstrated to inhibit the staining of human neutrophils and of mouse macrophages by fluorescent anti-CR3 and anti-dectin-1 antibodies, respectively, and to stimulate phagocytosis, all in a linkage-dependent manner suggestive of binding to the lectin domains of complement receptor 3 (CR3) and dectin-1. The ability of these relatively short mimetics to bind to CR3 and dectin-1, as compared to the greater degree of polymerization required in β-(1→3)-glucans, is discussed in terms of the increased hydrophobicity of the α-face on replacement of the glycosidic bond by the hydroxylamine linkage.



INTRODUCTION

The β-(1→3)-glucans (Figure 1) are well-known immunomodulating agents that occur widely in nature, with yeasts,

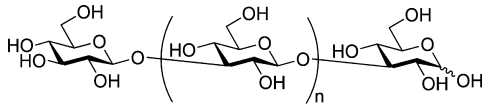


Figure 1. β-(1 → 3)-Glucan structure.

seaweeds, fungi, and grains as the most common sources.[1−12] The immunostimulating properties of the β-(1→3)-glucans are considered to arise primarily from their affinity for the lectin regions of complement receptor 3 (CR3)[13−20] and dectin-1[21−23] to which their binding triggers a cascade of effects including phagocytosis.

Despite their widespread availability in nature, the heterogeneity of natural isolates complicates the isolation of pure homogeneous glycoforms of β-(1→3)-glucans for biological studies and the establishment of structure activity relationships. Both enzymatic[24] and chemical[25] partial depolymerization of naturally occurring β-glucans enables the isolation of short oligomers, but extensive chromatographic purification is required to obtain single molecular entities.[26] Despite these difficulties, controlled acidic hydrolysis and extensive chromatographic purification were used to demonstrate that the shortest β-(1→3)-glucan capable of detectable binding to recombinant murine dectin-1 in a microarray format was the 10- or 11-mer.[25] Subsequent work with a combination of degraded natural and fully synthetic β-(1→3)-glucans employing a surface plasmon resonance-based assay revealed the heptasaccharide to be the minimum binding unit for recombinant murine dectin-1.[27]

The combination of the immunostimulating properties of the β-(1→3)-glucans and difficulties in the isolation of pure oligomers from degradative methods has stimulated considerable interest in the chemical synthesis of such oligomers, while revealing the difficulties inherent therein.[26−40] With the aid of homogeneous synthetic β-(1→3)-glucans it has been demonstrated that even the 4- and especially the 5-mer are sufficient to show immunostimulatory effects, such as the potentiation of phagocytosis, approaching those of phycarine, a β-(1→3)-glucan isolated from brown algae.[28] Chemical synthesis has also enabled the preparation of short homogeneous β-(1→3)-glucans modified at the reducing end by the replacement of the terminal glucopyranose residue by its manno-stereoisomer, by a 4-deoxyglucopyranose moiety, and by gluco- and manno-configured glycitols, with 5- and 6-mers carrying each of these modifications retaining the ability to promote phagocytosis.[41,42] The availability of defined synthetic β-(1→3)-glucans has also enabled their detailed conformational analysis by NMR spectroscopy.[30] Interestingly, particularly in view of the immunostimulatory effects observed with 5- and 6-mers,[41,42] STD NMR experiments revealed little or no binding between a synthetic 6-mer and recombinant CR3 and dectin-1.[43] On the other hand STD-NMR experiments demonstrated binding of laminarin, a natural β-(1→3)-glucan from brown algae with degree of polymerization from 18 to 31, to

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recombinant dectin-1. A hydrophobic binding patch was identified on the α-face of the two terminal pyranose rings at both the reducing and nonreducing ends consistent with an hydrophobic interaction with the side chains of Trp 221 and His 223 in the crystallographically revealed[44] shallow carbohydrate binding groove of the protein.[43]

In one of our laboratories, bearing in mind the well-known difficulties in the efficient and fully stereocontrolled synthesis of oligosaccharides, we have adopted the common medicinal chemistry approach in which a biologically active natural product, in this case the β-(1→3)-glucans, inspires the development of new constructs with potential therapeutic applications. Toward this end we have begun synthetic studies directed at the synthesis of oligomeric phostones[45,46] and oligomeric hydroxylamines (Figure 2)[47,48] as potential glycan

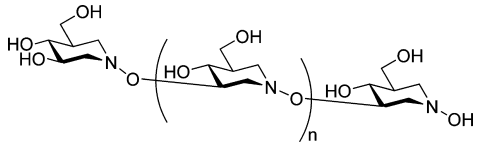


Figure 2. Oligomeric hydroxylamine-linked polyhydroxypiperidine structure.

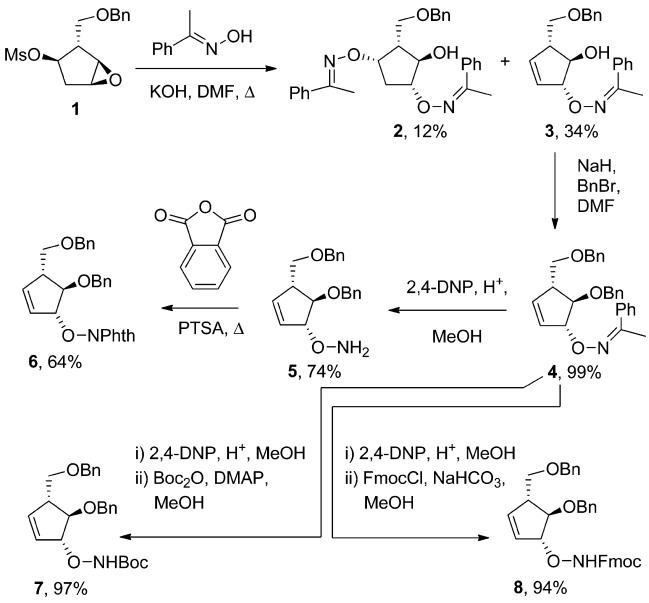
mimetics. Continuing our interest in the use of the hydroxylamine N−O bond as an achiral surrogate for the glycosidic bond, we describe here the synthesis of hydroxylamine-linked di- and trimeric polyhydroxypiperidines and preliminary evaluation of their affinity to CR3 and dectin-1 as well as their ability to promote phagocytosis.

RESULTS

Chemical Synthesis. Adapting our existing asymmetric synthesis of monomeric *N*-alkoxy polyhydroxypiperidines, the enantiomerically pure cyclopentadiene-derived mesyloxy epoxide **1**[47,48] was subject to ring opening with potassium hydroxide and acetophenone oxime[49] in hot DMF to give 12% of the disubstitution product **2** and the desired *O*-cyclopentenyl oxime **3** in 34% yield on a gram scale (Scheme 1). Subsequent benzylation then afforded the dibenzyl ether **4** in very high yield, from which the hydroxylamine **5** was liberated in 74% yield on exposure to 2,4-dinitrophenylhydrazine (2,4-DNP) in methanol with catalysis by sulfuric acid[49] (Scheme 1). Subsequent reaction with phthalic anhydride afforded the *N*-alkoxyphthalimide **6** in 64% yield. Alternatively, oxime cleavage followed immediately by standard carbamate-forming reactions converted **4** to the *N*-Boc and *N*-Fmoc-protected hydroxylamines **7** and **8** in 94% and 97% yield, respectively (Scheme 1).

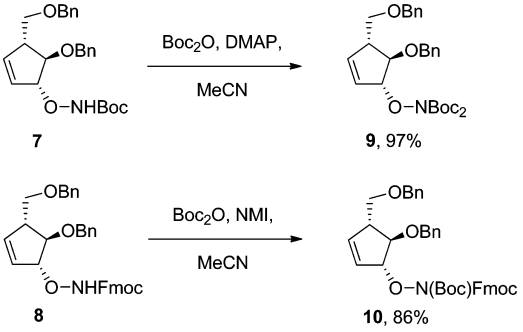
Attempted application of **6** or **8** as substrates in the previously established oxidative cleavage and subsequent double ring closing reductive amination with *O*-allylhydroxylamine[47] each gave complex mixtures. In the case of **6** the problems were traced to the incompatibility of the phthalimide function with the conditions of the reductive amination, whereas the problematic ring closures observed with the carbamates were considered to arise from the stabilization of intermediate hemiaminals by hydrogen bonding with the carbamate N−H group. In the face of this problem we elected to convert the carbamates **7** and **8** to the *N*,*N*-diBoc and *N*-Boc-*N*-Fmoc imides **9** and **10**, respectively, in which the bulky acyclic imide functionality was expected to be more compatible with the reductive amination protocol than the less hindered

Scheme 1. Synthesis and Protection of the Enantiomerically Pure *O*-Cyclopentenyl Hydroxylamines



and more reactive phthalimide **6**. While treatment of **7** with Boc_2O and DMAP in acetonitrile readily gave the imide **9** in 97% yield, the conversion of **8** to **10** required considerable optimization but was eventually achieved using Boc_2O and *N*-methylimidazole (NMI) in acetonitrile in 86% yield (Scheme 2). The attempted conversion of **8** into the corresponding *N*,*N*-diFmoc derivative failed under all conditions attempted including the use of the mild base *N*-methylimidazole.

Scheme 2. Imide Formation from Carbamates



Ozonolytic cleavage of cyclopentene **10** and reductive workup with dimethylsulfide gave a dialdehyde that existed primarily as a diastereomeric mixture of cyclic monohydrates and which consequently was taken forward to the next step without further characterization. Accordingly, after filtration on silica gel, the dialdehyde formed in 94% yield on cleavage of **10** was exposed first to an excess of *O*-allyl hydroxylamine HCl salt and sodium acetate in methanol, so as to form a dioxime,[47,48] and then to sodium cyanoborohydride and acetic acid.[50] In this manner a relatively complex reaction mixture was obtained that, according to LC-MS analysis, contained the anticipated product of double ring closing reductive amination and several related products lacking the Fmoc group. Accordingly, the crude reaction mixture was treated with piperidine and then subjected to chromatographic purification when the anticipated cyclic hydroxylamine **11** was isolated albeit in 20% yield (Scheme 3).

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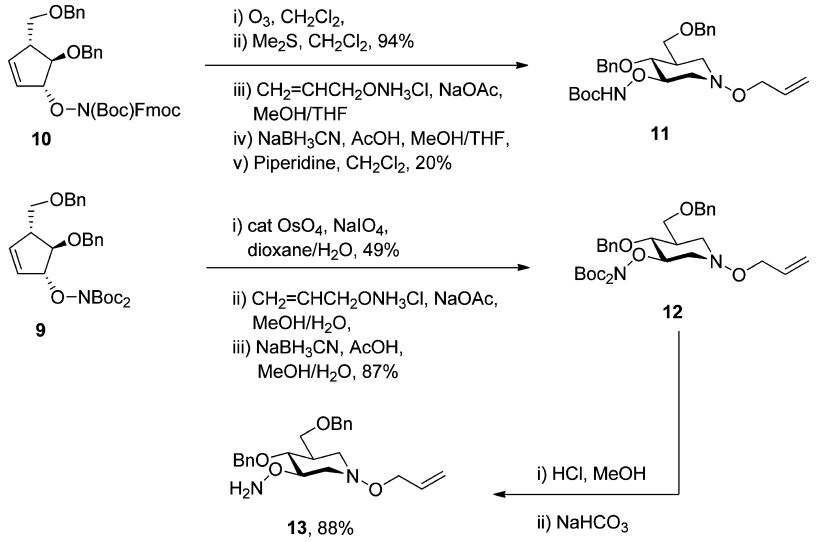
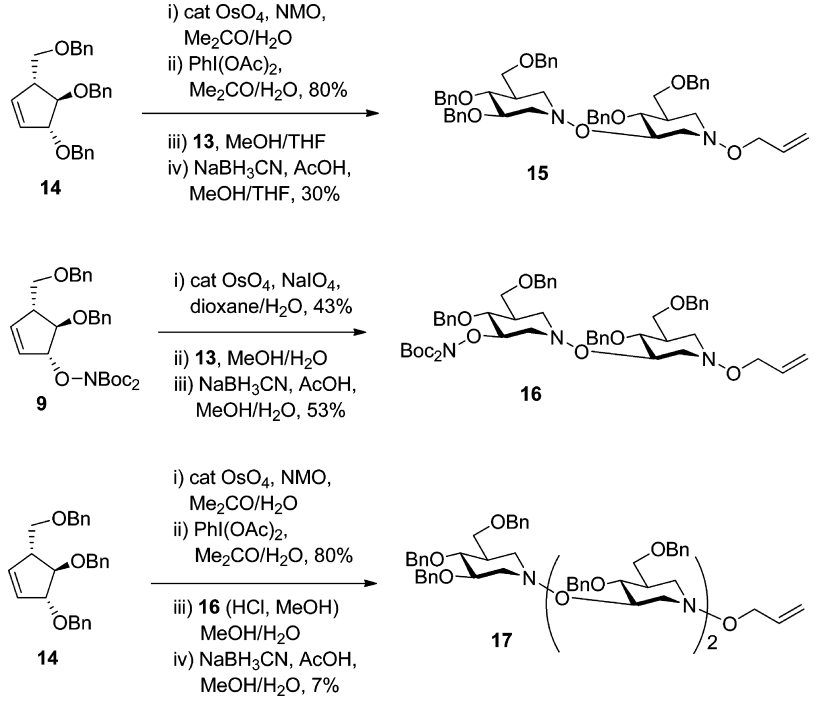
Scheme 3. Monomer Formation by Oxidative Cleavage and Double Ring Closing Reductive Amination



Scheme 4. Synthesis of Protected Di- and Trimeric Hydroxylamine-Based Glucan Mimetics



Cleavage of the *N*,*N*-diBoc cyclopentenyl hydroxylamine **9** with catalytic osmium tetroxide and sodium metaperiodate in aqueous dioxane,[51] followed by extractive workup, and filtration on silica gel gave a crude dialdehyde in 49% yield. This dialdehyde was subjected directly to the double ring closing reductive amination with sodium cyanoborohydride and acetic acid in methanol to afford 87% of the anticipated *N*,*N*-diBoc protected product **12** (Scheme 3). The ozonolytic cleavage of **9** followed by the reductive amination protocol also afforded **12**, but in the lower yield of 26%. Exposure of **12** to HCl in methanol, concentration, and washing with aqueous $NaHCO_3$ enabled the isolation of the novel dihydroxylamine **13** as the free base in 88% yield (Scheme 3) ready for application to the formation of di- and trimers.

Treatment of **14**[47,48] with catalytic osmium tetroxide and *N*-methyl morpholine *N*-oxide according to the Upjohn protocol[52] gave a diol that was not isolated but immediately cleaved with iodobenzene diacetate[53] to give a dialdehyde in 80% yield. This was subjected directly to the double ring closing reductive amination protocol with 2 equiv of hydroxylamine **13** to afford a first protected disaccharide mimetic **15** in 30% yield, in which both glycosidic linkages have been replaced by the hydroxylamine moiety (Scheme 4). Reductive amination of the hydroxylamine **13** with 2 equiv of the dialdehyde obtained in 43% yield on oxidative cleavage of **9** gave a second protected disaccharide mimetic **16** in 53% yield (Scheme 4). Removal of the Boc groups from **16** with HCl in methanol gave a free hydroxylamine, which, without further purification, was coupled to the dialdehyde derived in 80% yield from cleavage of

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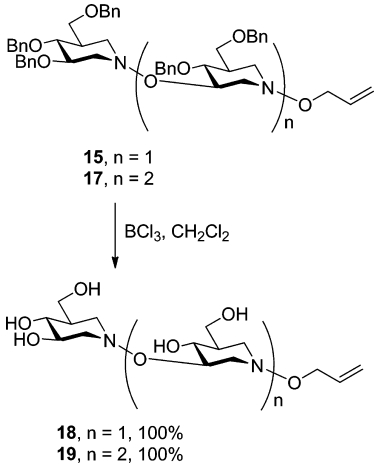
14 to give the trisaccharide mimetic **17**, albeit in only 7% yield (Scheme 4).

Finally, the di- and trihydroxylamines **15** and **17** were deprotected by treatment with boron trichloride in dichloromethane followed by filtration over silica gel to give the hydroxylamine-based di- and trisaccharide mimetics **18** and **19** in essentially quantitative yield (Scheme 5). As anticipated on

Scheme 5. Final Deprotection Providing the Hydroxylamine-Based Di- and Trisaccharide Mimetics 18 and 19



the basis of the barrier to inversion of the *N*-alkoxypiperidine moiety, previously determined to be ∼15 kcal·mol^{-1} for the simple monosaccharide mimetics,[48] the NMR spectra of all *N*-alkoxy piperidines described here are broad and unresolved at room temperature. However, sharp spectra were obtained in perdeuterio-DMF at 90 °C. By design[48] an inversion barrier of this magnitude, which equates to a half-life for inversion of tens of microseconds at room temperature, renders the hydroxylamine achiral and ideally affords the oligomeric species based on this linkage the ability to adapt to range of lectin binding sites, including, perhaps, those for both α- and β-linked oligosaccharides.

Assessment of CR3 and Dectin-1 Binding Affinity and Stimulation of Phagocytosis. The affinity of the di- and trihydroxylamine-based mimetics **18** and **19** for CR3 and dectin-1 was probed through their ability to inhibit anti-CR3 or anti-dectin-1 fluorescein isothiocyanate (FITC) conjugated antibody staining of human neutrophils and mouse macrophages, respectively. For comparison purposes the previously prepared[48] monohydroxylamines **20** and **21** (Figure 3) were also screened. At the 0.1 μg·mL^{-1} concentration employed in these assays the β-(1→3)-trimer mimetic **19**, with its three hydroxylamine linkages, caused a 34% inhibition in the staining of human neutrophils by the anti-CR3 FITC antibody (Table 1). Under the same conditions the β-(1→3)-dimer mimetic **18**

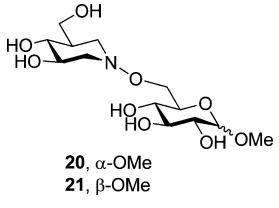


Figure 3. Structures of the monohydroxylamines **20** and **21**.

Table 1. Percentage Inhibition of Anti-CR3 and Anti-Dectin-1-FITC Antibody Staining of Neutrophils and Macrophages by 0.1 μg·mL^{-1} Substrate

entry	cmpd	linkage mimicked	oligomer no.	% inhibition of anti-CR3-FITC staining of human neutrophils[a]	% inhibition of anti-dectin 1-FITC staining of mouse macrophages[a]
1	**20**	1→6	dimer	19.7 ± 1.7	29.3 ± 2.2
2	**21**	1→6	dimer	22.3 ± 1.9	20.6 ± 2.1
3	**18**	1→3	dimer	26.4 ± 2.7	28.2 ± 2.9
4	**19**	1→3	trimer	34.2 ± 3.3	43.1 ± 3.5

[a]Mean ± SD.

and the anomeric β-(1→6)-dimer mimetic **20** and **21** resulted in only 26, 19, and 22% inhibition of staining by the anti-CR3 fluorescent antibody. Incubation of an 0.1 μg·mL^{-1} solution of the β-(1→3)-trimer mimetic **19** with mouse macrophages led to a 43% decrease in the subsequent staining by an anti-dectin-1 fluorescent antibody, while the β-(1→3)-dimer mimetic **18** caused a 28% drop in inhibition of staining and the two β-(1→6)-dimer mimetics **20** and **21** a 29 and 21% decrease, respectively (Table 1). Overall, these results suggest the hydroxylamine glucan mimetics bind to the lectin domains of both CR3 and dectin-1 in both a length- and linkage-dependent manner similar to that found for the glucans themselves but which is sufficiently strong to manifest itself even at the dimer level.

Solutions of compounds **18**–**21** (10 μg.mL^{-1}) were also assayed for their ability to stimulate phagocytosis of synthetic polymeric 2-hydroxyethyl methacrylate microspheres[54] by human macrophage-like RAW 264 cells. Commercial yeast-derived insoluble whole glucan particles (WGP, hollow spheres of long polymers of primarily β-(1→3)-glucan)[20] were used as comparison standard (Table 2). As with the inhibition of anti

Table 2. Percentage Stimulation of Phagocytosis

entry	cmpd	linkage mimicked	oligomer no.	% stimulation of phagocytosis (RAW 264 macrophages, 10 μg/mL, 24 h)[a]
1	**20**	1→6	dimer	6.7 ± 0.9
2	**21**	1→6	dimer	4.1 ± 0.5
3	**18**	1→3	dimer	7.8 ± 1.1
4	**19**	1→3	trimer	16.6 ± 2.0
5	WGP	1→3	Insol polymer	30.1 ± 2.8

[a]Mean ± SD; significant difference from PBS control (2.3 ± 0.2) at $P < 0.05$ level.

CR3 and dectin-1 antibody staining assays, stimulation of phagocytosis was found to occur in a length- and linkage-dependent manner, with the β-(1→3)-trimer mimetic **19** proving to be more effective than the comparable dimer **18**, which in turn was more effective than the two anomeric β-(1→6)-dimers **20** and **21** (Table 2). Noteworthy is the fact that the level of phagocytosis induced by the β-(1→3)-trimer mimetic **19** was more than 50% of that induced by the insoluble β-(1→3)-glucan.

■ DISCUSSION

The ability of compounds **18**-**21** to inhibit the binding of anti-CR3 and anti-dectin-1 binding fluorescent antibodies and to stimulate phagocytosis provides proof of principle of the use of oligomeric hydroxylamines as glucan mimetics. The shortness

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of the chains involved, when compared to the minimal pentasaccharides previously found necessary with synthetic β-(1→3)-glucans and their close analogues, begs the question of how the hydroxylamine linkage leads to increased activity. In the case of the dectin-1 binding site, for which crystallographic information is available,[44] STD-NMR studies have provided evidence of a terminal disaccharide unit at either end of β-(1→3)-glucan as the principle binding motif and suggest a hydrophobic interaction between the α-face of the disaccharide and the aromatic side chains of Trp 221 and His 223 in the binding site.[43] Accordingly, it is reasonable to suggest that the absence of the 2α-hydroxy group (carbohydrate numbering) in the hydroxylamine glucan mimetics **18** and **19** results in an increase in hydrophobicity of the α-face and hence a greater affinity for the lectin binding site (Figure 4). This is supported

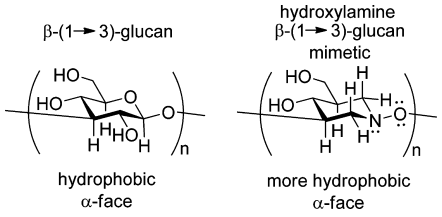

Figure 4. Proposed increased potential for hydrophobic on the α-face of oligomeric hydroxylamine as compared to β-(1→3)-glucans.

by the noncritical nature of the configuration at C2 at the reducing end of synthetic penta- and hexasaccharyl β-(1→3)-glucans and by NMR work from the Asensio laboratory indicating that even equatorial hydroxyl groups are detrimental to hydrophobic CH−π interactions between adjacent cofacial C−H bonds and aromatic rings.[55,56] Similarly, it is reasonable to suggest that the replacement of the polar glycosidic bond by the relatively soft and polarizable hydroxylamine unit, as manifest in the well-known increased nucleophilicity of hydroxylamines over amines (α-effect),[57] enhances the interaction of the ligand with the hydrophobic pocket of the receptor. While simple hydroxylamines units are frequently used to assemble neoglycoconjugates[58−62] and are components of some antitumor antibiotics,[63−65] their potential to mediate and possibly increase hydrophobic interactions has not been considered previously to our knowledge. The analysis of the CR3 and dectin-1-binding properties of the oligomeric hydroxylamines suggests other avenues for the enhancement of small molecule glucan mimetics, either alone or following incorporation into multivalent constructs.[60,66−68]

CONCLUSION

A set of simply di- and trimeric hydroxylamine-based mimetics of β-(1→3)-glucans have been prepared and found to inhibit the binding of anti-CR3 and anti-dectin-1 fluorescent antibodies to their respective binding sites and to stimulate phagocytosis. The length- and linkage-dependent nature of these properties suggests that the mimetics bind to the lectin domains of CR3 and dectin-1, while their structures suggest further ways to improve the affinity for the target proteins and opens up the prospect of small molecule therapeutics exhibiting glucan-like properties.

ASSOCIATED CONTENT

Supporting Information

Full experimental details and copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

dcrich@chem.wayne.edu

Notes

The authors declare no competing financial interest.

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