Synthesis and evaluation of iminocoumaryl and coumarylderivatized glycosides as galectin antagonists

Vishal Kumar Rajput, Hakon Leffler, Ulf J. Nilsson, Balaram Mukhopadhyay

PII: S0960-894X(14)00563-0
DOI: http://dx.doi.org/10.1016/j.bmcl.2014.05.063
Reference: BMCL 21677

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 30 January 2014
Revised Date: 3 May 2014
Accepted Date: 16 May 2014

Please cite this article as: Rajput, V.K., Leffler, H., Nilsson, U.J., Mukhopadhyay, B., Synthesis and evaluation of iminocoumaryl and coumarylderivatized glycosides as galectin antagonists, *Bioorganic & Medicinal Chemistry Letters* (2014), doi: http://dx.doi.org/10.1016/j.bmcl.2014.05.063

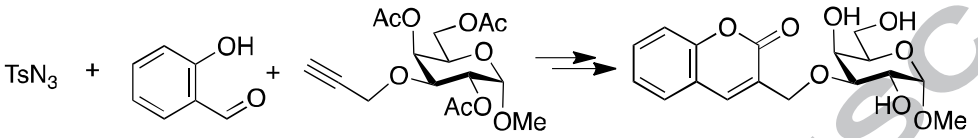
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis and evaluation of iminocoumaryl and coumarylderivatized glycosides as galectin antagonists

Leave this area blank for abstract info.

Vishal Kumar Rajput, Hakon Leffler, Ulf J. Nilsson, Balaram Mukhopadhyay*



Galectin	K_D (μM)
1	1900
3	78
7	850
8N	180
9N	180

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Synthesis and evaluation of iminocoumaryl and coumarylderivatized glycosides as galectin antagonists

Vishal Kumar Rajput[a,b], Hakon Leffler[c], Ulf J. Nilsson[a] and Balaram Mukhopadhyay[b]*

[a]*Centre for Analysis and Synthesis, Department of Chemistry, Lund University, POB 124, SE-221 00 Lund, Sweden;* [b]*Indian Institute of Science Education and ResearchKolkata, Mohanpur, Nadia 741252, India;* [c]*Section MIG, Department of Laboratory Medicine, Lund University, Sölvegatan 23, SE-223 62 Lund, Sweden*

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

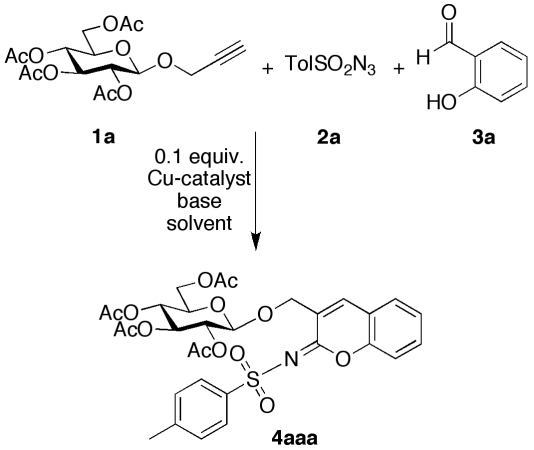
Keywords:
iminocoumarine
coumarine
galectin
antagonist
multicomponent reaction

ABSTRACT

A collection of iminocoumarylmethyl glycoside derivatives have been prepared by copper-catalyzed multi-component reaction of carbohydrate propargyl derivatives, sulfonyl azides, and salicylaldehyde or *o*-hydroxy acetophenone. The method is simple, versatile to all three components, and exceptionally high yielding. The carbohydrate *N*-sulfonyl iminocoumarine hybrid molecules were evaluated for binding galectin-1, -2, -3, -4N, -4C, -7, -8N, -9N, and 9C using a competitive fluorescence polarisation assay. Selective compounds were identified against galectin-3, 7, 8N, and 9N with up to 40-fold affinity enhancements relative to methyl α-D-galactopyranoside due to the coumarylmethyl moieties.

* Corresponding author. Tel.: +91 9748 261742; fax: +91 33 2334 8092; e-mail: sugarnet73@hotmail.com

Coumarines, widely abundant in nature, are versatile in applications as medicine, fluorescent indicators, dyes in laser technology and perfumery.[1-4] Many of them posses medicinally relevant character including antifungal, anticancer and anti-HIV activities.[5-6]Among the coumarin derivatives, iminocoumarins are reported to be potential protein tyrosine kinase (PTK) inhibitors[7] and therefore attractive compoundsfor the treatment of diseases involving excess cell proliferation and antitumor processes. Considering the plethora of biological functions associated with carbohydrates, it is a reasonable postulation that carbohydrate-heterocycle hybrids can provide target-specific drug candidates. In continuation to our recent research involving carbohydrate-heterocycle hybrids,[8] here we report an application of a facile multicomponent protocol for the synthesis of glycosylated iminocoumarins and coumarines. As an example of biomedical use we tested the compounds as antagonists of galectins. The galectins are a sub-class of lectins defined by having specific affinity for β-galactosides having a wide variety of biologically important functions including induction of apoptosis for T-cells, anti-apoptotic and pro-inflammatory functions, modulation of cell adhesion and migration.[9-11] Hence, there is a clear demand of molecules that would antagonize galectin activity and, therefore, enable evaluation of galectin functions in more detail and lead to the development of galectin blocking drugs.[12-15]



Scheme 1. Copper-catalyzed multi-component reaction of acetylated propargyl glucoside **1a**, *p*-toluenesulfonylazide **2a** and salicylaldehyde **3a**

Literature methods for the synthesis of coumarins such as Knoevenagel reaction and derivation of coumarins are often troublesome and limited for a narrow range of substituents.[16] Therefore, a practical synthesis of glycosylated iminocoumarins will be timely and useful. Recent development of multicomponent reactions (MCR) generated some excellent routes towards the synthesis of complex molecules by forming more than one covalent bonds in a single pot reaction.[17] In parallel to the extensive use of copper-catalysed Huisgen cycloaddition reaction between alkyl/aryl azides and terminal alkynes,[18-19]sulfonylazides are found to react in a different fashion in similar conditions. By exploiting this difference in reactivity, various MCR approaches have been reported in the literature to form highly substituted and complex molecules.[20-21]Recently, Wang *et al*[22] reported an efficient route towards formation of substituted iminocoumarines via copper-catalyzed multi-component domino reaction with terminal alkyne, sulfonylazide and salicylaldehyde or *o*-hydroxyacetophenone, which recently was applied on propargyl glycosides.[23-24] Taking the cue from their observations, we opted for propargylated carbohydrate derivatives of various carbohydrates as the terminal alkyne source for the synthesis of glycosylated *N*-sulfonyliminocoumarins and coumarines as potential galectin antagonists.

Initially, the scope and limitations of the method were investigated with per-acetylated propargyl glucoside (**1a**), *p*-toluenesulfonylazide (**2a**) and salicylaldehyde (**3a**), which were subjected to the copper-catalyzed multi-component reaction (Scheme 1). To optimize the reaction conditions, various bases, solvents and copper catalysts (CuI or CuCl) were used (Table 1). The best result (92% isolated yield) was obtained when the reaction was carried out in THF in the presence of triethylamine as base and CuI as catalyst at ambient temperature for 12h (Table 1, entry 3). Changing the solvent to CH_2Cl_2 or CH_3CN resulted in loss of yield and formation of inseparable by-products (Table 1, entry 1 and 2). Use of other bases, such as pyridine (Table 1, entry 5) or K_2CO_3 (Table 1, entry 6), also proved to be detrimental to yields and purity. CuCl as catalyst failed to deliver the desired product in good yield (Table 1, entry 4). Elevation of the reaction temperature to 50 °C and shortening the reaction time to 6h (Table 1, entry 7) led to a significant decrease in yield (56%) of the desired product.

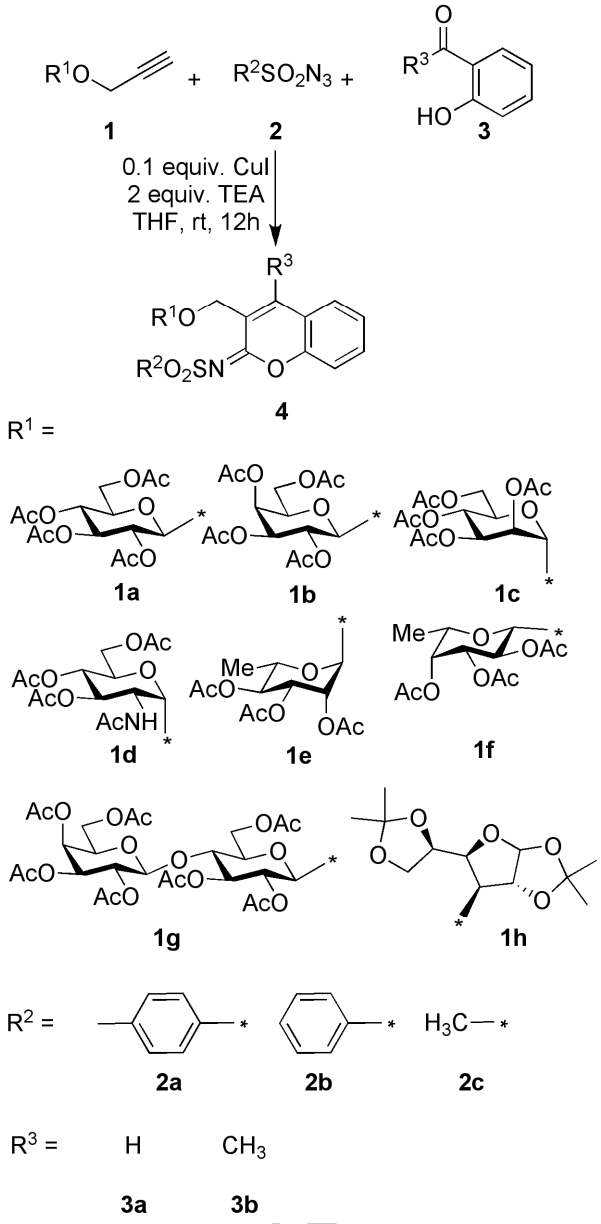
Table 1. Optimization of copper-catalyzed multi-component reaction conditions[a] of acetylated propargyl glucoside**1a**, *p*-toluenesulfonylazide**2a** and salicylaldehyde**3a.**

Entry	Base	Solvent	Catalyst	Time	Yield[b]
1	Et_3N	CH_2Cl_2	CuI	12h	71%
2	Et_3N	CH_3CN	CuI	12h	44%
3	Et_3N	THF	CuI	12h	92%
4	Et_3N	THF	CuCl	12h	≈20%
5	Pyridine	THF	CuI	12h	62%
6	K_2CO_3	CH_2Cl_2	CuI	12h	38%
7	Et_3N	THF	CuI	6h[c]	56%

[a]Alkyne (1 mmol), sulfonylazide (1 mmol), salicylaldehyde (1.1 mmol), base (2 mmol) and Cu-catalyst (0.1 mmol) in THF (10 mL) at RT. [b]Isolated yield on the basis of the alkyne. [c]Reaction was performed at 50 °C.

Having the optimized conditions in hand, we next focused our attention to investigate the generality of the reaction for different carbohydrate alkynes. Thus, a series of propargyl glycosides (**1a-1g**)[25] including 6-deoxy, 2-deoxy-2-acetamido and disaccharide were examined and to our satisfaction, excellent yield of the corresponding iminocoumarin derivative was obtained in each case (Scheme 2, Table 2). Propargyl ethers (**1h**) of carbohydrates attached to positions other than anomeric also gave similar results. In addition to *p*-toluenesulfonylazide (Table 2, entry 8), the reaction is equally effective with other sulfonylazides (Table2, entry 9, 11-12, and 14). Replacement of salicylaldehyde to *o*-hydroxyacetophenone merely affects the outcome of the reaction (Table 2, entries 13-14). Hence, the reaction is general with respect to choice of all three substrates.

In order to assess biological activity, it was essential to deprotect the acetate groups. The initial concern associated with the stability of the *N*-sulfonyls during NaOMe catalyzed de-*O*-acetylation was proved to be safe with low NaOMe concentration and controlled reaction time (Scheme 3). Completely de-*O*-acetylated products **5** were obtained in good yields using 0.005M NaOMe in MeOH (Table 3).

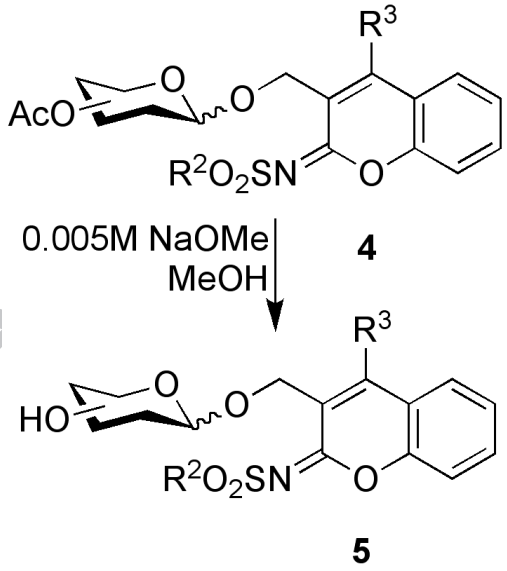


Scheme 2. Copper-catalyzed multi-component reaction of panels of propargyl derivatives **1a-h**, sulfonylazides**2a-c**, and salicyaldehyde**3a** or hydroxyacetophenone**3b**

Table 2. Synthesis of carbohydrate-iminocoumarin hybrids **4** by CuI-catalyzed multi-component reactions of carbohydrate alkynes **1**, sulfonylazides**2**, and salicylaldehyde or *o*-hydroxyacetophenone**3.**

Entry	Alkyne **1**	Sulfonylazide**2**	Carbonyl **3**	Imino-coumarine**4**	Yield [a]
1	**1a**	**2a**	**3a**	**4aaa**	92%
2	**1b**	**2a**	**3a**	**4baa**	90%
3	**1c**	**2a**	**3a**	**4caa**	91%
4	**1d**	**2a**	**3a**	**4daa**	86%
5	**1e**	**2a**	**3a**	**4eaa**	87%
6	**1f**	**2a**	**3a**	**4faa**	89%
7	**1g**	**2a**	**3a**	**4gaa**	81%
8	**1h**	**2a**	**3a**	**4haa**	91%
9	**1a**	**2b**	**3a**	**4aba**	84%
10	**1a**	**2c**	**3a**	**4aca**	87%
11	**1h**	**2b**	**3a**	**4hba**	88%
12	**1h**	**2c**	**3a**	**4hca**	87%
13	**1h**	**2a**	**3b**	**4hab**	88%
14	**1h**	**2b**	**3b**	**4hbb**	86%

[a]Isolated yields are calculated based on **1**. [b]Imino-coumarine**4** numberingis accompanied with threeletter combinationsdefining the source ofcarbohydrate propargyl ether,sulfonylazide, and salicylaldehyde or *o*-hydroxyacetophenone, respectively. See scheme 2 legend for letter definitions.



Scheme 3. General de-*O*-acetylation of the carbohydrate-iminocoumarines**4** with NaOMe in MeOH.

Table 3. De-*O*-acetylation of the carbohydrate-iminocoumarines**4** with NaOMe in MeOH.

Entry	**4**	**5**	Yield[a]
1	**4aaa**	**5aaa**	82%
2	**4baa**	**5baa**	77%
3	**4caa**	**5caa**	79%
4	**4daa**	**5daa**	80%
5	**4eaa**	**5eaa**	78%
6	**4faa**	**5faa**	81%
7	**4gaa**	**5gaa**	74%
8	**4aba**	**5aba**	78%

[a]Yields after chromatographic purification.

Once the library of glycosylated-iminocoumarines **5** was in hand, we focused our attention to evaluate their activities with galectins. The deprotected glycosylated iminocoumarins **5** were evaluated as antagonists against human galectin-1, -3, -7, -8N (N-terminal domain), and -9N (N-terminal domain).This selection of galectins to evaluate is based on their well-documented relevance in immunity, inflammation and cancer. Galectin-4, -8 C-terminal

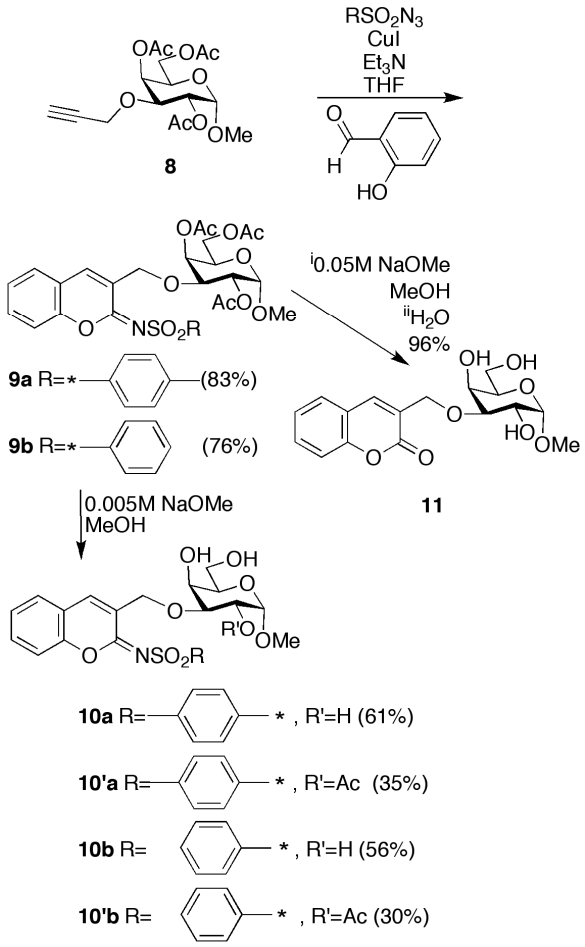
domain, -9 C-terminal domain, and -12 would also qualify as galectins of interest to evaluate, however adequately accurate assays for these galectins were not available. The data generated from these experiments clearly revealed that galactose and lactose-derived compounds **5baa** and **5gaa** posses binding

Table 4. K_d-values (mM)[a] of binding compounds **5baa** and **5gaa**against human galectin-1, 3, 7, 8N, and 9N as measured by a fluorescence polarization assay.[26-28] Methyl β-D-galactopyranoside**6** and methyl β-lactoside**7** are included as references.

Compound	Galectin				
	1	3	7	8N	9N
5baa	3.6±1.3	10±0.5	nb[b]	3.9±0.9	7.1±0.4
5gaa	0.5±0.09	0.13±0.06	nb	0.14±0.01	0.080±0.010
Me β-D-gal(6)[26]	10	4.4	4.8	5.3	3.3
Me β-lac(7)[29]	0.19	0.22	0.11	0.062	0.023

[a]The data are average and standard deviation of 4-8 single point measurements. [b]Non-binding.

activities against galectin-1, 3, 8N, and 9N in the same range as reference methyl β-D-galactoside **6** and methyl β-lactoside**7** (Table 4). On the contrary, galectin-7 did not bind by the anomeric coumarines **5baa** and **5gaa**. The other carbohydrate iminocoumarine compounds **5** as expected did not show any significant binding as they do not posses the key galactose or lactose moiety needed



Scheme 4. Synthesis of 3-*O*-iminocoumarine and coumarine derivatives **10**-**11** of methyl α-D-galactopyranoside..

Next, we synthesized the 3-*O*-iminocoumarine derivatives of galactose as an alternative strategy, because galectin:ligand X ray structures[30-36] reveal no clear contact between galactose 3-OH and galectin CRDs. This suggests that galactose 3-O is ideal as point of attaching putative affinity-enhancing coumaryl structures pointing into an extended binding pocket, as has been demonstrated with other structures in a series of publications.[36-42]Hence, 3-*O*-propargylated galactopyranoside**8**[43]was subjected to the Cu-catalyzed three-component protocol to afford the desired 3-*O*-iminocoumarine galactosides**9a** and **9b** in good yields. These derivatives were de-*O*-acetylated to afford compounds **10a**and **10'b**, respectively, using the same controlled de-*O*-acylation strategy with low sodium methoxide concentration (Scheme 4). Interestingly, the 2-*O*- acetyl group showed unexpectedly high stability and the partially de-*O*-acetylated **10'a** and**10'b** were isolated together with the fully de-*O*-acetylated compounds **10a** and **10b**. As 2-*O*-substituted galactopyranose derivatives have proven better antagonists, as compared to parent galactosides, against galectin-3[44-48], it was of interest to study the effect of 2-*O*-acetyl protecting group on galectin binding. Alternatively, forcing the de-*O*-acetylation conditions by using 0.05M in MeOH for 12h, followed by addition of water yielded the corresponding coumarine derivatives after an additional 12h. Hence, increasing the sodium methoxide concentration, followed by addition of water, allowed for simultaneous de-*O*-acetylation and de-*N*-sulfonylation to yield the coumarine**11**.

Evaluation of **10a**,**10'a**,**10b**, **10'b**,and **11** as galectin antagonists revealed only a marginal, but significant, affinity enhancement for galectin-1. However, to our satisfaction, all five compounds indeed showed binding(Table 5)to galectin-3, 8N, and 9N with efficiencies approaching or even surpassing the hitherto most promising galactose 3-C-modifications based on aromatic amides and triazoles (*e.g.*methyl 3-deoxy-3-(4-methylbenzamido)-1-thio-β-D-galactopyranoside **12**[46] and methyl 3-deoxy-3-(4-benzylaminocarbonyl-1*H*-[1,2,3]-triazol-1-yl)-1-thio-β-D-galactopyranoside **13**,[40](Figure 1). For galectin-8N the result was possibly even more intriguing because while the *N*-sulfonylatediminocoumarines**10a** and **10b** were more than20

Table 5. K_d-values (μM)[a] of **10a**, **10'a**, **10b**, **10'b**, **11**, **12**, **13**, and methyl α-D-galactoyranoside**14**against human galectin-1, 3,7, 8N, and 9N, as measured by a fluorescence polarization assay.[26-28]

	Galectin				
	1	3	7	8N	9N
10a	1700±640	120±25	1700±720	250±55	140±13
10'a	5100±590	97±22	180±18	170±46	36±13
10b	650±110	81±13	1100±270	390±46	76±16
10'b	4500±100	130±49	230±50	270±70	45±5
11	1900±290	78±15	850±130	180±17	180±27
12[40]	980	220	>2000	>2000	1500
13[39,40]	n.b.[b]	150	2100	>5000	>5000
14	>10000[c]	2700±420	11000±2800	6300±970	2800±450

[a]The data are average and standard deviation of 4-8 single point measurements. [b]Non-binding. [c]No inhibition observed at 10 mM concentration.

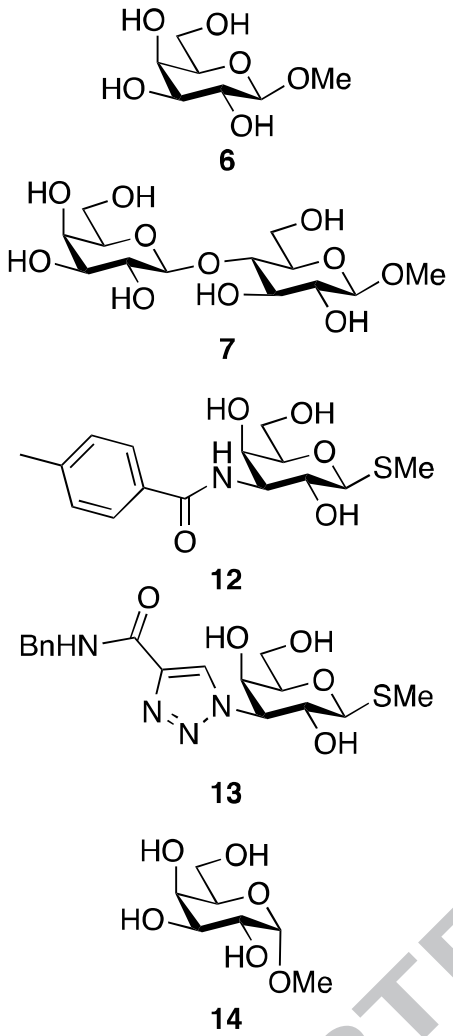


Figure 1. Galectin-binding reference 3-C-modified galactosides**12**, **13** and **14**.

times better ligands than methyl α-D-galactopyranoside**14**, the reference amide**12** and triazole**13** were virtually non-binding. Surprisingly, the compounds with 2-*O*-acetyl protection **10'a** and**10'b** were proved better ligands against galectins-7 and 9N, than de-protected iminosulfonyl-cumarines (**10a** and **10b**). They showed similar affinity as the coumarine**11** for galectin-3 and galectin-8N and considerably increased affinity against galectin-7 (**10'a**K_d=180 μM and **10'b**K_d=230 μM), galectin-9 (**10'a**K_d=36 μM and **10'b**K_d=45 μM), but rendered neutral or slightly adverse effect against galectin-1 in comparison to compound **11**,albeit in no case did the substitution cause abolished binding. Taken together, these results open up a promising avenue towards exploiting galactose 3-*C*-coumarines as galectin antagonists.

In conclusion, we have employed a highly efficient multi-component method for the synthesis of iminocoumarylmethyland coumarylmehtylderivatised carbohydrates for evaluation as galectin antagonists. While iminocoumarylmethylgalactosides and lactosides derivativesshowedbinding activity against galectin-1, 3, 7, 8N, and 9N in the same range as methyl β-D-galactoside and β-lactoside, respectively, the 3-*O*-iminocoumarylmethyl and coumarylmethyl galactoside derivatives showed greatly enhanced affinity over methyl α-D-galactoside for galectin-3, 7, 8N, and 9N, but less so for galectin-1. The affinity enhancements for galectin-3, 7, 8N, and 9N surpasses those of earlier discovered 3-benzamido- and 3-triazolyl galactosides, which clearly points to the 3-*O*-iminocoumarylmethyl and 3-*O*-coumarylmethyl derivatization being an attractive route towards efficient antagonists against these galectins.

Acknowledgments

VKR thanks CSIR, New Delhi, India for Senior Research Fellowship. The work wassupported by the Swedish Research Council program Swedish Links sponsored by SIDA (Swedish International Development Cooperation Agency), the Swedish Research Council (Grant No. 621-2009-5326), and the Department of Science and Technology, New Delhi, India (Grant No. SR/S1/OC-67/2009).

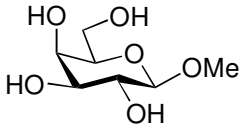
References and notes

1. Venugopala, K. N.; Rashmi, V.; Odhav, B. *BioMed Res. Int.* 2013, 1.
2. Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S. L.; Lee, K.-H. *Med. Res. Rev.* 2003, *23*, 322.
3. O´Kennedy, R.; Thomas, R. D., Eds. *Coumarins: Biology, Applications, and Mode of Action*; Wiley: Chichester, UK, 1997.
4. Brun, M. P.; Bischoff, L.; Garbay, C. *Angew. Chem. Int. Ed. Engl.* 2004, *43*, 3432.
5. Hariprassad, V.; Talele, T. T.; Kulkarni, V. *Pharm. Pharmacol. Comun.* 1998, *4*, 365.
6. Lacy, A.; Kennedy, R. *Curr. Phar. Des.* 2004, *10*, 3797.
7. Burke, T. R.; Lim, B.; Marquez, V. E.; Li, Z.-H.; Bolen, J. B.; Bolen, J. B.; Stefanova, I.; Horak, I. D. *J. Med. Chem.* 1993, *36*, 425..
8. Mandal, S.; Gauniyal, H. M.; Kausikisankar, P.; Mukhopadhyay, B. *J. Org. Chem.* 2007, *72*, 9753.
9. Leffler, H.; Carlsson, S.; Hedlund, M.; Qian, Y.; Poirier, F. *Glycoconj. J.* 2004, *19*, 433.
10. Rabinovich, G. A.; Croci, D. O. *Immunity* 2012, *36*, 322.
11. Rabinovich, G. A.; Toscano, M. A. *Nat. Rev. Immunol.* 2009, *9*, 338.
12. Ingrassia, L.; Camby, I.; Lefranc, F.; Mathieu, V.; Nshimyumukiza, P.; Darro, F.; Kiss, R. *Curr. Med. Chem.* 2006, *13*, 3513.
13. Leffler, H.; Nilsson, U. J., Eds. *Galectins and Disease - Implications for Targeted Therapies*, 2013.
14. Oberg, C.; Leffler, H.; Nilsson, U. J. *Chimia* 2011, *65*, 1.
15. Pieters, R. J. *ChemBioChem* 2006, *7*, 721.
16. Volmajer, J.; Toplak, R.; Bittner, S.; Leban, I.; Le Marechal, A. M. *Tetrahedron Lett.* 2003, *44*, 2363.
17. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* 2000, *39*, 3168.
18. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* 2013, *8*, 1128.
19. Meldal, M.; Tornøe, W. *Chem. Rev.* 2008, *108*, 2952.
20. Murugavel, G.; Punniyamurthy, T. *Org. Lett.* 2013, *15*, 3828.
21. Whiting, M.; Fokin, V. V. *Angew. Chem. Int. Ed. Engl.* 2006, *45*, 3157.
22. Cui, S.-L.; Lin, X.-F.; Wang, Y.-G. *Org. Lett.* 2006, *8*, 4517.
23. Mandal, P. K. *RSC Adv.* 2014, *4*, 5803.
24. Palanichamy, K.; Suravarapu, S. R.; Kaliappan, K. P. *Synthesis,* 2012, *2012*, 1841.
25. Roy, B.; Mukhopadhyay, B. *Tetrahedron Lett.* 2007, *48*, 3783.
26. Cumpstey, I.; Carlsson, S.; Leffler, H.; Nilsson, U. J. *Org. Biomol. Chem.* 2005, *3*, 1922.
27. Sörme, P.; Kahl-Knutsson, B.; Huflejt, M.; Nilsson, U. J.; Leffler, H. *Anal. Biochem.* 2004, *334*, 36.
28. Sörme, P.; Kahl-Knutsson, B.; Wellmar, U.; Nilsson, U. J.; Leffler, H. *Meth. Enzymol.* 2003, *362*, 504.
29. Cumpstey, I.; Salomonsson, E.; Sundin, A.; Leffler, H.; Nilsson, U. J. *ChemBioChem* 2007, *8*, 1389.
30. Bianchet, M. A.; Ahmed, H.; Vasta, G. R.; Amzel, L. M. *Proteins* 2000, *40*, 378.
31. Leonidas, D. D.; Vatzaki, E. H.; Vorum, H.; Celis, J. E.; Madsen, P.; Acharya, K. R. *Biochemistry* 1998, *37*, 13930.
32. López-Lucendo, M. F.; Solís, D.; André, S.; Hirabayashi, J.; Kasai, K.-i.; Kaltner, H.; Gabius, H.-J.; Romero, A. *J. Mol. Biol.* 2004, *343*, 957.
33. Nagae, M.; Nishi, N.; Nakamura-Tsuruta, S.; Hirabayashi, J.; Wataksuki, S.; Kato, R. *J. Mol. Biol.* 2008, *375*, 119.

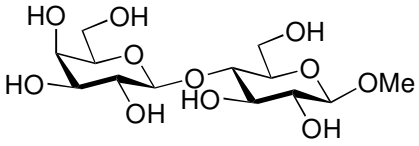
34. Saraboji, K.; Håkansson, M.; Genheden, S.; Diehl, C.; Qvist, J.; Weininger, U.; Nilsson, U.; Leffler, H.; Ryde, U.; Akke, M.; Logan, D. *Biochemistry* 2011, *51*, 296.
35. Seetharaman, J.; Kanigsberg, A.; Slaaby, R.; Leffler, H.; Barondes, S. H.; Rini, J. M. *J. Biol.Chem.* 1998, *273*, 13047.
36. Sörme, P.; Arnoux, P.; Kahl-Knutsson, B.; Leffler, H.; Rini, J. M.; Nilsson, U. J. *J. Am. Chem. Soc.* 2005, *127*, 1737.
37. Cumpstey, I.; Salomonsson, E.; Sundin, A.; Leffler, H.; Nilsson, U. J. *Chem. Eur. J.* 2008, *14*, 4233.
38. Cumpstey, I.; Sundin, A.; Leffler, H.; Nilsson, U. J. *Angew. Chem. Int. Ed.* 2005, *44*, 5110.
39. Salameh, B. A.; Cumpstey, I.; Sundin, A.; Leffler, H.; Nilsson, U. J. *Bioorg. Med. Chem.* 2010, *18*, 5367.
40. Salameh, B. A.; Leffler, H.; Nilsson, U. J. *Bioorg. Med. Chem. Lett.* 2005, *15*, 3344.
41. Salameh, B. A.; Sundin, A.; Leffler, H.; Nilsson, U. J. *Bioorg. Med. Chem.* 2006, *14*, 1215.
42. Sörme, P.; Qian, Y.; Nyholm, P.-G.; Leffler, H.; Nilsson, U. J. *ChemBioChem* 2002, *3*, 183.
43. Campo, V. L.; Sesti-Costa, R.; Carneiro, Z. A.; Silva, J. S.; Schenkman, S.; Carvalho, I. *Bioorganic & Medicinal Chemistry* 2012, *20*, 145.
44. Collins, P. M.; Oberg, C. T.; Leffler, H.; Nilsson, U. J.; Blanchard, H. *Chem. Biol. Drug Design* 2012, *79*, 339.
45. Öberg, C. T.; Blanchard, H.; Leffler, H.; Nilsson, U. J. *Bioorg. Med. Chem. Lett.* 2008, *18*, 3691.
46. Öberg, C. T.; Leffler, H.; Nilsson, U. J. *J. Med. Chem.* 2008, *51*, 2297.
47. Öberg, C. T.; Noresson, A.-L.; Leffler, H.; Nilsson, U. J. *Chem. Eur. J.* 2011, *17*, 8139.
48. Öberg, C. T.; Noresson, A.-L.; Leffler, H.; Nilsson, U. J. *Tetrahedron* 2011, *67*, 9164.

Supplementary Material

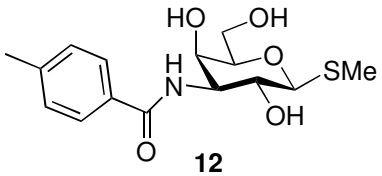
Synthetic experimental procedures, NMR data, ms data, and copies of NMR spectra.



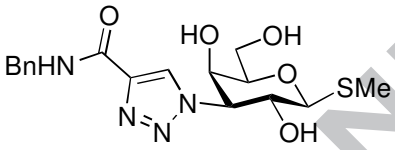
6



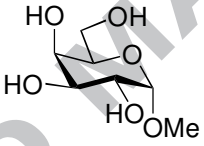
7



12



13



14