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Synthesis of stable and selective inhibitors of human galectins-1 and -3

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ABSTRACT

The syntheses of glycolytically stable galactosides and lactosides have been made toward the selective inhibition of human galectins-1 and -3. Transition metal-catalyzed cross-coupling reactions were used to create carbon–carbon bond formation (Sonogashira, Suzuki, Heck, Glaser). Additionally, Hantzsch condensation was used to create novel 2-aminothiazoles which reacted with a panel of acylating and sulfonylating reagents. Moreover, dimeric galactosides and lactosides bearing triazoles, regiospecifically prepared using copper-catalyzed Huisgen azide-alkyne [1,3]-dipolar cycloaddition, provided efficient galectins-1 and -3 inhibitors. Best monovalent inhibitor among the tested series was (*E*)-methyl 2-phenyl-4-(β-D-galactopyranosyl)-but-2-enoate **15** with inhibitory potency of 313 μM against galectin-1 and best dimers were bis-lactoside **68** and **75** having both inhibitory properties of 160 μM against Galectin-3.

1. Introduction

Galectins[1] are a family of cytosolic β-D-galactoside binding proteins for which fourteen members have been identified in mammals.[2] Galectin-1 (Gal-1) is a homo-dimer composed of subunits of approximately 130 amino acids and each subunit folds as one compact globular domain.[1] Galectin-3 (Gal-3) is quite unique and has one carbohydrate recognition domain (CRD) ending with a collagen-like repeat of peptides rich in proline and glycine capable of self association and receptor clustering after binding to galactoside clusters.[3] The roles of the galectin family are numerous, but a striking common feature of all galectins is the strong modulation of their expression during development, differentiation stages, and under different physiological or pathological conditions.[4] Studies have demonstrated that Gal-3 is involved in colon cancer metastasis,[5] brain tumor progression,[6] inhibition of metastasis-associated cancer cell adhesion,[7] is playing a key role in innate immunity,[8] and can regulate apoptotic processes[9] together with Gal-1[10] which can additionally act as a soluble host factor that promotes HIV-1 infectivity through stabilization of virus attachment to host cells.[11] Moreover, a recent study suggests that Gal-1, but not Gal-3, can facilitate HIV-1 infection in monocyte-derived macrophages (MDMs) by promoting early events of the virus replicative cycle.[12]

Naturally occurring carbohydrate ligands for galectins bind to galectins and can inhibit their biological activity. Among their simple analogs, methyl β-D-*N*-acetyllactosaminide, methyl β-D-lactoside, and methyl β-D-galactoside (Fig. 1) have low affinities, are too polar to be used as oral drugs, and possess low physiological stabilities due to their acid sensitive glycosidic bonds.[13] Although the CRDs of galectins show structural homologies and a binding preference toward the β-D-galactoside residues in subsite C (particularly OH-4′ and 6′), flexibility exists for the design of specific inhibitors bearing variable pharmacophores in subsites B (OH-3′) and D (Glc residue).[14] Moreover, when administered intraperitoneally (2 mg/g body weight in mice), D-galactose can completely abolish L-1 sarcoma cells metastasis to liver.[15] Hence, relatively high IC_{50}s do not necessarily reflect low in vivo potency. A rational design approach for the development of a new class of glycomimetic inhibitors with high affinity, stability, and specificity to target Gal-1 versus Gal-3 is thus needed.[16] Chemical modification at the anomeric position led us to the discovery of stable *C*-galactoside methyl 2-{4-(β-D-galactopyranosyl)-[1,2,3]triazole-2-yl-methyl}acetate **1**[17] (Fig. 1) with binding affinities of 5 mM against Gal-1. Moreover, β-D-lactosyl naphthyl sulfone **2**[18] and dimeric lactoside **3**[19] had binding affinities and IC_{50} of 40 μM against Gal-1 and 163 μM against Gal-3, respectively. As exemplified by the success encountered with analogs **4** (0.3 μM), **5** (33 nM), and **6** (110 μM) against Gal-3,[20] it is anticipated that further development in galactoside and lactoside modifications should provide efficient and selective galectin inhibitors.

Transition metal-catalyzed cross-couplings have proven to be powerful tools for mild, highly efficient carbon–carbon bond formations. Among these processes, those involving palladium

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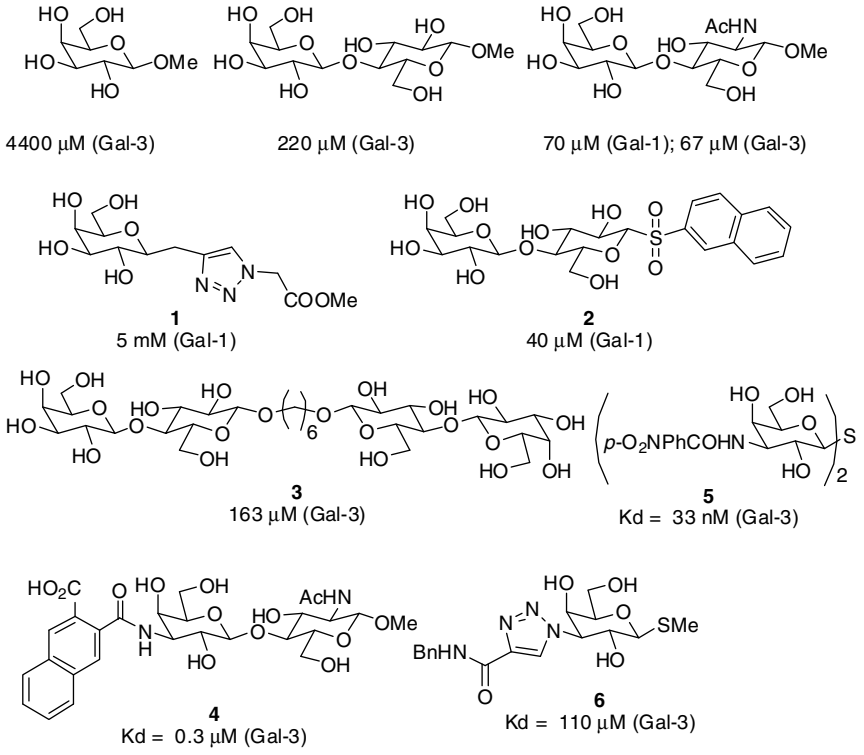


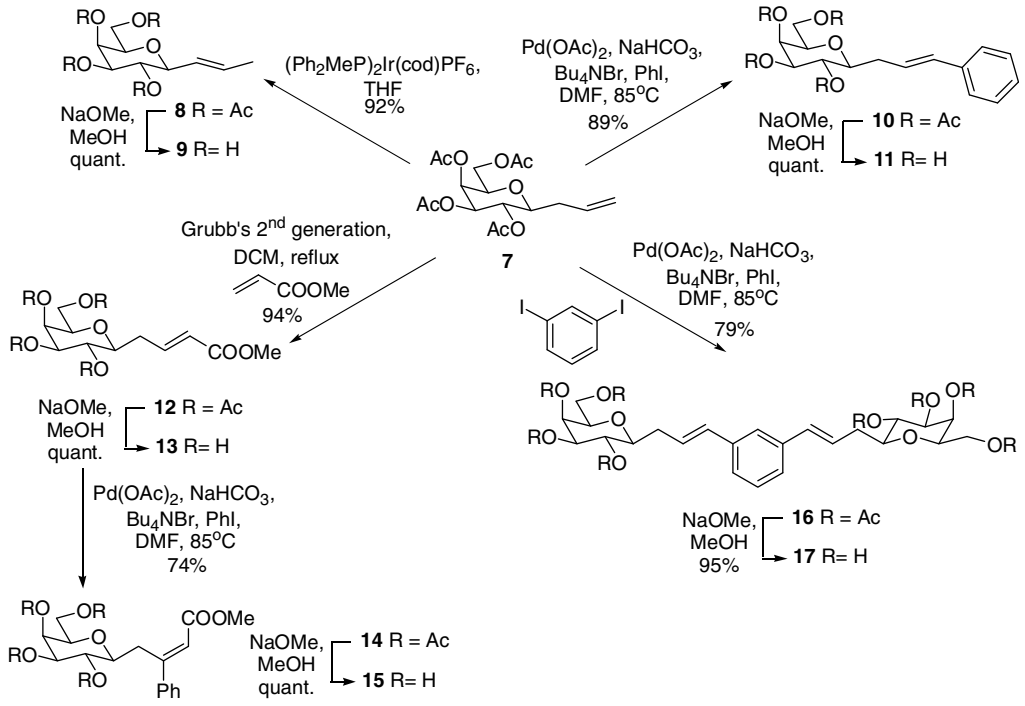
Figure 1. Simple and synthetic ligands for galectins: methyl β-D-galactoside, methyl β-D-lactoside, methyl *N*-acetyllactosaminide, triazolyl galactoside 1,[17] sulfonaphthyl lactoside 2,[18] dimeric lactoside 3,[19] and best candidates from varied libraries 4–6.[20]

(Heck[21] or Sonogashira[22]) catalysis are particularly powerful for the synthesis of complex molecules, owing to their excellent level of selectivity and high functional group compatibility. Consequently and on the basis of previous expertises,[23] the palladium(0)-catalyzed Heck or Sonogashira reactions were used to synthesize *C*-galactoside modified aglycons and a small family of dimeric glycoclusters. Moreover, dimeric galactosides and lactosides bearing triazoles, regiospecifically prepared using copper-catalyzed Huisgen azide-alkyne [1,3]-dipolar cycloaddition,[24] provided efficient Gal-1 and -3 inhibitors. Finally, first application of the Hantzsch 2-aminothiazole synthesis toward preparation of glycoside inhibitors is described.[25] We thus report herein the straightforward synthesis and evaluation of galectin inhibitors made by palladium coupling, Hantzsch 2-aminothiazole synthesis, and click chemistry.

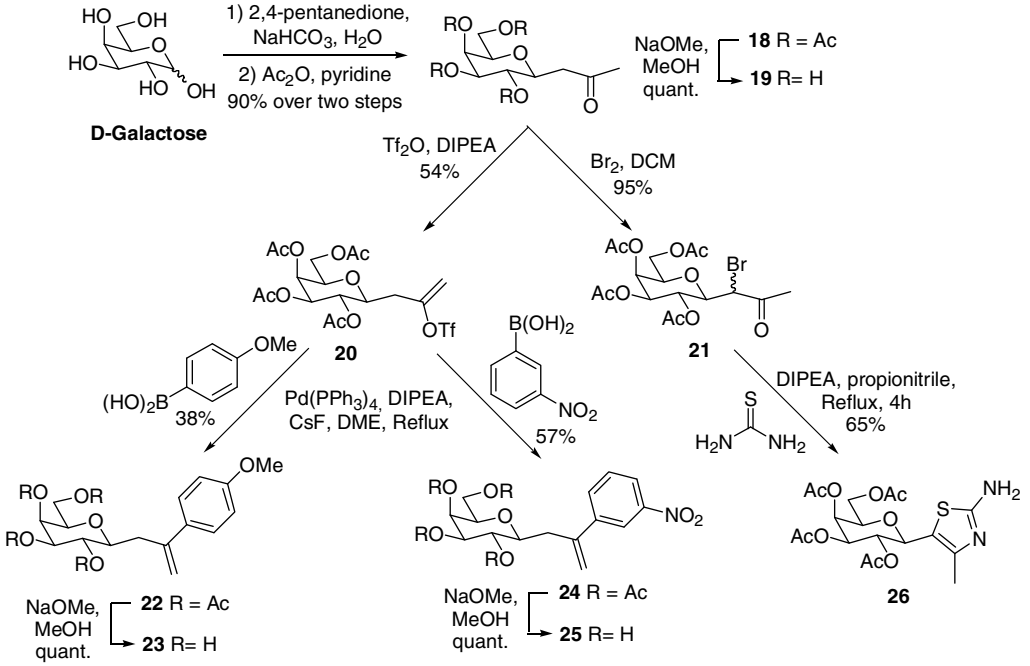
2. Results and discussions

The syntheses were initiated with the known β-*C*-allyl galactoside **7**,[26] which was subjected to a stereoselective isomerization in presence of the cationic iridium(I) catalyst to give the (*E*)-*C*-vinyl glycoside **8** in 92% yield (Scheme 1).[27] Under Heck conditions, allyl **7** was converted to (*E*)-styrene derivative **10** (89%) in presence of phenyl iodide. Cross metathesis[23a,28] was also used on allyl **7** to provide unsaturated ester **12** in 94% yield, which was transformed into compound **14** under palladium cross-coupling.[29] Finally, dimer **16** was easily prepared using the same Heck conditions between allyl **7** and *m*-diiodobenzene in 79% yield.[30] All acylated glycosides **8**, **10**, **12**, **14**, and **16** were deprotected using a catalytic amount of sodium methoxide in methanol to provide free alcohols **9**, **11**, **13**, **15**, and **17** in all almost quantitative yield.

In our ongoing effort to synthesize stable glycosides,[18,28] the Knoevenagel condensation under aqueous conditions could present a very convenient method for the preparation of pure β-*C*-glycosidic ketones directly from unprotected sugars in one step.[31] Thus, condensation of the carbanion of β-diketone with D-galactose followed by β-elimination of water and then cyclization to the intermediate *C*-galactoside which undergoes a retro-Claisen aldolisation under basic conditions with concomitant sodium acetate elimination provided ketone **18** after acetyl protection (90% over two steps, Scheme 2). Two transformations were initiated on ketone **18**: (1) vinyl triflate formation under basic condition provided compound **20** in 54% yield and (2) preparation of α-bromoketone **21** using Br_2 in 95% yield. Treatment of vinyl triflate **20** under Suzuki-coupling using two different arylboronic acids gave adducts **22** and **24** in moderate yields. Ketone **18** along with alkenes **22** and **24** was deprotected (NaOMe/MeOH) to afford free alcohols **19**, **23**, and **25**, respectively. α-Bromoketone **21** was treated with thiourea in propionitrile[32] to give galacto-aminothiazole **26** in 65% yield (32% of ketone **18** was also recovered).[33] 2-Aminothiazole-bearing *C*-galactoside **26** is expected to possess improved stability against hydrolysis under physiological pH and may provide improved cell membrane permeability. Moreover, **26** is a good candidate as a mimic of methyl *N*-acetyllactosaminide, having the amine in the same region in Gal-1 and -3 CRDs. Following the above rationale, derivatization of amine **26** could provide good candidate as galectin inhibitors. Table 1 shows the synthesis of a small library of modified 2-aminothiazoles along with deprotection of the newly formed compounds. 2-Aminothiazole **26** reacted with various sulfonyl chlorides (entries 1–6) to give a range of sulfonamides **27–32** in good to excellent yields 67–91%. Subsequently, imine formation with two aromatic aldehydes (entries 7 and 8) followed by reduction using sodium borohydride yielded secondary amines **33** and **34** in 42% and 47% yields over two steps. Then, amide formation with a variety of acyl chlorides (entries 9–14) provided final products in 44–92% yields (**35**–**40**). Finally, reaction of amine **26** with methyl chloroformate (entry 15) allowed the formation of carbamate **47** in 67% yield. Ultimately, 2-aminothiazole derivatives **27**–**41** were subjected to deprotection with methanolic sodium methoxide, followed by treatment with Amberlite



Scheme 1. Synthesis of various β-*C*-galactosides **9**, **11**, **13**, and **15** and β-*C*-galactoside dimer **17**.

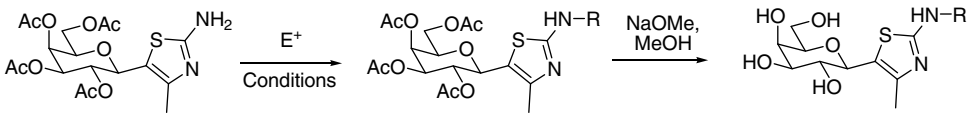


Scheme 2. Synthesis of various *C*-galactosides starting from D-galactose.

IR-120 (H^+) resin to give free alcohols **42**–**56** in yields ranging from 46% to 93%.[34]

Prop-2-ynyl galactoside and lactoside alkynes **57**, **58** along with galactosyl and lactosyl azides **59**, **60** were used for carbon–carbon coupling and/or click chemistry (Scheme 3). Unprotected lactoside **61** and galactoside **62** were used as control. Homo-coupling between sp and sp carbon atoms and cross-coupling between sp^2 and sp carbon atoms (such as Glaser[35] and Sonogashira reactions[36]) as methods to build such compounds have gained great interest. We recently described the use of transition metal-catalyzed syntheses of 'rod-like' thioglycoside dimers.[37] Sonogashira coupling between thiopropynyl lactoside **57**[37] and galactoside **58**[37] with 1,4-diiodobenzene and $Pd_2(dba)_3$, PPh_3 and Et_3N in DMF (1:1, v/v) under nitrogen at 60 °C for 2 h provided lactoside dimer **63** (89% yield) and galactoside dimer **66** (93% yield) (Scheme 4). Moreover, using the same strategy, we used the Glaser coupling, which is the Cu(I)-catalyzed homo-coupling of 2-propynyl glycoside. The reaction proceeded using

Table 1
Synthesis of sulfonamides **42**–**47**, amines **48**–**49**, amides **50**–**55** and carbamate **56**, followed by deprotection of alcohols, starting from 2-aminothiazole galactoside **26**



26 **27-41** **42-56**

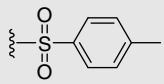
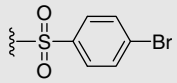
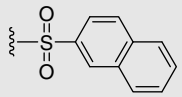
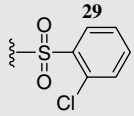
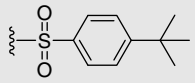
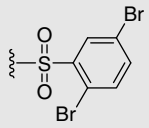
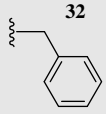
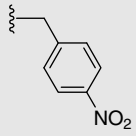
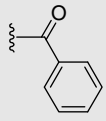
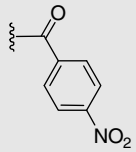
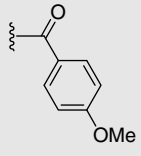
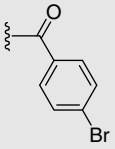
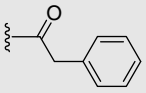
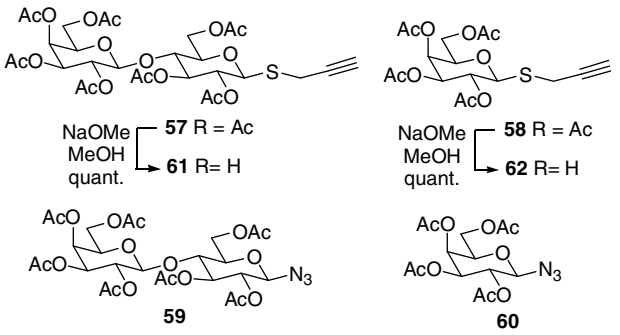
Entry	Reagent	Product (R)	Yield (%)[a]	Deprotected compound[a,e] (yield (%))
1[b]	*p*-Toluenesulfonyl chloride	 **27**	86	**42** (61)
2[b]	4-Bromobenzene-sulfonyl chloride	 **28**	91	**43** (64)
3[b]	2-Naphthalene-sulfonyl chloride	 **29**	76	**44** (92)
4[b]	2-Chlorobenzene-sulfonyl chloride	 **30**	83	**45** (85)
5[b]	4-*tert*-Butylbenzene-sulfonyl chloride	 **31**	80	**46** (74)
6[b]	2,5-Dibromobenzene-sulfonyl chloride	 **32**	67	**47** (83)
7[c]	Benzaldehyde	 **33**	42	**48** (69)
8[c]	4-Nitrobenzaldehyde	 **34**	47	**49** (75)
9[d]	Benzoyl chloride	 **35**	58	**50** (93)
10[d]	4-Nitrobenzoyl chloride	 **36**	80	**51** (74)
11[d]	4-Methoxybenzoyl chloride	 **37**	44	**52** (62)

Table 1 (*continued*)

Entry	Reagent	Product (R)	Yield (%)[a]	Deprotected compound[a,e] (yield (%))
12[d]	4-Bromobenzoyl chloride	 **38**	77	**53** (80)
13[d]	Phenylacetyl chloride	 **39**	59	**54** (46)
14[d]	Acetyl chloride	 **40**	92	**55** (60)
15[d]	Methyl chloroformate	 **41**	73	**56** (60)

[a] Yields refer to isolated pure products.
[b] Sulfonyl chloride was stirred under reflux to a solution of aminothiazole and DMAP in DCM.
[c] Aldehyde was heated at 140 °C neat with 2-aminothiazole, then dissolved in MeOH, and $NaBH_4$ was added.
[d] Acyl chloride was added to a solution of aminothiazole and Et_3N in THF.
[e] Acylated carbohydrate was dissolved in MeOH and a catalytic amount of sodium methoxide was added, and the mixture was stirred for less than overnight at room temperature. Treatment with Amberlite IR-120 (H^+) resin, followed by filtration and concentration afforded unprotected carbohydrates.



Scheme 3. Lactosides and galactosides alkynes **57**, **58**, and azides **59**, **60**.

CuCl as source of Cu(I) and tetramethylethylenediamine (TMEDA) as base at 40 °C in oxygenated DMF. Thiopropyl lactoside **57** and galactoside **58** were successfully coupled to afford lactoside dimer **67** and galactoside dimer **69** in 82% and 85% yields, respectively (Scheme 4). All acylated glycosides **63**, **65**, **67**, and **69** were subjected to deprotection with methanolic sodium methoxide to give, respectively, unprotected dimers **64**, **66**, **68**, and **70** in almost quantitative yields.

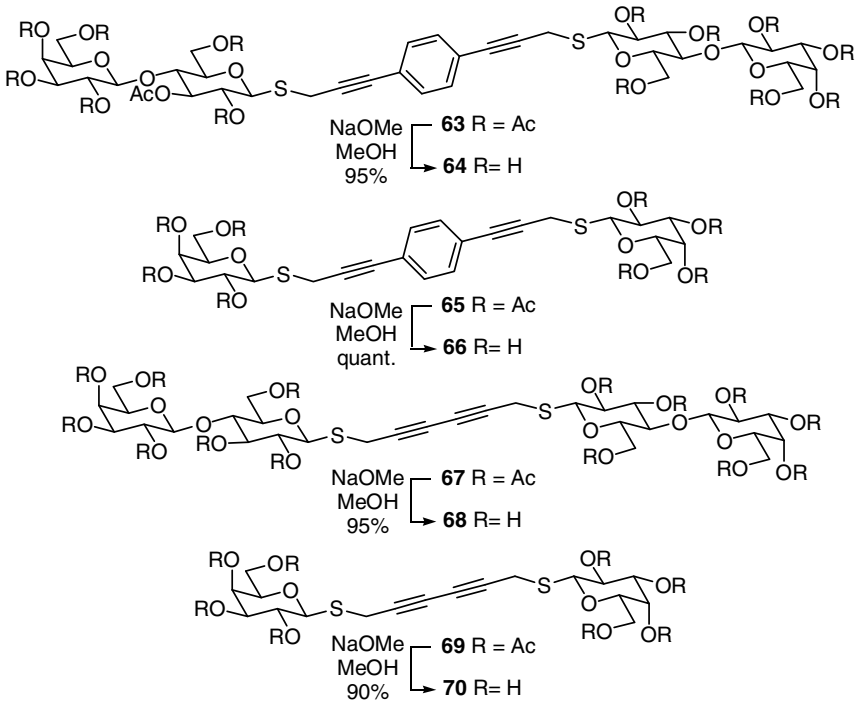
Recent developments have been reported in the synthesis of carbohydrate-based 1,2,3-triazoles.[38] Application of the Cu(I)-catalyzed Huisgen azide-alkyne [1,3]-dipolar cycloaddition[24] is powerful for the synthesis of non-natural heterocycles which are attractive due to their stability.[39] In our ongoing effort to make glycoclusters using click chemistry,[17,40] we used lactosyl azide **59** and galactosyl azide **60** as starting materials (Scheme 3). Table 2 shows reactions of these azides with both thiopropynyl lactoside **57** and galactoside **58** to give homo-dimers **71** and **74**, along with hetero-dimers **72** and **73** in yields ranging from 77% to 89%. Final de-O-acetylation occurred as above with methanolic sodium methoxide to give unprotected dimers **75–78** in high yields.

3. Bioassays

All compounds and controls (lactose and galactose) were tested by inhibition of hemagglutination assay at a concentration of 1 μM of both galectins. Hemagglutination assays were performed using red blood cells, type O, fixed with 3% glutaraldehyde–0.0025% NaN_3 in PBS[11a,41] to confer both lectins equal relative affinities. Table 3 shows inhibitory properties and relative activities of our derivatives toward Gal-1 and -3. The monosaccharides inhibitory potencies varied from inactive to moderately active with a IC_{50} of 313 μM for compound **15** (160 times better then galactose), indicating that a sp^2 carbon at the β-position to the anomeric carbon increases the affinity toward Gal-1 and, -3; this is consistent with other compounds having such scaffolds (compounds **13**, **23** and **25**). Best 2-aminothiazole derivatives toward Gal-1 and -3 were sulfonamide **46**, amines **48** and **49**, along with amides **52** and **53**. Most of the lactoside dimers were effective against Gal-1 and -3 and dimers **68** and **75** gave inhibitory properties as low as 160 μM against Gal-3 for a relative affinity of 5 (2.5 times better for each lactose unit). Surprisingly, in this assay, no multivalent effect was observed for hetero-dimers **76** and **77** (for a relative potency similar to methyl β-D-lactoside). It is important to note that compound **15** is not only the most promising candidate against galectin-1, but is also the most selective, being ineffective against Gal-3. This result compared well with β-D-lactosyl naphthyl sulfone **2**[18] which also have better affinity to Gal-1 (40 μM) compared to Gal-3 (313 μM).

4. Conclusions

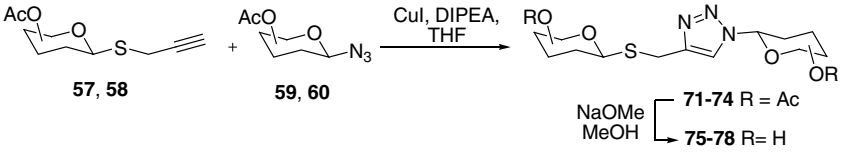
In conclusion, we described the synthesis of stable galactosides and lactosides which have potential Gal-1 and -3 inhibitory properties against galectins which compared well with known inhibitors.[17–20,42] The best monovalent inhibitor among the tested series was *C*-galactoside **15** with inhibitory properties of 313 μM

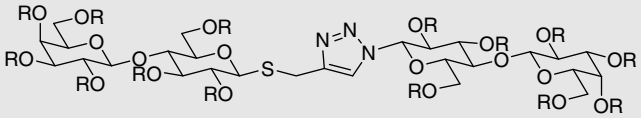
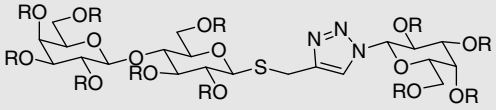
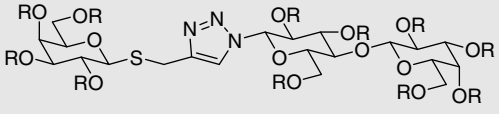
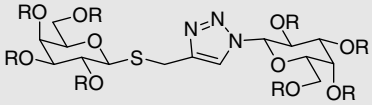


Scheme 4. Deprotection of acetylated dimeric glycosides **63**, **65** (made from palladium(0)-catalyzed Sonogashira coupling) and dimeric glycosides **67**, **69** (made from the Glaser Cu(I)-catalyzed homo-coupling reactions) afforded unprotected dimeric lactosides **64**, **68**, and dimeric galactosides **66**, **70**.

against Gal-1 and inhibitory >5 mM against Gal-3. Best dimers were bis-lactosides **68** and **75** having both inhibitory properties of160 μM. Although the above compounds are notably less efficient than those described by Nilsson et al. in solution assays,[20,42a] the present work described inhibition of hemagglutination assays usually known to require higher concentrations.

Table 2
Synthesis of triazole dimers **75**–**78** using the copper-catalyzed Huisgen azide-alkyne [1,3]-dipolar cycloaddition, followed by deprotection of alcohol



Entry	Alkynes	Azides	Products	R = Ac yield[a,b] (%)	R = H yield[a,c] (%)
1	**57**	**59**		**71** (81)	**75** (92)
2	**57**	**60**		**72** (89)	**76** (quant.)
3	**58**	**59**		**73** (77)	**77** (75)
4	**58**	**60**		**74** (88)	**78** (quant.)

[a] Yields refer to isolated pure products.
[b] Alkyne, azide, DIPEA and CuI were dissolved in THF and stirred at room temperature for less than 3 h.
[c] Acetylated carbohydrates were dissolved in MeOH and a catalytic amount of sodium methoxide was added and the mixture was stirred for less than overnight at room temperature.

Table 3
Inhibitory properties and relative activity of compounds **9**, **11**, **13**, **15**, **17**, **19**, **23**, **25**, **42-56**, **61**, **62**, **64**, **66**, **68**, **70**, **75**, **76**, **77**, and **78** against Gal-1 and -3

Compound	Inhibitory properties (mM)		Relative activity[a]	
	Galectin-1	Galectin-3	Galectin-1	Galectin-3
Lactose[b]	0.8	0.8	1	1
Galactose	50	50	1	1
9	>5	>5	<10	<10
11	>5	>5	<10	<10
13	5	5	10	10
15	0.313	>5	160	<10
17[c]	5	>5	10 (5)	<10
19	>5	5	<10	10
23	>5	5	<10	10
25	5	>5	10	<10
42	>5	5	<10	10
43	>5	5	<10	10
44	>5	2.5	<10	20
45	>5	5	<10	10
46	5	5	10	10
47	>5	2.5	<10	20
48	5	2.5	10	20
49	2.5	2.5	20	20
50	>5	2.5	<10	20
51	>5	>5	<10	<10
52	5	2.5	10	20
53	2.5	2.5	20	20
54	>5	>5	<10	<10
55	>5	5	<10	10
56	>5	>5	<10	<10
61	0.6	0.3	1.3	2.6
62	>5	2.5	<10	20
64[c]	0.3	0.3	2.6 (1.3)	2.6 (1.6)
66[c]	2.5	>5	20 (10)	<10
68[c]	0.3	0.16	2.6 (1.3)	5 (2.5)
70[c]	5	>5	10 (5)	<10
75[c]	0.3	0.16	2.6 (1.3)	5 (2.5)
76[c]	0.6	0.3	1.3 (0.7)	2.6 (1.3)
77[c]	0.3	0.6	2.6 (1.3)	1.3 (0.7)
78[c]	>5	2.5	<10	20 (10)

[a] All compounds were compared to galactose except for compounds **64**, **68**, and **75** which were compared to lactose.
[b] Lactose is ~50× better than galactose.
[c] Numbers in parentheses express the relative potency of each lactose unit in the divalent derivative compare to lactose for compounds **64**, **68**, and **75** and galactose for compounds **17**, **66**, **70**, **76**, **77**, and **78**.

5. Experimentals

5.1. Chemistry

5.1.1. General

All reactions in organic medium were carried out under nitrogen atmosphere using freshly distilled solvents. CH_2Cl_2 was dried over P_2O_5, THF and toluene were dried over sodium and benzophenone. Evolution of the reaction was monitored by analytical thin-layer chromatography using silica gel 60 F_{254} precoated plates (E. Merck). Purifications by column chromatography were performed using silica gel Si 60 (40–63 μM) with the indicated eluent. Optical rotations were measured with a JASCO P-1010 polarimeter. Melting points were measured on an Electrothermal MEL-TEMP apparatus. NMR spectra were recorded on a Varian Gemini 300 spectrometer. Proton and carbon chemical shifts (δ) are reported in ppm downfield from $CHCl_3$, CH_3OH, or DMSO. Coupling constants (J) are reported in Hertz (Hz) with singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m), and broad (br). Infrared were measured with a Bomem MB-series. Low-resolution (ESI-MS) and high-resolution mass spectra (HRMS) were achieved using a LC-MSD-TOF instrument from Agilent Technologies (by Dr. Alexandra Furtos and Karine Venne; Mass Spectrometry Laboratory, Université de Montréal, Québec, Canada or at the Université du Québec à Montréal). Either protonated molecular ions $[M+H]^+$ or sodium adducts $[M+Na]^+$ were used for empirical formula confirmation.

5.1.2. Typical de-O-acetylation procedure

The acetyls protected glycoside (0.1 mmol) was dissolved into methanol (2 mL), to which was added a catalytic amount of sodium methoxide. The solution was stirred at room temperature from 3 to 15 h. After neutralization of sodium methoxide with Amberlite IR-120 (H^+) resin, the solution was filtered and removal of the methanol under reduced pressure afforded the fully deprotected glycoside.

5.1.3. (*E*)-Methyl 4-(2,3,4,6-tetracetyl-β-D-galactopyranosyl)-but-2-enoate (12)

To a 0.04 M solution of β-*C*-allyl glycoside **7** (0.1 mmol) in CH_2Cl_2 were added methyl acrylate (0.3 mmol) and 5 mol% of Grubbs 2nd generation catalyst. The reaction mixture was heated under reflux (55 °C) under N_2 for 3 h. The solution was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give **12** as a yellow oil in 94% yield: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.94–6.84 (m, 1H), 5.88 (d, J = 14.3 Hz, 1H), 5.36 (d, J = 3.3 Hz, 1H), 5.07 (t, J = 9.9 Hz, 1H), 4.98 (dd, J = 3.3, 9.9 Hz, 1H), 4.12–3.97 (m, 2H), 3.84 (t, J = 6.3 Hz, 1H), 3.68 (s, 3H), 3.54–3.47 (m, 1H), 2.41 (m, 2H), 2.11 (s, 3H), 2.00 (s, 6H), 1.93 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.3, 170.2, 169.9, 169.6, 166.4, 143.4, 123.3, 76.6, 74.0, 71.8, 68.9, 67.4, 61.4, 51.4, 34.2, 20.6, 20.5, 20.4, 20.3; ESI-MS *m/z* : 431.3 $[M+H]^+$; HRMS *m/z* calcd $C_{19}H_{26}O_{11}$ $[M+H]^+$: 431.1555; found: 431.1538.

5.1.4. (*E*)-Methyl 4-(β-D-galactopyranosyl)-but-2-enoate (13)

Synthesis according to the typical de-O-acetylation procedure obtained in quantitative yield as a yellow solid: mp = 53–54 °C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 6.92–6.87 (m, 1H), 5.82 (d, J = 15.6 Hz, 1H), 3.93–3.75 (m, 1H), 3.52 (s, 1H), 3.37–3.05 (m, 6H), 2.58–2.38 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 174.8, 147.0, 122.5, 78.7, 78.4, 74.1, 71.0, 69.1, 61.3, 52.4, 38.7 HRMS *m/z* calcd $C_{11}H_{18}O_7$ $[M+H]^+$: 263.1132; found: 263.1125.

5.1.5. (*E*)-Methyl 2-phenyl-4-(2,3,4,6-tetracetyl-β-D-galactopyranosyl)-but-2-enoate (14)

To a 0.16 M solution of **12** (0.1 mmol) in DMF were added phenyl iodide (0.2 mmol), 10% palladium(II) acetate, tetrabutylammonium bromide (0.1 mmol), and sodium bicarbonate (0.3 mmol). The reaction mixture was heated at 85 °C under N_2 overnight. The solution was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to give **14** as a yellow oil; $[\alpha]_D^{25}$: −4.8° (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.44–7.40 (m, 2H), 7.36–7.33 (m, 3H), 6.09 (s, 1H), 5.33 (d, J = 3.3 Hz, 1H), 5.15 (t, J = 9.9 Hz, 1H), 4.95 (dd, J = 3.3, 10.2 Hz, 1H), 3.85 (d, J = 6.6 Hz, 2H), 3.74 (s, 3H), 3.65–3.49 (m, 3H), 3.21 (dd, J = 9.3, 14.0 Hz, 1H), 2.13 (s, 3H), 2.11 (s, 3H), 1.96 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.3, 170.2, 170.1, 166.5, 156.9, 141.5, 128.8, 128.2, 126.9, 118.8, 78.3, 73.8, 71.9, 69.4, 67.6, 61.3, 51.2, 33.2, 20.9, 20.7, 20.6; ESI-MS *m/z* : 507.3 $[M+H]^+$; HRMS *m/z* calcd $C_{25}H_{30}O_{11}$ $[M+H]^+$: 507.1868; found: 507.1855.

5.1.6. (*E*)-Methyl 2-phenyl-4-(β-D-galactopyranosyl)-but-2-enoate (15)

Synthesis according to the typical de-O-acetylation procedure obtained in quantitative yield as a yellowish solid: mp = 57–58 °C (ethanol); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.21–7.17 (m, 5H), 5.84 (s, 1H), 3.64 (s, 1H), 3.52 (s, 3H), 3.51–3.27 (m, 6H), 3.24–

2.96 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 169.1, 157.9, 140.6, 129.3, 128.8, 127.1, 118.9, 78.8, 78.3, 74.1, 71.7, 69.1, 60.9, 51.9, 33.1; HRMS *m/z* calcd $C_{17}H_{22}O_7$ $[M+H]^+$: 339.1445; found: 339.1438.

5.1.7. 1-(2,3,4,6-Tetracetyl-β-D-galactopyranosyl)-ace-tone (18)

2,4-Pentanedione (0.62 mL, 6.0 mmol) was added to a mixture of D-galactose (900 mg, 5.0 mmol) and $NaHCO_3$ (630 mg, 7.5 mmol) in water (20 mL). The mixture was stirred overnight at 90 °C, and then cooled to room temperature. The solution was washed with DCM (3× 20 mL), and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the crude *C*-galactoside in pyridine (15 mL) at 0 °C was added dropwise Ac_2O (7.5 mL) and the mixture was stirred at room temperature overnight. In the morning, ice (30 mL) and EtOAc (30 mL) were added to the solution, and the organic layer was washed with aqueous NH_4Cl (2× 30 mL), aqueous $NaHCO_3$ (2× 30 mL), brine (2× 30 mL), and water (2× 30 mL). The organic solution was dried over Na_2SO_4, filtered, concentrated, and chromatographed using a mixture of $Et_2O/CHCl_3$ (1:5) to give **18** in 90% yield over two steps as a colorless oil (1.523 g): ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.33 (dd, *J* = 3.0, 1.0 Hz, 1H), 5.04–4.91 (m, 2H), 4.04–3.78 (m, 4H), 2.69 (dd, *J* = 16.5, 9.0 Hz, 1H), 2.40 (dd, *J* = 16.5, 3.0 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 205.4, 170.5, 170.3, 170.2, 170.1, 74.5, 74.4, 72.0, 69.1, 67.8, 61.6, 45.6, 31.2, 20.9, 20.8, 20.7; HRMS *m/z* calcd $C_{17}H_{24}O_{10}$ $[M+H]^+$: 389.1449; found: 389.1435.

5.1.8. 2-Amino-5-(2,3,4,6-tetraacetyl-β-D-galactopyranosyl)-4-methylthiazole (26)

Bromoketone **21** (47.16 mmol), thiourea (3.58 g, 47.16 mmol) and DIPEA (15.78 mL, 94.32 mmol) were dissolved in propionitrile (300 mL) and the mixture was stirred under reflux for 4 h. After this time, the mixture was evaporated and chromatographed using a mixture of *t*-BuOH/$CHCl_3$ (1:9) to give **26** in 65% yield as a yellow oil (13.6 mg); $[\alpha]_D^{25}$: −8.0° (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.48 (d, *J* = 3.5 Hz, 1H), 5.35 (t, *J* = 10.0 Hz, 1H), 5.13 (dd, *J* = 3.5, 10.0 Hz, 1H), 4.63 (d, *J* = 9.5 Hz, 1H), 4.09 (m, 3H), 2.20 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.3, 170.2, 170.0, 169.3, 158.0, 144.4, 120.6, 74.6, 74.2, 71.7, 70.3, 67.4, 61.5, 20.6, 20.5, 20.5, 20.5, 15.3; IR (neat NaCl, cm^{-1}): 3735, 3400, 3118, 3020, 2962, 1749, 1521, 1371, 1226, 1051, 753; ESI-MS *m/z* : 445.1 $[M+H]^+$; HRMS *m/z* calcd $C_{18}H_{24}N_2O_9S$ $[M+H]^+$: 445.1282; found: 445.1265.

5.1.9. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-(4-methyl-phenyl)sulfonylaminothiazole (27)

Tosyl chloride (19 mg, 0.10 mmol) and DMAP (13 mg, 0.10 mmol) were added to a solution of aminothiazole **26** (45 mg, 0.10 mmol) in 3 mL of DCM. The mixture was stirred under reflux overnight, then concentrated. Flash chromatography was done using a mixture of *t*-BuOH/$CHCl_3$ (1:9). Sulfonamide **27** was obtained as a white solid in 86% yield (51 mg): mp = 91–92 °C; $[\alpha]_D^{25}$: −27.4° (*c* 1.3 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.64 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 5.43 (d, *J* = 3.0 Hz, 1H), 5.21 (dd, *J* = 10.0 Hz, 1H), 5.07 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.46 (dd, *J* = 9.5 Hz, 1H), 4.14–3.95 (m, 3H), 2.34 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.6, 170.5, 170.3, 169.8, 169.1, 143.0, 138.9, 133.1, 129.6, 126.5, 114.7, 75.1, 73.7, 71.8, 69.4, 67.5, 61.8, 21.7, 21.0, 20.9, 20.78, 12.5; IR (KBr, cm^{-1}): 1751, 1541, 1225, 1088; HRMS *m/z* calcd $C_{25}H_{30}N_2O_{11}S_2$ $[M+H]^+$: 599.1370; found: 599.1364.

5.1.10. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-(4-bromophenyl)sulfonylaminothiazole (28)

Synthesis according to the same procedure as for the synthesis of **27** obtained in 91% yield as a white solid: mp = 95–96 °C (ethanol); $[\alpha]_D^{25}$: −21.8° (*c* 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.61 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 9.0 Hz, 2H), 5.44 (d, *J* = 3.0 Hz, 1H), 5.19 (dd, *J* = 10.0 Hz, 1H), 5.08 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.46 (dd, *J* = 9.5 Hz, 1H), 4.14–3.95 (m, 3H), 2.27 (s, 3H), 2.18 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.6, 170.4, 170.2, 169.8, 169.1, 140.7, 133.0, 132.2, 128.0, 127.3, 115.3, 75.1, 73.6, 71.7, 69.5, 67.5, 61.8, 21.0, 20.8, 12.5; IR (KBr, cm^{-1}): 1751, 1540, 1221, 742; HRMS *m/z* calcd $C_{24}H_{27}BrN_2O_{11}S_2$ $[M+H]^+$: 663.0319; found: 663.0298.

5.1.11. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-(β-naphthyl)sulfonylaminothiazole (29)

Synthesis according to the same procedure as for the synthesis of **27** obtained in 76% yield as a white solid: mp = 92–93 °C; $[\alpha]_D^{25}$: −19.3° (*c* 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.36 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.64–7.43 (m, 4H), 5.43 (d, *J* = 3.5 Hz, 1H), 5.23 (dd, *J* = 10.0 Hz, 1H), 5.07 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.46 (dd, *J* = 9.5 Hz, 1H), 4.14–3.94 (m, 3H), 2.31 (s, 3H), 2.19 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.6, 170.5, 170.2, 169.8, 169.1, 138.6, 134.8, 133.2, 132.2, 129.5, 129.3, 128.6, 127.9, 127.4, 127.2, 122.2, 115.0, 75.1, 73.7, 71.8, 69.4, 67.6, 61.8, 21.0, 20.9, 20.8, 20.7, 12; IR (KBr, cm^{-1}): 1751, 1540, 1221, 770; HRMS *m/z* calcd $C_{28}H_{30}N_2O_{11}S_2$ $[M+H]^+$: 635.1370; found: 635.1351.

5.1.12. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-(2-chlorophenyl)sulfonylaminothiazole (30)

Synthesis according to the same procedure as for the synthesis of **27** obtained in 83% yield as a white solid: mp = 91–92 °C; $[\alpha]_D^{25}$: +16.0° (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.12–8.07 (m, 1H), 7.44–7.27 (m, 3H), 5.41 (d, *J* = 3.5 Hz, 1H), 5.16 (dd, *J* = 10.0 Hz, 1H), 5.06 (dd, *J* = 10.0, 3.5 Hz, 1H), 4.46 (dd, *J* = 9.5 Hz, 1H), 4.13–3.92 (m, 3H), 2.31 (s, 3H), 2.16 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.6, 170.4, 170.2, 170.0, 169.0, 138.6, 133.4, 133.2, 132.4, 131.8, 130.7, 126.8, 115.4, 75.1, 73.7, 71.7, 69.4, 67.5, 61.8, 21.0, 20.9, 20.8, 20.7, 12.6; IR (KBr, cm^{-1}): 1752, 1542, 1228, 1046, 753; HRMS *m/z* calcd $C_{24}H_{27}ClN_2O_{11}S_2$ $[M+H]^+$: 619.0824; found: 619.0805.

5.1.13. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-(4-*tert*-buthylphenyl)sulfonylaminothiazole (31)

Synthesis according to the same procedure as for the synthesis of **27** obtained in 80% yield as a white solid: mp = 97–98 °C; $[\alpha]_D^{25}$: −32.1° (*c* 1.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.78 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 3.3 Hz, 1H), 5.49 (dd, *J* = 10.0 Hz, 1H), 5.14 (dd, *J* = 3.3, 10.0 Hz, 1H), 4.50 (d, *J* = 9.5 Hz, 1H), 4.19–4.00 (m, 3H), 2.35 (s, 3H), 2.24 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.4, 170.3, 170.1, 169.6, 168.8, 155.9, 138.5, 132.9, 126.2, 125.7, 114.3, 74.9, 73.5, 71.6, 69.1, 67.3, 61.6, 35.04, 31.1, 20.8, 20.7, 20.6, 12.4; IR (KBr, cm^{-1}): 1752, 1540, 1222, 1086, 754; HRMS *m/z* calcd $C_{28}H_{36}N_2O_{11}S_2$ $[M+H]^+$: 641.1840; found: 641.1821.

5.1.14. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-(2,5-dibromophenyl)sulfonylaminothiazole (32)

Synthesis according to the same procedure as for the synthesis of **27** obtained in 67% yield as a white solid: mp = 90–91 °C; $[\alpha]_D^{25}$: −17.0° (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.30–8.27 (m, 1H), 7.46–7.41 (m, 2H), 5.44 (d, *J* = 3.0 Hz,

1H), 5.18 (dd, J = 10.0 Hz, 1H), 5.08 (dd, J = 10.0, 3.5 Hz, 1H), 4.47 (dd, J = 9.5 Hz, 1H), 4.15–3.95 (m, 3H), 2.33 (s, 3H), 2.18 (s, 3H), 2.00 (s, 3H), 1.94 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.6, 170.4, 170.2, 169.9, 169.1, 141.9, 136.7, 136.1, 133.6, 133.2, 121.2, 119.6, 115.9, 75.1, 73.7, 71.7, 69.4, 67.5, 61.8, 21.0, 20.8, 12.7; IR (KBr, cm^{-1}): 1752, 1540, 1222, 1054, 756; HRMS m/z calcd $C_{24}H_{26}Br_2N_2O_{11}S_2$ $[M+H]^+$: 740.9424; found: 740.9407.

5.1.15. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-(benzyl)sulfonylaminothiazole (33)

Aminothiazole **26** (120 mg, 0.27 mmol) was heated in a sealed tube at 140 °C in presence of benzaldehyde (0.81 mmol) for 1 h. After this time, crude imine was dissolved in THF (2 mL) and $NaBH_4$ (40 mg, 1.08 mmol) was added. The mixture was stirred at room temperature for 30 min. Aqueous NH_4Cl (5 mL) and EtOAc (5 mL) were added, and the aqueous layer was extracted with EtOAc (3× 5 mL). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography was done using a mixture of EtOAc/toluene (1:1). Benzyl **33** was obtained as a colorless oil in 42% yield (61 mg): ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.32–7.22 (m, 5H), 5.41 (d, J = 3.0 Hz, 1H), 5.19 (dd, J = 10.0 Hz, 1H), 5.07 (dd, J = 10.0, 3.5 Hz, 1H), 4.52 (d, J = 9.5 Hz, 1H), 4.41 (d, J = 14.5 Hz, 1H), 4.33 (d, J = 14.5 Hz, 1H), 4.13–3.94 (m, 3H), 2.13 (s, 3H), 2.08 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.6, 170.5, 170.3, 169.5, 169.1, 147.6, 147.3, 137.49, 128.9, 127.9, 127.7 (2C), 74.8, 74.7, 72.2, 70.3, 67.8, 61.8, 50.0, 20.9, 20.7, 15.5; HRMS m/z calcd $C_{25}H_{30}N_2O_9S$ $[M+H]^+$: 535.1751; found: 535.1812.

5.1.16. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-(4-nitrobenzyl)sulfonylaminothiazole (34)

Synthesis according to the same procedure as for the synthesis of **33** obtained in 47% yield as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.13 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 5.40 (d, J = 2.5 Hz, 1H), 5.14 (dd, J = 10.0 Hz, 1H), 5.05 (dd, J = 10.0, 3.5 Hz, 1H), 4.54–4.45 (m, 3H), 4.10–3.94 (m, 3H), 2.10 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H), 1.91 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.6, 170.4, 170.3, 169.3, 169.1, 147.6, 147.3, 128.1, 124.1, 114.9, 74.8, 74.6, 72.1, 70.3, 67.7, 61.8, 49.0, 20.9, 20.8, 20.7, 15.6; HRMS m/z calcd $C_{25}H_{29}N_3O_{11}S$ $[M+H]^+$: 580.1602; found: 580.15849.

5.1.17. 2-Benzamido-5-(2,3,4,6-tetraacetyl-β-D-galactopyranosyl)-4-methylthiazole (35)

Aminothiazole **26** (226 mg, 0.509 mmol) and DMAP (93 mg, 0.764 mmol) were dissolved in 2 mL of THF at 0 °C. Benzoyl chloride (0.764 mmol) was added, and the mixture was stirred at 0 °C overnight. After this time, saturated $NaHCO_3$ (6 mL) was added and the mixture was extracted with ethyl acetate (3× 6 mL). The combined organic solution was dried over Na_2SO_4, filtered, concentrated, and chromatographed using a mixture of t-BuOH/$CHCl_3$ (1:9). Amide **35** was obtained as a yellow oil in 58% yield (162 mg); $[\alpha]_D^{25}$: −27.1° (c 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.89 (d, J = 7.0 Hz, 2H), 7.57 (t, J = 7.5 Hz, 3H), 7.46 (t, J = 7.5 Hz, 2H), 5.49 (d, J = 3.5 Hz, 1H), 5.36 (dd, J = 10.0 Hz, 1H), 5.14 (dd, J = 3.5, 10.0 Hz, 1H), 4.63 (d, J = 9.5 Hz, 1H), 4.09 (m, 3H), 2.21 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.7, 170.6, 170.4, 169.1, 165.6, 159.0, 145.1, 132.9, 129.2, 128.3, 125.5, 121.5, 74.9, 74.4, 72.2, 70.5, 67.7, 61.9, 21.6, 20.9, 20.9, 20.8, 15.0; IR (neat NaCl, cm^{-1}): 3303, 3032, 2956, 1751, 1671, 1537, 1370, 1294, 1225, 1054, 756; ESI-MS m/z : 549.1 $[M+H]^+$; HRMS m/z calcd $C_{25}H_{28}N_2O_{10}S$ $[M+H]^+$: 549.1544; found: 549.15243.

5.1.18. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-*p*-nitrobenzamidothiazole (36)

Synthesis according to the same procedure as for the synthesis of **35** obtained in 80% yield as a yellow oil; $[\alpha]_D^{25}$: −27.1° (c 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.27 (d, 2 H, J = 9.0 Hz, 2H), 8.09 (d, J = 9.0 Hz, 2H), 5.49 (d, J = 3.5 Hz, 1H), 5.32 (dd, J = 10.0 Hz, 1H), 5.16 (dd, J = 3.5, 10.0 Hz, 1H), 4.65 (d, J = 9.5 Hz, 1H), 4.10 (m, 3H), 2.18 (s, 3H), 2.03 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.3, 170.1, 169.9, 169.8, 163.3, 158.0, 149.9, 144.3, 137.5, 129.0, 123.6, 121.6, 74.5, 73.9, 71.5, 70.3, 67.4, 61.5, 20.6, 20.4, 20.4, 20.4, 14.,9; IR (neat NaCl, cm^{-1}): 3298, 3022, 2982, 1751, 1675, 1547, 1369, 1229, 1052, 756; ESI-MS m/z : 594.1 $[M+H]^+$; HRMS m/z calcd $C_{25}H_{27}N_3O_{12}S$ $[M+H]^+$: 594.1395; found: 594.1382.

5.1.19. 2-*p*-Anisamido-5-(2,3,4,6-tetraacetyl-β-D-galactopyranosyl)-4-methylthiazole (37)

Synthesis according to the same procedure as for the synthesis of **35** obtained in 44% yield as a yellow oil; $[\alpha]_D^{25}$: −21.5° (c 1.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.86 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 5.48 (d, J = 3.5 Hz, 1H), 5.35 (dd, J = 10.0 Hz, 1H), 5.14 (dd, J = 3.5, 10.0 Hz, 1H), 4.64 (d, J = 9.5 Hz, 1H), 4.09 (m, 3H), 3.84 (s, 3H), 2.20 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.96 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.3, 170.2, 170.1, 168.8, 164.6, 158.8, 144.8, 129.8, 128.8, 128.1, 125.1, 124.3, 120.1, 114.0, 74.5, 74.1, 70.2, 67.5, 61.6, 55.4, 20.6, 20.5, 20.5, 20.4, 14.9; IR (neat NaCl, cm^{-1}): 3313, 3022, 2941, 1756, 1664, 1608, 1516, 1373, 1256, 1225, 1056, 766; ESI-MS m/z : 579.1 $[M+H]^+$; HRMS m/z calcd $C_{26}H_{30}N_2O_{11}S$ $[M+H]^+$: 579.1650; found: 579.1631.

5.1.20. 2-*p*-Bromobenzamido-5-(2,3,4,6-tetraacetyl-β-D-galactopyranosyl)-4-methylthiazole (38)

Synthesis according to the same procedure as for the synthesis of **35** obtained in 77% yield as a yellow oil; $[\alpha]_D^{25}$: −25.2° (c 1.1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.77 (d, J = 9.0 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 5.50 (d, J = 3.5 Hz, 1H), 5.35 (dd, J = 10.0 Hz, 1H), 5.16 (dd, J = 3.5, 10.0 Hz, 1H), 4.63 (d, J = 9.5 Hz, 1H), 4.11 (m, 3H), 2.20 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.4, 170.3, 170.1, 169.0, 164.4, 158.6, 144.7, 132.9, 131.1, 129.4, 128.9, 128.1, 127.7, 121.6, 74.7, 74.2, 71.8, 70.3, 67.5, 61.6, 20.7, 20.6, 20.6, 20.6, 14.9; IR (neat NaCl, cm^{-1}): 3303, 2971, 1751, 1669, 1540, 1369, 1225, 1053, 750; ESI-MS m/z : 627.1 $[M+H]^+$ (Br79); 629.0 $[M+H]^+$ (Br81); HRMS m/z calcd $C_{25}H_{27}N_2O_{10}SBr$ $[M+H]^+$: 627.0649; found: 627.0633.

5.1.21. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-4-methyl-2-phenylacetamidothiazole (39)

Synthesis according to the same procedure as for the synthesis of **35** obtained in 59% yield as a yellow oil; $[\alpha]_D^{25}$: −17.0° (c 1.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.47 (d, J = 3.5 Hz, 1H), 5.31 (dd, J = 9.5 Hz, 1H), 5.14 (dd, J = 3.5, 10.0 Hz, 1H), 4.64 (d, J = 9.5 Hz, 1H), 4.09 (m, 3H), 3.76 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.4, 170.3, 170.1, 168.9, 168.6, 157.1, 144.8, 132.9, 129.5, 129.2, 127.8, 121.3, 74.7, 74.3, 71.8, 70.3, 67.5, 61.6, 43.2, 20.7, 20.6, 20.5, 20.5, 15.3; IR (neat NaCl, cm^{-1}): 3277, 2952, 2926, 2868, 1750, 1541, 1371, 1225, 1052, 758; ESI-MS m/z : 563.1 $[M+H]^+$; HRMS m/z calcd $C_{25}H_{28}N_2O_{10}S$ $[M+H]^+$: 563.1700; found: 563.1684.

5.1.22. 2-Acetamido-5-(2,3,4,6-tetraacetyl-β-D-galactopyranosyl)-4-methylthiazole (40)

Synthesis according to the same procedure as for the synthesis of **35** obtained in 92% yield as a yellow oil; $[\alpha]_D^{25}$: −9.9° (c 1.6 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.46 (d, J = 3.0 Hz,

1H), 5.29 (dd, J = 10.0 Hz, 1H), 5.13 (dd, J = 3.5, 10.0 Hz, 1H), 4.62 (d, J = 9.5 Hz, 1H), 4.06 (m, 3H), 2.25 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.3, 170.2, 170.0, 169.3, 167.9, 158.0, 144.4, 120.6, 74.6, 74.2, 71.7, 70.3, 67.4, 61.5, 22.8, 20.6, 20.5, 20.5, 20.5, 15.3; IR (neat NaCl, cm^{-1}): 3287, 3028, 2977, 1751, 1692, 1543, 1370,1228, 1053, 756; ESI-MS m/z : 487.1 [M+H]$^+$; HRMS m/z calcd $C_{20}H_{26}N_2O_{10}S$ [M+H]$^+$: 487.1388; found: 487.1387.

5.1.23. 5-(2,3,4,6-Tetraacetyl-β-D-galactopyranosyl)-2-methylcarbamate-4-methylthiazole (41)

Synthesis according to the same procedure as for the synthesis of **35** obtained in 73% yield as a yellow oil; $[\alpha]_D^{25}$: −8.2° (c 1.4 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 5.48 (d, J = 3.5 Hz, 1H), 5.32 (dd, J = 10.0 Hz, 1H), 5.15 (dd, J = 3.5, 10.0 Hz, 1H), 4.66 (d, J = 9.5 Hz, 1H), 4.09 (m, 3H), 3.82 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 2.03 (s, 3H), 1.98 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.4, 170.3, 170.2, 168.7, 160.8, 154.0, 145.2, 120.3, 74.7, 74.3, 71.9, 70.3, 67.5, 61.6, 52.9, 20.7, 20.7, 20.6, 20.4, 14.9; IR (neat NaCl, cm^{-1}): 3180, 2961, 1751, 1559, 1370, 1230, 1086, 1053, 760; ESI-MS m/z : 503.1 [M+H]$^+$; HRMS m/z calcd $C_{20}H_{26}N_2O_{11}S$ [M+H]$^+$: 503.1337; found: 503.1330.

5.1.24. 5-(β-D-Galactopyranosyl)-4-methyl-2-(4-methyl-phenyl) sulfonylaminothiazole (42)

Synthesis according to the typical de-O-acetylation procedure obtained in 61% yield as a white solid: mp = 131–132 °C (ethanol); $[\alpha]_D^{25}$: −13.9° (c 1.0 in DMSO); ^{1}H NMR (300 MHz, D_2O, δ ppm): 7.49 (d, J = 7.1 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 4.21 (d, J = 8.8 Hz, 1H), 3.79–3.78 (m, 1H), 3.58–3.41 (m, 5H), 2.04 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 169.3, 144.5, 137.3, 134.8, 129.9, 126.4, 117.1, 79.2, 74.9, 73.9, 71.7, 69.1, 61.3, 20.8, 11.9; IR (KBr, cm^{-1}): 3462, 1655, 1432, 1060; HRMS m/z calcd $C_{17}H_{22}N_2O_7S_2$ [M+H]$^+$: 431.0947; found: 431.0938.

5.1.25. 5-(β-D-Galactopyranosyl)-4-methyl-2-(4-bromophenyl) sulfonylaminothiazole (43)

Synthesis according to the typical de-O-acetylation procedure obtained in 64% yield as a white solid: mp = 149–150 °C (ethanol); $[\alpha]_D^{25}$: +14.0° (c 1.0 in DMSO); ^{1}H NMR (300 MHz, D_2O, δ ppm): 7.49 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 4.23 (d, J = 9.1 Hz, 1H), 3.81 (dd, J = 2.3 Hz, 1H), 3.58–3.46 (m, 5H), 2.00 (s, 3H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 168.7, 139.1, 132.5, 128.1, 127.5, 117.2, 116.1, 79.6, 76.6, 75.9, 73.9, 71.7, 61.3, 11.6; IR (KBr, cm^{-1}): 3473, 1657, 1428, 1061; HRMS m/z calcd $C_{16}H_{19}BrN_2O_7S_2$ [M+H]$^+$: 494.9896; found: 494.9889.

5.1.26. 5-(β-D-Galactopyranosyl)-4-methyl-2-(β-naphthyl) sulfonylaminothiazole (44)

Synthesis according to the typical de-O-acetylation procedure obtained in 92% yield as a white solid: mp = 126–127 °C (ethanol); $[\alpha]_D^{25}$: +41.0° (c 1.0 in DMSO); ^{1}H NMR (300 MHz, CD_3OD, δ ppm): 8.40 (s, 1H), 7.92–7.79 (m, 4H), 7.55–7.47 (m, 2H), 4.86 (s, 4H), 4.26 (d, J = 9.1 Hz, 1H), 3.89 (dd, J = 3.0 Hz, 1H), 3.76–3.51 (m, 5H), 2.06 (s, 3H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 169.8, 140.3, 135.9, 133.4, 133.0, 130.1, 130.0, 129.4, 128.8, 128.4, 127.8, 123.3, 118.7, 80.8, 76.5, 75.9, 73.0, 70.7, 62.9, 12.1; IR (KBr, cm^{-1}): 3492, 1675, 1437, 1067; HRMS m/z calcd $C_{20}H_{22}N_2O_7S_2$ [M+H]$^+$: 467.0947; found: 467.0937.

5.1.27. 5-(β-D-Galactopyranosyl)-4-methyl-2-(2-chloro-phenyl) sulfonylaminothiazole (45)

Synthesis according to the typical de-O-acetylation procedure obtained in 85% yield as a white solid: degrade at 217–218 °C (ethanol); $[\alpha]_D^{25}$: −4.4° (c 1.0 in DMSO); ^{1}H NMR (300 MHz, D_2O, δ ppm): 7.82 (d, J = 8.5 Hz, 1H), 7.29–7.16 (m, 3H), 4.23 (d, J = 9.1 Hz, 1H), 3.79 (dd, J = 3.0 Hz, 1H), 3.60–3.40 (m, 5H), 1.96 (s, 3H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 167.4, 136.8, 134.5, 134.1, 132.2, 131.6, 130.5, 127.5, 117.3, 79.3, 74.8, 73.4, 71.6, 69.2, 61.2, 11.5; IR (KBr, cm^{-1}): 3467, 1652, 1438, 1063; HRMS m/z calcd $C_{16}H_{19}ClN_2O_7S_2$ [M+H]$^+$: 451.0401; found: 451.0395.

5.1.28. 5-(β-D-Galactopyranosyl)-4-methyl-2-(4-*tert*-Butylphenyl)sulfonylaminothiazole (46)

Synthesis according to the typical de-O-acetylation procedure obtained in 74% yield as a white solid: mp = 164–165 °C (ethanol); $[\alpha]_D^{25}$: +1.1° (c 1.0 in DMSO); ^{1}H NMR (300 MHz, CD_3OD, δ ppm): 7.77 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 4.95 (s, 4H), 4.28 (d, J = 8.8 Hz, 1H), 3.91 (dd, J = 2.7 Hz, 1H), 3.76–3.54 (m, 5H), 2.09 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (75.5 MHz, CD_3OD, δ ppm): 169.7, 156.9, 140.5, 133.2, 127.2, 126.7, 118.6, 80.7, 76.5, 75.9, 73.0, 70.6, 62.8, 35.8, 31.4, 12.2; IR (KBr, cm^{-1}): 3480, 1660, 1439, 1045; HRMS m/z calcd $C_{20}H_{28}N_2O_7S_2$ [M+H]$^+$: 473.1417; found: 473.1408.

5.1.29. 5-(β-D-Galactopyranosyl)-4-methyl-2-(2,5-dibromophenyl)sulfonylaminothiazole (47)

Synthesis according to the typical de-O-acetylation procedure obtained in 83% yield as a yellow oil; $[\alpha]_D^{25}$: −3.9° (c 1.2 in DMSO); ^{1}H NMR (300 MHz, D_2O, δ ppm): 7.92 (s, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 4.21 (d, J = 8.2 Hz, 1H), 3.82–3.81 (m, 1H), 3.54–3.44 (m, 5H), 2.00 (s, 3H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 168.3, 141.2, 137.0, 136.9, 136.4, 132.9, 121.0, 118.5, 117.9, 78.9, 75.0, 73.9, 71.8, 68.9, 60.9, 12.3; IR (Neat NaCl) cm^{-1}: 3476, 1653, 1437, 1061; HRMS m/z calcd $C_{16}H_{18}BrN_2O_7S_2$ [M+H]$^+$: 572.9002; found: 572.8985.

5.1.30. 5-(β-D-Galactopyranosyl)-4-methyl-2-benzylaminothiazole (48)

Synthesis according to the typical de-O-acetylation procedure obtained in 69% yield as a yellow solid: mp = 83–84 °C (ethanol); $[\alpha]_D^{25}$: −5.0° (c 0.1 in DMSO); ^{1}H NMR (300 MHz, D_2O, δ ppm): 7.22–7.18 (m, 4H), 4.29 (s, 3H), 4.27 (d, J = 7.7 Hz, 1H), 3.81 (d, J = 3.0 Hz, 1H), 3.62–3.42 (m, 5H), 1.96 (m, 3H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 170.4, 146.5, 138.0, 129.2, 128.1, 127.8, 115.8, 79.2, 75.7, 74.3, 72.5, 69.4, 61.5, 48.9, 14.2; IR (KBr, cm^{-1}): 3470, 1657, 1455, 1009; HRMS m/z calcd $C_{17}H_{22}N_2O_5S$ [M+H]$^+$: 367.1328; found: 367.1319.

5.1.31. 5-(β-D-Galactopyranosyl)-4-methyl-2-4-nitrobenzylaminothiazole (49)

Synthesis according to the typical de-O-acetylation procedure obtained in 75% yield as a yellow solid: mp = 127–128 °C (ethanol); $[\alpha]_D^{25}$: +19.6° (c 0.2 in DMSO); ^{1}H NMR (300 MHz, D_2O, δ ppm): 8.01 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 4.42 (s, 2H), 4.30 (d, J = 9.6 Hz, 1H), 3.83 (d, J = 3.0 Hz, 1H), 3.64–3.41 (m, 5H), 1.95 (s, 3H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 147.7, 146.6, 128.4, 127.5, 124.3, 116.2, 79.2, 75.7, 74.3, 72.6, 69.4, 61.5, 48.0, 14.5; IR (KBr, cm^{-1}): 3459, 1653, 1447, 1071; HRMS m/z calcd $C_{17}H_{21}N_3O_7S$ [M+H]$^+$: 412.1179; found: 412.1169.

5.1.32. 2-Benzamido-5-(β-D-galactopyranosyl)-4-methylthiazole (50)

Synthesis according to the typical de-O-acetylation procedure obtained in 93% yield as a yellow oil; $[\alpha]_D^{25}$: +13.0° (c 1.1 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8,03 (d, J = 7,5 Hz, 2H), 7,51 (m, 3H), 4,80 (m, 2H), 4,54 (m, 2H), 4,25 (m, 1H), 3,71 (m, 1H), 3,40 (m, 5H), 2,22 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 166.8, 158.0, 144.6, 133.4, 132.7, 129.4, 128.5, 124.4, 79.6, 75.7, 74.9, 73.1, 69.3, 61.5, 15.4; IR (neat NaCl, cm^{-1}): 3410, 2921, 2858, 1653, 1541, 1293, 1091, 894, 706; ESI-MS m/z : 381.2 [M+H]$^+$; HRMS m/z calcd $C_{17}H_{20}N_2O_6S$ [M+H]$^+$: 381.1122; found: 381.11095.

5.1.33. 5-(β-D-Galactopyranosyl)-4-methyl-2-*p*-nitro-benzamidothiazole (51)

Synthesis according to the typical de-O-acetylation procedure obtained in 74% yield as a yellow oil; $[\alpha]_D^{25}$: +0.8° (*c* 1.0 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.27 (m, 4H), 4.79 (m, 2H), 4.52 (m, 2H,), 4.27 (m, 1H), 3.71 (m, 1H), 3.43 (m, 5H), 2.22 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 166.3, 160.1, 149.9, 142.0, 139.3, 130.0, 124.1, 123.9, 79.6, 75.7, 74.9, 72.9, 69.3, 61.6, 14.7; IR (neat NaCl, cm^{-1}): 3413, 2924, 2890, 1670, 1525, 1346, 1052, 851, 714; ESI-MS *m/z* : 426.2 $[M+H]^+$; HRMS *m/z* calcd $C_{17}H_{19}N_3O_8S$ $[M+H]^+$: 426.0972; found: 426.0962.

5.1.34. 2-*p*-Anisamido-5-(β-D-galactopyranosyl)-4-methylthiazole (52)

Synthesis according to the typical de-O-acetylation procedure obtained in 62% yield as a yellow oil; $[\alpha]_D^{25}$: +10.5° (*c* 1.3 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 8.03 (d, *J* = 9.5 Hz, 2H), 7.00 (d, *J* = 9.5 Hz, 2H), 4.75 (m, 2H), 4.47 (m, 2H), 4.26 (m, 1H), 3.78 (s, 3H), 3.70 (m, 1H), 3.32 (m, 5H), 2.20 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 165.5, 163.2, 157.7, 144.2, 130.5, 124.9, 124.3, 114.5, 79.6, 75.9, 75.0, 73.0, 69.3, 61.5, 55.9, 15.5; IR (neat NaCl, cm^{-1}): 3439, 2922, 2842, 1655, 1606, 1547, 1514, 1311, 1260, 1177, 1025, 845, 761; ESI-MS *m/z* : 411.1 $[M+H]^+$; HRMS *m/z* calcd $C_{18}H_{22}N_2O_7S$ $[M+H]^+$: 411.1227; found: 411.1214.

5.1.35. 2-*p*-Bromobenzamido-5-(β-D-galactopyranosyl)-4-methylthiazole (53)

Synthesis according to the typical de-O-acetylation procedure obtained in 80% yield as a yellow oil; $[\alpha]_D^{25}$: +7.2° (*c* 1.4 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.96 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 4.78 (m, 2H), 4.51 (m, 2H), 4.26 (m, 1H), 3.71 (m, 1H), 3.37 (m, 5H), 2.21 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 166.1, 158.5, 143.5, 132.4, 132.1, 130.8, 127.1, 124.5, 79.8, 75.9, 75.1, 73.2, 69.4, 61.6, 15.5; IR (neat NaCl, cm^{-1}): 3411, 2922, 2858, 1664, 1591, 1547, 1313, 1070, 893, 747; ESI-MS *m/z* : 459.1 $[M+H]^+$ (Br79); 461.1 $[M+H]^+$ (Br81); HRMS *m/z* calcd $C_{17}H_{19}N_2O_6S$ $[M+H]^+$: 459.0227; found: 459.0211.

5.1.36. 5-(β-D-Galactopyranosyl)-4-methyl-2-phenylacetamidothiazole (54)

Synthesis according to the typical de-O-acetylation procedure obtained in 46% yield as a yellow oil; $[\alpha]_D^{25}$: +17.0° (*c* 0.5 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.21 (m, 5H), 4.75 (m, 2H), 4.50 (m, 2H), 4.21 (m, 1H), 3.69 (m, 1H), 3.36 (m, 5H), 2.44 (s, 2H), 2.16 (s, 3H); IR (neat NaCl, cm^{-1}): 3402, 2922, 2858, 1678, 1551, 1312, 1282, 1052, 788, 728, 698; ESI-MS *m/z* : 395.1 $[M+H]^+$; HRMS *m/z* calcd $C_{18}H_{22}N_2O_6S$ $[M+H]^+$: 395.1278; found: 395.1270.

5.1.37. 2-Acetamido-5-(β-D-galactopyranosyl)-4-methylthiazole (55)

Synthesis according to the typical de-O-acetylation procedure obtained in 60% yield as a yellow oil; $[\alpha]_D^{25}$: +10.6° (*c* 1.1 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.70 (m, 2H), 4.42 (m, 2H), 4.20 (m, 1H), 3.69 (m, 1H), 3.39 (m, 5H), 2.15 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 169.8, 156.7, 144.9, 124.2, 79.6, 75.8, 74.9, 73.1, 69.3, 61.5, 22.9, 15.6; IR (neat NaCl, cm^{-1}): 3497, 3318, 2922, 2854, 1690, 1551, 1288, 1036, 785; ESI-MS *m/z* : 319.1 $[M+H]^+$; HRMS *m/z* calcd $C_{12}H_{18}N_2O_6S$ $[M+H]^+$: 319.0965; found: 319.0957.

5.1.38. 5-(β-D-Galactopyranosyl)-2-methylcarbamate-4-methylthiazole (56)

Synthesis according to the typical de-O-acetylation procedure obtained in 60% yield as a yellow oil; $[\alpha]_D^{25}$: +6.5° (*c* 0.3 in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 4.72 (m, 2H), 4.,42 (m, 2H), 4.20 (m, 1H), 3.69 (m, 1H), 3.65 (s, 3H,), 3.38 (m, 5H), 2.12 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 158.9, 155.2, 145.0, 123.9, 79.6, 75.7, 74.9, 73.1, 69.3, 61.5, 53.5, 15.49; IR (neat NaCl, cm^{-1}): 3468, 3402, 2927, 2858, 1733, 1559, 1315, 1245, 1079, 764; ESI-MS *m/z* : 335.1 $[M+H]^+$; HRMS *m/z* calcd $C_{12}H_{18}N_2O_7S$ $[M+H]^+$: 335.0914; found: 335.0903.

5.1.39. Dimeric lactoside (64)

Synthesis according to the typical de-O-acetylation procedure obtained in 95% yield as a orange solid: mp = 173–174 °C (ethanol); $[\alpha]_D^{25}$: −93.2° (*c* 1.0 in DMSO); ^{1}H NMR (300 MHz, CD_3OD, δ ppm): 7.64–7.53 (m, 4H), 4.50 (d, *J* = 9.6 Hz, 2H), 4.32 (d, *J* = 7.7 Hz, 2H), 3.86–3.36 (m, 28H); ^{13}C NMR (75.5 MHz, CD_3OD, δ ppm): 131.9, 131.4, 128.7, 103.9, 84.5, 79.6, 76.8, 75.9, 73.7, 72.9, 71.3, 71.2, 69.2, 61.3, 60.9, 23.0; IR (KBr, cm^{-1}): 3406, 1576, 1419, 1088; HRMS *m/z* calcd $C_{36}H_{50}O_{20}S_2$ $[M+Na]^+$: 889.2235; found: 889.2223.

5.1.40. Dimeric galactoside (66)

Synthesis according to the typical de-O-acetylation procedure obtained in quantitative yield as a brown solid: mp = 172–173 °C (ethanol); $[\alpha]_D^{25}$: −117.8° (*c* 1.0 in DMSO); ^{1}H NMR (300 MHz, CD_3OD, δ ppm): 7.33–7.26 (m, 4H), 4.52 (d, *J* = 9.8 Hz, 2H), 3.85–3.28 (m, 16H); ^{13}C NMR (75.5 MHz, CD_3OD, δ ppm): 131.4, 116.2, 85.2, 79.6, 75.2, 70.2, 69.4, 61.5, 23.0; IR (KBr, cm^{-1}): 3339, 1576, 1410, 1085; HRMS *m/z* calcd $C_{24}H_{30}O_{10}S_2$ $[M+Na]^+$: 565.1178; found: 565.1167.

5.1.41. Dimeric lactoside (68)

Synthesis according to the typical de-O-acetylation procedure obtained in 95% yield as a brown solid: mp = 160–161 °C (ethanol); $[\alpha]_D^{25}$: −68.6° (*c* 1.0 in DMSO); ^{1}H NMR (300 MHz, D_2O, δ ppm): 4.53 (d, *J* = 9.8 Hz, 2H), 4.25 (d, *J* = 7.7 Hz, 2H), 3.79–3.62 (m, 6H), 3.59–3.22 (m, 24H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 102.9, 84.4, 78.8, 78.1, 75.9, 75.4, 75.2, 72.6, 71.8, 71.0, 70.7, 68.7, 61.1, 60.3, 18.1; IR (KBr, cm^{-1}): 3477, 1576, 1421, 1078; HRMS *m/z* calcd $C_{30}H_{46}O_{20}S_2$ $[M+Na]^+$: 813.1922; found: 813.1912.

5.1.42. Dimeric galactoside (70)

Synthesis according to the typical de-O-acetylation procedure obtained in 90% yield as a brown solid: mp = 76–77 °C (ethanol); $[\alpha]_D^{25}$: −110.4° (*c* 1.0 in DMSO); ^{1}H NMR (300 MHz, D_2O, δ ppm): 4.45 (d, *J* = 9.0 Hz, 2H), 3.80–3.35 (m, 16H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 85.5, 79.4, 75.9, 74.5, 69.9, 69.3, 67.4, 61.5, 18.5; IR (KBr, cm^{-1}): 3548, 1560, 1437; HRMS *m/z* calcd $C_{18}H_{26}O_{10}S_2$ $[M+H]^+$: 467.1046; found: 467.1037.

5.1.43. Dimeric lactoside (71)

Alkyne lactoside **57** (0.302 mmol) was dissolved in THF (0.1 M) and CuI (0.03 mmol), DIPEA (0.606 mmol) and azide **59** (0.332 mmol) were added and stirred, at room temperature. The green solution was stirred until disappearance of the starting material (maximum 3 h), and then evaporated under reduced pressure, dissolved with ethyl acetate, and filtered through a pad of Celite. The organic solution was washed with aqueous HCl (10%), dried over sodium sulfate, filtered, evaporated under reduced pressure, and chromatographed using a mixture of ethyl acetate/hexane (2:1) to give **71** in 81% yield as a white solid: mp = 125–126 °C (EtOAc/hexanes); $[\alpha]_D^{25}$: −41.4° (*c* 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.64 (s, 1H), 5.79 (d, *J* = 8.8 Hz, 1H), 5.43–5.31 (m, 3H), 5.19 (dd, *J* = 9.3 Hz, 1H), 5.10 (dd, *J* = 8.2 Hz, 2H), 4.97–4.88 (m, 2H), 4.55–4.40 (m, 4H), 4.17–3.73 (m, 17H), 3.68–3.65 (m, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.03 (s, 6H), 2.02 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.94 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.4, 170.2, 170.1, 170.0, 169.9, 169.6, 169.5, 169.4, 169.3, 168.9, 144.9, 120.7, 100.9, 85.5, 81.8,

76.2, 76.1, 75.9, 75.5, 73.5, 72.3, 70.8, 70.6, 70.3, 68.9, 66.5, 62.0, 61.6, 60.8, 24.1, 20.9, 20.7, 20.6, 20.5, 20.4, 20.0; IR (neat NaCl) cm^{-1}: 1752, 1371, 1237, 1055; HRMS *m/z* calcd $C_{55}H_{73}N_3O_{34}S$ $[M+H]^+$: 1352.3875; found: 1352.3848.

5.1.44. Heterodimer (72)

Synthesis according to the same procedure as for the synthesis of **71** obtained in 89% yield as a yellow solid: mp = 108–109 °C (EtOAc/hexanes); $[\alpha]_D^{25}$: −35.6° (*c* 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.76 (s, 1H), 5.83 (d, *J* = 9.1 Hz, 1H), 5.57 (dd, *J* = 3.0, 1H), 5.50 (dd, *J* = 9.3 Hz, 1H), 5.34 (dd, *J* = 2.5 Hz, 1H), 5.29–5.21 (m, 2H), 5.11 (dd, *J* = 7.9 Hz, 1H), 4.99–4.93 (m, 2H), 4.57–4.46 (m, 3H), 4.24–4.06 (m, 7H), 3.89–3.75 (m, 4H), 2.22 (s, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.3, 170.1, 169.9, 169.8, 169.6, 169.4, 169.1, 147.7, 120.8, 101.2, 86.4, 81.3, 76.4, 76.2, 74.1, 73.7, 71.0, 70.7, 70.6, 70.4, 69.1, 67.8, 66.8, 66.6, 62.2, 61.1, 60.7, 23.9, 20.9, 20.8, 20.6, 20.5, 20.2; IR (neat NaCl) cm^{-1}: 1752, 1371, 1233, 1056; HRMS *m/z* calcd $C_{43}H_{57}N_3O_{26}S$ $[M+H]^+$: 1064.3030; found: 1064.3006.

5.1.45. Heterodimer (73)

Synthesis according to the same procedure as for the synthesis of **71** obtained in 77% yield as a white solid: mp = 112–113 °C (EtOAc/hexanes); $[\alpha]_D^{25}$: −40.9° (*c* 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ *ppm);* ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.62 (s, 1H), 5.76 (d, *J* = 9.1 Hz, 1H), 5.36–5.21 (m, 4H), 5.12–4.96 (m, 3H), 4.87 (dd, *J* = 3.0, 10.4 Hz, 1H), 4.46 (d, *J* = 7.7 Hz, 1H), 4.39–4.35 (m, 1H), 4.27 (d, *J* = 9.3 Hz, 1H), 4.13–3.83 (m, 8H), 3.74–3.69 (m, 1H), 2.03 (s, 6H), 1.96 (s, 9H), 1.94 (s, 3H), 1.92 (s, 3H), 1.85 (s, 3H), 1.83 (s, 6H), 1.76 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 170.1, 169.9, 169.8, 169.7, 169.6, 169.2, 169.0, 168.6, 144.1, 120.6, 100.6, 85.3, 81.4, 75.7, 75.3, 73.7, 72.0, 71.3, 70.6, 68.9, 67.2, 67.1, 66.5, 61.5, 61.2, 60.6, 23.3, 20.3, 20.2, 19.7; IR (neat NaCl) cm^{-1}: 1754, 1457, 1263; HRMS *m/z* calcd $C_{43}H_{57}N_3O_{26}S$ $[M+H]^+$: 1064.3030; found: 1064.3016.

5.1.46. Dimeric galactoside (74)

Synthesis according to the same procedure as for the synthesis of **71** obtained in 88% yield as a white solid: mp = 81–82 °C (EtOAc/hexanes); $[\alpha]_D^{25}$: −48.4° (*c* 1.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 7.71 (s, 1H), 5.82 (d, *J* = 9.1 Hz, 1H), 5.48–5.34 (m, 3H), 5.25–5.04 (m, 3H), 4.32 (d, *J* = 9.3 Hz, 1H), 4.25–4.10 (m, 1H), 4.08–3.97 (m, 4H), 3.78–3.73 (m, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.93 (s, 6H), 1.85 (s, 3H), 1.86 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 169.9, 169.6, 169.5, 169.4, 169.2, 144.2, 120.6, 86.1, 81.2, 73.9, 71.4, 70.4, 67.9, 67.4, 67.3, 66.8, 61.6, 60.9, 23.4, 20.3, 20.2, 20.1, 19.8; IR (neat NaCl) cm^{-1}: 1757, 1372, 1251; HRMS *m/z* calcd $C_{31}H_{41}N_3O_{18}S$ $[M+H]^+$: 776.2185; found: 776.2176.

5.1.47. Dimeric lactoside (75)

Synthesis according to the typical de-O-acetylation procedure obtained in 92% yield as a white solid: mp = 122–123 °C (ethanol); $[\alpha]_D^{25}$: −6.3° (*c* 1.0 in DMSO); ^1H NMR (300 MHz, D_2O, δ ppm): 8.02 (s, 1H), 5.57 (d, *J* = 9.1 Hz, 1H), 4.30 (d, *J* = 8.5 Hz, 2H), 4.23 (d, *J* = 7.7 Hz, 1H), 3.97–3.16 (m, 26H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 146.1, 123.9, 103.4, 103.3, 100.2, 87.6, 85.2, 78.9, 78.6, 78.1, 78.0, 76.1, 75.8, 75.7, 75.0, 73.0, 72.4, 72.3, 71.4, 69.0, 61.4, 60.7, 60.3, 24.1; IR (KBr, cm^{-1}): 3340, 1580, 1410, 1080; HRMS *m/z* calcd $C_{27}H_{45}N_3O_{20}S$ $[M+H]^+$: 764.2396; found: 764.2382.

5.1.48. Heterodimer (76)

Synthesis according to the typical de-O-acetylation procedure obtained in quantitative yield as a white solid: mp = 118–119 °C (ethanol); $[\alpha]_D^{25}$: −12.6° (*c* 0.5 in DMSO); ^1H NMR (300 MHz, D_2O, δ ppm): 8.06 (s, 1H), 5.49 (d, *J* = 9.1 Hz, 1H), 4.33 (d, *J* = 9.6 Hz, 1H), 4.25 (d, *J* = 7.7 Hz, 1H), 4.03–3.83 (m, 5H), 3.73–3.72 (m, 2H), 3.67–3.19 (m, 13H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 146.1, 123.7, 103.3, 88.5, 85.1, 78.7, 76.2, 75.8, 73.5, 73.0, 72.3, 71.4, 70.1, 69.0, 61.4, 61.3, 60.7, 24.1; IR (KBr, cm^{-1}): 3547, 1566, 1442; HRMS *m/z* calcd $C_{21}H_{35}N_3O_{15}S$ $[M+H]^+$: 602.1868; found: 602.1855.

5.1.49. Heterodimer (77)

Synthesis according to the typical de-O-acetylation procedure obtained in 75% yield as a white solid: mp = 161–162 °C (ethanol); $[\alpha]_D^{25}$: −14.4° (*c* 1.0 in DMSO); ^1H NMR (300 MHz, D_2O, δ ppm): 8.05 (s, 1H), 5.59 (d, *J* = 9.3 Hz, 1H), 4.32 (d, *J* = 7.7 Hz, 1H), 4.23 (d, *J* = 6.6 Hz, 1H), 3.99–3.37 (m, 21H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 145.9, 123.8, 103.3, 87.6, 85.6, 79.2, 77.9, 75.8, 74.9, 74.3, 72.9, 72.3, 71.4, 69.8, 68.9, 61.3, 60.2; IR (KBr, cm^{-1}): 3535, 1498, 1413; HRMS *m/z* calcd $C_{21}H_{35}N_3O_{15}S$ $[M+H]^+$: 602.1868; found: 602.1859.

5.1.50. Dimeric galactoside (78)

Synthesis according to the typical de-O-acetylation procedure obtained in quantitative yield as a white solid: mp = 60–61 °C (ethanol); $[\alpha]_D^{25}$: −20.4° (*c* 1.0 in DMSO); ^1H NMR (300 MHz, D_2O, δ ppm): 8.07 (s, 1H), 5.49 (d, *J* = 8.2 Hz, 1H), 4.24 (d, *J* = 6.3 Hz, 1H), 4.07–3.42 (m, 14H); ^{13}C NMR (75.5 MHz, D_2O, δ ppm): 146.0, 123.6, 88.4, 85.6, 79.2, 78.6, 74.3, 73.4, 70.1, 69.9, 69.2, 68.9, 61.3, 61.2, 24.0; IR (KBr, cm^{-1}): 3548, 1559, 1432; HRMS *m/z* calcd $C_{15}H_{25}N_3O_{10}S$ $[M+H]^+$: 440.1334; found: 440.1333.

5.2. Biological assay

5.2.1. General procedure for glycoside inhibition experiments

Recombinant galectins-1 and -3 were purified using a lactose-agarose affinity column (Sigma–Aldrich).[11a,43] Hemagglutination assays were performed using human O-type red blood cells (RBCs) as described previously.[41] RBCs (final concentration at 0.0025%), which were fixed with 3% glutaraldehyde (around 0.625% in PBS), were incubated with 1 μM of galectin in the presence or absence of the various concentrations of inhibitors in U-shaped 96-well plate. After incubation at 37 °C for 30 min, aggregation of RBCs was evaluated and performed in triplicate.

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