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Design, Synthesis, and Structure−Affinity Relationships of Novel Series of Sialosides as CD22-Specific Inhibitors

Hajjaj H. M. Abdu-Allah,*[,†] Taichi Tamanaka,[‡] Jie Yu,[‡,§] Lu Zhuoyuan,[‡,§] Magesh Sadagopan,[||] Takahiro Adachi,[‡] Takeshi Tsubata,[‡,⊥] Soerge Kelm,[#] Hideharu Ishida,[†] and Makoto Kiso*[,†,||,⊥]

Department of Applied Bio-organic Chemistry, The United Graduate School of Agricultural Sciences, Gifu University, Gifu 501-1193, Japan, Laboratory of Immunology, School of Biomedical Science, Tokyo Medical and Dental University, Japan, Department of Immunology, School of Basic Medical Sciences, Peking University Health Science Center, China, Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University, Kyoto, Japan, CREST, Science and Technology Agency (JST), Saitama, Japan, Centre for Biomolecular Interactions, Department of Biology and Chemistry, Bremen University, Bremen, Germany

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Sialosides incorporating substituted amides or amines at 9-position of sialic acid moiety have been synthesized and evaluated as CD22 inhibitors. Several derivatives exhibited inhibitory potency in sub- to low micromolar range (e. g., **8o**, **9d**, **9g**, and **9k** showed IC_{50} values 0.40, 0.47, 0.24, and 0.23 μM, respectively, for hCD22, while **8p**, **8q**, and **9f**, showed IC_{50} values 1.70, 2.90, and 4.10 μM, respectively, for mCD22). The most significant result was the strongly enhanced affinity of **9g** and **9k** containing 9-(2′ or 4′-hydroxy-4-biphenyl) methylamino substituents (600-fold more potent for hCD22 than the corresponding 9-hydroxy derivative; **7a**). Molecular modeling study was carried out to get some insights into the molecular basis of CD22 inhibition. To the best of our knowledge, this is the first systematic structure−affinity relationship study on inhibition of CD22.

Introduction

The Siglec[a] (Sialic acid-binding immunoglobulin [Ig]-like lectins) proteins are subset of the Ig superfamily of cell recognition molecules that bind to sialic acid-containing glycans of cell surface glycoconjugates as ligands.[1,2] Each Siglec has a N-terminal V-set sialic acid-binding Ig domain, a variable number of additional C-set Ig domains, a transmembrane domain, and a cytoplasmic domain that typically contains tyrosine-based motifs. These motifs are implicated in the regulation of cell signaling and endocytosis. Each Siglec has a characteristic cell-type-dependent expression pattern and a distinct binding specificity for sialylated glycoconjugates.[3,4] The recognition of Siglecs for sialylated glycoconjugates was found to depend on the nature of sialic acid, its linkage to substituted sugars, and the underlying neutral oligosacchrides. In general, Siglecs show low affinity (a K_d of 0.1−3 mM) for Neu5Acα2-3Gal and Neu5Acα2-6Gal.[1] This typifies the relatively low affinity values reported for monovalent cell surface receptor−carbohydrate interactions.

CD22 (Siglec-2) is a well-characterized B cell−specific transmembrane protein of the Siglec family. It is a B-cell inhibitory receptor that regulates multiple B-cell functions, including the cellular activation thresholds and survival.[1] Therefore, CD22 modulates B-cell dependent immune response, prevents autoimmunity, and controls the homing of recirculating B cells back to the bone marrow.[5] Also, binding of CD22 to glycoprotein ligands on T cells modulates T cell signaling.[5] Importantly, many of these CD22 functions depend on its ligand binding ability.[1]

A number of studies have established the key structural features for binding to CD22.[6−12] CD22 is unique in having a strong preference for Neu5Gcα2-6Gal and Neu5Acα2-6Gal structures.[6,7] Powell et al.[8] reported that the minimal motif required for recognition by human CD22 is a disaccharide α-D-Neu5Ac-2,6-Hex(NAc), Hex(NAc) being Gal, GalNAc, or GlcNAc. Recent data from NMR experiments, computational docking model, X-ray data of a complex of α2-3-sialyllactose and sialoadhesin (Sn)/Siglec-1 revealed that Sn mainly recognizes the Neu5Ac and a small part of the Gal moiety.[12] The interaction of Siglecs with sialosides modified at the fifth position of sialic acid moiety varies from Siglec to Siglec significantly. While mCD22 showed strong preference for Neu5Gc, hCD22 binds Neu5Gc and Neu5Ac equally well. In contrast, Sn and myelin-associated glycoprotein (MAG)/Siglec-4 do not show significant binding to Neu5Gc and bind well to cells carrying Neu5Ac.[10]

CD22 binding, as for all Siglecs, requires the recognition of not only the sialic acid negative charge but also the side chain that comprises the C-7, C-8, and C-9 positions. It has been shown that substitution of the hydroxyl group at the 9-position of sialic acid by halogens or esterification abolished binding, suggesting the important role of a hydrogen donor at this position.[10] Furthermore, substitution of this group by an amino group enhanced binding, and acylation of this amino group by

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[*] To whom correspondence should be addressed. Phone/Fax: +81-(0) 58-293-2919/2840. E-mail: Kiso@gifu-u.ac.jp (M.K.); moazhajjaj@yahoo.com (H.H.M.A.).

[†] Department of Applied Bio-organic Chemistry, The United Graduate School of Agricultural Sciences, Gifu University.

[‡] Laboratory of Immunology, School of Biomedical Science, Tokyo Medical and Dental University.

[§] Department of Immunology, School of Basic Medical Sciences, Peking University Health Science Center.

[||] Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University.

[⊥] CREST, Science and Technology Agency (JST).

[#] Centre for Biomolecular Interactions, Department of Biology and Chemistry, Bremen University.

[a] Abbreviations: Siglec, sialic acid-binding immunoglobulin-like lectin; Ig, immunoglobulin; hCD22, human CD22; mCD22, murine CD22; Sn, sialoadhesin (Siglec-1); MAG, myelin-associated glycoprotein (Siglec-4); Neu5Gc, *N*-glycolylneuraminic acid; Neu5Ac, *N*-acetylneuraminic acid; GalNAc, *N*-acetyl-*β*-D-galactosamine; Gal, *β*-D-galactose; GlcNAc, *N*-acetyl-*β*-D-glucosamine; BPC, biphenylcarboxamido; BPA, biphenylacetamido; LacNAc, *N*-acetyllactoseamine (Gal*β*1-4GlcNAc); Sia, sialic acid type unspecified; MP, *p*-methoxyphenyl; SE, 2-(trimethylsilyl)ethyl; IC_{50}, concentration giving 50% inhibition of binding.

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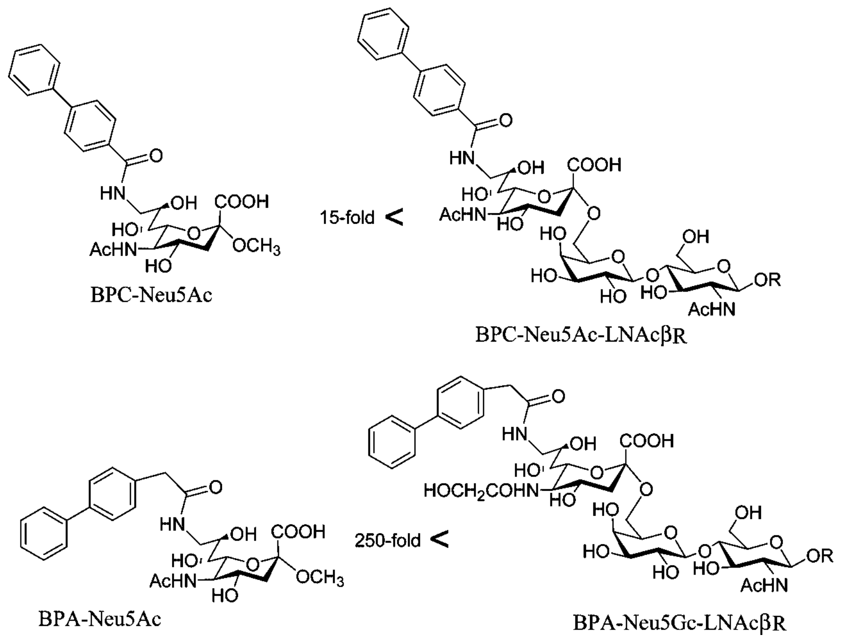


Figure 1. Chemical structures of the known 9-biphenyl derivatives of Neu5Ac or Neu5Gc and their comparative inhibitory potencies.[13,16]

hydrophobic moieties has yielded increased binding to CD22, MAG, and sialoadhesin.[13,14] Interestingly, 9-biphenyl-4-carboxamido derivative of Neu5Ac (BPC-Neu5Ac)[13] showed high affinity and selectivity for hCD22 and was found to augment B cell receptor (BCR) signaling by inhibiting CD22-mediated signal inhibition and in turn enhances B cell response. In contrast, biphenylacetamido derivative (BPA-Neu5Ac)[13] was more potent and selective inhibitor for mCD22 than BPC-Neu5Ac (Figure 1).

Molecular modeling studies of Zaccai et al.[15] explored a hydrophobic pocket in CD22 adjacent to the 9-position of sialic acid. They further identified biphenyl substituents at that position, BPC and BPA, that increased the affinity and selectively of Neu5Ac for hCD22 and mCD22, respectively. Moreover, the sequence alignment and the structural analysis of members of the Siglec family showed that variations in the amino acid residues that create this hydrophobic pocket (which are not well conserved) might contribute to the differences in binding affinity and specificity.[15] Such differences provide promising opportunity for the design of siglec-specific sialosides. Recently, BPC-Neu5Ac and BPA-Neu5Gc were assembled, chemoenzymatically, into the sequences 9-BPC-NeuAcα2-6Galβ1-4GlcNAcβ-ethylamine (BPC-Neu5Ac-LNAcβR) and 9-BPA-NeuGc-α2-6Gaβ1-4GlcNAcβ-ethylamine (BPA-Neu5Gc-LNAcβR) (Figure 1).[16] This assembly resulted in high-affinity sialoside ligands that could compete with cis ligands, bind to CD22 on native B cells, and served as a ligand-based markers of CD22 endocytosis. Conjugation of these sialoside probes to the toxin saporin resulted in toxin uptake and toxin-mediated killing of B lymphoma cell lines, suggesting an alternative approach to antibody-mediated therapy for targeting CD22 for the treatment of B cell lymphoma. This interesting finding indicates that any therapeutic agent or radioisotope could be targeted to B cells by attaching it to high affinity CD22 ligands.[16] Thus, synthetic CD22 ligands could be useful in developing a novel strategy to regulate the immune responses and can also be used as delivery agents for treating B cell-related diseases (e.g., lymphoma).[13,16,17]

The above-mentioned facts gave us an insight into the factors govern the ligand binding of CD22, possible routes for inhibitor design, and the crucial importance of gaining potent and selective CD22 inhibitors. As part of our continuing research into exploring sialoside specificity of Siglec binding,[18] the present study was aimed at the systematic investigation of the structure−affinity relationship and eventually developing more potent and selective CD22 inhibitors. Herein we report the synthesis and CD22 inhibitory potencies of a series of synthesized compounds of the general scaffold shown in (Figure 2). This library of compounds (35 compounds) has allowed us to carry out the first systematic structure−affinity relationship study on inhibition of CD22.

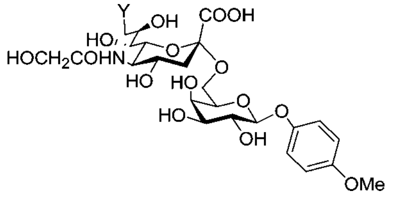


Figure 2. Target compounds. Y = OH, NH$_2$, substituted amide, or substituted amine.

Rational Design. Crystal structure analysis of two Siglecs, Sn[19] and Siglec 7,[20] have revealed a shallow surface with highly flexible amino acids and this feature is predicted to be present in all siglecs.[15] This means that CD22 belongs to a class of molecules which are not readily amenable to receptor- or structure-based drug design for virtual screening as recently reported for selectins.[21] Instead, structurally similar analogues of natural ligand can increase the possibility of getting more selective and higher affinity ligands. Therefore, analogue-based design approach and chemical synthesis have been employed based on sialic acid template. The basic binding motif in endogenous ligands for CD22 has been identified as Neu5Acα2-6-LacNAc.[22] Further studies by Powell et al.[8] suggested that this basic binding motif for CD22 could be further stripped to the disaccharide Neu5Acα2-6-Hex(NAc) without loss of affinity. Moreover, compound Neu5Acα2-6GalNAcONP (ONP, *o*-nitrophenyl) displayed a 3-fold higher affinity for CD22 compared with the reference trisaccharide structure Neu5Acα2-6LacNAc.[8] The same study revealed that CD22 binding was significantly influenced by the structure of the group at the reducing terminus of Gal. For example a sialoside with *o*-nitrophenyl group as aglycone, was 40-fold better than the same sialoside with a benzyl group instead.[8]

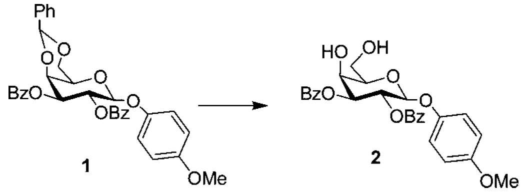
Because CD22 does not recognize α2-3 sialosides, the Gal C_5-C_6 face of Neu5Acα2-6Gal must be involved in CD22 binding as these positions are the key structural features which distinguish α2-6 from α2-3 sialosides. The unfavorable effect of C_6 methylation of Gal likewise indicates that this region of the disaccharide faces the binding site.[8] An X-ray crystallographic analysis of the N-terminal domain of Sn complexed with α2-3-sialyllactose showed a network of close interactions between the protein, the Sia, and Gal residues, while the GlcNAc residue is bonded via water molecules.[19] Furthermore, combined NMR experiments with a molecular modeling study revealed that Sn mainly recognizes the sialic acid moiety and a small part of the Gal moiety.[12] This binding model is probably also representative for CD22 because the binding sites of Sn and CD22 possess a high degree of sequence similarity.[23] These findings indicate that CD22 mainly recognizes Siaα2-6Gal motif while GlcNAc residue is of less importance.

As already mentioned above, BPC-Neu5Ac and BPA-Neu5Ac displayed strong affinity with high selectivity for hCD22 and mCD22, respectively.[13] Furthermore, incorporation of BPC-Neu5Ac into BPC-Neu5Ac-LNAc*β*R sequence resulted in an inhibitory potency for hCD22 15-fold more than BPC-Neu5Ac alone.[16] Similarly, incorporation of BPA-Neu5Ac into BPA-Neu5Gc-LNAc*β*R sequence resulted in an inhibitory potency for mCD22 250-fold more than BPA-Neu5Ac alone.[16] Accordingly, the affinity for CD22 can be enhanced by further optimization of the structure attached to the reducing end of the sialic acid moiety.

To maintain the functionality while improving binding affinity, selectivity, and structural simplicity, we combined all the structural requirements for CD22 receptor recognition (Figure 2). Therefore, our lead optimization strategy was based on the following modifications: (1) Employing Siaα2-6Gal as the principal motif for CD22 binding. (2) N-Gc as the substituent at the fifth position, which is recognized mainly by CD22, Neu5Gcα2−6Gal is the main source of specificity. (3) Introducing free or substituted NH_2 group at 9-position of sialic acid moiety to enhance the affinity and selectivity. The inclusion of varying functionality at this position was designed to explore the effects of hydrophobic, hydrophilic, and sterically demanding groups upon their interaction with CD22. (4) Inserting a *p*-methoxyphenyl moiety as the aglycon, which is not only expected to enhance the affinity but also it is advantageous from synthetic point of view. The phenyl group will be useful for the detection of the oligosaccharides and serve as a marker to check the purity of the product by NMR.

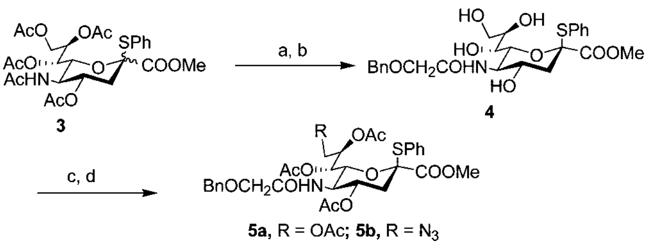
Chemistry. The target sialosides **7a**, **7b**, **8a−s,** and **9a−n** (Tables 1−7) were synthesized as described in Schemes 1−4. Scheme 1 depicts the synthesis of Gal acceptor **2** by the acid hydrolysis of the known 4-methoxyphenyl 4,6-*O*-benzylidene-2,3-di-*O*-benzoyl-*β*-D- galactopyranoside **1**.[23] Neu5Gc donor **5** was obtained from methyl (phenyl 5-actamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-α- and -*β*-D-*galacto*-2-nonulopyranoside)onate **3**, which is known as one of the most useful Neu5Ac donors, and the anomeric phenylthio group is stable in many organic manipulations.[24] Therefore, we synthesized the thioglycoside of Neu5Gc **4** as a potential good donor by exchanging the *N*-acetyl group of **3** with the *N*-glycolyl group (Scheme 2). The thioglycoside **3** was deacetylated with methanesulfonic acid (MsOH), and the resulting amine was treated with *N*-hydroxysuccinimide ester of *O*-benzylglycolic acid[25] to give the *N*-glycolyl derivative **4** in 75% yield in two steps (Scheme 2). The succinimidyl ester was prepared by DCC coupling acylation in analogy to that of *O*-acetyl glycolic acid.[26]

Scheme 1. Preparation of Gal Acceptor[a]



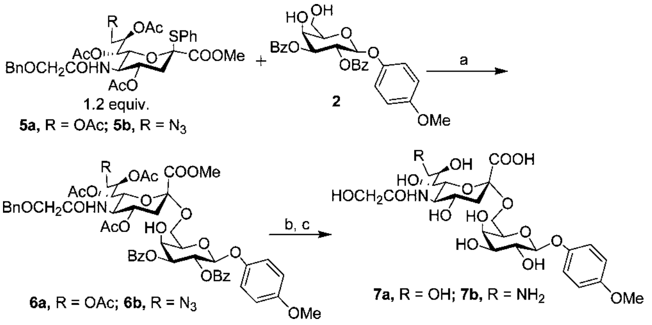
[a] Reagents and conditions: 80% AcOH, 60 °C for 24 h, 89%.

Scheme 2. Synthesis of Neu5Gc Donors **5a**, **b**[a]



[a] Reagents and conditions: (a) MsOH, CH_3OH, 65 °C, 24 h; (b) $BnOCH_2COONSu$, TEA, r.t., 24 h, two steps 75%; (c) Ac_2O, pyr., 0 °C−rt, 94.5%; (d) 1- CBr_4, Ph_3P, NaN_3, DMF; 2- Ac_2O, pyr, 0 °C−rt, two steps 83.5%.

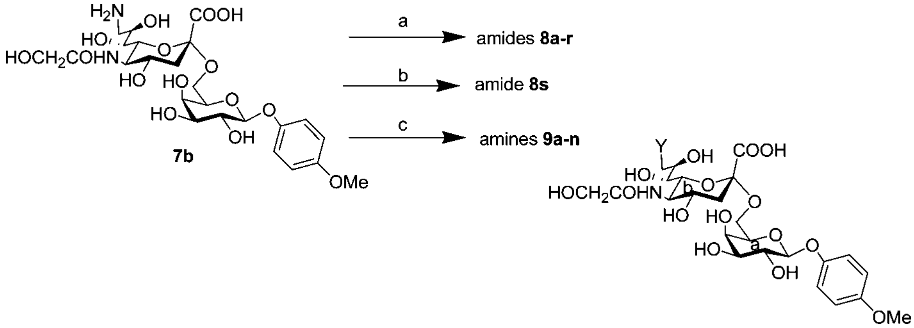
Scheme 3. Sialylation and Deprotection **7**[a]



[a] Reagents and conditions: (a) NIS, TfOH, MS 3 A, (MeCN/DCM; 5/1), −20 °C, 16 h, 64%; (b) LiOH, aq.EtOH, 6 h, rt; (c) H_2, $Pd(OH)_2$, EtOH, AcOH, H_2O, 40 °C, 48 h, two steps 84.5%.

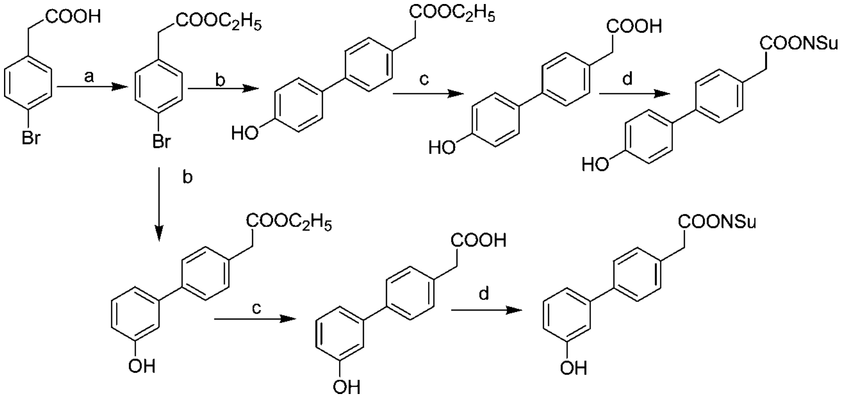
Acetylation of **4** afforded **5a** in quantitative yield. The synthesis of **5b** required the synthesis of 9-azido derivative of **4.** To achieve this purpose, **4** was reacted with *p*-toluenesulfonyl chloride in pyridine to give 9-*O*-tosyl derivative in 55% yield. Azidation of this tosylate ester with sodium azide in aqueous acetone provided 9-azido derivative in 90% yield. In an alternative approach toward improving the overall yield, we attempted to employ direct selective replacement of primary hydroxyl group by azide.[27] Accordingly, treatment of **4** with sodium azide in the presence of triphenyphosphine (Ph_3P) and carbon tetrabromide (CBr_4) followed by acetylation gave the desired 9-azido derivative **5b** in an excellent yield (83.5%). Direct acetylation gave the donor **5b** and made it easier to get rid of the problematic triphenylphosphine oxide. We decided to introduce azido group at this stage because of its stability during other manipulations. The structure of **5b** from one-pot reaction was identical to that from azidation of tosylate ester and confirmed by IR (2100 cm^{-1}, azide), ^{13}C NMR (δ 50.0, C-9), and by ^1H NMR in comparison with **5a**.

Scheme 4. Amidation or Reductive Alkylation **8a**−**s** and **9a**−**n**[a]



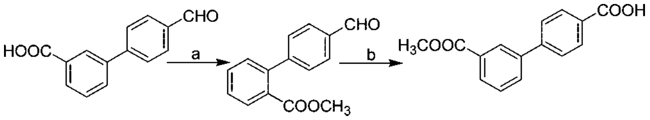
[a] Reagents and conditions: (a) appropriate succinimidyl ester, $NaHCO_3$ ($MeCN/H_2O$; 5/1), rt, 24 h, 70−85%; (b) 4,4′-biphenyl dicarboxylic acid, DMF, *N*-methylmorpholine, isobutyl choroformate, 12 h, rt, 65%; (c) appropriate aldehyde, $NaBH_3CN$ either in phosphate buffer pH 7, rt, 48 h, and then AcOH, 3 h (compds **9a**−**c**), or in MeOH/AcOH (compds **9d**−**n**), 70−80%.

Scheme 5. Synthesis of 3′ and 4′-Hydroxybiphenyl-4-acetic Acid-NHS esters[a]



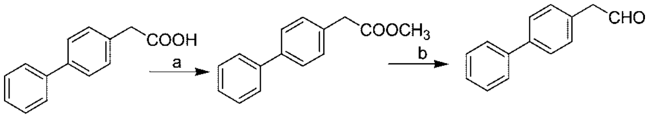
[a] Reagents and conditions: (a) TsOH, EtOH, 96%; (b) 3- or 4-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, benzene, reflux, dark condition, 85%; (c) LiOH, EtOH, H_2O, 6 h; (d) *N*-hydroxysuccinimide, DCC, AcOEt, 0 °C, 24 h, two steps 80%.

Scheme 6. Synthesis of 3′-Methoxycarbonyl-biphenyl-4-carboxylic Acid[a]



[a] Reagents and conditions: (a) MeOH, $SOCl_2$, 90%; (b) $NaClO_2$, H_2NSO_3H, 70%.

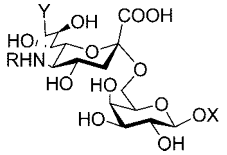
Scheme 7. Synthesis of 4-Biphenylacetaldehyde[a]



[a] Reagents and conditions: (a) $(MeO)_3CH$, TsOH, MeOH, reflux, 4 h, 99%; (b) DIBAL, toluene, −78°C, 2 h, 96%.

Sialylation of **2** with **5** was promoted by *N*-iodosuccinimide/triflic acid (NIS/TfOH)[28] in $CH_3CN-CH_2Cl_2$ at −20 °C, furnishing the α-sialoside **6** in 64% and *β*-form in 14% yield (Scheme 3). The anomeric configuration of the resulting sialosides were determined by analysis of ^1H NMR spectra based on the chemical shift values of the H_{3beq} and H_{4b} signals, the coupling constant $J_{7b,8b}$, and the value of $\Delta\delta$ ($H_{9b}''-H_{9b}'$); for α-sialoside these values are 2.66 ppm, 4.91 ppm, 7.4 Hz, and 0.38 ppm, respectively, while for the *β*-form, the values are 2.55 ppm, 5.28 ppm, 2.0 Hz, and 0.88 ppm, respectively. These values are in accordance with the empirical rules for defining the anomeric configuration of sialosides.[29]

Table 1. Influence of the Substituents at 5,9 Positions of Sialic Acid Moiety and at the Reducing End of Gal on Affinity (compds **7a**, **7b**, **10**, **11**): Building the Main Scaffold

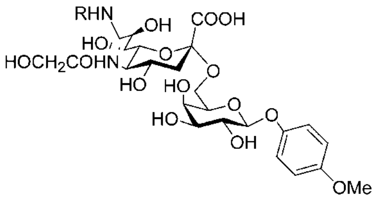


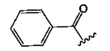
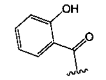
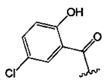
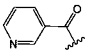
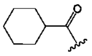
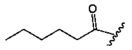
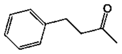
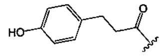
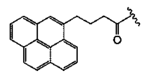
				IC_{50} (μM)[a] ± SD	
compd no.	Y	R	X	hCD22	mCD22
11	OH	Ac	SE	683.33 ± 28.87	ND[b]
10	OH	Gc	SE	550.00 ± 45.09	833.33 ± 57.74
7a	OH	Gc	MP	148.33 ± 59.65	496.67 ± 28.87
7b	NH_2	Gc	MP	85.00 ± 43.30	93.10 ± 54.1

[a] Sialoside concentration which leads to 50% inhibition of binding. The values are means of at least three independent determinations. [b] ND means that 50% inhibition was not observed until 1000 μM "IC_{50} > 1000 μM".

To minimize the number of steps required for the synthesis of substituted amides at 9-position of **6b**, we decided to use reductive acylation under modified Staudinger conditions as commonly used for preparation of sugar amides.[30] Unfortunately, attempts at forming 9-*N*-Bz derivative by treatment of **6b** under different conditions failed to furnish any of the desired product. ^1H NMR and mass data referred to the occurrence of *O* to *N* acetyl migration. So we concluded that reduction of azide to amine followed by acylation is the best route to get our target compounds. Disappointingly, Zemplen deacetylation, followed by catalytic hydrogenation and acylation with acid chloride or active ester using standard acylation conditions,

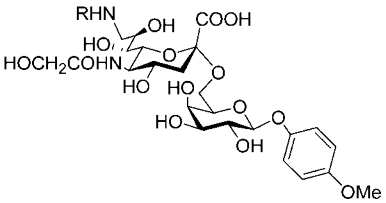
Table 2. Inhibitory Potencies of Aryl, Heteroraryl, Arylalkyl, Alicyclic, and Aliphatic Carboxylic Acid Derivatives (Compds **8a**−**i**)

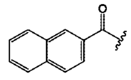
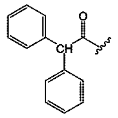
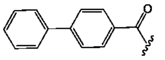
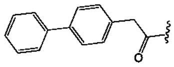
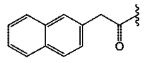


Compd.	R	IC$_{50}$ (μM)[a] ± SD	
		hCD22	mCD22
8a		125.16 ± 9.08	114.77 ± 106.80
8b		192.67 ± 21.03	137.82 ± 56.50
8c		115.85 ± 10.34	161.11 ± 62.90
8d		132.32 ± 1.70	32.23 ± 22.60
8e		16.00 ± 10.20	65.33 ± 27.20
8f		40.85 ± 1.34	88.50 ± 36.70
8g		10.40 ± 4.45	167.88 ± 108.40
8h		7.65 ± 0.85	138.88 ± 12.90
8i		21.06 ± 9.75	66.76 ± 26.70

[a] Sialoside concentration which leads to 50% inhibition of binding. The values are means of at least three independent determinations.

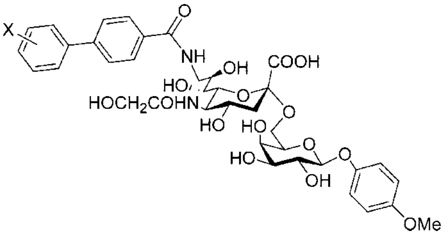
Table 3. Inhibitory Potencies of Dicyclic Aromatic Carboxylic Acid Derivatives (compds **8j**−**n**)



Compd,	R	IC$_{50}$ (μM)[a] ± SD	
		hCD22	mCD22
8j		2.60 ± 1.40	90.03 ± 58.40
8k		8.85 ± 2.05	63.53 ± 30.00
8l		1.10 ± 0.22	52.93 ± 9.60
8m		3.70 ± 1.41	6.20 ± 0.50
8n		1.00 ± 0.01	24.7 ± 10.01

[a] Sialoside concentration which leads to 50% inhibition of binding. The values are means of at least three independent determinations.

Table 4. Inhibitory Potencies of 9-Biphenylcarboxamido Derivatives (compds **8l**, **8o**, **8r**, and **8s**)



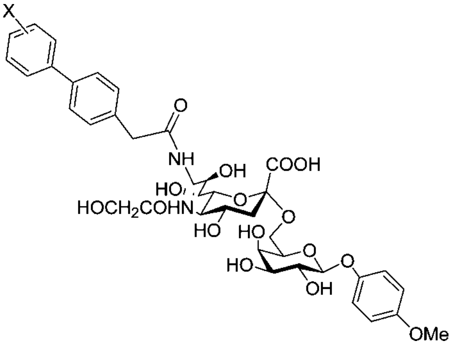
compd	X	IC$_{50}$ (μM)[a] ± SD	
		hCD22	mCD22
8l	H	1.10 ± 0.22	52.93 ± 9.60
8o	4-OH	0.40 ± 0.06	8.63 ± 3.50
8r	3-COOH	7.13 ± 2.00	16.60 ± 6.40
8s	4-COOH	73.25 ± 5.44	23.43 ± 5.70

[a] Sialoside concentration which leads to 50% inhibition of binding. The values are means of at least three independent determinations.

failed to afford any of the desired compounds instead resulted in a complex reaction mixture. We expected that the methyl ester of the sialic acid moiety may undergo lactamization during reduction and under acylation condition. This expectation is confirmed by the usual use of free sialic acid to prepare 9-*N*-acylated derivatives.[31] Also, lactamization of methyl ester during azide reduction was used as a one-pot reaction for the synthesis of GM3-Lactam, while for azide reduction in presence of free carboxylic group, no lactamization occurred.[32] Accordingly, de-esterifiction with lithium hydroxide (LiOH) in aq ethanol. followed by catalytic hydrogenation in weakly acidic medium. afforded the **7** in 84.5% yield (Scheme 3). For amidation, at first we tried nitrophenyl active ester; thereby, nitrophenyl-4-biphenylcarboxylate[14] was used to prepare amide **8l**. The main problem was the laborious purification of the target from *p*-nitrophenol. To overcome this problem, we tried succinimidyl ester, which afforded the corresponding amides (**8a**−**r**) in good to excellent yields (Scheme 4). *N*-Hydroxysuccinimidyl (NHS) esters required as acylating agents were prepared via DCC-mediated coupling of NHS with the corresponding carboxylic acids essentially as reported.[33] Synthesis of compounds **8p** and **8q** required the synthesis of 3′- and 4′-hydroxybiphenyl-4-acetic acid, respectively (Scheme 5), which were synthesized from phenylacetic acid by esterification followed by Suzuki coupling with 3- or 4-hydroxyphenylboronic acid in analogy to reported procedures.[34] On the other hand, compound **8r** was obtained by amidation of **7b** with succinimidyl ester of 3′-methoxycarbonyl-biphenyl-4-carboxylic acid, followed by de-esterification with LiOH. This succinimidyl ester was synthesized from 3-(*p*-formylphenyl)benzoic acid by esterification, aldehydic oxidation, and then NHS esterification (Scheme 6) as reported for the preparation of monomethyl ester of terephthalic acid.[35] Acylation of **7b** with 4,4′-biphenyl dicarboxylic acid under mixed anhydride condition afforded **8s** (Scheme 4) in analogy to acylation of a uracil derivative with 2,6-naphthalene dicarboxylic acid.[36]

To study the effect of replacing the amidic carbonyl with methylene group on affinity, compounds **9a**−**n** (Scheme 4) were

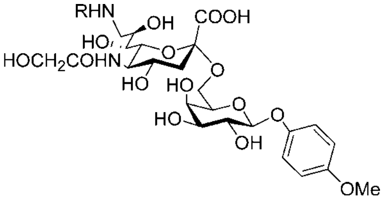
Table 5. Inhibitory Potencies of 9-Biphenylacetamido Derivatives (compds **8m**, **8p**, and **8q**)

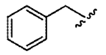
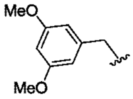
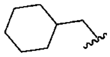
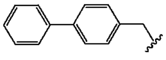
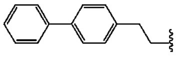
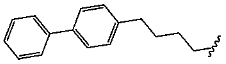


compd	X	IC$_{50}$ (μM)[a] ± SD	
		hCD22	mCD22
8m	H	3.70 ± 1.41	6.20 ± 0.50
8p	4-OH	0.90 ± 0.01	1.70 ± 0.30
8q	3-OH	4.30 ± 1.20	2.90 ± 0.40

[a] Sialoside concentration which leads to 50% inhibition of binding. The values are means of at least three independent determinations.

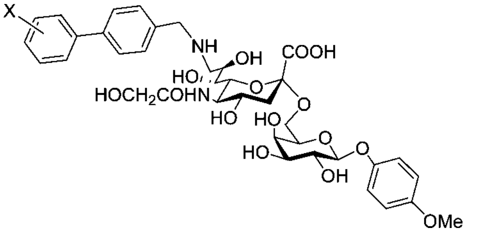
Table 6. Inhibitory Potencies of 9-Amino Derivatives (compds **9a**−**f**)



Compd	R	IC$_{50}$ (μM)[a] ± SD	
		hCD22	mCD22
9a		122.57 ± 21.42	25.70 ± 16.10
9b	 MeO MeO	24.76 ± 8.20	77.52 ± 56.00
9c		37.70 ± 9.1	9.50 ± 0.70
9d		0.47 ± 0.20	16.33 ± 3.33
9e		5.48 ± 2.40	11.24 ± 1.30
9f		6.22 ± 2.54	4.10 ± 1.50

[a] Sialoside concentration which leads to 50% inhibition of binding. The values are means of at least three independent determinations.

Table 7. Effect of Varying Outer Ring Substituent on Inhibitory Potency (compds **9d** and **9g**−**n**)



compd	X	IC$_{50}$ (μM)[a] ± SD	
		hCD22	mCD22
9d	H	0.47 ± 0.20	16.33 ± 3.33
9g	4-OH	0.24 ± 0.02	6.43 ± 1.74
9h	4-COOH	43.00 ± 24.00	10.00 ± 3.00
9i	3-COOH	7.48 ± 3.50	32.7 ± 12.1
9j	3-OH	1.73 ± 0.21	16.50 ± 3.91
9k	2-OH	0.23 ± 0.02	12.50 ± 1.80
9l	4-OMe	1.76 ± 0.68	30.00 ± 3.61
9m	4-Me	9.83 ± 3.75	27.00 ± 1.00
9n	4-CF$_3$	45.00 ± 8.89	48.00 ± 4.36

[a] Sialoside concentration which leads to 50% inhibition of binding. The values are means of at least three independent determinations.

prepared by reductive alkylation of **7b** with the appropriate aldehyde, following the procedures described in ref 37. The aldehydes, when not commercially available, were synthesized as shown for 4-biphenylacetaldehyde (Scheme 7), which was synthesized in two steps from biphenylacetic acid by DIBAL reduction[38] of its methyl ester.[39] The other substituted biphenyl-4-carbaldehydes were prepared by Suzuki coupling of *p*-bromobenzaldehyde and the appropriate phenylboronic acid by adaptation of published procedures.[40] Compounds **10** (Neu5Gcα2-6Gal*β*SE, 2-(trimethylsilyl)ethyl (3,5-dideoxy-5- glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2-6)-*β*-D-galactopyranoside, and **11** (Neu5Acα2-6Gal*β*SE, 2-(trimethylsilyl)ethyl (5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2,6)-*β*-D-galactopyranoside) were already synthesized by our group and used for exploring the biological roles of CD22.[17]

Results and Discussion

Biological Evaluation. The inhibitory potencies (IC$_{50}$) of the synthesized compounds were determined by measuring the binding inhibition of IgG fusion protein of mCD22 and hCD22 (mCD22-Fc and hCD22-Fc, respectively) to their cellular ligands expressed on the mouse myeloma transfectants J558LST6.[17] The parent line J558L do not express α2,6-sialic acid due to lack of the expression of ST6GalI, a sialyl transferase required for the synthesis of α2,6-sialic acid-containing glycans, whereas its ST6GalI transfectants (J558LST6) restore expression of α2,6-sialic acid. By using these cells, specific binding of mCD22-Fc and hCD22-Fc to α2,6-sialic acid can be measured. Thus when J558LST6 cells incubated with CD22-Fc in the presence of various concentrations of synthetic α2,6-sialosides, binding of CD22-Fc to J558LST6 cells was reduced in a dose-dependent manner. Results are shown in Tables 1−7 for different classes of compounds.

Structure−Affinity Relationships. IC$_{50}$ of the target compounds **7a**,**7b**, **8a**−**s**, and **9a**−**n** are reported in Tables 1−7. Compounds **10** and **11**[17] were included in the present study for the evaluation of the influence of the substituents at the reducing end of Gal and at C-9 of sialic acid moiety and in turn a more complete SAR investigation.

As shown in Table 1, mCD22 has strong specificity for *N*-Gc (**10**) over *N*-Ac (**11**) while hCD22 can bind both. Compound **7a** showed higher potency than **10**. This result displays the contribution of the substituent at the reducing end of Gal to the binding affinity and the favorable effect of MP group over SE. Interestingly, replacement of the 9-hydroxy of **7a** with amino group (**7b**) resulted in a further improvement in affinity. Thus

7b exhibited 5-fold higher potency than **7a** for mCD22. This result is in accordance with the reported data.[10] On the basis of these findings, compound **7b** was taken as a valuable structural basis for optimization of the affinity. To study the influence of 9-amino derivatives of **7b** on affinity, divergent substituents with different requirements in space and interaction possibilities were synthesized and evaluated for their inhibition potencies. Our design is primary based on molecular modeling studies and molecular features previously reported to enhance the affinity for CD22.[13,15]

As can be seen in Table 2, substitution of the amino group of **7b** with benzoyl **8a**, salicyloyl **8b**, or chlorosalicyloyl **8c** resulted in little change in affinity. While introduction of nicotinoyl **8d** seems to improve the affinity for mCD22 (3-fold more potent), the cyclohexanecarbonyl (**8e**) and hexanoyl (**8f**) showed, to some extent, better affinity for hCD22 (6- and 2-fold, respectively). These results could suggest that aliphatic chain can bind hCD22 with higher affinity than mCD22. Accordingly, inserting alkyl side chain between the amidic carbonyl and the aromatic ring improved the affinity for hCD22; **8g** and **8h** were 10-fold more potent than **7b**. However, these compounds did not show improved affinity for mCD22 (2-fold loss of potency). Unexpectedly, increasing the bulkiness of the aromatic moiety did not improve the affinity for CD22 (**8i** vs **8g**).

Next we switched to study the effect of dicyclic aromatic substituents based on the presence of a relatively large pocket about 9-position of sialic acid moiety.[15] The results shown in Table 3 show that this class of compound has much higher affinity for hCD22 and mCD22. Of special note is that biphenylcarbonyl (**8l**) exhibited the most promising affinity for hCD22 (IC_{50} = 1.10 μM; 77-fold more potent than **7b**). Importantly, this compound was less active for mCD22 (IC_{50} = 52.93 μM).

Because of the promising assay data on compound **8l**, the biphenyl motif was considered as the backbone for further homologous and isomeric derivatives where spacers and biphenyl substitution pattern were changed. Therefore, inserting methylene (CH_2) between the biphenyl ring and amidic carbonyl group of compound **8l** gave compound **8m**, which showed lower affinity than **8l** for hCD22 but showed strong promising affinity for mCD22 (IC_{50} = 6.20 μM, 8-fold more potent than **8l**). The improved affinity of **8m** may be due to better flexibility and favorable fitting to the binding site. Similarly, introducing CH_2 between the naphthyl ring and the amidic carbonyl group of compound **8j** gave **8n** with promising affinity for hCD22 (IC_{50} = 1.00 μM, 9-fold more potent), but it was not so effective for mCD22 (IC_{50} = 25.00 μM, 3.6-fold more potent). It can be concluded from the above-mentioned data that **8l** (9-biphenylcarbonyl) is the lead compound for hCD22 inhibition, while **8m** (9-biphenylacetyl) is the lead compound for mCD22 inhibition.

As a consequence, the influences of some ring substituents of **8l** and **8m** on affinity were studied and the results are shown in Tables 4 and 5, respectively. Interestingly, introducing 4′-OH to the biphenyl ring of **8l** gave **8o** with improved affinity for hCD22 (IC_{50} = 0.40 μM) and was 6-fold more potent for mCD22 (IC_{50} = 8.63 vs 52.90 μM). However, introducing a carboxyl group at 3′-position (**8r**) decreased the affinity for hCD22, while at 4′-position (**8s**) led to dramatic drop in affinity (IC_{50} = 73.25 μM). This decrease in affinity may be due to an unfavorable stereochemical interaction inside the ligand binding site. In contrast, the carboxyl derivatives of **8l** showed slight improvement in affinity for mCD22 (**8r** and **8s** vs **8l**).

On the other hand, the 4′-hydroxyl group at the biphenyl ring of **8m** gave **8p** with better affinity for hCD22 and mCD22 ((IC_{50} = 0.90 and 1.70 μM, respectively). Accordingly, compound **8p** showed the highest potency of this series for mCD22 (290-fold more potent than **7a**). Compound **8q**, a regioisomer of **8p**, showed little change in potency.

Zaccai et al.[15] clearly showed that the amidic NH at 9-position is involved in a key hydrogen bond between the ligand and the main chain carbonyl of amino acid residue at the binding side, but the amidic carbonyl group does not seem to form a hydrogen bond. These features may imply that the amide moiety is exposed for recognition, but it is not clear if it has the structural role of maintaining the substituent in a particular geometry. Therefore, we envisaged that the replacement of the amidic carbonyl (CO) with CH_2 would be very interesting. It may alter the position of the substituent in the binding groove as a result of the different geometry, electronic, and steric characters. As a consequence, the affinity and selectivity could be modulated. Table 6 shows that replacing the amidic carbonyl with CH_2 was found to improve the affinity for mCD22 with comparable affinity for hCD22 (**9a** and **9c** vs **8a** and **8e**). Thereby, we decided to replace the amidic carbonyl in **8l** with CH_2, which gave **9d**. Interestingly, **9d** showed better affinity for hCD22 (IC_{50} = 0.47 μM) and mCD22 (16.33 μM; 3-fold more potent than **8l**). This result may be due to increased rotational flexibility of the biphenyl ring, which can make it easier to adopt the appropriate conformation to enter the pocket. Furthermore, **9d** was modified to investigate the effect of increasing the chain length of the spacer between the biphenyl ring and the amino group on affinity. The results suggest that increasing the chain length decreases the affinity for hCD22 (**9d** vs **9e** and **9f**), while it is tolerated by mCD22.

At this point, we decided to study the additive effect of combining 4′-hydroxylation of biphenyl ring and replacement of amidic carbonyl with the CH_2 group on inhibition of CD22. Accordingly, compound **9g** with 4′-hydroxyl group at biphenyl ring of **9d** revealed the highest potency for hCD22 (IC_{50} = 0.24 μM) and better affinity for mCD22. The favorable effect of introducing 4′-OH (**8o**, **8p**, and **9g**) may be due to its ability to form additional hydrogen bond interactions.

The promising affinity of **9d** encouraged us to investigate the steric and electronic effects of structural modifications of the biphenyl ring (Table 7). Therefore, substitution by *o*-hydroxyl (**9k**) exhibited promising affinity similar to **9g**. In contrast, *m*-hydroxyl derivative **9j** displayed lower potency (7-fold loss of potency). This variation in affinity may be due to correct spatial orientations of the dipole originated by the hydroxyl groups in the para and ortho position of **9g** and **9k**, which may allow the formation of a hydrogen bond with the corresponding receptor site. Moreover, substitution by electron donating groups, 4′-OMe (**9l**) or 4′-Me (**9m**), diminished the affinity. In a similar manner, replacement of the *p*-hydroxyl (**9g**) by an electron withdrawing substituent; COOH (**9h**) or CF_3 (**9n**), diminished the inhibitory affinity dramatically probably due to unfavorable stereochemical interactions. The results discussed above suggest that the binding site for our compounds is not so deep as to accept a large substituent at the para position and could suggest that small polar group at this site could be better.

Molecular Modeling. To rationalize the above-described results, the structural basis of observed affinity was investigated by means of combined approach of homology modeling and receptor−ligand docking. The homology models of hCD22 and mCD22 were constructed using the crystal structure of Sn in complex with BPC-Neu5Ac.[15] These ligand bound models were

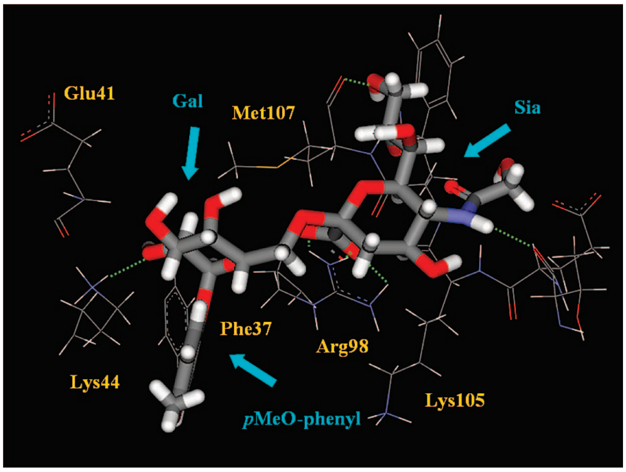


Figure 3. Binding mode of compound **10** in hCD22. Green line represents the hydrogen bonding.

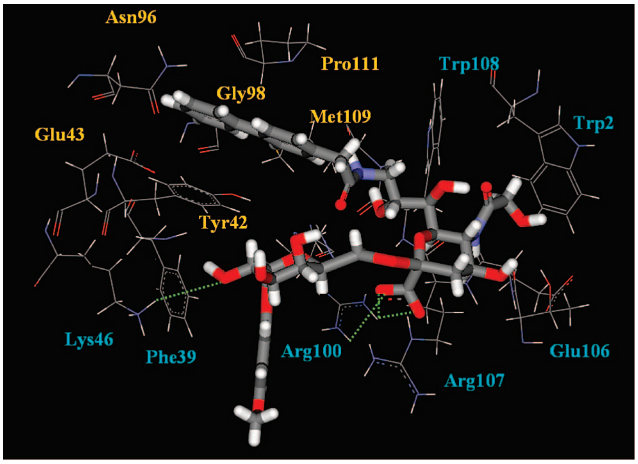


Figure 4. Binding mode of compound **8m** in the binding site of mCD22. The amino acids residues which interact with the C9 substituent are given in yellow color. Green line represents the hydrogen bonding.

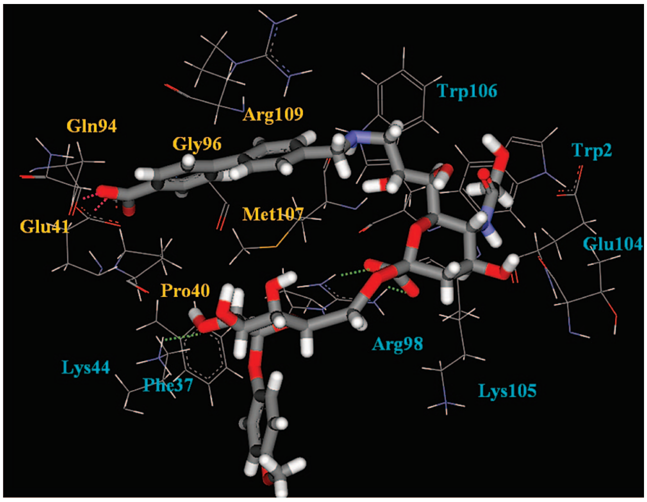


Figure 5. Binding mode of compound **9h** in the binding site of hCD22. The amino acids residues which interact with the C9 substituent are given in yellow color. Green and pink lines represent the hydrogen bonding and steric clash, respectively.

built according to the reported sequence alignment of N-terminal domain, which contains the groups responsible for ligand recognition and binding.[15] A series of antagonists (**10**, **8l**, **8m**, **9d**, **9g**, **9h**, and **9i**) were manually docked into homology models in a proposed binding mode. The resulting complexes were energetically refined to maximize the interactions and also to reduce the steric clashes.

To look into the key modification of present study, i.e., *p*-methoxyphenyl substitution at the reducing end of the Siaα2-6Gal, the binding pose of the compound **7a** in both of the models was examined. In the hCD22 model, the *p*-methoxyphenyl group may interact with the hydrophobic patch formed by the residues Phe37, Lys44, Arg98, and Lys105 at the vicinity of the binding site via steric and/or noncovalent interactions (Figure 3). This hydrophobic patch also conserved in mCD22, where only Lys105 is replaced with equivalent substitution Arg107. This observation suggests that these interactions of ligand with the hydrophobic patch of the receptor could increase the binding affinity as compared to the control compound **10**.

The docked pose of **8l** revealed that the biphenyl group sterically fits into the hydrophobic channel in hCD22 and it appears to be more favorable than mCD22, where side chain rigid Pro111 in mCD22 is replaced by flexible Arg109 in hCD22. This finding is in line with a previous study, which suggested that the biphenyl substituent could be sandwiched between the side chain residues of hCD22 hydrophobic pocket.[15] This fact could be a reason for the increased affinity of **8l** to hCD22 over mCD22. Conversely, the side chain residues of mCD22 at the ligand binding site preclude this highly favorable packing mode.

Interestingly, the binding pose of **8m** in mCD22 seems as favorable as hCD22, as the tail phenyl group of biphenyl can form more stable stacking interactions with Tyr42 because of its increased flexibility fetched in by the CH_2 group between the aromatic ring and the amidic carbonyl group (Figure 4).

Another interesting observation is that the binding mode of **9d** in both models looks favorable, probably differentiated shape of the binding sites and the rotational flexibility at C9 of **9d** could be responsible for the slight differences in the binding affinities and the same is applicable for **9g**. It is worth noting that three out of the six amino acid residues that accommodate C9 substituents are different although they offer comparable hydrophobic face.

Additionally, the docked pose of **9h** in hCD22 (Figure 5) shows some possible steric clashes with the distal end of the binding site which could be accounted for by its slight decrease in the binding affinity and these steric clashes are apparently not observed in mCD22. Conversely, the docked pose of **9i** in hCD22 looks more favorable than mCD22, where biphenyl ring orientation with the mCD22 Tyr42 is slightly disturbed and that is reasonable to apprehend the decreased binding affinity (Figure 6). Another possibility not to negate is that different amino acid substitutions at identical positions (Gln94 (hCD22) and Asn96 (mCD22)) can create differential steric volume, which also could be speculated for the differential binding of **9h** and **9i**. The lower activities exhibited by **9l**−**n** can be attributed to the presence of relatively bulky substituents (methoxy, methyl, and triflurom-ethyl, respectively) in proximity to the polar amino acid residues, Gln94 (hCD22) and Asn96 (mCD22), which can potentially form unfavorable interactions.

Conclusions

In summary, we have documented the development and structural optimization of a new series of sialosides as CD22-specific inhibitors. The steric space around 9-position of sialic

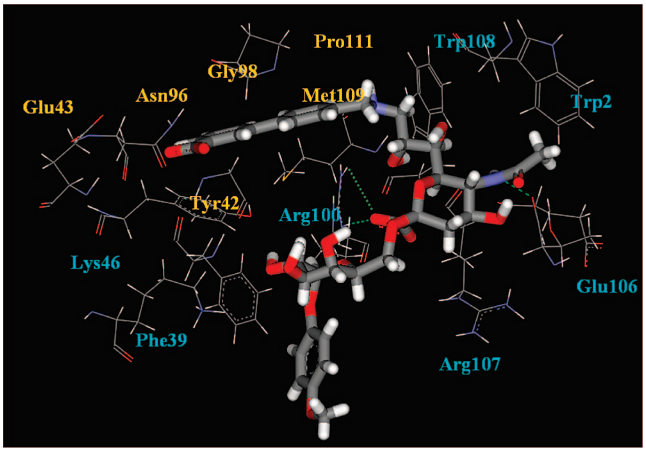


Figure 6. Binding mode of compound **9i** in the binding site of mCD22. The amino acids residues which interact with the C9 substituent are given in yellow color. Green line represents the hydrogen bonding.

acid moiety has been explored using relatively small and large bulky substituents. As concluded from the preliminary SAR studies, the presence of biphenyl ring at 9-position of sialic acid moiety is the key structural element for the affinity. 2′- and 4′-Hydroxyl derivative of biphenyl ring and the replacement of amidic carbonyl group with methylene yielded the most potent compounds in this series (**9g** and **9k**). Replacement of hydroxyl group of **9g** with electron donating or electron withdrawing substituents decreased the inhibitory activities. The effect of these modifications was more pronounced for mCD22 than for hCD22, while the later responded better for alkyl chain modifications. The best results of our lead optimization efforts are compounds **8o**, **9d**, **9g**, and **9k** (IC_{50} values 0.40, 0.47, 0.24, 0.23 μM, respectively) for hCD22 and **8p**, **8q**, and **9f** (IC_{50} values 1.70, 2.90, and 4.10 μM, respectively) for mCD22. Docking studies were carried out to visualize the possible interactions at the molecular level and therefore help in extending our understanding of the nature of interactions with the proposed binding site.

These CD22 specific inhibitors may be useful tools to study the biology of B-cells, modulate B-cell dependent immune response, and deliver therapeutic agents or toxins to B-cells, including cancerous B-cells (B-cell targeting).

Experimental Section

Chemistry. General. Specific rotations were recorded in a 1 dm cell with a JASCO DIP-360 polarimeter. Elemental analyses were performed by using Micro Corder (MT-6) of J Science Lob. at the Life Science Research Centre, Gifu University. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-EX-400 (400 MHz) or JEOL JNM-ECA-500 (500 MHz). Chemical shifts are expressed in ppm (δ) relative to the signal of Me_4Si. Gal protons assigned a, while those of sialic acid assigned b. In some spectra, H_{1a} overlapped with the water signal from D_2O (**8r**, **9h**, and **9i**). MALDI-TOF MS spectra were recorded in positive ion mode on a Bruker Autoflex with the use of α-cyano-4-hydroxycinnamic acid (CHCA) as a matrix. Some spectra were recorded in negative ion mode. Solvents and reagents were used as received from commercial distributors without further purification. Anhydrous reactions were conducted under an argon atmosphere. TLC analysis was carried out on Merck TLC (silica gel $60F_{254}$ on glass plate), and compounds were visualized by exposure to UV light and/or by charring with 10% H_2SO_4 in ethanol. Silica gel (80 mesh and 300 mesh) manufactured by Fuji Silysia Co. was used for flash column chromatography. The quantity of silica gel was usually estimated as 100- to 150-fold weight of the sample to be charged. Reversed phase silica gel (Wakogel 50C18) was purchased from Wako Pure Chemical Industries, Ltd. HPLC grade water and methanol (WAKO) were used for separation of the final compounds. Solvent systems in chromatography were specified in v/v. All evaporations and concentrations were carried out in vacuo.

***p*-Methoxyphenyl 2,3-di-*O*-benzoyl-*β*-D-galactopyranoside (2).** A solution of compound **1** (3.07 g, 5 mmol) in AcOH/H_2O (20 mL, 8:2, v/v) was heated at 60 °C and monitored by TLC. The excess solvent was removed under reduced pressure and the residue chromatographed on silica gel (2% methanol/chloroform) to afford compound **2** (1.97 g, 89%) as a colorless solid: R_f 0.49 (1:9 methanol/chloroform); $[\alpha]_D^{26}$ +106.3° (*c* 4.8, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 8.01−7.96 (m, 4 H, Ar−H), 7.54−7.48 (m, 2 H, Ar−H), 7.40−7.37 (m, 4 H, Ar−H), 6.94 (d, 2 H, Ar−H), 6.76 (d, 2 H, Ar−H), 5.99 (dd, J = 8.0, 10.3 Hz, 1 H, H_2), 5.26 (dd, J = 2.8, 10.3 Hz, 1 H, H_3), 5.15 (d, J = 8.0 Hz, 1 H, H_1), 4.97 (d, J = 5.1 Hz, 1 H, C4-OH), 4.44 (m, 1 H, H_4), 4.37 (t, J = 6.0, 5.7 Hz, 1 H, H_5), 3.91 (m, J = 5.7 Hz, 2 H, H_{6a}, H_{6b}), 3.83 (t, J = 5.7 Hz, 1 H, 6-OH), 3.74 (s, 3 H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 165.8, 151.1, 133.5, 133.2, 129.7, 129.4, 128.4, 101.2, 74.4, 74.2, 69.4, 68.3, 62.6, 55.6. MALDI-TOF MS calcd for $C_{27}H_{26}O_9Na$ $(M + Na)^+$, 517.14; found, 517.21.

Methyl (phenyl 5-benzyloxyacetamido-3,5-dideoxy-2-thio-D-*glycero*-*β*-D-*galacto*-2- nonulopyranosid)onate (4). To a stirred solution of **3** (11 g, 18.83 mmol) in dry methanol (125 mL) was added methanesulfoic acid (3 mL, 46.25 mmol). The mixture was stirred for 24 h at 60 °C, then neutralized with triethylamine (6.2 mL) and concentrated in vacuo. To a solution of the residue in CH_3CN-H_2O (15:1, 200 mL) were added succinimidyl ester of *O*-benzylglycolic acid (6.25 g, 23.78 mmol) and triethylamine (4 mL). After being stirred for 24 h at room temperature, the mixture was concentrated in vacuo.

Column chromatography (2% methanol/chloroform) of the residue on silica gel followed by crystallization from ethanol−water gave **4** (6.94 g, 75%) as a colorless solid: R_f 0.64 (1:5 methanol/chloroform); $[\alpha]_D^{23}$ −60.8 (*c* 10.2, CH_3OH). ^{1}H NMR (CD_3OD): δ 7.60−7.58 (m, 2 H, Ar−H), 7.42−7.30 (m, 8 H, Ar−H), 4.64−4.62 (m, 3 H, $PhCH_2$, H_6), 4.22 (td, J = 4.6, 12.0 Hz, 1 H, H_4), 4.03 (s, 2 H, CH_2CO), 3.97 (t, J = 10.3 Hz, 1 H, H_5), 3.82 (dd, J = 3.4, 14.3 Hz, 1 H, H_{9a}), 3.79 (dt, J = 3.4, 5.1 Hz, 1 H, H_8), 3.67 (dd, J = 5.1, 14.3 Hz, 1 H, H_{9b}), 3.57 (br-d, J = 10.3 Hz, 1 H, H_7), 3.49 (s, 3 H, OCH_3), 2.70 (dd, J = 4.6, 13.7 Hz, 1 H, H_{3eq}), 1.96 (t, J = 12.0, 13.7 Hz, 1 H, H_{3ax}). ^{13}C NMR (CD_3OD): δ 173.8, 170.7, 138.6, 137.5, 137.3, 131.5, 130.5, 129.9, 129.8, 129.7, 129.5, 129.3, 129.0, 74.5, 74.4, 73.2, 71.3, 70.6, 70.1, 67.7, 65.1, 53.9, 52.9, 42.4, 36.6. MALDI-TOF MS calcd for $C_{25}H_{31}NO_9SNa$ $(M + Na)^+$, 544.16; found, 544.24.

Methyl (phenyl 4,7,8,9-tetra-*O*-acetyl-5-benzyloxyacetamido 3,5-dideoxy-2-thio-D-*glycero*-*β*-D-*galacto*-2-nonulopyranosid)-onate (5a). Compound **4** (1.2 g, 2.3 mmol) was treated with acetic anhydride (4 mL) and pyridine (4 mL) for 6 h at room temperature. The solution concentrated in vacuo. The residue was subjected for column chromatography (4:5 ethyl acetate/hexane) to yield **5a** (1.5 g, 94.5%) as a colorless solid: R_f 0.34 (1:1 ethyl acetate/hexane); $[\alpha]_D^{22}$ −131.4 (*c* 10.2, CH_3OH). ^{1}H NMR ($CDCl_3$): 7.47−7.32 (m, 10 H, Ar−H), 6.66 (d, J = 10.8 Hz, 1 H, NH), 5.50 (dd, J = 2.3, 4.6 Hz, 1 H, H_7), 5.43 (td, J = 6.5, 10.5 Hz, 1 H, H_4), 4.70 (dd, J = 2.3, 10.5 Hz, 1 H, H_8), 4.63 (d, J = 11.4 Hz, 1 H, PhCH), 4.54 (d, J = 11.4 Hz, 1 H, PhCH), 4.48 (dd, J = 2.3, 10.3 Hz, 1 H, H_6), 4.19 (q, J = 10.8 Hz, 1 H, H_5), 4.02 (dd, J = 8.6, 12.0 Hz, 1 H, H_{9a}), 3.87 (d, J = 9.7 Hz, 2 H, glycolyl $C\underline{H_2}CO$), 3.60 (s, 3 H, OCH_3), 3.35 (dd, J = 9.1, 13.1 Hz, 1 H, H_{9b}), 2.71 (dd, J = 4.6, 13.7 Hz, 1 H, H_{3eq}), 2.13−2.00 (m, 13 H, 4 OAc, H_{3ax}). ^{13}C NMR ($CDCl_3$): δ 170.7, 170.4, 170.3, 170.2, 170.1, 168.1, 136.7, 136.1, 129.7, 129.0, 128.8, 128.6, 128.3, 128.2, 128.0, 73.4, 72.9, 68.9, 68.7, 68.6, 68.0, 67.05, 62,5, 52.6, 52.1, 51.3, 48.5, 37.4, 21.0, 20.8, 20.7, 20.6. MALDI-TOF MS calcd for $C_{33}H_{39}NO_{13}SNa$ $(M + Na)^+$, 712.20; found, 712.21.

Methyl (phenyl 4,7,8-tri-*O*-acetyl-9-azido-5-benzyloxyacetamido 3,5,9-trideoxy-2-thio-D-*glycero*-*β*-D-*galacto*-2-nonulopyranosid)-onate (5b). To a mixture of compound **4** (6.4 g, 12.30 mmol), triphenylphosphine (3.6 g, 13.66 mmol) and sodium azide (4.01 g, 61.54 mmol) in dry DMF (50 mL) was added carbon tetrabromide (4.53 g, 13.66 mmol) at room temperature. The mixture was stirred at room temperature for 24 h,and then methanol was added until the mixture turned into a clear solution. Stirring was continued for another 3 h. The solution concentrated in vacuo, and the residue was treated with acetic anhydride (20 mL) and pyridine (20 mL) for 6 h at room temperature. The solution concentrated in vacuo. The residue was subjected for column chromatography (1:1 ethyl acetate/hexane) to yield **5b** (6.88 g, 83.5%) as a colorless solid: R_f 0.3 (5:4 ethyl acetate/hexane); $[\alpha]_D^{26}$ −151.4 (*c* 10.8, CH_3OH).IR (KBr) 3361, 3030, 2950, 2360, 2100, 1746, 1687, 1525, 1237, 750, 696 cm^{-1}.^{1}H NMR ($CDCl_3$): δ 7.46−7.35 (m, 10 H, Ar−H), 6.51 (d, J = 10.8 Hz, 1 H, NH), 5.46 (dd, J = 2.3, 4.6 Hz, 1 H, H_7), 5.39 (m, 1 H, H_4), 4.79 (m, 1 H, H_8), 4.60 (d, J = 11.4 Hz, 2 H, PhCH, H_6), 4.54 (d, 1 H, PhCH), 4.17 (q, J = 10.8 Hz, 1 H, H_5), 3.87−3.83 (2 d, 2 H, glycolyl C$\underline{H}_2$CO), 3.67−3.64 (m, 4 H, OCH_3, H_{9a}), 3.32 (dd, J = 9.1, 13.1 Hz, 1 H, H_{9b}), 2.73 (dd, J = 4.5, 13.7 Hz, 1 H, H_{3eq}), 2.13−2.00 (m, 10 H, 3 OAc, H_{3ax}). ^{13}C NMR ($CDCl_3$): δ 170.6, 170.3, 170.2, 170.1, 168.1, 135.9, 130.1, 129.3, 128.6, 128.4, 128.2, 128.0, 88.6, 76.6, 74.2, 73.4, 72.9, 68.9, 68.8, 68.7, 52.6, 49.8, 48.5, 37.5, 20.9, 20.8, 20.7. MALDI-TOF MS calcd for $C_{31}H_{36}N_4O_{11}SNa$ $(M + Na)^+$, 695.20; found, 695.36.

General Procedure for Sialylation. To a solution of **2** (0.644 g, 1.26 mmol, 1.0 equiv and **5** (1.041 g, 1.51 mmol, 1.2 equiv) in dry acetonitrile−dichloromethane (5:1, 48 mL) was added molecular sieves 3 Å (8.0 g), and the mixture was stirred for 6 h at room temperature under argon atmosphere then cooled to −20 °C. *N*-Iodosuccinimide (NIS, 1.024 g, 4.54 mmol, 3.0 equiv) was added to the cooled mixture while stirring. After 20 min,trifluoromethanesulfonic acid (TfOH, 45.5 μL, 0.45 mmol) was added dropwise to the reaction mixture. After 16 h at −20 °C, the precipitate was filtered off and thoroughly washed with chloroform. The filterate and washings were combined and the solution was successively washed with 1 M Na_2CO_3, 1 M $Na_2S_2O_3$,and brine, dried (Na_2SO_4),and concentrated. The residue was applied to a silica gel column (0:1 to 1:99 methanol-chloroform) to furnish compound **6** (0.85 g, 64%) as a colorless solid.

***p*-Methoxyphenyl (methyl 4,7,8,9-tetra-*O*-acetyl-5-benzyloxyacetamido 3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-2,3-di-*O*-benzoyl-*β*-D-galactopyranoside (6a).** R_f 0.38 (1% methanol/chloroform); $[\alpha]_D^{23}$ +29.9 (*c* 11.2, CH_3OH). ^{1}H NMR ($CDCl_3$): δ 8.01 (dd, J = 7.2, 8.3 Hz, 4 H, Ar−H), 7.50−7.48 (m, 2 H, Ar−H), 7.39−7.26 (m, 9 H, Ar−H), 7.02 (d, J = 9.2 Hz, 2 H, Ar−H), 6.77 (d, J = 9.2 Hz, 2 H, Ar−H), 6.37 (d, J = 9.7 Hz, 1 H, N$\underline{H}$), 6.00 (dd, J = 8.0, 10.5 Hz, 1 H, H_{2a}), 5.43 (m, 1 H, H_{8b}), 5.37 (dd, J = 3.4, 10.3 Hz, 1 H, H_{3a}), 5.32 (d, J = 7.4 Hz, 1 H, H_{7b}), 5.15 (d, J = 8.0 Hz, 1 H, H_{1a}), 4.92 (m, 1 H, H_{4b}), 4.56 (q, J = 12.0, 25.2 Hz, 2 H, $PhCH_2$), 4.42−4.39 (m, 2 H, H_{4a}, $H_{9b'}$), 4.16−4.10 (m, 2 H, H_{5b}, H_{6b}), 4.06(dd, J = 6.3, 12.6 Hz, 1 H, $H_{9b''}$), 3.99−3.95 (m, 2 H, H_{5a}, $H_{6a'}$), 3.92−3.83 (m, 6 H, $H_{6a''}$, glycolyl C$\underline{H}_2$CO, COOC$\underline{H}_3$), 3.74 (s, 3 H, OCH_3), 3.15 (br. s, 1 H, 4a-OH), 2.65 (dd, J = 4.6, 12.6 Hz, 1 H, H_{3beq}), 2.14, 2.12, 2.08 (3s, 9 H, 3 OAc), 2.04−1.97 (m, 4 H, OAc, H_{3bax}).^{13}C NMR ($CDCl_3$): δ 170.9, 170.3, 170.2, 170.1, 170.0, 167.8, 165.8, 165.3, 155.5, 151.4, 136.7, 133.2, 133.0, 129.8, 129.7, 129.5, 129.2, 128.5, 128.3, 128.2, 128.1, 128.0, 118.9, 114.3, 101.2, 98.9, 74.3, 73.4, 72.9, 72.7, 69.6, 69.0, 68.7, 68.6, 67.2, 66.7, 62.8, 62.6, 55.5, 53.0, 48.4, 21.0, 20.7, 20.6, 20.5. MALDI-TOF MS calcd for $C_{54}H_{59}NO_{22}Na$ $(M + Na)^+$, 1096.34; found, 1096.45.

***p*-Methoxyphenyl (methyl 4,7,8-tri-*O*-acetyl-9-azido-5-benzyloxyacetamido 3,5,9-trideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-2,3-di-*O*-benzoyl-*β*-D-galactopyranoside (6b).** R_f 0.30 (1% methanol/chloroform); $[\alpha]_D^{31}$ +45.4 (*c* 12.0, CH_3OH). IR (KBr) 3300, 3030, 2950, 2100, 1717, 1507, 1217, 712 cm^{-1}.^{1}H NMR ($CDCl_3$): δ 8.02−7.97 (dd, 4 H, Ar−H), 7.52−7.48 (m, 2 H, Ar−H), 7.40−7.33 (m, 9 H, Ar−H), 7.02 (d, J = 9.2 Hz, 2 H, Ar−H), 6.78 (d, J = 9.2 Hz, 2 H, Ar−H), 6.34 (d, J = 9.2 Hz, 1H, N$\underline{H}$), 5.97 (dd, J = 8.0, 10.5 Hz, 1 H, H_{2a}), 5.37 (m, 1 H, H_{8b}), 5.34 (dd, J = 3.4, 10.3 Hz, 1 H, H_{3a}), 5.30 (d, J = 7.4 Hz, 1 H, H_{7b}), 5.14 (d, J = 8.0 Hz, 1 H, H_{1a}), 4.91 (m, 1 H, H_{4b}), 4.56 (q, J = 11.4, 32.5 Hz, 2 H, $PhCH_2$), 4.41 (br. d, 1 H, H_{4a}), 4.16−4.13 (m, 2 H, H_{5b}, H_{6b}), 4.02−3.96 (m, 2 H, H_{5a}, $H_{6a'}$), 3.92−3.81 (m, 6 H, $H_{6a''}$, glycolyl C$\underline{H}_2$CO, COOC$\underline{H}_3$), 3.75 (s, 3 H, OCH_3), 3.64 (dd, J = 6.0, 13.7 Hz, 1 H, $H9_{b'}$), 3.26 (dd, J = 6.0, 13.7 Hz, 1 H, $H_{9b''}$), 2.82 (br d, J = 5.5, 1 H, 4a-OH), 2.66 (dd, J = 4.5, 12.5 Hz, 1 H, H_{3beq}), 2.17, 2.03, 2.00 (3s, 9 H, 3 OAc), 1.99 (t, J = 12.6 Hz, 1 H, H_{3bax}).^{13}C NMR ($CDCl_3$): δ 170.3, 170.2, 170.1, 167.8, 165.9, 165.3, 155.6, 136.7, 133.4, 133.1, 129.8, 129.7, 129.5, 129.1, 128.6, 128.4, 128.3, 128.2, 128.0, 119.1, 114.4, 101.4, 99.0, 73.4, 72.9, 72.8, 69.9, 69.5, 69.0, 68.6, 67.9, 67.0, 63.2, 50.9, 48.4, 21.0, 20.7, 20.6. MALDI-TOF MS calcd for $C_{52}H_{56}N_4O_{20}Na$ $(M + Na)^+$, 1079.34; found, 1079.43.

General Procedure for Deprotection and Catalytic Hydrogenation. To a solution of compound **6** (0.85 g, 0.8 mmol) in ethanol (20 mL) was added solution of $LiOH{\cdot}H_2O$ (0.2 g, 4.8 mmol, 6 equiv) in water (5 mL). After stirring at room temperature for 6 h, the reaction mixture was treated with acidic (Dowex 50, H^+) and the suspension was filtered. The filterate was concentrated in vacuo. The residue was dissolved in ethanol/water (1:1 v/v; 20 mL). Palladium hydroxide on carbon 20% (0.9 g) and acetic acid (80 μL) were added to the solution. The reaction mixture was hydrogenolyzed under H_2 gas atmosphere with stirring at 50 °C for 24 h. The mixture was filtered through a plug of celite. The filterate was concentrated in vacuo, reconstituted into water, and applied onto a silica reversed-phase column. The compound was eluted with a gradient of methanol−water (0:1 to 10:90 methanol/water) to afford compound **7** (0.4 g, 84.5%) as a white fluffy solid after a final lyophilization from water. The solvent system (ethyl acetate/methanol/water/acetic acid 10:3:3:1) was used for following up the reaction and determining R_f values.

***p*-Methoxyphenyl (3,5-dideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (7a).** According to general procedure without employing acetic acid during hydrogenation. R_f 0.1; $[\alpha]_D^{23}$ −44.2 (*c* 2.6, MeOH). ^{1}H NMR (CD_3OD): δ 7.03 (d, J = 9.16 Hz, 2 H, Ar−H), 6.83 (d, J = 9.16 Hz, 2 H, Ar−H), 4.69 (d, J = 7.44 Hz, 1 H, H_{1a}), 4.03 (d, J = 2.30 Hz, 2 H, glycolyl C$\underline{H}_2$CO), 3.95−3.93 (m, 2 H, $H_{6a'}$, H_{8b}), 3.85 (m, 1 H, H_{4b}), 3.83−3.67 (m, 10 H, H_{2a}, H_{3a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, OCH_3), 3.60 (dd, J = 5.7, 9.6 Hz, 1 H, H_{9a}), 3.57−3.54 (m, 1 H, H_{7b}), 3.50 (d, J = 9.6 Hz, 1 H, $H_{9b'}$), 2.86 (dd, J = 4.6, 12.6 Hz, 1 H, H_{3beq}), 1.62 (t, J = 12.6 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.8, 177.3, 156.5, 153.2, 119.3, 115.5, 103.8, 75.2, 74.5, 73.8, 72.3, 72.2, 69.9, 69.0, 64.1, 62.5, 56.2, 53.6, 43.8, 42.4. MALDI-TOF MS calcd for $C_{24}H_{35}NO_{16}Na$ $(M + Na)^+$, 616.18; found, 616.17. Anal. ($C_{24}H_{35}NO_{16}{\cdot}3H_2O$) N, H. C: calcd, 44.51; found, 44.00.

***p*-Methoxyphenyl (9-amino-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (7b).** R_f 0.25; $[\alpha]_D^{25}$ −49.5 (*c* 10.2, H_2O). ^{1}H NMR (D_2O with a few drops of CD_3OD): δ 7.07 (d, J = 9.2 Hz, 2 H, Ar−H), 6.85 (d, J = 9.2 Hz, 2 H, Ar−H), 4.73 (d, J = 7.8 Hz, 1 H, H_{1a}), 4.07−4.02 (m, 3 H, glycolyl C$\underline{H}_2$CO, H_{8b}), 3.94−3.93 (m, 2 H, H_{4a}, $H_{6a'}$), 3.85 (m, 1 H, H_{4b}), 3.80−3.72 (m, 8 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}, OCH_3), 3.59 (dd, J = 3.2, 9.6 Hz, 1 H, H_{3a}), 3.43(d, J = 8.5 Hz, 1 H, H_{7b}), 3.27 (dd, 1 H, $H_{9b'}$), 2.95 (dd, J = 12.0 Hz, 1 H, $H_{9b''}$), 2.86 (dd, J = 5.0, 12.0 Hz, 1 H, H_{3beq}), 1.65 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.3, 156.5, 153.2, 119.3, 115.5, 103.8, 75.2, 74.5, 73.8, 72.3, 72.2, 69.9, 69.0, 64.1, 62.5, 56.2, 53.6, 43.8, 42.4. MALDI-TOF MS calcd for $C_{24}H_{38}N_2O_{15}$ $(M + H)^+$, 593.22; found, 593.30. Anal. ($C_{24}H_{36}N_2O_{15}{\cdot}2H_2O$) H, C. N: calcd, 4.46; found, 4.03.

General Procedure for Amidation. *p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-substituted carboxamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8a−r). To compound **7** (40 mg, 0.067 mmol) in water (1 mL) was added solution of the appropriate *N*-hydroxysuccinimidyl ester (0.08 mmol) in acetonitrile (5 mL) while maintaining the pH between 8.0−9.0 with saturated sodium hydrogen carbonate. The mixture was stirred at room temperature for 48 h. The solvent was evaporated, and the residue was reconstituted into water and applied onto a silica reversed phase column pre-equilibrated in water. The compound was eluted with a gradient of methanol−water (0:1 to

40:100) to afford the title compounds **8a−r** in (70−85%) yields as a white fluffy solid after a final lyophilization from water. The solvent system (ethyl acetate/methanol/water/acetic acid 10:3:3:1) was used for following up the reaction and determining R_f values.

***p*-Methoxyphenyl (9-benzamido-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8a).** The yield was 85%; R_f 0.35; $[\alpha]_D^{26}$ −17.1 (*c* 6.7, H_2O). ^1H NMR (CD_3OD): *δ* 7.68 (d, 2 H, Ar−H), 7.38−7.30 (m, 3 H, Ar−H), *δ* 6.89 (d, J = 8.6 Hz, 2 H, Ar−H), 6.67 (d, J = 8.6 Hz, 2 H, Ar−H), 4.59 (d, J = 7.4 Hz, 1 H, H_{1a}), 3.94−3.59 (m, 15 H, glycolyl $C\underline{H}_2CO$, H_{8b}, H_{4b}, H_{6b}, H_{5b}, H_2, H_{4a}, H_{5a}, $H_{6a'}$, $H_{6a''}$, OCH_3, H_{3a}), 3.59−3.25 (m, 3 H, H_{7b}, $H_{9b'}$, $H_{9b''}$), 2.75 (br. s, 1 H, H_{3beq}), 1.56 (br. s, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): *δ* 156.5, 153.2, 135.5, 132.6, 129.5, 128.3, 119.1, 115.4, 103.8, 75.0, 74.6, 74.0, 72.4, 69.8, 69.7, 63.7, 62.5, 56.0, 53.8, 44.4, 42.5. MALDI-TOF MS calcd for $C_{31}H_{40}N_2O_{16}Na$ (M + Na)$^+$, 719.22; found, 719.30. Negative ion mode calcd for $C_{31}H_{39}N_2O_{16}$ (M − H)$^-$, 695.64; found, 695.41. Anal. ($C_{31}H_{40}N_2O_{16}\cdot 3H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(2-hydroxybenzamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8b).** The yield was 75%; R_f 0.40; $[\alpha]_D^{27}$ −15.1° (*c* 10.9, H_2O). ^1H NMR (CD_3OD): *δ* 7.76 (m, 1 H, Ar−H), 7.33 (m, 1 H, Ar−H), 7.01 (d, J = 8.6 Hz, 2 H, Ar−H), 6.88−6.86 (m, 2 H, Ar−H), 6.77 (d, J = 8.6 Hz, 2 H, Ar−H), 4.69 (d, J = 7.4 Hz, 1 H, H_{1a}), 4.03−3.69 (m, 15 H, H_{2a}, H_{3a}, H_{4a}, H_{5a}, $H_{6a'}$, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, H_{8b}, glycolyl $C\underline{H}_2CO$, OCH_3), 3.59−3.25 (m, 3 H, H_{7b}, $H_{9b'}$, $H_{9b''}$), 2.79 (br-d, 1 H, H_{3beq}), 1.77 (br-d, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): *δ* 156.5, 153.2, 134.6, 129.5, 120.2, 119.2, 119.1, 118.2, 115.4, 103.9, 75.0, 74.7, 74.3, 72.3, 69.8, 63.8, 56.0, 53.6, 49.8, 49.6, 49.5, 49.4, 49.3, 48.5, 44.4. MALDI-TOF MS calcd for $C_{31}H_{39}ClN_2O_{17}Na$ (M + Na)$^+$, 769.183; found, 769.240. Negative ion mode calcd for $C_{31}H_{38}ClN_2O_{17}$ (M − H)$^-$, 745.186; found, 745.460. Anal. ($C_{31}H_{40}N_2O_{17}\cdot 3H_2O$) C, H, N.

***p*-Methoxyphenyl (9-(5-chloro-2-hydroxybenzamido)-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8c).** The yield was 70%; R_f 0.38, $[\alpha]_D^{27}$ −15.1 (*c* 10.9, H_2O). ^1H NMR (CD_3OD): *δ* 7.82 (d, J = 2.5 Hz, 1 H, Ar−H), 7.29 (dd, J = 2.5, 9.0 Hz, 1 H, Ar−H), 7.00−6.98 (m, 2 H, Ar−H), 6.85 (d, J = 9.0 Hz, 2 H, Ar−H), 6.7 (d, J = 9.0 Hz, 2 H, Ar−H), 4.68 (d, J = 7.5 Hz, 1 H, H_{1a}), 4.05−4.00 (m, 3 H, glycolyl $C\underline{H}_2CO$, H_{8b}), 3.96−3.80 (m, 2 H, H_{4a}, $H_{6a'}$), 3.83−3.69 (m, 11 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, H_{7b}, OCH_3), 3.57 (dd, J = 5.0, 9.0 Hz, 1 H, H_{3a}), 3.46−3.39 (m, 2 H, $H_{9b'}$, $H_{9b''}$), 2.85 (dd, J = 4.0, 12.0 Hz, 1 H, H_{3beq}), 1.63 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): *δ* 177.1, 156.4, 153.2, 134.0, 129.4, 124.8, 119.9, 119.1, 118.2, 115.3, 103.9, 75.0, 74.6, 74.0, 72.4, 72.2, 71.3, 69.7, 69.3, 63.7, 62.5, 56.0, 53.7, 49.8, 49.5, 49.2, 48.4, 43.9, 42.6. MALDI-TOF MS calcd for $C_{31}H_{39}ClN_2O_{17}Na$ (M + Na)$^+$, 769.18; found, 769.24. Negative ion mode calcd for $C_{31}H_{38}ClN_2O_{17}$ (M − H)$^-$, 745.18; found, 745.46. Anal. ($C_{31}H_{39}ClN_2O_{17}\cdot 3.5H_2O$) C, N. H: calcd, 5.72; found, 5.18.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-nicotinoylamino-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8d).** The yield was 78%; R_f 0.38; $[\alpha]_D^{27}$ −3.12 (*c* 11.2, H_2O). ^1H NMR (CD_3OD): *δ* 8.93 (d, J = 2.3 Hz, 1 H, Ar−H), 8.60 (dd, J = 1.7, 5.1 Hz, 1 H, Ar−H), 8.18 (d, J = 8.6 Hz, 1 H, Ar−H), 7.45 (t, J = 4.0, 8.0 Hz, 1 H, Ar−H), 6.97 (d, J = 9.0 Hz, 2 H, Ar−H), 6.75 (d, J = 9.0 Hz, 2 H, Ar−H), 4.68 (d, J = 7.4 Hz, 1 H, H_{1a}), 4.02 (m, 3 H, glycolyl $C\underline{H}_2CO$, H_{8b}), 3.95 (d, J = 3.5 Hz, 1 H, H_{4a}), 3.92 (dd, J = 5.0, 9.0 Hz 1 H, $H_{6a'}$), 3.89−3.70 (m, 11 H, H_{4b}, H_{5b}, H_{6b}, H_{7b}, H_{2a}, H_{5a}, $H_{6a''}$, OCH_3), 3.58 (dd, J = 3.5, 10.0 Hz, 1 H, H_{3a}), 3.47−3.38 (m, 2 H, $H_{9b'}$, $H_{9b''}$), 2.84 (dd, J = 4.0, 12.0 Hz, 1 H, H_{3beq}), 1.63 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): *δ* 177.1, 168.0, 156.4, 153.2, 152.4, 149.2, 137.0, 132.0, 125.0, 119.0, 119.1, 115.4, 103.8, 102.1, 75.0, 74.7, 74.1, 72.4, 71.4, 69.7, 69.3, 63.7, 62.6, 56.0, 53.7, 49.7, 49.5, 48.4, 44.6, 42.6. MALDI-TOF MS calcd for $C_{30}H_{39}N_3O_{16}Na$ (M + Na)$^+$,720.22; found, 720.30. Negative ion mode calcd for $C_{30}H_{38}N_3O_{16}$ (M − H)$^-$, 696.22; found, 696.46. Anal. ($C_{30}H_{39}N_3O_{16}\cdot 4H_2O$) C, N. H: calcd, 6.15; found, 5.64.

***p*-Methoxyphenyl (9-cyclohexanecarboxamido-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8e).** The yield was 80%; R_f 0.30; $[\alpha]_D^{27}$ −34.3 (*c* 10.2, H_2O). ^1H NMR (CD_3OD): *δ* 6.93 (d, J = 9.0 Hz, 2 H, Ar−H), 6.73 (d, J = 9.0 Hz, 2 H, Ar−H), 4.59 (d, J = 7.4 Hz, 1 H, H_{1a}), 3.94 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.86 (d, J = 3.4 Hz, 1 H, H_{4a}), 3.85−3.75 (m, 2 H, H_{8b}, $H_{6a'}$), 3.73−3.6 (m, 9 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, OCH_3), 3.50−3.46 (m, 2 H, H_{7b}, H_{3a}), 3.23 (d, J = 12.0 Hz, 1 H, $H_{9b'}$), 3.11 (dd, J = 8, 12 Hz, 1 H, $H_{9b''}$), 2.75 (dd, J = 5.0, 13.0 Hz, 1 H, H_{3beq}), 2.10−2.00 (m, 1 H, cyclohexane H), 1.61 (m, 6 H, cyclohexane 5 H, H_{3bax}), 1.35−1.02 (m, 5 H, cyclohexane H). ^{13}C NMR (CD_3OD): *δ* 179.4, 177.0, 174.6, 156.4, 153.2, 119.1, 115.4, 103.8, 102.1, 75.0, 74.6, 74.0, 72.4, 72.0, 71.4, 69.6, 69.3, 63.6, 62.6, 56.0, 53.7, 49.5, 48.4, 46.3, 43.5, 42.6, 30.7, 30.6, 26.8, 26.77, 26.7. MALDI-TOF mass for $C_{31}H_{46}N_2O_{16}Na$ (M + Na)$^+$, 725.27; found, 724.95. Negative ion mode calcd for $C_{31}H_{45}N_2O_{16}$ (M − H)$^-$, 701.27; found, 701.44. Anal. ($C_{31}H_{46}N_2O_{16}\cdot 4H_2O$) C, N. H: calcd, 7.03; found, 6.52.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-hexanamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8f).** The yield was 77%; R_f 0.54; $[\alpha]_D^{26}$ −30.2 (*c* 10.4, H_2O). ^1HNMR (CD_3OD): *δ* 6.93 (d, J = 9.5 Hz, 2 H, Ar−H), 6.73 (d, J = 9.5 Hz, 2 H, Ar−H), 4.59 (d, J = 8.0 Hz, 1 H, H_{1a}), 3.94 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.86 (d, J = 3.5 Hz, 1 H, H_{4a}), 3.82−3.80 (m, 2 H, H_{8b}, $H_{6a'}$), 3.69−3.60 (m, 9 H, H_{4b}, H_{5b}, H_{6b}, H_{2a}, H_5a, H_{6b}, OCH_3), 3.54 (dd, J = 11.0 Hz, 1 H, H_{7b}), 3.47 (dd, J = 3.5, 10.0 Hz, 1 H, H_{3a}), 3.23 (d, J = 13.5 Hz, 1 H, $H_{9b'}$), 3.07 (dd, J = 8.0, 13.5 Hz, 1 H, $H_{9b''}$), 2.75 (dd, J = 4.5, 12.5 Hz, 1 H, H_{3beq}), 2.04 (t, J = 7.5 Hz, 2 H, hexane CH_2), 1.52 (t, J = 12.5 Hz, 1 H, H_{3bax}), 1.46 (m, 2 H, hexane CH_2), 1.19 (m, 4 H, hexane CH_2CH_2), 0.78 (t, J = 6.5, 7.5 Hz, 3 H, hexane CH_3). ^{13}C NMR (CD_3OD): *δ* 177.1, 176.5, 174.6, 156.5, 153.3, 119.1, 115.4, 103.9, 102.1, 75.0, 74.6, 74.0, 72.4, 72.1, 71.3, 69.6, 69.3, 63.6, 62.6, 56.0, 53.7, 49.5, 48.4, 43.8, 42.6, 37.0, 32.5, 26.7, 23.3, 14.2. MALDI-TOF MS calcd for $C_{30}H_{46}N_2O_{16}Na$ (M + Na)$^+$, 713.27; found, 713.18. Negative ion mode calcd for $C_{30}H_{45}N_2O_{16}$ (M − H)$^-$, 689.28; found, 689.38. Anal. ($C_{30}H_{52}N_2O_{19}\cdot 3H_2O$) N. C: calcd, 48.38; found, 47.93. H: calcd, 7.04; found, 6.57.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(3-phenylpropionamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8g).** The yield was 76%; R_f 0.57; $[\alpha]_D^{27}$ −32.9 (*c*. 4.1, H_2O). ^1H NMR (CD_3OD): *δ* 7.14−7.04 (m, 5 H, Ar−H), 6.92 (d, J = 9 Hz, 2 H, Ar−H), 6.70 (d, J = 9 Hz, 2 H, Ar−H), 4.6 (d, J = 7.5 Hz, 1 H, H_{1a}), 3.93 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.86 (d, J = 3.0 Hz, 1 H, H_{4a}), 3.82−3.78 (m, 2 H, H_{8b}, $H_{6a'}$), 3.68−3.59 (m, 9 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, OCH_3), 3.55 (dd, J = 11.0 Hz, 1 H, H_{7b}), 3.47 (dd, J = 3.0, 10.0 Hz, 1 H, H_{3a}), 3.24 (d, J = 11.5 Hz, 1 H, $H_{9b'}$), 3.03 (dd, J = 8.5, 11.5 Hz, 1 H, $H_{9b''}$), 2.77−2.73 (m, 3 H, propionyl CH_2, H_{3beq}), 2.34 (t, J = 9.0, 7.5 Hz, 2 H, propionyl CH_2), 1.51 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): *δ* 177.1, 175.4, 174.6, 162.1, 156.5, 153.3, 142.3, 129.4, 129.3, 127.1, 119.1, 115.4, 103.9, 102.1, 75.0, 74.7, 74.0, 72.4, 72.2, 71.3, 69.6, 69.3, 63.6, 62.6, 56.0, 53.7, 49.6, 49.5, 48.4, 43.8, 42.7, 38.9, 32.9. MALDI-TOF MS calcd for $C_{33}H_{44}N_2O_{16}Na$ (M + Na)$^+$, 747.26; found, 747.44. Negative ion mode calcd for $C_{33}H_{43}N_2O_{16}$ (M − H)$^-$, 723.26; found, 723.630. Anal. ($C_{33}H_{44}N_2O_{16}\cdot 3.5H_2O$) C, N. H: calcd, 6.53; found, 6.10.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(3-(*p*-hydroxyphenyl) propionamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8h).** The yield was 70%; R_f 0.56; $[\alpha]_D^{27}$ −30.9 (*c* 10, H_2O). ^1H NMR (CD_3OD): *δ* 6.92 (d, J = 9.0 Hz, 2 H, Ar−H), 6.88 (d, J = 9.0 Hz, 2 H, Ar−H), 6.70 (d, J = 9.0 Hz, 2 H, Ar−H), 6.57 (d, J = 9.0 Hz, 2 H, Ar−H), 4.6 (d, J = 7.5 Hz, 1 H, H_{1a}), 3.94 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.86 (d, J = 3.0 Hz, 1 H, H_{4a}), 3.82−3.78 (m, 2 H, H_{8b}, $H_{6a'}$), 3.68−3.59 (m, 9 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, OCH_3), 3.55 (dd, J = 11.0 Hz, 1 H, H_{7b}), 3.47 (dd, J = 3.5, 10.0 Hz, 1 H, H_{3a}), 3.22 (br-d, 1 H, $H_{9b'}$), 3.03 (dd, J = 8.0, 13.0 Hz, 1 H, $H_{9b''}$), 2.74 (dd, J = 8.0, 12.0 Hz, 1 H, H_{3beq}), 2.66 (t, J = 7.5 Hz, 2 H, propionyl CH_2), 2.28 (t, J = 8.0, 7.5 Hz, 2 H, propionyl CH_2), 1.53 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): *δ* 177.1, 175.7, 174.6, 156.6, 156.5, 153.2, 133.0, 130.2, 119.1, 116.2, 115.4, 103.9, 102.1, 75.0, 74.6, 74.0, 72.4, 72.1, 71.3, 69.6, 69.3, 63.7, 62.6, 56.0, 53.7, 49.6, 49.5, 48.4, 43.8, 42.7, 39.9, 32.2. MALDI-TOF MS calcd for $C_{33}H_{44}N_2O_{17}Na$ $(M + Na)^+$, 763.25; found, 763.02. Negative ion mode calcd for $C_{33}H_{43}N_2O_{17}$ $(M - H)^-$, 739.25; found, 739.43. Anal. ($C_{33}H_{44}N_2O_{17}\cdot 3.5H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(4(1-pyrenyl)butanoylamino)-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranoside (8i).** The yield was 70%; R_f 0.63; $[\alpha]_D^{27}$ −18.4 (*c* 10.3, H_2O). ^1H NMR (CD_3OD): δ 8.22−7.98 (m, 8 H, Ar−H), 7.82 (d, *J* = 8.0 Hz, 1 H, Ar−H), 6.94 (d, *J* = 9.0 Hz, 2 H, Ar−H), 6.71 (d, *J* = 9.0 Hz, 2 H, Ar−H), 4.66 (d, *J* = 8.0 Hz, 1 H, H_{1a}), 4.10 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.98 (d, *J* = 3.5 Hz, 1 H, H_{4a}), 3.97 (dd, *J* = 8.0 Hz, 1 H, $H_{6a'}$), 3.91 (dd, *J* = 6.0, 9.5 Hz, 1 H, H_{8b}), 3.87−3.78 (m, 3 H, H_{5a}, $H_{6a''}$, H_{4b}), 3.74−3.65 (m, 4 H, H_{2a}, H_{5b}, H_{6b}, H_{7b}), 3.61 (d, *J* = 3.5, 10.5 Hz, 1 H, H_{3a}), 3.59 (s, 1 H, 3 H, OCH_3), 3.47 (d, *J* = 9.5 Hz, 1 H, $H_{9b'}$), 3.27−3.21 (m, 3 H, $H_{9''}$, $CH_2C\underline{H}_2CO$), 2.85 (dd, *J* = 4.0, 12.5, Hz, H_{3beq}), 2.42 (dd, *J* = 7.5, 15.0 Hz, 2 H, $C\underline{H}_2CH_2CH_2CO$), 2.16−1.98 (m, 2 H, $CH_2C\underline{H}_2CH_2CO$), 1.70 (t, *J* = 12.5 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 175.6, 175.3, 154.5, 151.3, 131.0, 130.6, 127.0, 126.9, 126.1, 125.6, 124.5, 124.4, 124.3, 122.9, 117.6, 114.1, 101.97, 100.58, 73.2, 72.7, 72.3, 70.6, 70.3, 70.1, 67.9, 67.7, 62.1, 60.9, 54.9, 51.9, 42.3, 40.7, 35.3, 32, 27.4. MALDI-TOF MS calcd for $C_{33}H_{44}N_2O_{16}Na$ $(M + Na)^+$, 747.26; found, 747.44. Negative ion mode calcd for $C_{33}H_{43}N_2O_{16}$ $(M - H)^-$, 723.26; found, 723.630. Anal. ($C_{44}H_{50}N_2O_{16}\cdot 4H_2O$) C, N. H: calcd, 6.25; found, 5.75.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(2-naphtamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranoside (8j).** The yield was 74%; R_f 0.38; $[\alpha]_D^{26}$ −17.9 (*c* 10.3, H_2O). ^1H NMR (CD_3OD): δ 8.34 (s, 1 H, Ar−H), 7.92−7.85 (m, 4 H, Ar−H), 7.55−7.52 (m, 2 H, Ar−H), 6.95 (d, *J* = 9.0 Hz, 2 H, Ar−H), 6.69 (d, *J* = 9.0 Hz, 2 H, Ar−H), 4.68 (d, *J* = 8.0 Hz, 1 H, H_{1a}), 4.12−3.95 (m, 4 H, $H_{6a'}$, H_{8b}, glycolyl $C\underline{H}_2CO$), 3.98−3.70 (m, 7 H, H_{2a}, H_{4a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, H_{7b}), 3.61−3.58 (m, 4 H, H_{3a}, OCH_3), 3.52 (m, 2 H, $H_{9b'}$, $H_{9b''}$), 2.85 (br-d, 1 H, H_{3beq}), 1.65 (t, 1 H, H_{3bx}). ^{13}C NMR (CD_3OD): δ 177.1, 156.4, 153.1, 136.2, 134.0, 132.9, 130.1, 129.2, 128.8, 128.7, 127.7, 124.9, 119.0, 115.3, 103.8, 75.0, 74.6, 74.1, 72.5, 72.4, 71.6, 69.6, 69.3, 63.7, 62.6, 55.9, 53.7, 49.8, 44.6, 42.7. MALDI-TOF MS calcd for $C_{35}H_{42}N_2O_{16}Na$ $(M + Na)^+$, 769.24; found, 769.25. Negative ion mode calcd for $C_{35}H_{41}N_2O_{16}$ $(M - H)^-$, 745.24; found, 745.46. Anal. ($C_{35}H_{42}N_2O_{16}\cdot 4.5H_2O$) C, N. H: calcd, 6.21; found, 5.76.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-diphenylacetamido-D-*glycero*-D-α-*galacto*-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranoside (8k).** The yield was 76%; R_f 0.52; $[\alpha]_D^{26}$ −17.9 (*c* 11.2, H_2O). ^1H NMR (CD_3OD): δ 7.26−7.18 (m, 10 H, Ar−H), 7.03 (d, *J* = 9.0 Hz, 2 H, Ar−H), 6.80 (d, *J* = 9.0 Hz, 2 H, Ar−H), 4.99 (s, 1 H, acetyl CH), 4.70 (d, *J* = 7.5 Hz, 1 H, H_{1a}), 3.98 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.94−3.90 (m, 2 H, $H_{6a'}$, H_{8b}), 3.82−3.60 (m, 11 H, H_{2a}, H_{4a}, H_5a, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, H_{7b}, OCH_3), 3.55 (td, *J* = 6.5 Hz, H_{3a}), 3.34−3.25 (m, 2 H, $H_{9b'}$, $H_{9b''}$), 2.8 (br-d, 1 H, H_{3beq}), 1.6 (t, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.1, 174.9, 156.5, 153.3, 141.2, 130.0, 129.9, 129.4, 128, 119.2, 115.5, 103.9, 75.0, 74.6, 74.0, 72.4, 72.1, 71.2, 69.7, 69.3, 63.6, 62.6, 59.1, 55.9, 53.7, 44.0, 42.6. MALDI-TOF MS calcd for $C_{38}H_{46}N_2O_{16}Na$ $(M + Na)^+$, 809.27; found, 809.49. Negative ion mode calcd for $C_{38}H_{45}N_2O_{16}$ $(M - H)^-$, 785.27; found, 785.63. Anal. ($C_{38}H_{46}N_2O_{16}\cdot 3.5H_2O$) C, H, N.

***p*-Methoxyphenyl (9-(4-biphenylcarboxamido)-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranoside (8l).** The yield was 80%; R_f 0.40; $[\alpha]_D^{24}$ −41.4 (*c* 10.5, H_2O). ^1H NMR (CD_3OD): δ 7.87 (d, *J* = 8.5 Hz, 2 H, Ar−H), 7.76−7.63 (m, 4 H, Ar−H), 7.45 (m, 2 H, Ar−H), 7.36 (m, 1 H, Ar−H), 7.01 (d, *J* = 7.0 Hz, 2 H, Ar−H), 6.77 (d, *J* = 7.0 Hz, 2 H, Ar−H), 4.71 (d, *J* = 8.0 Hz, 1 H, H_{1a}), 4.1−3.95 (m, 4 H, $H_{6a'}$, H_{8b}, glycolyl $C\underline{H}_2CO$), 3.94−3.78 (m, 7 H, H_{4b}, H_{6b}, H_{5b}, H_{2a}, H_{4a}, H_{5a}, $H_{6a''}$), 3.74 (dd, *J* = 8.0, 9.5 Hz, 1 H, H_{7b}), 3.66 (s, 3 H, OCH_3), 3.51 (dd, *J* = 7.5, 14.0 Hz, 1 H, $H_{9b'}$), 3.46 (d, *J* = 7.5 Hz, 1 H, $H_{9b''}$), 2.73 (br-d, 1 H, H_{3beq}), 1.80 (t, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 156.4, 153.1, 145.5, 141.3, 129.9, 128.9, 128.1, 127.9, 119.0, 115.3, 103.8, 75.0, 74.6, 74.1, 72.4, 69.7, 69.2, 62.6, 55.9, 53.8, 49.5, 48.4, 44.5, 42.6. MALDI-TOF MS calcd for $C_{37}H_{44}N_2O_{16}Na$ $(M + Na)^+$, 795.26; found, 795.31. Negative ion mode calcd for $C_{37}H_{43}N_2O_{16}$ $(M - H)^-$, 771.26; found, 771.36. Anal. ($C_{37}H_{44}N_2O_{16}\cdot 4.5H_2O$) C, H, N.

***p*-Methoxyphenyl (9-(4-biphenyl)acetamido-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranoside (8m).** The yield was 76%; R_f 0.59; $[\alpha]_D^{29}$ −35.5 (*c* 10.0, H_2O). ^1H NMR (CD_3OD): δ 7.47 (d, *J* = 7.5 Hz, 2 H, Ar−H), 7.42 (d, *J* = 9.0 Hz, 2 H, Ar−H), 7.32−7.28 (m, 2 H, Ar−H), 7.22−7.20 (m, 3 H, Ar−H), 6.94 (d, *J* = 9.0 Hz, 2 H, Ar−H), 6.73 (d, *J* = 9.0 Hz, 2 H, Ar−H), 4.61 (d, *J* = 8.0 Hz, 1 H, H_{1a}), 3.93 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.86−3.78 (m, 3 H, H_{4a}, $H_{6a'}$, H_{8b}), 3.72−3.60 (m, 1 H, H_{2a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, acetyl CH_2, OCH_3), 3.50−3.39 (m, 3 H, H_3, H_{5a}, H_{7b}), 3.21−3.20 (m, 1 H, $H_{9b'}$), 3.09 (dd, *J* = 8.0, 13.0 Hz, $H_{9b''}$), 2.75 (dd, *J* = 4.5, 12.0 Hz,1 H, H_{3beq}), 1.53 (t, *J* = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.1, 174.5, 174.1, 156.5, 153.3, 142.0, 141.0, 136.0, 130.7, 129.8, 128.2, 128.1, 127.9, 119.2, 115.5, 103.9, 102.2, 75.0, 74.7, 74.0, 72.4, 72.2, 71.3, 69.6, 69.3, 63.7, 62.6, 56.0, 53.7, 44.0, 43.3, 42.7. MALDI-TOF MS calcd for $C_{38}H_{46}N_2O_{16}Na$ $(M + Na)^+$, 809.27; found, 809.28. Negative ion mode calcd for $C_{38}H_{45}N_2O_{16}$ $(M - H)^-$, 785.27; found, 785.53. Anal. ($C_{38}H_{46}N_2O_{16}\cdot 3.5H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(2-naphtyl)-acetamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranoside (8n).** The yield was 75%; R_f 0.58; $[\alpha]_D^{27}$ −32.9 (*c* 10.5, H_2O). ^1H NMR (CD_3OD): δ 7.67 (m, 3 H, Ar−H), 7.61 (s, 1 H, Ar−H), 7.33−7.27 (m, 3 H, Ar−H), 6.94 (d, *J* = 8.5 Hz, 2 H, Ar−H), 6.72 (d, *J* = 8.5 Hz, 2 H, Ar−H), 4.60 (d, *J* = 8.0 Hz, 1 H, H_{1a}), 3.90 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.87−3.78 (m, 3 H, H_4, $H_{6a'}$, H_{8b}), 3.75−3.52 (m, 12 H, H_{2a}, $H_{5a,}$ $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, H_{7b}, acetyl CH_2, OCH_3), 3.46 (dd, *J* = 3.5, 10.0 Hz, 1 H, H_{3a}), 3.21−3.20 (m, 1 H, $H_{9b'}$), 3.01 (dd, *J* = 10.0, 12.0 Hz, $H_{9b''}$), 2.75 (dd, *J* = 4.5, 12.0 Hz, 1 H, H_{3beq}), 1.53 (t, *J* = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.1, 174.5, 174.1, 156.5, 153.3, 135.0, 134.4 133.8, 129.1, 128.8, 128.7, 128.6, 128.3, 127.1, 126.6, 119.2, 115.5, 103.9, 102.2, 75.0, 74.7, 74.0, 72.4, 72.2, 71.3, 69.6, 69.3, 63.7, 62.6, 56.0, 53.7, 49.8, 44.0, 43.8, 42.6. MALDI-TOF MS calcd for $C_{36}H_{44}N_2O_{16}Na$ $(M + Na)^+$, 783.26; found, 783.26. Negative ion mode calcd for $C_{36}H_{43}N_2O_{16}$ $(M - H)^-$, 759.26; found, 759.50. Anal. ($C_{36}H_{44}N_2O_{16}\cdot 2.5H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(4′-hydroxy-4-biphenyl-carboxamido)-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranoside (8o).** The yield was 70%; R_f 0.60; $[\alpha]_D^{27}$ −12.6 (*c* 10.3, H_2O). ^1H NMR (CD_3OD): δ 7.72 (d, *J* = 9.0 Hz, 2 H, Ar−H), 7.48 (d, *J* = 9.0 Hz, 2 H, Ar−H), 7.39 (d, *J* = 9.0 Hz, 2 H, Ar−H), 6.88 (d, *J* = 9.0 Hz 2 H, Ar−H), 6.77 (d, *J* = 9.0 Hz, 2 H, Ar−H), 6.65 (d, *J* = 9.0 Hz, 2 H, Ar−H), 4.59 (d, *J* = 7.5 Hz, 1 H, H_{1a}), 3.98−3.92 (m, 3 H, glycolyl $C\underline{H}_2CO$, H_{8b}), 3.88 (d, *J* = 3.0 Hz, 1 H, H_{4a}), 3.83 (dd, *J* = 6.0 Hz, 1 H, $H_{6a'}$), 3.78−3.68 (m, 5 H, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}), 3.65−3.60 (m, 2 H, H_2, H_{7b}), 3.54 (s, 3 H, OCH_3), 3.49 (dd, *J* = 3.5, 9.5 Hz, 1 H, H_{3a}), 3.37−3.30 (m, 2 H, $H_{9b'}$, $H_{9b''}$), 2.76 (dd, *J* = 4.5, 12.0 Hz, 1 H, H_{3beq}), 1.55 (t, *J* = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.1, 174.6, 174.1, 170.2, 159.0, 156.4, 153.2, 145.0, 133.3, 132.4, 129.2, 128.8, 127.2, 119.0, 116.8, 115.4, 103.8, 102.2, 75.0, 74.7, 74.1, 72.5, 72.4, 71.5, 69.6, 69.3, 63.7, 62.6, 56.0, 53.7, 44.5, 43.3, 42.7. MALDI-TOF MS calcd for $C_{37}H_{44}N_2O_{17}Na$ $(M + Na)^+$, 811.25, found, 811.56. Negative ion mode calcd for $C_{37}H_{43}N_2O_{17}$ $(M - H)^-$, 787.25; found, 787.44. Anal. ($C_{37}H_{44}N_2O_{17}\cdot 4.5H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(4′-hydroxy-4-biphenyl)-acetamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-β-D-galactopyranoside (8p).** The yield was 72%; R_f 0.61; $[\alpha]_D^{32}$ −31.7 (*c* 10.1, H_2O). ^1H NMR (CD_3OD): δ 7.45−7.40 (m, 4 H, Ar−H), 7.26 (d, *J* = 9.0 Hz, 2 H, Ar−H), 7.03 (d, *J* = 9.0 Hz, 2 H, Ar−H), 6.84−6.81 (m, 4 H, Ar−H), 4.70 (d, *J* = 7.2 Hz, 1 H, H_{1a}), 4.02 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.95−3.91 (m, 3 H, H_{4a}, $H_{6a'}$, H_{8b}), 3.85−3.63 (m, 9 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, OCH_3), 3.60−3.52 (m, 2 H, H_{3a}, H_{7b}), 3.50 (s, 2 H, acetyl CH_2), 3.35−3.30 (m, 1 H, $H_{9b'}$), 3.20 (dd, *J* = 8.0, 12.0 Hz, 1 H, $H_{9b''}$) 2.84 (dd, *J* = 4.5, 12.0 Hz,1 H, H_{3beq}), 1.63 (t,

J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.1, 174.5, 174.3, 158.2, 156.5, 153.3, 140.9, 134.9, 133.3, 130.6, 128.9, 128.1, 127.5, 119.1, 116.6, 115.5, 103.9, 102.2, 75.0, 74.7, 74.1, 72.4, 72.1, 71.4, 69.7, 69.3, 63.7, 62.6, 56.0, 53.7, 44.0, 43.3, 42.7. MALDI-TOF MS calcd for $C_{38}H_{46}N_2O_{17}Na$ $(M + Na)^+$, 825.27, found, 825.28. Anal. ($C_{38}H_{46}N_2O_{17}\cdot 5H_2O$) C, N. H: calcd, 6.32; found, 5.84.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(3′-hydroxy-4-biphenyl)-acetamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8q).** The yield was 75%; R_f 0.61; $[\alpha]_D^{32}$ −31.5 (c 10.8, H_2O). ^1H NMR (CD_3OD): δ 7.48 (m, 2 H, Ar−H), 7.29 (d, J = 8.5 Hz, 2 H, Ar−H), 7.21 (t, J = 8.5 Hz, 1 H, Ar−H), 7.03 (d, J = 9.0 Hz, 4 H, Ar−H), 6.82 (d, J = 9.0 Hz, 2 H, Ar−H), 6.75 (dd, J = 2.5, 6.0 Hz, 1 H, Ar−H), 4.70 (d, J = 7.5 Hz, 1 H, H_{1a}), 4.04 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.95−3.92 (m, 3 H, H_{4a}, $H_{6a'}$, H_{8b}), 3.79−3.66 (m, 10 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, H_{7b}, OCH_3), 3.58 (dd, J = 3.5, 9.5 Hz, 1 H, H_{3a}), 3.52 (s, 2 H, acetyl CH_2), 3.35 (br-d, J = 8.0 Hz,, $H_{9b'}$), 3.20 (dd, J = 8.0 Hz, 1 H, $H_{9b''}$), 2.85 (dd, J = 4.5, 12.0 Hz,1 H, H_{3beq}), 1.64 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.1, 174.6, 174.2, 158.8, 156.5, 153.2, 143.5, 141.0, 136.0, 130.8, 130.6, 128.0, 119.2, 119.1, 115.5, 115.2, 114.7, 103.8, 102.2, 75.0, 74.6, 74.0, 72.4, 72.1, 71.5, 69.7, 69.3, 63.7, 62.6, 56.0, 53.7, 44.0, 43.3, 42.6. MALDI-TOF MS calcd for $C_{38}H_{46}N_2NaO_{17}Na$ $(M + Na)^+$, 825.27; found, 825.26. Anal. ($C_{38}H_{46}N_2O_{17}\cdot 4.5H_2O$) C, H, N.

***p*-Methoxyphenyl (9-(3′-carboxy-4-biphenylcarboxamido)-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8r).** Obtained after LiOH hydrolysis of methyl ester. The yield was 70%; R_f 0.59; $[\alpha]_D^{29}$ −8.3 (c 10.8, H_2O). ^1H NMR (CD_3OD): δ 8.00 (s, 1 H, Ar−H), 7.91 (d, 1 H, Ar−H), 7.67−7.66 (m, 3 H, Ar−H), 7.44−7.41 (m, 3 H, Ar−H), 6.90 (d, J = 9.0 Hz, 2 H, Ar−H), 6.22 (d, J = 9.0 Hz, 2 H, Ar−H), 4.76 (br-d, 1 H, H_{1a}), 4.17−4.08 (m, 4 H, H_{4a}, glycolyl $C\underline{H}_2CO$, H_{8b}), 4.05−3.88 (m, 5 H, H_{2a}, $H_{6a'}$, H_{4b}, H_{5b}, H_{6b}), 3.85−3.75 (m, 3 H, H_{5a}, $H_{6a''}$, H_{7b}), 3.61 (d, J = 9.0 Hz, 1 H, H_{3a}) 3.60 (s, 3 H, OCH_3), 3.45−3.32 (m, 2 H, $H_{9b'}$, $H_{9b''}$), 2.77 (br-d, 1 H, H_{3beq}), 1.85 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 169.3, 154.1, 150.9, 142.3, 139.3, 132.1, 131.5, 130.0, 129.0, 128.8, 127.5, 127.4, 126.5, 117.2, 114.3, 101.5, 73.1, 72.5, 70.5, 70.3, 70.1, 67.8, 67.3, 62.3, 60.9, 55.0, 51.5. MALDI-TOF MS calcd for $C_{38}H_{44}N_2O_{18}Na$ $(M + Na)^+$, 839.25; found, 839.39. Anal. ($C_{38}H_{44}N_2O_{18}\cdot 5H_2O$) C, H, N.

Mixed Anhydride Method. *p*-Methoxyphenyl (9-(4′-carboxy-4-biphenylcarboxamido)-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (8s). To a suspension of 4,4′-biphenyl dicarboxylic acid (16.2 mg, 0.067 mmol) in DMF (2 mL), *N*-methylmorpholine (7.3 μL, 0.067 mmol) and isobutyl chloroformate (9 μL, 0.067 mmol) were added under cooling on an ice bath. To the obtained mixture compound **7** (48 mg, 0.08 mmol) was added portionwise, and the mixture was stirred at room temperature for 12 h. DMF was removed under vacuum and the residue was reconstituted into water and applied onto a silica reversed-phase column pre-equilibrated in water. The compound was eluted with a gradient of methanol/water (0:1 to 20:100) to afford compound **8s** (65%) as a colorless solid: R_f 0.58 (ethyl acetate/methanol/water/acetic acid 10:3:3:1); $[\alpha]_D^{31}$ −14.44 (c 10.4, H_2O). ^1H NMR (CD_3OD): δ 7.83 (d, J = 8.0 Hz, 2 H, Ar−H), 7.59−6.49 (m, 6 2 H, Ar−H), 6.73 (d, J = 9.0 Hz, 2 H, Ar−H), 6.54 (d, J = 9.0 Hz, 2 H, Ar−H), 4.78 (d, J = 7.5 Hz, 1 H, H_{1a}), 3.97−3.90 (m, 4 H, H_{4a}, glycolyl $C\underline{H}_2CO$, H_{8b}), 3.82−3.38 (dd, J = 6.0 Hz, 1 H,), 3.78−3.68 (m, 8 H, H_{2a}, H_{5a}, $H_{6a'}$, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}, H_{7b}), 3.60 (s, 3 H, OCH_3), 3.49 (d, J = 9.0 Hz, 1 H, H_{3a}), 3.47−3.38 (m, 2 H, $H_{9b'}$, $H_{b''}$), 2.77 (d, J = 12.0 Hz, 1 H, H_{3beq}), 1.84 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 169.3, 154.1, 150.9, 142.3, 139.3, 132.1, 131.5, 130.0, 129.0, 128.8, 127.5, 127.4, 126.5, 117.2, 114.3, 101.5, 73.1, 72.5, 70.5, 70.3, 70.1, 67.8, 67.3, 62.3, 60.9, 55.0, 51.5. MALDI-TOF MS calcd for $C_{38}H_{44}N_2O_{18}$ $(M + H)^+$, 839.25; found, 839.29. Anal. ($C_{38}H_{44}N_2O_{18}\cdot 5H_2O$) N. C: calcd, 50.33; found, 49.86. H: calcd, 6.00; found, 5.45.

General Procedures for Reductive Alkylation. *p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-substituted amino-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic Acid)-(2→6)-*β*-D-galactopyranoside (9a−n). For compounds **9a−c**: To a mixture of the amine **7b** (40 mg, 0.067 mmol) and appropriate aldehyde (0.043 mmol) in 0.2 M phosphate buffer pH = 7 (1 mL) was added sodium cyanoborohydride; $NaBH_3CN$ (5.8 mg, 0.093 mmol). The reaction mixture was stirred at room temperature for 48 h then acetic acid (11 μL) was added and stirring was continued for further 3 h. For compounds **9d−n**: To a mixture of the amine **7** (50 mg, 0.084 mmol) and appropriate aldehyde (0.043 mmol) in dry MeOH (3 mL) was added acetic acid (0.1 mL), followed by $NaBH_3CN$ (1.0 M in THF, 60 μL, 0.060 mmol). A total of 24 h later, a TLC indicated a complete disappearance of the aldehyde. The reaction mixture was concentrated, reconstituted into water, and loaded on a silica reversed-phase column pre-equilibrated in water. The compounds were eluted with a gradient of methanol−water (0:1 to 60:100) to afford the title compounds **9a−n** in (70−80%) as a a white fluffy solid after a final lyophilization from water. The solvent system (ethyl acetate/methanol/water/acetic acid 10:3:3:1) was used for following up the reaction and determining R_f values.

***p*-Methoxyphenyl (9-benzylamino-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9a).** The yield was 73%; R_f 0.61; $[\alpha]_D^{26}$ −41.9 (c 7.5, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 7.35−7.31 (m, 5 H, Ar−H), 6.95 (d, J = 9.0 Hz, 2 H, Ar−H), 6.70 (d, J = 9.0 Hz, 2 H, Ar−H), 4.60 (d, J = 8.0 Hz, 1 H, H_{1a}), 4.45 (brs, 1 H, NH), 4.10 (s, 2 H, glycolyl $C\underline{H}_2CO$), 4.02 (td, J = 8.5 Hz, 1 H, H_{8b}), 3.94 (s, 2 H, benzylic $C\underline{H}_2$), 3.83−3.81 (m, 2 H, H_{4a}, $H_{6a'}$), 3.75 (m, 1 H, H_{4b}), 3.65−3.55 (m, 8 H, H_2, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}, OCH_3), 3.46 (dd, J = 3.5, 9.5 Hz, 1 H, H_{3a}), 3.28 (d, J = 8.5 Hz, 1 H, H_{7b}), 3.25 (dd, 1 H, $H_{9b'}$), 2.86 (dd, J = 10.0, 12.0 Hz, 1 H, $H_{9b''}$), 2.76 (dd, J = 4.5, 12.0 Hz, 1 H, H_{3beq}), 1.53 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 174.6, 156.6, 153.3, 132.6, 131.0, 130.5, 130.2, 119.3, 115.4, 103.9, 102.0, 75.3, 74.7, 74.0, 72.7, 72.4, 69.9, 69.1, 68.4, 64.1, 62.6, 56.0, 53.7, 52.3, 51.3, 42.6. MALDI-TOF MS calcd for $C_{31}H_{43}N_2O_{15}$ $(M + H)^+$, 683.26; found, 683.25. Anal. ($C_{31}H_{42}N_2O_{15}\cdot 3H_2O$) C, N. H: calcd, 6.57; found, 6.12.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(3,5-dimethoxybenzyl)amino-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9b).** The yield was 75%; R_f 0.54; $[\alpha]_D^{26}$ −104.4 (c 10.2, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 7.03 (d, J = 9.0 Hz, 2 H, Ar−H), 6.80 (d, J = 9.0 Hz, 2 H, Ar−H), 6.61 (d, J = 2.5 Hz, 2 H, Ar−H), 6.50 (s, 1 H, Ar−H), 4.70 (d, J = 7.5 Hz, 1 H, H_{1a}), 4.16−4.08 (m, 3 H, H_{8b}, glycolyl $C\underline{H}_2CO$), 4.04 (s, 2 H, benzylic $C\underline{H}_2$), 3.94−3.91 (m, 2 H, H_{4a}, $H_{6a'}$), 3.83 (m, 1 H, H_{4b}), 3.75−3.65 (m, 14 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}, 3 $OC\underline{H}_3$), 3.55 (dd, J = 3.5, 10.0 Hz, 1 H, H_{3a}), 3.38 (d, J = 8.5 Hz, 1 H, H_{7b}), 3.31 (dd, 1 H, $H_{9b'}$), 2.96 (dd, J = 12.0 Hz, 1 H, $H_{9b''}$), 2.86 (dd, J = 4.5, 12.0 Hz, 1 H, H_{3beq}), 1.63 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 174.6, 162.8, 156.6, 153.2, 134.6, 119.3, 115.4, 108.7, 103.9, 102.1, 102.0, 75.2, 74.7, 74.0, 72.7, 72.4, 69.9, 69.1, 68.4, 64.0, 62.6, 56.0, 53.7, 52.3, 51.3, 42.5. MALDI-TOF MS calcd for $C_{33}H_{47}N_2O_{17}$ $(M + H)^+$, 743.28; found 743.41. Anal. ($C_{33}H_{46}N_2O_{17}\cdot 3H_2O$) N. C: calcd, 49.75; found, 49.29. H: calcd, 6.58; found, 6.11.

***p*-Methoxyphenyl (9-cyclohexylmethylamino-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9c).** The yield was 80%; R_f 0.55; $[\alpha]_D^{25}$ −45.2 (c 10.5, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 7.05 (d, J = 9.0 Hz, 2 H, Ar−H), 6.83 (d, J = 9.0 Hz, 2 H, Ar−H), 4.71 (d, J = 8.0 Hz, 1 H, H_{1a}), 4.08−4.05 (m, 3 H, glycolyl $C\underline{H}_2CO$, H_{8b}), 3.95−3.87 (m, 2 H, H_{4a}, $H_{6a'}$), 3.83 (m, 1 H, H_{4b}), 3.74−3.70 (m, 8 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}, OCH_3), 3.56 (dd, J = 3.5, 9.5 Hz, 1 H, H_{3a}), 3.38 (d, J = 8.5 Hz, 1 H, H_{7b}), 3.18 (dd, J = 12.5 Hz, 1 H, $H_{9b'}$), 2.87 (m, 2 H, $H_{9b''}$, H_{3beq}), 2.71 (d, J = 7.0 Hz, 2 H, $\underline{CH}_2NH$), 1.74−1.61 (m, 7 H, cyclohexane $CH_2CH_2CH_2$, H_{3bax}), 1.28−1.18 (m, 3 H, cyclohexane $\underline{CH}_2\underline{CH}$), 0.95−0.92 (m, 2 H, cyclohexane $\underline{CH}_2$). ^{13}C NMR (CD_3OD): δ 177.3, 174.6, 156.5, 153.3, 119.2, 115.4, 103.9, 102.0, 75.2, 74.7, 74.0, 72.7, 72.4, 69.8, 69.2, 69.0, 63.9, 62.6, 56.0, 55.8, 53.7, 53.0, 42.6, 36.8, 31.8, 31.7, 27.2, 26.7, 26.6. MALDI-TOF MS calcd for $C_{31}H_{49}N_2O_{15}$ $(M + H)^+$, 689.31; found, 689.20. Anal. ($C_{31}H_{48}N_2O_{15}\cdot 2.5H_2O$) C, H, N.

***p*-Methoxyphenyl (9-(4-biphenyl)methylamino-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9d).** The yield was 70%; R_f 0.61; $[\alpha]_D^{25}$ −52.5 (*c* 8.0, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 7.65 (d, J = 8 Hz, 2 H, Ar−H), 7.60 (d, J = 9 Hz, 2 H, Ar−H), 7.52 (d, J = 8.0 Hz, 2 H, Ar−H), 7.44 (t, J = 7.5 Hz, 2 H, Ar−H), 7.35 (m, 1 H, Ar−H), 7.04 (d, J = 9.0 Hz, 2 H, Ar−H), 6.80 (d, J = 9.0 Hz, 2 H, Ar−H), 4.70 (d, J = 7.5 Hz, 1 H, H_{1a}), 4.24 (s, 2 H, glycolyl $C\underline{H}_2CO$), 4.16 (td, J = 7.5 Hz, 1 H, H_{8b}), 4.04 (s, 2 H, $C\underline{H}_2NH$), 4.00−3.90 (m, 2 H, H_{4a}, $H_{6a'}$), 3.84 (m, 1 H, H_{4b}), 3.78−3.68 (m, 8 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}, OCH_3), 3.55 (dt, J = 9.5 Hz, 1 H, H_{3a}), 3.41 (d, J = 8.5 Hz, 1 H, H_{7b}), 3.36 (dd, J = 12.0 Hz, 1 H, $H_{9b'}$), 3.00 (brt, J = 12.0 Hz, 1 H, $H_{9b''}$), 2.88 (dd, J = 12.0 Hz, 1 H, H_{3beq}), 1.64 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 174.6, 156.6, 153.3, 143.6, 141.4, 131.7, 131.5, 130.0, 128.8, 128.7, 128.0, 119.3, 115.4, 104.0, 102.0, 75.3, 74.7, 74.0, 72.7, 72.4, 69.9, 69.1, 68.4, 64.1, 62.6, 56.0, 53.8, 52.0, 51.2, 42.6. MALDI-TOF MS calcd for $C_{37}H_{47}N_2O_{15}$ $(M + H)^+$, 759.30; found, 759.38. Anal. ($C_{37}H_{46}N_2O_{15}\cdot 3H_2O$) C, N. H: calcd, 6.45; found, 6.01.

***p*-Methoxyphenyl (9-2(4-biphenyl)ethylamino-3,5, 9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9e).** The yield was 70%; R_f 0.61; $[\alpha]_D^{25}$ −39.3 (*c* 7.5, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 7.58−7.55 (m, 4 H, Ar−H), 7.43−7.40 (m, 2 H, Ar−H), 7.33−7.32 (m, 3 H, Ar−H), 7.04 (d, J = 9.0 Hz, 2 H, Ar−H), 6.80 (d, J = 9.0 Hz, 2 H, Ar−H), 4.70 (d, J = 8.0 Hz, 1 H, H_{1a}), 4.13 (td, J = 3.0 Hz, 1 H, H_{8b}), 4.05 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.95 (dd, J = 3.5 Hz, 1 H, $H_{6a'}$), 3.92 (d, J = 3.5 Hz, 1 H, H_{4a}), 3.85 (m, 1 H, H_{4b}), 3.76−3.70 (m, 8 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}, OCH_3), 3.55 (dd, J = 3.5, 10.0 Hz, 1 H, H_{3a}), 3.44 (d, J = 6.5, 1 H, H_{7b}), 3.40 (dd, J = 3.0, 12.5 Hz, 1 H, $H_{9b'}$), 3.28−3.25 (m, 2 H, $C\underline{H}_2CH_2NH$), 3.08 (brd, J = 12.5 Hz, 1 H, $H_{9b''}$), 3.05−3.01 (m, 2 H, $CH_2C\underline{H}_2NH$), 2.88 (dd, J = 5.5, 12.0 Hz, 1 H, H_{3beq}), 1.65 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 174.6, 156.6, 153.3, 142.0, 141.4, 136.9, 130.3, 129.9, 128.5, 128.4, 127.9, 119.3, 115.5, 104.0, 102.0, 75.3, 74.7, 74.0, 72.7, 72.4, 69.9, 69.1, 68.6, 64.1, 62.6, 56.0, 53.8, 52.1, 50.2, 42.6, 32.8. MALDI-TOF MS calcd for $C_{38}H_{49}N_2O_{15}$ $(M + H)^+$, 773.31; found, 773.39. Anal. ($C_{38}H_{48}N_2O_{15}\cdot 3H_2O$) C, N. H: calcd, 6.58; found, 6.03.

***p*-Methoxyphenyl (9-4(4-biphenyl)butylamino-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9f).** The yield was 70%; R_f 0.62; $[\alpha]_D^{25}$ −41.0 (*c* 5.0, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 7.58−7.55 (m, 4 H, Ar−H), 7.42−7.39 (m, 2 H, Ar−H), 7.31−7.25 (m, 3 H, Ar−H), 7.04 (d, J = 9.0 Hz, 2 H, Ar−H), 6.81 (d, J = 9.0 Hz, 2 H, Ar−H), 4.70 (d, J = 8.0 Hz, 1 H, H_{1a}), 4.09 (td, 1 H, H_{8b}), 4.05 (s, 2 H, glycolyl $C\underline{H}_2CO$), 3.93−3.90 (m, 2 H, H_{4a}, $H_{6a'}$), 3.84 (brs, 1 H, H_{4b}), 3.77−3.65 (m, 8 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}, OCH_3), 3.54 (dd, J = 3.5, 9.5 Hz, 1 H, H_{3a}), 3.41 (d, J = 8.5, 1 H, H_{7b}), 3.31−3.30 (m, 1 H, $H_{9b'}$), 3.00−3.96 (m, 3 H, $H_{9b''}$, $C\underline{H}_2CH_2CH_2CH_2NH$), 2.88 (dd, J = 5.5, 12.0 Hz, 1 H, H_{3beq}), 2.67 (m, 2 H, $CH_2CH_2CH_2C\underline{H}_2NH$), 1.68 (m, 5 H, $CH_2C\underline{H}_2C\underline{H}_2CH_2NH$, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 156.5, 153.3, 142.3, 142.0, 140.2, 130.0, 129.8, 128.1, 128.0, 127.8, 119.2, 115.5, 103.8, 102.0, 75.3, 74.7, 74.0, 72.6, 72.4, 69.9, 69.1, 68.5, 64.1, 62.6, 56.0, 53.8, 52.0, 50.2, 42.6, 35.8, 29.3, 26.6. MALDI-TOF MS calcd for $C_{40}H_{53}N_2O_{15}$ $(M + H)^+$, 801.34; found, 801.43. Anal. ($C_{41}H_{62}N_2O_{18}\cdot 3H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(4′-hydroxy-4-biphenyl)-methylamino-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9g).** The yield was 75%; R_f 0.40; $[\alpha]_D^{31}$ −41.0 (*c* 10.0, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 7.58 (d, J = 8.0 Hz, 2 H, Ar−H), 7.45 (m, 4 H, Ar−H), 7.04 (d, J = 7.0 Hz, 2 H, Ar−H), 6.86 (d, J = 9 Hz, 2 H, Ar−H), 6.78 (d, J = 9.0 Hz, 2 H, Ar−H), 4.70 (d, J = 8.0 Hz, 1 H, H_{1a}), 4.20 (d, J = 4.0 Hz, 2 H, glycolyl $C\underline{H}_2CO$), 4.15 (td, J = 7.5, 15.0 Hz, 1 H, H_{8b}), 4.04 (s, 2 H, $C\underline{H}_2NH$), 3.95−3.91 (m, 2 H, H_{4a}, $H_{6a'}$), 3.85 (m, 1 H, H_{4b}), 3.75−3.71 (m, 5 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}), 3.67 (s, 3 H, OCH_3), 3.55 (dd, J = 3.5, 10.0 Hz, 1 H, H_{3a}), 3.40 (br-dd, J = 8.5, 1 H, H_{7b}), 3.35 (dd, 1 H, $H_{9b'}$), 2.99 (dd, J = 12.0 Hz, 1 H, $H_{9b''}$), 2.88 (dd, J = 4.5, 12.0 Hz,1 H, H_{3beq}), 1.64 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 158.7, 156.6, 153.3, 143.6, 132.6, 131.6, 130.3, 129.1, 128.0, 119.3, 116.8, 115.4, 104.0, 75.3, 74.7, 74.0, 72.7, 72.4, 69.9, 69.1, 68.4, 64.1, 62.6, 56.0, 53.8, 52.0, 51.2, 42.6. MALDI-TOF MS calcd for $C_{37}H_{47}N_2O_{16}$ $(M + H)^+$, 775.29; found, 775.27. Anal. ($C_{37}H_{46}N_2O_{16}\cdot 3H_2O$) C, H, N.

***p*-Methoxyphenyl (9-(4′-carboxy-4-biphenyl)methylamino-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9h).** The yield was 75%; R_f 0.60; $[\alpha]_D^{25}$ −30.3 (*c* 10.4, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 8.07 (d, J = 7.0 Hz, 2 H, Ar−H), 7.73 (m, 4 H, Ar−H), 7.58 (d, J = 7.5 Hz, 2 H, Ar−H), 7.05 (d, J = 9.0 Hz, 2 H, Ar−H), 6.81 (d, J = 9.0 Hz, 2 H, Ar−H), 4.28 (s, 2 H, glycolyl $C\underline{H}_2CO$), 4.16 (td, 1 H, H_{8b}), 4.06 (s, 2 H, $C\underline{H}_2NH$), 3.98−3.87 (m, 2 H, H_{4a}, $H_{6a'}$), 3.82 (m, 1 H, H_{4b}), 3.80−3.64 (m, 8 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}, OCH_3), 3.61 (dd, 1 H, H_{3a}), 3.44−3.39 (m, 2 H, H_{7b}, $H_{9b'}$), 3.04 (dd, J = 12.0 Hz, 1 H, $H_{9b''}$), 2.83 (dd, J = 12.0 Hz, 1 H, H_{3beq}), 1.64 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 174.7, 156.1, 152.8, 142.0, 131.7, 131.3, 128.8, 127.9, 119.2, 115.6, 74.9, 74.1, 72.0, 72.4, 56.3, 48.3. MALDI-TOF MS calcd for $C_{38}H_{47}N_2O_{17}$ $(M + H)^+$, 803.29; found, 803.34. Anal. ($C_{38}H_{46}N_2O_{17}\cdot 2H_2O$) C, H, N.

***p*-Methoxyphenyl (9-(3′-carboxy-4-biphenyl)methylamino-3,5,9-trideoxy-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9i).** The yield was 70%; R_f 0.60; $[\alpha]_D^{26}$ −22.7 (*c* 11.0, H_2O). ^1H NMR (D_2O with a few drops of CD_3OD): δ 8.19 (s, 1 H, Ar−H), 7.92 (d, J = 7.6 Hz, 1 H, Ar−H), 7.72−7.71 (m, 3 H, Ar−H), 7.55−7.52 (m, 3 H, Ar−H), 7.08 (d, J = 9.0, 2 H, Ar−H), 6.85 (d, J = 9.0 Hz, 2 H, Ar−H), 4.27 (s, 2 H, glycolyl $C\underline{H}_2CO$), 4.18 (td, 1 H, H_{8b}), 4.10 (s, 2 H, $C\underline{H}_2NH$), 3.99−3.95 (m, 2 H, H_{4a}, $H_{6a'}$), 3.89−3.73 (m, 5 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{6b}), 3.72−3.57 (m, 5 H, H_{5b}, OCH_3, H_{3a}), 3.51 (d, J = 7.6 Hz, 1 H, H_{7b}), 3.43 (br-d, J = 12.8 Hz,, 1 H, $H_{9b'}$), 3.09 (dd, J = 10.0, 12.8 Hz, 1 H, $H_{9b''}$), 2.80 (br-d, J = 12.4 Hz,1 H, H_{3beq}), 1.68 (t, J = 12.4 Hz, 1 H, H_{3bax}). ^{13}C NMR (D_2O): δ 176.4, 175.7, 174.0, 155.0, 151.5, 141.6, 140.0, 137.5, 131.0, 130.1, 130.0, 129.5, 128.8, 128.0, 127.9, 118.6, 115.4, 102.3, 101.1, 74.0, 73.0, 72.8, 71.1, 70.8, 68.8, 68.4, 67.8, 63.4, 61.5, 56.1, 52.1, 51.0, 49.7, 40.8. MALDI-TOF MS calcd for $C_{38}H_{47}N_2O_{17}$ $(M + H)^+$, 803.29; found, 803.36. Anal. ($C_{38}H_{46}N_2O_{17}\cdot 5.5H_2O$) C, N. H: calcd, 6.37; found, 5.95.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(3′-hydroxy-4-biphenyl)-methylamino-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9j).** The yield was 72%; R_f 0.42; $[\alpha]_D^{24}$ −54.4 (*c* 10.2, MeOH). ^1H NMR (CD_3OD): δ 7.61 (d, J = 8.3 Hz, 2 H, Ar−H), 7.48 (d, J = 8.3 Hz, 2 H, Ar−H), 7.25 (t, J = 8.0 Hz, 1 H, Ar−H), 7.07−7.03 (m, 4 H, Ar−H), 6.79−6.77 (m, 3 H, Ar−H), 4.70 (d, J = 8.0 Hz, 1 H, H_{1a}), 4.20 (br. s, 2 H, glycolyl $C\underline{H}_2CO$), 4.14 (td, J = 8.6 Hz, 1 H, H_{8b}), 4.04 (s, 2 H, $C\underline{H}_2NH$), 3.95−3.91 (m, 2 H, H_{4a}, $H_{6a'}$), 3.83 (m, 1 H, H_{4b}), 3.74−3.71 (m, 5 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}), 3.67 (s, 3 H, OCH_3), 3.55 (dd, J = 3.4, 9.7 Hz, 1 H, H_{3a}), 3.40 (dd, J = 8.6, 1 H, H_{7b}), 3.34 (dd, 1 H, $H_{9b'}$), 2.97 (dd, J = 12.6 Hz, 1 H, $H_{9b''}$), 2.87 (dd, J = 4.6, 12.0 Hz,1 H, H_{3beq}), 1.64 (t, J = 12.0 Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 175.2, 153.2, 142.8, 131.5, 131.02, 128.6, 119.3, 115.7, 115.4, 75.2, 72.7, 72.4, 68.5, 56.0, 52.0, 42.6. MALDI-TOF MS calcd for $C_{37}H_{47}N_2O_{16}$ $(M + H)^+$, 775.29; found, 775.27. Anal. ($C_{37}H_{46}N_2O_{16}\cdot H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(2′-hydroxy-4-biphenyl)-methylamino-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9k).** The yield was 70%; R_f 0.40; $[\alpha]_D^{24}$ −42.4 (c 10.6, MeOH). ^1H NMR (CD_3OD): δ 7.60 (d, J = 8.0 Hz, 2 H, Ar−H), 7.44 (d, J = 8.0 Hz, 2 H, Ar−H), 7.24 (dd, J = 8.0 Hz, 1 H, Ar−H), 7.17−7.14 (m, 1 H, Ar−H), 7.05−7.03 (m, 2 H, Ar−H), 6.90−6.88 (m, 2 H, Ar−H), 6.87−6.78

(m, 2 H, Ar−H), 4.70 (d, $J = 8.0$ Hz, 1 H, H_{1a}), 4.22 (br. s, 2 H, glycolyl $C\underline{H}_2CO$), 4.15 (td, $J = 9.7, 8.6, 6.3$ Hz, 1 H, H_{8b}), 4.04 (s, 2 H, $C\underline{H}_2NH$), 3.97−3.91 (m, 2 H, H_{4a}, $H_{6a'}$), 3.84 (m, 1 H, H_{4b}), 3.74−3.70 (m, 5 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}), 3.67 (s, 3 H, OCH_3), 3.54 (dd, $J = 3.4, 9.7$ Hz, 1 H, H_{3a}), 3.40 (dd, $J = 8.6$, 1 H, H_{7b}), 3.35 (br. d, 1 H, $H_{9b'}$), 2.99 (dd, $J = 9.7, 12.6$ Hz, 1 H, $H_{9b''}$), 2.88 (dd, $J = 4.6, 12.0$ Hz,1 H, H_{3beq}), 1.64 (t, $J = 12.0$ Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 156.6, 155.5, 153.2, 141.6, 131.6, 131.1, 130.7, 130.6, 129.9, 128.8, 121.0, 119.3, 117.0, 115.5, 103.9, 75.2, 74.7, 74.0, 72.7, 72.4, 69.9, 69.1, 68.5, 64.1, 62.6, 56.0, 53.7, 52.1, 51.2, 42.6. MALDI-TOF MS calcd for $C_{37}H_{47}N_2O_{16}$ $(M + H)^+$, 775.29; found, 775.23. Anal. ($C_{37}H_{46}N_2O_{16}\cdot 2H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(4′-methoxy-4-biphenyl)-methylamino-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9l).** The yield was 75%; R_f 0.50; $[\alpha]_D^{22}$ −101.8 (*c* 10.9, MeOH). ^1H NMR (CD_3OD): δ 7.60 (d, $J = 8.0$ Hz, 2 H, Ar−H), 7.54 (d, $J = 1.7, 6.8$ Hz, 2 H, Ar−H), 7.05−6.9 (m, 4 H, Ar−H), 6.8 (dd, $J = 1.7, 6.8$ Hz, 2 H, Ar−H), 4.70 (d, $J = 8.0$ Hz, 1 H, H_{1a}), 4.20 (br. s, 2 H, glycolyl $C\underline{H}_2CO$), 4.17−4.12 (m, Hz, 1 H, H_{8b}), 4.04 (s, 2 H, $C\underline{H}_2NH$), 3.97−3.91 (m, 2 H, H_{4a}, $H_{6a'}$), 3.85−3.78 (m, 4 H, H_{4b}, OCH_3), 3.74−3.69 (m, 5 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}), 3.67 (s, 3 H, OCH_3), 3.54 (dd, $J = 3.4, 9.7$ Hz, 1 H, H_{3a}), 3.40 (dd, $J = 8.6$, 1 H, H_{7b}), 3.35 (br. d, 1 H, $H_{9b'}$), 2.99 (dd, $J = 9.7, 12.6$ Hz, 1 H, $H_{9b''}$), 2.88 (dd, $J = 4.6, 12.0$ Hz,1 H, H_{3beq}), 1.64 (t, $J = 12.0$ Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 174.7, 161.1, 156.5, 153.3, 143.2, 133.7, 131.6, 130.6, 129.1, 128.1, 119.3, 115.4, 103.9, 102.0, 75.2, 74.6, 74.0, 72.6, 72.4, 69.9, 69.1, 68.4, 64.1, 62.5, 56.0, 55.7, 53.7, 52.0, 51.1, 42.6. MALDI-TOF MS calcd for $C_{38}H_{49}N_2O_{16}$ $(M + H)^+$, 789.30; found, 789.32. Anal. ($C_{38}H_{48}N_2O_{16}\cdot H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-5-glycolamido-9-(4′-methyl-4-biphenyl)-methylamino-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9m).** The yield was 69%; R_f 0.58; $[\alpha]_D^{22}$ −44.6 (*c* 10.3, MeOH). ^1H NMR (CD_3OD): δ 7.60 (d, $J = 8.0$ Hz, 2 H, Ar−H), 7.47 (d, $J = 8.0$ Hz, 2 H, Ar−H), 7.22 (m, $J = 8.6$ Hz, 2 H, Ar−H), 7.03 (d, $J = 9.2$ Hz, 2 H, Ar−H), 6.77 (d, $J = 9.2$ Hz, 2 H, Ar−H), 4.69 (d, $J = 8.0$ Hz, 1 H, H_{1a}), 4.22−4.17 (m, 3 H, glycolyl $C\underline{H}_2CO$, H_{8b}), 4.05 (s, 2 H, $C\underline{H}_2NH$), 3.96−3.91 (m, 2 H, H_{4a}, $H_{6a'}$), 3.85−3.78 (m, 1 H, H_{4b}), 3.75−3.72 (m, 5 H, H_{2a}, H_{5a}, $H_{6a''}$, H_{5b}, H_{6b}), 3.65 (s, 3 H, OCH_3), 3.55 (dd, $J = 3.4, 9.7$ Hz, 1 H, H_{3a}), 3.42 (dd, $J = 8.2$, 1 H, H_{7b}), 3.34 (br. d, 1 H, $H_{9b'}$), 2.99 (t, $J = 12.6$ Hz, 1 H, $H_{9b''}$), 2.89 (dd, $J = 12.0$ Hz,1 H, H_{3beq}), 1.64 (t, $J = 12.0$ Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.4, 174.7, 156.5, 153.3, 143.3, 138.8, 138.4, 131.6, 131.1, 130.6, 128.4, 127.8, 119.2, 115.5, 103.9, 102.0, 75.2, 74.6, 73.9, 72.6, 72.4, 69.9, 69.0, 68.5, 64.1, 62.6, 56.0, 51.2, 42.6. MALDI-TOF MS calcd for $C_{38}H_{49}N_2O_{16}$ $(M + H)^+$, 773.31; found, 773.32. Anal. ($C_{38}H_{48}N_2O_{15}\cdot 0.5H_2O$) C, H, N.

***p*-Methoxyphenyl (3,5,9-trideoxy-9-(4′-trifluromethyl-4-biphenyl)methylamino-5-glycolamido-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→6)-*β*-D-galactopyranoside (9n).** The yield was 70%; R_f 0.52; $[\alpha]_D^{22}$ −25.7 (*c* 9.7, MeOH). ^1H NMR (CD_3OD): δ 7.78 (d, $J = 8.6$ Hz, 2 H, Ar−H), 7.72 (d, $J = 8.02$ Hz, 2 H, Ar−H), 7.62 (d, $J = 8.6$ Hz, 2 H, Ar−H), 7.43 (d, $J = 8.02$ Hz, 2 H, Ar−H), 7.03 (d, $J = 2.3, 6.3$ Hz, 2 H, Ar−H), 6.78 (d, $J = 2.3, 6.3$ Hz, 2 H, Ar−H), 4.71 (d, $J = 8.0$ Hz, 1 H, H_{1a}), 4.08−4.04 (m, 3 H, glycolyl $C\underline{H}_2CO$, H_{8b}), 3.96−3.94 (m, 2 H, H_{4a}, $H_{6a'}$), 3.89−3.72 (m, 8 H, $C\underline{H}_2NH$, H_{2a}, H_{5a}, $H_{6a''}$, H_{4b}, H_{5b}, H_{6b}), 3.71 (s, 3 H, OCH_3), 3.58 (dd, $J = 3.4, 9.7$ Hz, 1 H, H_{3a}), 3.35 (dd, $J = 8.2$, 1 H, H_{7b}), 2.99 (dd, $J = 8.6, 12.0$ Hz, 1 H, $H_{9b'}$), 2.85 (dd, $J = 4.6, 12.0$ Hz,1 H, H_{3beq}), 2.99 (t, $J = 8.6, 12.0$ Hz, 1 H, $H_{9b''}$), 1.63 (t, $J = 12.0$ Hz, 1 H, H_{3bax}). ^{13}C NMR (CD_3OD): δ 177.2, 174.6, 156.5, 153.3, 145.9, 140.4, 139.7, 138.4, 130.4, 128.5, 128.3, 126.7, 119.2, 115.4, 103.9, 102.0, 75.07, 74.6, 72.9, 72.7, 72.4, 70.5, 69.6, 69.3, 63.6, 62.6, 56.0, 53.7, 52.9, 51.2, 42.6. MALDI-TOF MS calcd for $C_{38}H_{46}F_3N_2O_{15}$ $(M + H)^+$, 827.28; found, 827.32. Anal. ($C_{38}H_{45}F_3N_2O_{15}\cdot 2.5H_2O$) C, H, N.

Inhibition Assay. Materials and Methods. The binding assay was performed as previously described with slight modifications.[17] Mouse myeloma line J558L,[41] which do not express α2-6 linked sialic acid due to lack of ST6GalI expression, and its ST6GalI transfectants (J558LST6), which express α2-6 linked sialic acids, were cultured as previously described.[42] The chimeric protein containing the N-terminal three domains of murine or human CD22 and the Fc fragment of human IgG1 (mCD22-Fc and hCD22-Fc, respectively) were prepared and biotinylated as reported.[43] Cells were incubated with 1 μg biotinylated mCD22-Fc or hCD22-Fc alone or together with synthetic sialosides at 1.00, 0.10, 0.01, 0.001, 0.0001, and 0.00001 mM. After washing, the cells were stained with 1% Alexa Fluor 647-streptavidin conjugate (Molecular Probes, Eugene, Oregon) for 30 min on ice and then analyzed by flow cytometry using a FACS Calibur (Becton−Dickinson, San Jose, CA). The percentage of binding was calculated according to the following equation: % binding = $(A - B)/(C - B) \times 100\%$, where A is the mean of fluorescent intensity (MFI) of J558LST6 cells in the presence of the synthetic sialoside (sample), B is MFI of J558L cells (negative control), and C is MFI of J558LST6 cells (positive control). Obviously, the lower the binding rates, the higher the inhibitory affinity of the synthetic sialosides.

Molecular Modeling. Model construction and antagonist docking were carried out on an Intel P4 based Microsoft Windows 2000 workstation using Discovery Studio Modeling 1.5 and 2.0 packages (Accelrys, Inc., San Diego, CA). The X-ray structure of the Sn in complex with a substrate-analogue inhibitor BPC-Neu5Ac (coded 1oda) obtained from the Protein Data Bank was used for modeling analysis. The sequence comparisons between Sn and the equivalents regions of hCD22 and mCD22 have been described in detail elsewhere.[15] Homology models of hCD22 and mCD22 in complex with BPC-Neu5Ac were constructed using the MODELER program, based upon the individual sequence/template alignments. The obtained complexes were then subjected to geometry optimization using the following parameters: CHARMm force field, conjugate gradient minimization, distance-dependent dielectric constant 4, 10 Å nonbonded cutoff, and 2000 maximum iterations. Fitness of the models sequence in their current 3D environment was evaluated by Profiles-3D, and the stereochemical quality of the final structure was analyzed using the program PROCHECK.

For the manual docking of antagonists (**8m**, **9h**, **9i**, **10**), their structures were built using BPC-Neu5Ac in the model complexes as a template. The individual antagonists were superimposed onto the BPC-Neu5Ac in the models, confirming that interactions which are essential for competitive binding are maintained throughout the docking process and a special emphasis was given to core carboxylic acid group's salt-bridge formation with Arginine residue (hCD22 Arg98, mCD22 Arg100). The obtained complexes were then energetically minimized with 500−1000 iterations of "in situ ligand minimization algorithm" using the Smart Minimizer program. The antagonist binding modes were analyzed to investigate the relative differences between interactions to understand the selectivity differences.

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Supporting Information Available: ^1H NMR spectra, combustion analysis data of the target compounds, and molecular modeling coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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