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Multivalency To Inhibit and Discriminate Hexosaminidases

Dimitri Alvarez-Dorta,[a] Dustin T. King,[b] Thibaut Legigan,[c] Daisuke Ide,[d] Isao Adachi,[d] David Deniaud,[a] Jérôme Désiré,[c] Atsushi Kato,[d] David Vocadlo,[b] Sébastien G. Gouin,*[a] and Yves Blériot*[c]

Dedicated to Professor Charles Tellier on the occasion of his retirement

Abstract: A set of multivalent polyhydroxylated acetamidoazepanes based on ethylene glycol, glucoside, or cyclodextrin scaffolds was prepared. The compounds were assessed against plant, mammalian, and therapeutically relevant hexosaminidases. Multimerization was shown to improve the inhibitory potency with synergy, and to fine tune the selectivity profile between related hexosaminidases.

Introduction

exo-*N*-Acetyl-β-glucosaminidases are found in diverse organisms ranging from bacteria to humans. These enzymes catalyze the removal of terminal *N*-acetylglucosamine residues (GlcNAc) from a wide range of glycoconjugates and saccharides. Humans express three exo-*N*-acetyl-β-glucosaminidases,[1] namely the isoenzymes β-hexosaminidase A (HexA) and β-hexosaminidase B (HexB), as well as O-GlcNAcase (OGA), and considerable attention has been given to these enzymes because of their involvement in various diseases. HexA and HexB share high sequence similarity and belong to glycoside hydrolase (GH) family 20 (GH20) of the CAzy classification system.[2] Heritable deficiencies in HexA activity cause GM2-ganglioside to accumulate in the nervous system, resulting in lethal neurodegenerative disorders known as Tay-Sachs and Sandhoff diseases.[3] O-GlcNAcase (OGA) belongs to GH family 84 (GH84) and removes O-GlcNAc residues from particular hydroxyls of serine and threonine residues of nuclear and cytoplasmic proteins.[4] O-GlcNAc has been implicated in a range of cellular processes and inhibitors of OGA have been proposed as a potential therapeutic strategy to treat neurodegenerative diseases.[5,6] Although of nonhuman origin, NagZ, a fourth functionally related exo-*N*-acetyl-β-glucosaminidase from family 3 (GH3), has also been implicated in human diseases. NagZ is involved in the highly conserved Gram-negative peptidoglycan cell wall recycling pathway. NagZ releases GlcNAc from the cytosolic GlcNAc-1,6-anhydroMurNAcpeptide peptidoglycan recycling intermediates to yield 1,6-anhydroMurNAcpeptides that act as signalling molecules to promote resistance of Gram-negative bacteria to a wide range of β-lactam antibiotics. Noteworthy GH3 enzymes, including NagZ,[7] use a catalytic mechanism that differs from that used by GH20[8] and GH84[9] enzymes, which use substrate-assisted catalysis. Furthermore, significant differences in the active site structures of all of these enzymes have been noted. These various differences have enabled the generation of selective inhibitors of each enzyme. Accordingly, specific inhibitors have been designed, including potent bicyclic derivatives such as Thiamet-G **1** that mimic the oxazolinium-like transition state of the substrate-assisted mechanism.[10] Similarly, modification of the acetamido group has resulted in potent hexosaminidase inhibitors derived from PUGNAc **2**, nagstatin **3**,[11] and DNJNAc **4**,[12] and these have also been reported to yield selective NagZ inhibitors (Figure 1). Furthermore, the *N*-alkylation of DNJNAc **4** with elaborated pharmacophores have afforded potent HexA and B (HexAB) inhibitors.[13] Other structural modifications on GlcNAc mimics have been recently explored to target hexosaminidases.[14–18]

An alternative promising approach has recently emerged for developing potent and selective inhibitors of glycosidases and glycosyltransferases. Carbohydrate-binding proteins, lectins,

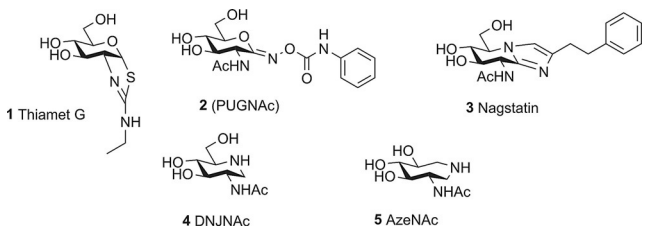


Figure 1. Structure of potent hexosaminidase inhibitors.

[a] *Dr. D. Alvarez-Dorta, Prof. D. Deniaud, Dr. S. G. Gouin*
LUNAM Université, CEISAM, Chimie Et Interdisciplinarité, Synthèse, Analyse, Modélisation, UMR CNRS 6230, UFR des Sciences et des Techniques
2, rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3 (France)
E-*mail: sebastien.gouin@univ-nantes.fr*

[b] *Dr. D. T. King, Prof. D. Vocadlo*
Department of Chemistry, Simon Fraser University
8888 University Drive, Burnaby, British Columbia, V5S 1P6 (Canada)

[c] *Dr. T. Legigan, Dr. J. Désiré, Prof. Y. Blériot*
Equipe Synthèse Organique, Groupe Glycochimie, IC2MP, UMR CNRS 7285, Université de Poitiers
4 rue Michel Brunet, 86073 Poitiers cedex 09 (France)
E-*mail: yves.bleriot@univ-poitiers.fr*

[d] *Dr. D. Ide, Dr. I. Adachi, Prof. A. Kato*
Department of Hospital Pharmacy, University of Toyama
2630 Sugitani, Toyama 930-0194 (Japan)

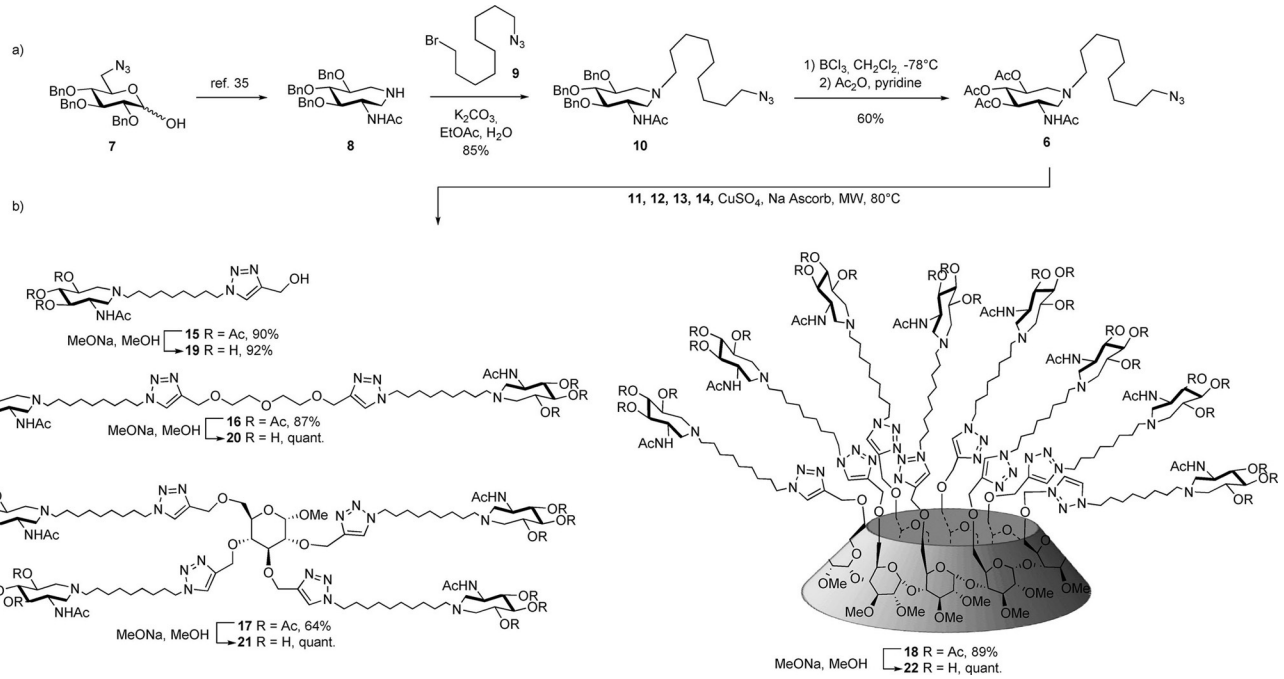
are generally multimeric and interact in a multivalent manner with their sugar ligands, which enables high avidity despite their generally weak affinity for monomeric ligands.[19] This highly synergistic multivalent effect inspired the development of synthetic glycoclusters bearing multiple copies of sugar epitopes on a single scaffold,[20,21] leading to affinity enhancements of several orders of magnitude over the corresponding monovalent binding interaction.[22,23] Although this so-called "glycocluster effect" was coined more than twenty years ago,[24] this concept only progressed recently from carbohydrate-binding lectins to carbohydrate-processing enzymes.[25–28] In 2009, conducting a systematic evaluation of multivalent iminosugars based on the deoxymannojirimycin (DMJ) moiety against commercial glycosidases,[29] we observed a significant multivalent effect on the α-mannosidase from jack bean (JbMan). Since then, higher avidities have been reached by using multivalent DNJ constructs with higher valency,[30–32] and much effort was dedicated to unravel the JbMan binding mode.[33–35] The concept was then extended to other targets, including biologically relevant classes of glycosidases and glycosyltransferases.[36,37] Interestingly, the initial ligand specificity of lectin and glycosidases may also fade out with multivalency, as recently probed with multivalent constructs based on carbohydrates and iminosugars that bind/inhibit the mismatching proteins.[38,39] Here, we assess the potential sensitivity of various hexosaminidases of biological interest to the effect of multivalent inhibitor clusters.

Results and Discussion

We have contributed to the development of a new class of seven-membered iminosugars, the polyhydroxylated azepanes, that inhibit glycosidases in a competitive manner.[40,41] Introduction of a NHAc group on the azepane ring as in AzeNAc **5** led to potent and broadly effective inhibitors of hexosaminidases,[42] including OGA[43] and NagZ[44] (Figure 1). AzeNAc **5** was exploited here to synthesize a set of multivalent iminosugar clusters with varied valencies that are based on the trihydroxylated acetamidoazepane moiety. Copper-catalyzed azide alkyne cyclization (CuAAc) was used as a robust methodology to construct the multivalent entities. The azido-functionalized azepane **6** was first designed (Scheme 1) as a protected epitope to be grafted onto alkynyl-armed scaffolds.

Starting from acetamido azepane **8**, which is available in five steps from known azidolactol **7**,[42] N-alkylation with 1-azido-9-bromononane **9**[45] in EtOAc/H_2O in the presence of K_2CO_3 furnished azepane **10** in 85% yield. For ease of deprotection, this derivative was then debenzylated using BCl_3 in CH_2Cl_2 at $-78\,^{\circ}C$ and subsequently per-*O*-acetylated (Ac_2O, pyr) to produce azepane **6**. The CuAAc protocol was first implemented with **6** and propargyl alcohol **11** to form protected cycloadduct **15** with 90% yield (Scheme 1). This protocol was successfully repeated with previously described alkyne-derived ethylene glycol **12**,[46] methyl glucoside **13**,[47] and γ-cyclodextrin **14**[33] to form the corresponding di-, tetra-, and octavalent cycloadducts **16**–**18**. Acetates were removed under Zemplèn conditions to furnish monovalent **19** alongside multivalent iminosugar clusters **20**–**22** in quantitative yields.

In preliminary screening, compounds **19**–**22** were assayed as inhibitors of three hexosaminidases isolated from jack bean, bovine kidney, and HL60 (Table 1). The relative potency (Rp) of the multivalent derivatives can be obtained by dividing the measured IC_{50} values by the value obtained for monovalent reference **19**. Dividing the Rp by the valency (*n*) of the cluster enables one to estimate if the enhancements in binding are truly synergistic or only statistical. A true multivalent effect is



Scheme 1. Synthesis of the mono- **19** and multivalent azepanes **20**–**22**.

Table 1. Inhibitory activities of **19**–**22** against plant and mammalian hexosaminidases.

Cmpd	Val.	IC_{50} [μM] Hexosaminidases (Rp/*n*) Jack bean	Bovine kidney	HL60
19	1	43	20	27
20	2	9.3 (2)	0.5 (20)	0.3 (45)
21	4	1 (11)	0.6 (8)	0.4 (17)
22	8	0.3 (18)	0.5 (5)	0.3 (11)

observed if Rp/*n* is higher than 1. The Rp/*n* and IC_{50} values of compounds **19**–**22** that we obtained are presented in Table 1. All the multivalent azepanes proved more potent than monovalent reference **19**, with IC_{50} values in the submicromolar range. Importantly, all compounds showed significant Rp/*n* values, which indicates the sensitivity of the three hexosaminidases towards multivalent inhibitors. A higher Rp/*n* was obtained with the low valency compound **20** showing 90-fold improved inhibition compared to **19** (27 vs. 0.3 μM), meaning that each azepane on **20** is 45-fold more potent than **19** on its own.

Multivalency also offers an opportunity to tune selectivity toward hexosaminidases. As an example, monomer **19** is equipotent towards HL60 and jack bean hexosaminidase (27 vs. 43 μM), whereas dimer **20** is 33-fold more selective for HL60 (9.3 vs. 0.3 μM). Thus, and as previously observed with other glycosidases,[29,33] multivalency can be used to discriminate between related hexosaminidases.

These promising preliminary data encouraged us to assess the inhibitory activity of compounds **19**–**22** against relevant human hexosaminidases hOGA, HexAB, and bacterial NagZ (Table 2). PUGNAc was included in the assay as a potent control inhibitor of the three hexosaminidases. We first determined the mode of hOGA inhibition by **19**–**22** and found that compounds **19** and **20** displayed unambiguous evidence for competitive inhibition as expected. In contrast, the tetra- and octavalent compounds **21** and **22** displayed mixed-model inhibition (see Figure S1 in the Supporting Information for Lineweaver–Burke plots). Future investigations are required to define the molecular mechanism that governs the observed mixed-model inhibition of hOGA by these multivalent inhibitors but this effect may stem from a combination of the geometry of the inhibitor cluster and the dimeric structure of OGA.[48]

Table 2. Inhibitory activities of PUGNAc and iminosugars **19**–**22** against relevant human and bacterial hexosaminidases.

Cmpd	Val	IC_{50} [μM] Hexosaminidases (Rp/*n*) hOGA	NagZ	HexAB
PUGNAc	1	0.24 (–)	0.030 (–)	0.037 (–)
19	1	4.2 (1)	106 (1)	4.2 (1)
20	2	0.14 (15)	29 (1.8)	0.016 (131)
21	4	0.43 (2.4)	17 (1.6)	0.033 (32)
22	8	0.32 (1.6)	10 (1.3)	0.007 (75)

Standard deviation from triplicate reactions, errors bars are less than 10% in most cases (see the Supporting Information, Figures S2–S4).

Multivalent iminosugars **20**–**22** showed low, moderate, and strong multivalent effects against NagZ, hOGA, and HexAB, respectively. The most significant effect was obtained with HexAB with Rp/*n* values of 131, 32, and 75 observed for compounds **20**, **21**, and **22** with increasing valency of 2, 4, and 8, respectively. Previously, several studies have found that higher valency does not necessarily correlate with improved multivalent binding avidity for targeted carbohydrate-binding or carbohydrate-processing proteins.[49,50] To improve potency, fine tuning of the spatial distribution of the azepane ligands through altering the scaffold may be a more effective strategy than simply increasing multivalency.

Results obtained with multivalent derivatives **20**–**22** on the isoenzyme HexAB are particularly striking. Indeed, the multivalent presentation of the seven-membered iminosugar was shown to convert the micromolar inhibitor **19** (IC_{50} 4.2 μM) into nanomolar inhibitors **20** (IC_{50} 16 nM), **21** (IC_{50} 33 nM), and **22** (IC_{50} 7 nM). Monovalent iminosugars bearing hydrophobic aglycons were previously shown to enhance HexaB affinity and selectivity.[13] However, such an impact on the enhanced affinity should be limited here compared to a multivalent effect as a long hydrophobic tail is already present on the monovalent reference **19**.

Notably, the three multivalent compounds **20**–**22** surpass the inhibitory activity of PUGNAc towards HexAB. The development of glycosidase inhibitors is generally hampered by unwanted inhibition of related enzymes. PUGNAc inhibits HexAB and NagZ to the same extent (37 vs. 30 nM). Monovalent compound **19** is significantly less potent than PUGNAc but showed a 25-fold higher inhibitory activity for HexAB over NagZ (4.2 vs. 106 μM). This selectivity trend was dramatically enhanced with the multivalent compounds, as illustrated by octavalent derivative **22** being 1430-fold more selective toward HexAB over NagZ. A greater multivalent enhancement effect was observed for hOGA and HexAB, which are both expected to be dimeric in solution. In contrast, the monomeric NagZ displayed reduced Rp/*n* values for the multivalent inhibitor panel (Table 2). In the hOGA crystallographic dimer (PDB ID: 5M7R), the distance between the catalytic D175 CA atom in the two chains is 41 Å with the two active sites juxtaposed on opposite sides of the dimer. Similarly, in the human beta-hexosaminidase A crystallographic heterodimer structure (PDB ID: 2GJX), the distance between the equivalent catalytic Glu (E323 alpha subunit and E355 beta subunit) is 48 Å with the two active sites oriented on the same face of the dimer. The maximal distance between the azepane motifs (estimated to 26 Å for the dimer **20**) being too short to span this large distance, a chelate binding mode can be ruled out. The multivalent effects observed are most likely due to additional binding of the azepanes in enzyme subsites, or to an aggregative process.

Conclusion

In conclusion, we developed a set of multivalent polyhydroxylated acetamidoazepane clusters based on hydrophilic and biocompatible scaffolds. Multivalent inhibitory effects were observed for the first time on plant, mammalian, and therapeuti-

cally relevant hexosaminidase targets. The strategy proved effective in designing nanomolar inhibitors of HexAB with a high selectivity profile and without the need of intensive structure–activity relationship studies. These results further expand the scope of multivalent iminosugars able to interfere with glycosidase activity.

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Conflict of interest

The authors declare no conflict of interest.

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