Title: Exploring the structural space of galectin-1-ligand interaction

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Exploring the structural space of galectin-1-ligand interaction

Nadja Bertleff-Zieschang[‡], Julian Bechold[‡], Clemens Grimm, Michael Reutlinger, Petra Schneider, Gisbert Schneider and Jürgen Seibel**

Abstract: Galectin-1 is a tumor-associated protein which, recognizing the Gal*β*1-4Glc*N*Ac motif of cell surface glycoconjugates. Here, we report on the stepwise expansion of a multifunctional natural scaffold based on *N*-acetyllactosamine (Lac*N*Ac). We obtained a Lac*N*Ac mimetic equipped with an alkyne function on the 3'-hydroxyl group of the disaccharide facing towards a binding pocket adjacent to the carbohydrate recognition domain. It served as an anchor motif for further expansion *via* Sharpless-Huisgen-Meldal reaction, resulting in ligands with an almost identical binding mode to the natural carbohydrate template. X-ray crystallography provided a structural understanding of the galectin-1-ligand interactions. The results of this study enable the development of bespoke ligands for members of the galectin target family.

Human galectin-1 is a homodimer of 14.5 kDa subunits and a member of carbohydrate binding lectins.[1] It has been associated with tumor proliferation, angiogenesis and metastasis.[2] Galectin-1 secreting tumors gain immune privilege by inducing apoptosis in T-helper cells,[3] and its expression level correlates with the aggressiveness of certain tumors.[4] Many of these processes are mediated by the sophisticated interplay between the lectin and the *β*-galactosides of complex glycan structures presented on the cell surface. Due to the overexpression of galectin-1 in numerous types of cancer cell lines, the protein has been suggested as a potential target for therapeutic intervention[5] and a diagnostic marker[6]. Recent studies have demonstrated that multivalent presentation of natural *β*-galactosides (*N*-acetyllactosamine (Lac*N*Ac), lactose) compensates for the weak affinity (low mM range) of galectin-1 to the carbohydrate ligand and results in high-avidity binding.[7] In this context, the development of synthetic galectin-1 ligands, based on the natural binding motif Lac*N*Ac to interfere with physiological interactions or to probe for elevated galectin-1 levels, has previously been pursued by combinatorial approaches.[8]

The galectin-1 carbohydrate recognition domain (CRD) features a main binding site for the respective *β*-galactoside, (defined by His44, Asn46, Arg48, His52, Trp68, Asp54, Val59, Asn61, Glu71, Arg73, surface area depicted in blue, Figure 1a), which also accommodates the *N*-acetylglucosamine residue of Lac*N*ac (Figure 1a). However, previous studies have shown that oligosaccharides like Neu5Ac-*α*-(2,3)-Lac*N*Ac[9] bind to an adjacent pocket to the left side (Ala121, Ala122, Asp123, Val31, Leu32, Asn33, Leu34, Gly35, green surface region). The goal of this present study was to gradually expand Lac*N*Ac into a tailor-made ligand able to reach this and a previously unexplored cleft on the protein surface (Asp25, Asp126, red surface region). This part of the galectin-1 surface had not been addressed previously, and was chosen to demonstrate our rational approach to design a ligand for a specific protein or binding site.

In a preliminary experiment using isothermal titration calorimetry (ITC), we observed that the interaction between galectin-1 and Lac*N*Ac (K_d = 81 ± 12 μM) is enthalpically driven and suffers from entropic losses (Supplementary Information, Table S2). Consequently, the predictability of synthetically extended disaccharide structures by computational methods is limited.[10][11] To avoid artefacts from structural modeling, we directly crystallized the complex of human galectin-1 bound to Lac*N*Ac and solved its structure with a resolution of 1.4 Å (Figure 1a, PDB ID: 4Q26). This crystal structure features high similarity to the complex of human galectin-1 with lactose (PDB ID: 1GZW, RMSD = 0.28 Å)[10a] as well as to bovine galectin-1 with Lac*N*Ac (PDB ID: 1SLT, RMSD = 0.55 Å)[12]. In all three structures, the disaccharide ligand displays a canonical binding mode within the binding site (highlighted in blue, Figure 1)[12].

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The crystallographic data suggested that the

functionalization of the 3'-OH of the galactosyl unit and the 1-OH

of the *N*-acetylglucosamine moiety (as *β*-anomer) would not

strongly influence the binding of the sugar and might yield a

template that mimics the Lac*N*Ac binding motif. The 3'-OH group

has already been proposed for modifications,[8, 13] and apparently

forms a favorable exit vector pointing away from the

N-acetylglucosamine core, facing towards the surface pocket

adjacent to the CRD. In order to provide a reactive and

synthetically accessible form of the natural galectin-1 ligand, we

chose the alkyne and alkene groups as modifications of the

3'-OH and 1-OH groups, respectively (Scheme 1). Both

functional groups can be converted under mild conditions with

excellent yields, high selectivity and compatibility with a wide

scope of other functional groups[14]. Terminal alkynes react in the

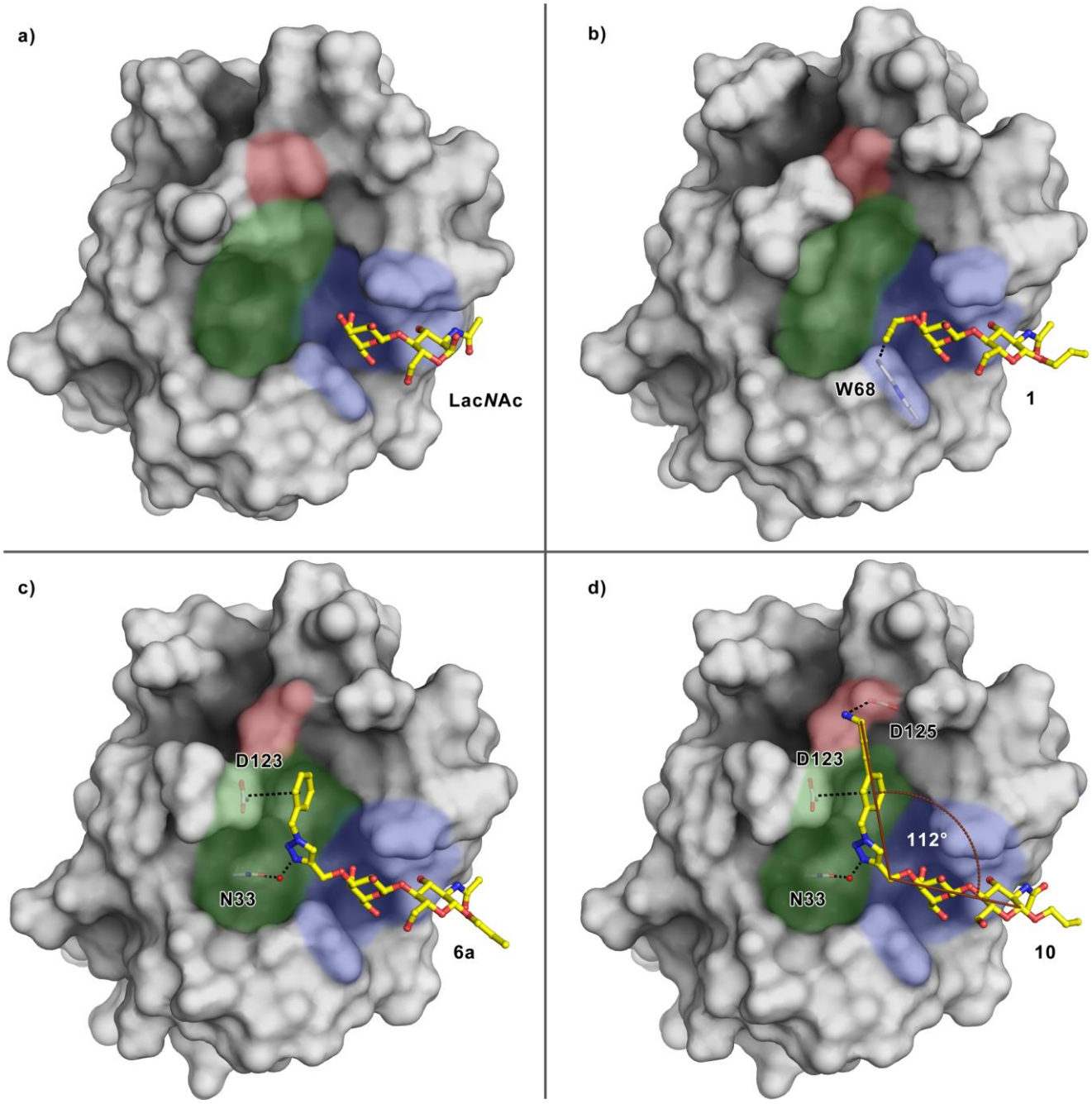
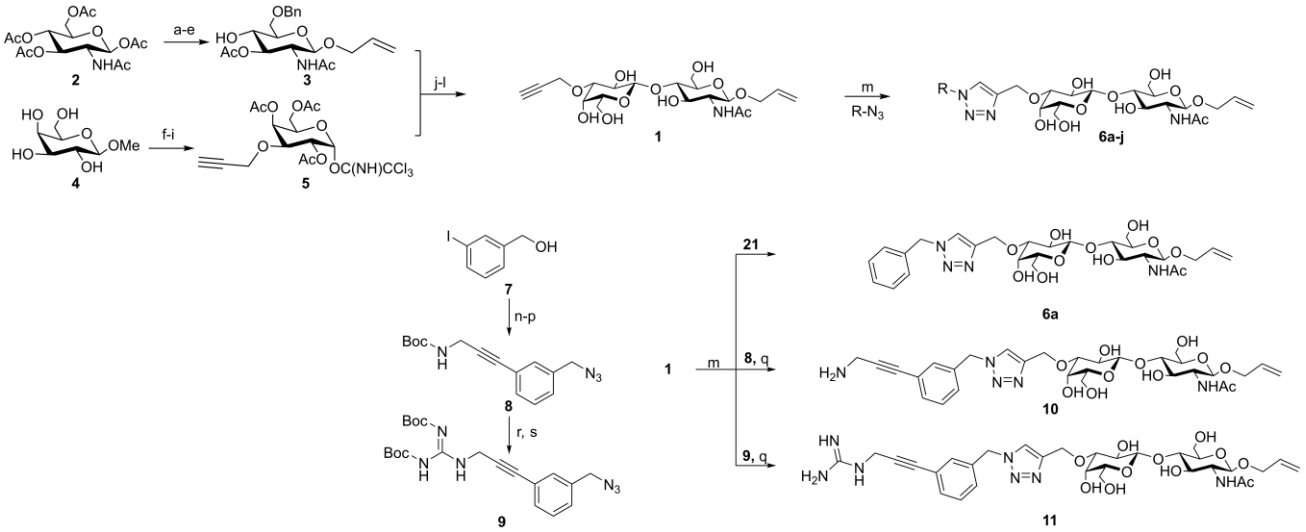


Figure 1. Crystallographic complexes of galectin-1 with synthetic *N*-acetyllactosamine-based ligands. The carbohydrate binding site is colored in blue, the adjacent binding site in green, and an Asp-rich region in red. a) Galectin-1 with Lac*N*Ac (PDB ID: 4Q26, resolution: 1.40 Å). b) Galectin-1 with the multifunctional Lac*N*Ac mimic **1** (PDB ID: 4Q27, resolution: 1.27 Å), the alkyne group forms an interaction with W68. c) Galectin-1 with triazole **6a** (PDB ID: 4Q1P, resolution: 1.42 Å), the triazole forms water mediated interaction with N33, and the benzyl moiety undergoes π-π stacking with D123. d) Galectin-1 with triazole **10** (PDB ID: 5MWX, resolution: 1.29 Å), a salt bridge is introduced between the amino residue of **9** and D125, the angle between the glucoside moiety and the alkyne group is 112°.

Cu(I)-catalyzed Sharpless-Huisgen-Meldal click reaction with

azides to 1,4-triazoles.[15] The alkene group modification at 1-OH is able to functionalize the resulting compounds with thiols[16], alkenes in the metathesis reaction,[17] or with tetrazines in an inverted Diels-Alder[18] reaction. This option offers opportunities for drug loading, microarray experiments or the formation of multivalent structures in future studies.

Surface plasmon resonance (SPR) studies suggested that the synthetic modifications apparently do not interfere with the natural ligand interactions and resulted in comparable dissociation constants for both disaccharides (Lac*N*Ac: 91 ± 5 μM; **1**: 107 ± 9 μM). This K_d value obtained for Lac*N*Ac is in agreement with our ITC data and a previously reported

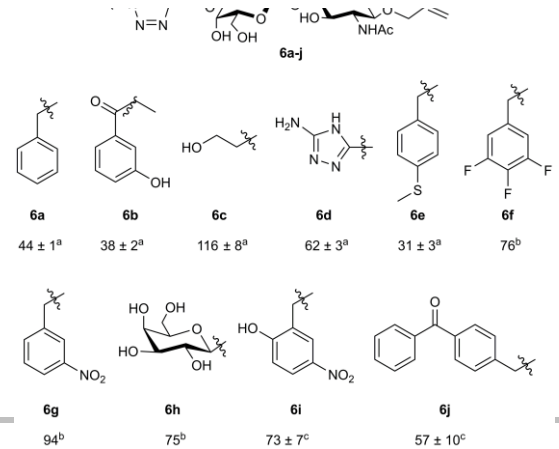


Scheme 1. Synthesis of alkyne precursor **1** and click products **10** and **11**. a) TMSOTf, CH_2Cl_2, 40 °C, 3 d, then allyl alcohol, 40 °C, 3 h, 62 %; b) NaOMe, MeOH, rt, 15 min, 95 %; c) benzaldehyde dimethylacetal, CSA, MeCN, rt, 12 h, quant.; d) acetic anhydride, pyridine, rt, 12 h, 98 %; e) TFA, TFAA, $HSiEt_3$, CH_2Cl_2, 0 °C to rt, 5 h, 85 %; f) Bu_2SnO, MeOH, reflux, 4 h, then propargyl bromide, dmf, 35 °C, 40 h, 67 %; g) acetic anhydride, cat. H_2SO_4, rt, 12 h, quant.; h) hydrazine acetate, dmf, 50 °C, 45 min, 69 %; i) trichloroacetonitrile, dbu, CH_2Cl_2, 0 °C, 1 h, 83 %; j) $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 1 h, 88 %; k) DDQ, CH_2Cl_2, 40 °C, 48 h, then H_2O, rt, 2 h, 83 %; l) NaOMe, MeOH, rt, 12 h, 87 %; m) $CuSO_4$, sodium ascorbate, ^{t}BuOH/H_2O 2:1, 36-99 %; n) *tert*-butyl-prop-2-in-1-yl-carbamate, CuI, $(PPh_3)_2PdCl_2$, thf/NEt_3,, rt, 16 h, 93 %; o) CBr_4, PPh_3, DCM, 0 °C to rt, 16 h, 68 %; p) NaN_3, H_2O, 110 °C MW, 1 h, 44 %; q) TFA/H_2O, rt, 30 min, 99 %; r). TFA/DCM, rt, 1 h, quant.; s) *N*,*N*'-di-bocthiourea , 2-chloro-1-methylpyridinium iodide, NEt_3, DMF, rt, 2 h.

In this regard, 3-*O*-propargyl-*β*-D-galactopyranosyl-(1,4)-2-acetamido-1-*O*-allyl-2-deoxy-*β*-D-glucopyranoside **1** was conceived as a multifunctional Lac*N*Ac mimic. Therefore, peracetylated *N*-acetyl-*β*-D-glucosamine **2** was converted to partially protected *N*-acetyl-*β*-D-glucosamine derivative **3**. We further functionalized 1-*O*-methyl-*β*-D-galactopyranoside **4** regioselectively at the 3'-OH group with Bu_2SnO and propargyl bromide *via* intermediate tin complexation,[19] and activated the galactosyl derivative with trichloroacetonitrile to yield galactosyl donor **5**. We arrived at compound **1** by a glycosylation reaction of **3** and **5** and subsequent deprotection steps (Scheme 1).

We probed the impact of the synthetic extensions on the binding mode by X-ray crystallography. The complex of galectin-1 and Lac*N*Ac mimic **1** (Figure 1b, PDB ID: 4Q27) shows a conserved geometry. The structural superposition of the sugars (Supplementary Information, Figure 1S) demonstrates that the galactosyl moiety is captured in the protein depression, as anticipated. Key interactions are formed between His44, Arg48, Asn46 and the axial 4-OH, and between Glu71, Asn61 and the 6-OH of the carbohydrate ligand (Figure 1S). Trp68 supports this ligand orientation by π-CH-stacking with the galactosyl ring. The allyl group of the Glc*N*Ac unit shows weak electron density, suggesting that this extension might be flexible and does not disturb the carbohydrate interactions. This observation will become relevant for galectin-1 recognition when exploiting the alkene functionality for further modification in future experiments. In contrast, the alkyne modification at 3'-OH features well-defined electron density within a distance of 3.7 Å to Trp68, which might be explained by weak T-shaped π-π-interactions.[20]

Scheme 2. Chemical structures of computationally prioritized click products **6a**-**6j**. K_d values (in μM) were determined by SPR with immobilized galectin-1 in [a]triplicates or [c]duplicates. [b]K_d values were estimated from a single concentration screen (at 10^{-4} M) and measured in



value.[10a]

The next goal of our design strategy was to extend the ligands across the galectin-1 CRD surface region (blue) to the adjacent cavity (green) and eventually address a new surface patch (red, Figure 1). To this end, we computationally generated a library of 397 derivatives from readily available azides and halogenide precursors, and ranked them according to the heavy-atom-corrected ChemPLP score obtained by ligand docking into the galectin-1 binding site (Supplementary Information). We chemically synthesized the ten top-ranking compounds (Scheme 1 and 2). SPR experiments of the novel ligands identified three click products with increased affinity, while the remaining compounds showed equivalent or improved affinity as Lac*N*Ac.

To elucidate their binding mode, we co-crystallized galectin-1 with the new inhibitors **6a** (PDB ID: 4Q1P), **6b** (PDB ID: 4Q1R) and **6d** (PDB ID: 4Q2F). The strong electron density of **6a** and **6b** underlines the conserved binding mode of the carbohydrate unit and its synthetic expansion towards the sub-pocket. (green patch Figure 1 and S1). The triazole fulfills its role as a linker unit and is fixated by a water-mediated interaction with Asn33 in all structures. The benzyl group of **6a** is positioned in a parallel orientation to the carboxyl group of Asp123 by π-π stacking and covers the hydrophobic area formed by Val31. In compound **6b**, the aromatic hydroxyl group undergoes hydrogen bonding with Asp125, while the acetophenone moiety is orientated for CH-π interaction with Gly124, covering the hydrophobic surface area formed by Val31.

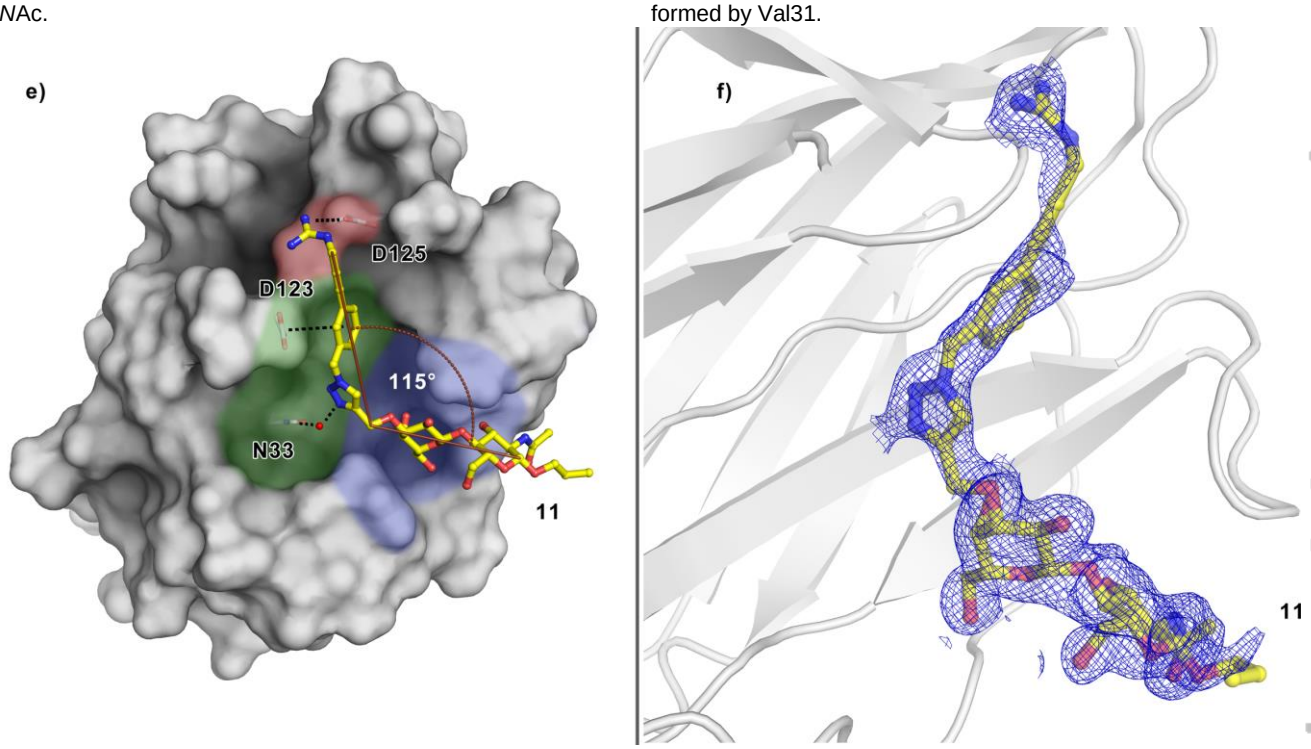


Figure 2. a) Complex of galectin-1 with the synthetic *N*-acetyllactosamine-based ligand **11** (PDB ID: 5MWT, resolution: 1.71 Å). a) The carbohydrate binding site is colored in blue, the adjacent binding site in green, and an Asp-rich region in red. b) Simulated annealing omit map for the bound ligand **11** contoured on the 0.5σ level, shown in blue.

Based on these results, we selected ligand **6a** for further elongation due to its favorable orientation on the protein surface, and identified feasible interactions that could be addressed by such an extended ligand. We focused on the introduction of a basic functionality to the ligand to address a carboxyl-rich region of the protein, which to our knowledge has not been targeted before. This part of the target pocket of galectin-1 hosts two aspartate residues (Asp26, Asp125, Figure 1c, red surface area). The main challenge we encountered was to devise a synthetic route that enables the integration of the cationic group while preserving the binding scaffold of **6a**. We extrapolated the structure and hypothesized that an alkyne connector attached to the benzyl ring in *meta*-position should be rigid enough to bridge the gap of about 5.9 Å to Asp125, and a Sonogashira coupling would allow the synthetic realization of the proposed structure.[21] Therefore, Boc-protected propargylamine was reacted with 3-iodobenzyl alcohol **7** and Bis(triphenylphosphine) palladium(II)dichloride as catalyst in 93 % yield (Scheme 1).[22] The subsequent steps included conversion of the alcohol into the azide **8** *via* the bromide compound and deprotection of the amine group, which afterwards was reacted with *N,N'*-Di-Bocthiourea to form the analogue guanidino compound **9**.[23] Triazole formation of **8** and **9** with precursor **1** and consecutive deprotection of the amine and guanidino functionality, respectively, lead to the expanded ligands **10** and **11** (Scheme 1). We also succeeded in co-crystallizing compounds **10** (Figure 1d) and **11 (**Figure 2), with the latter showing a good fit to the electron density (Figure 2b). The amino group reaches the targeted carboxylate of Asp125 and locates within a distance of 2.8 Å. The common structural elements of **6a** and the previous-generation ligand are well aligned and the alkyne extension fulfills its function as a rigid spacer, as demonstrated by the galectin-1-ligand complex. The angle between the Lac*N*Ac and the alkyne residue is about 115° (Figure 1d, 2a), which is unique for ligand-protein interactions. To further evaluate these results, we performed ITC experiments, obtaining similar ΔG values for ligand **10** and the previously probed structures **6a-d** and Lac*N*Ac respectively (Figure 3). This result is in agreement with the SPR data (Scheme 2).

In conclusion, we investigated and extended the binding modes of a growing carbohydrate ligand fragment to the tumor-associated protein galectin-1. Related combinatorial approaches have concentrated on the evaluation of ligands with a focus on their binding affinity. Here, we concentrated on the design of innovative ligands with a conserved orientation supported by X-ray crystallography. The alkyne-alkene modified Lac*N*Ac mimetic **1** proved to be a useful template as it allows the extension over the carbohydrate recognition site to unexplored sub-pockets in a predictable way. The alkene moiety did not interfere with sugar binding and could be used in future experiments for covalent conjugation with other compounds, *e.g.* drugs or biomarkers. Furthermore, it could serve as a tool to establish multivalency to compensate for the moderate affinity.

Keywords: galectin-1 • X-ray crystallography • carbohydrate-lectin interaction • ligand design • fragment-based design

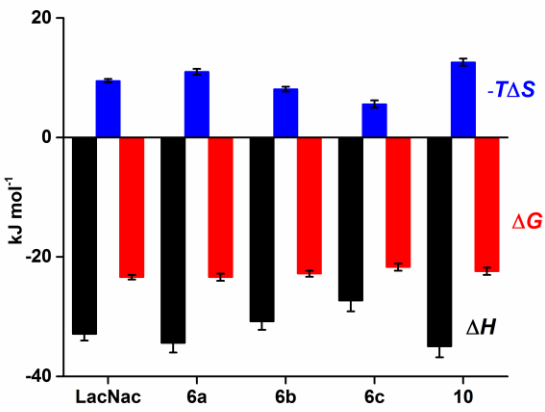


Figure 3. Thermodynamic data obtained by ITC for ligands **6a**, **6b**, **6c**, **10**, and Lac*N*ac at 298 K. Colored bars give the respective changes in Gibbs free energy ΔG (red), enthalpy ΔH (black) and the entropy term $-T\Delta S$ (blue). Error bars: stddev from model fitting (n = 1).

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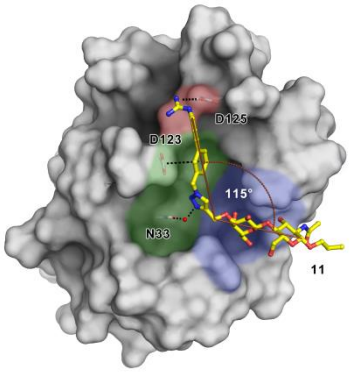
Entry for the Table of Contents

COMMUNICATION

Expansion of natural binding scaffold *N*-acetyllactosamine (Lac*N*ac), *via* a synthetic multifunctional Lac*N*Ac mimetic leads to expanded ligands, which share a highly conserved binding mode.



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Elucidating the structural space of galectin-1-ligand interaction

Author/s:
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