Mini Review: Oxazolidinone and Other Sialic Acid C5 Modifications over the Past Decade

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The potential of sialic acids as therapeutic agents has gradually been recognized due to its importance in the proper functioning of living systems, and likewise the virulence of several pathogens. However, synthesis of these compounds often result in poor yields and selectivities because of inherent characteristics associated with their structures. Use of various promoters, solvent systems and introduction of auxiliaries has since improved the outlook of chemical sialylation. Of these, attachment of various groups on C5 has notably resulted in improved α -selectivity. This mini review focuses on C5 structural modification of sialic acids over the past decade, most notably the oxazolidinone group protection.

Keywords: *sialic acid; C5 modification; oxazolidinone; α -sialylation*

PHYSIOLOGICAL SIGNIFICANCE OF SIALIC ACIDS

Sialic acids are cyclic nine-carbon monosaccharides discovered in the 1930s by Gunnar Blix as a product of the mild acid hydrolysis of salivary mucins but not introduced to the scientific community until 1952 (Varki and Schauer, 2009; Lundblad, 2015). These are also present in other body fluids such as serum, urine and human milk, with the highest concentration found in colostrum and decreasing as lactation progresses (Wang and Brand-Miller, 2003). Commonly found in the non-reducing, terminal positions of glycans and glycoconjugates, sialic acids have significant roles in cell interactions and the development of vertebrates (Varki, 1993; Schauer, 2000).

In humans, sialic acid in the form of 5-*N*-acetyl neuraminic acid (Neu5Ac) is found in high concentration in the brain gangliosides (Wang and Brand-Miller, 2003) with no significant differences between sexes. However, concentration variations observed in the left and right lobes of human and chimpanzee brains suggest its significance in the development of various neurological functions (Suzuki, Pattern, 1965; Wang *et al.*, Sialic, 1998). Although there are conflicting reports on whether the increase or decrease of sialic acid concentration in the brain leads to psychiatric and neurodegenerative disorders, in general, alterations in the level of brain sialic acid have been linked to conditions such as schizophrenia (Sirota *et al.*, 1988; Sato and Kitajima, 2013; Schnaar *et al.*, 2014; Piras *et al.*, 2015), phenylketonuria (Loo *et al.*, 1985) and Alzheimer's disease (Schedin-Weiss *et al.*, 2014).

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Gangliosides in the nervous system may also serve as markers of other medical conditions. In diabetic rat liver, increased expression of monosialogangliosides GM1 and GM3, disialoganglioside GD1b and trisialoganglioside GT1b, with a marked absence of GM2 were found (Sanchez *et al.*, 2000; Abregu *et al.*, 2002). Rats subjected under a high fructose and glucose diet showed elevated sialic acid synthesis in the liver and kidney with concomitant loss of sialic acids in the pancreas (Ibrahim *et al.*, 2016).

Cancerous tissues also express increased levels of bound sialic acid (Ingraham and Alhadeff, 1978). Elevated concentrations were seen in the brain, liver, testes and kidney of Dalton's lymphoma-bearing mice (Nicol and Prasad, 2002). While in human melanomas, the disialogangliosides GD2 and GD3 are reported to be largely expressed (Hussain *et al.*, 2011).

In addition, sialic acids were found to be important receptors in the entry of viruses, such as influenza, into humans and other hosts. Influenza A and B, of avian origin, both have hemagglutinin and neuraminidase which interact with Neu5Ac, while influenza C contains hemagglutinin-esterase-fusion (HEF) protein and interacts primarily with Neu5,9Ac₂. Sialic acid linkages to galactose (Gal), N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc) also affect the binding of influenza viruses. Avian influenza viruses primarily bind to Neu5Ac in α 2-3 linkage with Gal while human influenza viruses bind to Neu5Ac in α 2-6 Gal linkage (Matrosovich *et al.*, 2015; Stencel-Baerenwald *et al.*, 2014; Sauer *et al.*, 2014; Mandal *et al.*, 2015; Varki and Gagneux, 2012). Studies utilizing other animal models such as mice (Pekosz *et al.*, 2009) and horses (Suzuki *et al.*, 2000) have shown that receptor specificity is important in the replication of the virus. The extracellular matrix glycoprotein called fibronectin was reportedly essential in the entry of viruses with α 2-6 linkage preference (Leung *et al.*, 2012).

Due to the importance of sialic acids in physiology and pathogenesis, researches are now targeting the potential of these

compounds in the production of pharmaceuticals (Liao *et al.*, 2015; Spence *et al.*, 2015; Zhang *et al.*, 2014; Byrne *et al.*, 2007; Kiefel and von Itzstein, 2002). Unfortunately, extraction of sialic acids and its derivatives in adequate amounts from natural sources is very challenging. Synthetic strategies have also been limited by the inherent characteristics of sialic acid which include the destabilization of the oxocarbenium ion due to the presence of carboxylic acid and the absence of a directing group near the anomeric position. Thus, synthetic chemists have continuously sought for ways to improve chemical sialylation. These include investigations on various promoter systems (Salmasan *et al.*, 2014; Crich and Li, 2006; Ress and Linhardt, 2004) and structural variations via attachment of auxiliaries (in C1, C3, C5) or modification of the hydroxyl groups (at C4, C7, C8, C9) (Ress and Linhardt, 2004; Boons and Demchenko, 2000). Among these modifications, the attachment of various electron-withdrawing groups on C5 have brought significant improvements in yield and α -selectivity (Hanashima, 2011; Crich, 2011; Hemeon and Bennet, 2007; Halcomb and Chappell, 2002; Boons and Demchenko, 2000). Much of the current researches are still exploring this potential in the hopes of achieving a more efficient sialylation, sometimes even without the assistance of nitrile solvents. Acetonitrile or propionitrile have been commonly employed as solvents in α -sialylation as these interact with the β -face of the oxocarbenium ion thereby improving α -selectivity (Hasegawa *et al.*, 1991). This mini review focuses on C5 sialic acid modifications over the past decade, most notably the effect of oxazolidinone-protection on C4,5 and its combination with other protecting groups aimed towards better yield and stereoselectivity.

OXAZOLIDINONE PROTECTION

The 5-*N*,4-*O*-oxazolidinone protection of sialic acids is usually achieved by treatment of the free amine with *p*-nitro-phenyl chloroformate (NPCC), while deprotection is performed under basic conditions (Farris and De Meo, 2007; De Meo and Priyadarshani, 2008; Tanaka *et al.*, Oligo, 2006).

Figure 1. $\alpha(2,8)$ -sialylation of oxazolidinone-protected donor and acceptor.

Protection of both donors and acceptors have facilitated the synthesis of $\alpha(2,8)$ -tetrasialic acid even without the help of nitrile solvent effects. Coupling of **1** and **2** via *N*-iodosuccinimide/ trifluoromethanesulfonic acid (NIS/TfOH) activation (Figure 1) resulted in disialic acid **3** as the α -anomer in 86% yield. Deprotection of the chloroacetyl groups afforded acceptor **4**. After subsequent iterative sialylation and deprotection, tetrasialic acid **6** was obtained in perfect stereoselectivity although in a lower yield of 57% (Tanaka *et al.*, Oligo, 2006).

The same method was also employed in the synthesis of $\alpha(2,9)$ -di-, tri- and tetrasialic acids with excellent stereoselectivity ($\alpha:\beta = >95:5$) in overall yields of 87%, 89% and 69%, respectively (Tanaka *et al.*, Tetrasialic, 2009). These show that the oxazolidinone ring effectively enhances the reactivity of the hydroxyl group at C8 and that it provides an alternative in the sialylation of primary alcohols without the need for nitrile solvents. In both syntheses, removal of the oxazolidinone ring was done using lithium hydroxide (Tanaka *et al.*, Oligo, 2006; Tanaka *et al.*, Tetrasialic, 2009). In a similar set of reaction conditions but with

the use of CH₂Cl₂/CH₃CN as solvent, Lin and co-workers also reported the synthesis of $\alpha(2,9)$ -tetrasialic acid by combining the effects of the oxazolidinone ring with tri-*O*-chloroacetyl protecting groups on C7, 8 and 9 of the thiosialoside donor. Utilizing acceptors with free hydroxyl groups on C7, 8 and 9, the fully deprotected $\alpha(2,9)$ -tetrasialic acid was likewise obtained in perfect stereoselectivity although in lower overall yield (Lin *et al.*, 2010). As evident in Tanaka and co-workers' results, the same trend of diminishing yield as the number of sialic acid residues on the chain increased was also observed. Ensuring the α -selectivity of all linkages and prevention of random removal of the protecting groups are some of the factors that may hinder the elongation of the oligosialic acid chain. One way to overcome this is by using sialyl phosphate donors in a convergent block synthetic strategy. Coupling tetrasialic acid donor **7** and octasialoside acceptor **8** via trimethylsilyl trifluoromethanesulfonate (TMSOTf) activation (Figure 2), the $\alpha(2,9)$ dodecasialic acid **9** was obtained in 45% yield (Chu *et al.*, 2011). This is by far the longest oligosialic acid chain synthesized with an impressive yield.

Figure 2. Synthesis of $\alpha(2,9)$ dodecasialic acid.

Aside from $\alpha(2,8/9)$, $\alpha(2,3/6)$ linkages are also common in glycoconjugates. While the latter can be synthesized in excellent yields, stereocontrol remains a challenge. Improvement in the stereoselectivity of $\alpha(2,6)$ sialylation was successful when the effects of oxazolidinone was combined with *S*-benzoxazolyl (SBox) at C2 in donor **10** (Figure 3). Selective activation of the sialyl thioimide donor over the thioethyl galactoside acceptor **11** via bismuth (III) triflate activation in $\text{CH}_2\text{Cl}_2/\text{THF}$ afforded disaccharide **12** in 66% yield and 20:1 α/β ratio (Harris *et al.*, 2011).

In the case of $\alpha(2,3)$ sialylations (Table 1), *p*-toluenethiosialoside **13** (Liang *et al.*, 2009) with an acetyl group attached to the oxazolidinone-protected nitrogen afforded comparable yields

but markedly better selectivities than the previously reported phenylthiosialoside **14** (Crich and Li, *O*-Sialylation, 2007). Changing the activation method of **13** from NIS/TfOH to diphenylsulfoxide/trifluoromethanesulfonic anhydride/2,4,6-tri-*tert*-butylpyridine ($\text{Ph}_2\text{SO}/\text{Tf}_2\text{O}/\text{TfBPy}$) afforded better selectivity (α/β ratio from 6.1:1 to 9.9:1) in $\alpha(2,6)$ sialylation with a 6-OH glucopyranoside acceptor (Wang *et al.*, 2011).

Oxidation of the STol group in **13** using *meta*-chloroperoxybenzoic acid (*m*-CPBA) resulted in sialyl sulfoxide **15** (Figure 4). While sulfoxides have already been utilized in glycosylation, the potential of sialyl sulfoxides as donors have not been fully explored. Pioneering work by Gu and co-workers

Figure 3. $\alpha(2,6)$ sialylation of oxazolidinone-protected *S*-benzoxazolyl sialyl donor.

showed that activation of **15** using trifluoromethanesulfonic anhydride/ ditolyl sulfoxide ($\text{Tf}_2\text{O}/(\text{ToI})_2\text{SO}$) facilitated the synthesis of $\alpha(2,3)$ - and $\alpha(2,4)$ -sialosides (**16-18**) in good yields (60-78%) and complete α selectivity (Gu *et al.*, 2012).

On the other hand, it was possible to synthesize non-natural GM4 derivatives via (2-2) and (2-4) sialylation using phenylthiosialoside **14** (Figure 5). Activation of **14** via NIS/TfOH in $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ afforded the (2-2) linked GM4 derivative **19** in excellent yield with the predominance of the α -anomer. This is in contrast to the result of the synthesis of (2-4) linked GM4 derivative **20** which only gave the β -anomer in 58% yield (Kurimoto *et al.*, 2015).

The presence of 5*N*-*tert*-butoxycarbonyl (5-*N*-Boc) group on the oxazolidinone ring **22** instead of acetyl has also been reported in the synthesis of a tetrasaccharide bearing a fucosyl linkage (Figure 6). While Boc and the fucosyl linkage are usually labile in acidic conditions, these were found to be stable under NIS/TMSOTf activation affording the tetrasaccharide **23** in 73% yield. The oxazolidinone group can also be selectively cleaved without affecting the Boc carbamate allowing further functionalization of the

resulting amine (Boltje *et al.*, 2013).

Further modification done by double-locking sialic acid **24** with oxazolidinone and silicon-protecting groups di-*tert*-butylsiloxydiphenylsilane (DTBS) on C5,7 and tetraisopropyl-disiloxydiphenylsilane (TIPDS) on C8, 9 (Figure 7) gave trisaccharide **26** as the α -anomer in 80% yield without the need for nitrile solvent. Using molecular modelling, the excellent α -selectivity observed can be explained as a consequence of the clearly defined *Re* and *Si* faces of the oxonium ion due to the oxazolidinone and silylene groups. The latter blocking the *Si* face thereby exposing the *Re* face to TfOH during activation. The OH group of the acceptor then approaches the *Si* face which leads to the α -anomer (Hanashima *et al.*, 2009).

OTHER MODIFICATIONS ON C5

Significant improvements in sialylation observed when oxazolidinone is trans-fused to pyranose rings result from the strong influence of its dipole moment which creates an electron-withdrawing effect that causes the destabilization of the oxocarbenium ion. This destabilization then favors $\text{S}_{\text{N}}2$ -like mechanistic pathways (Kancharla *et al.*, 2012). Capitalizing on this and the thiocarbonyl

Table 1. Comparison of *p*-Toluenethiosialoside **13 and Phenylthiosialoside **14** $\alpha(2,3)$ Sialylations**

Donor	Acceptor	Conditions	% Yield (α/β)
13		A	72 (1.8/1)
	A	81 (1.2/1)
14		B	78 (1/1.3)
	B	85 (1/8)

Conditions: A (Liang *et al.*, 2009): NIS/TfOH, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$, MS 4Å, -40°C ; B (Crich and Li, O-Sialylation, 2007): NIS/TfOH, CH_2Cl_2 , MS 5Å, -40°C .

Figure 4. Synthesis of $\alpha(2,3)$ - and $\alpha(2,4)$ -sialosides using sialyl sulfonate donor **15**. Sialylation conditions: $\text{Tf}_2\text{O}/(\text{Tol})_2\text{SO}$ (2.0 equiv), MS 4 Å, CH_2Cl_2 , -70 to -50°C .

Figure 5. Synthesis of (2,2)- and (2,4) linked GM4 derivatives. Sialylation conditions: NIS/ TfOH , MS 3 Å, $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$, -40°C .

Figure 6. Synthesis of a tetrasaccharide bearing a fucose residue using 5-*N*-Boc-protected 5*N*,4*O*-oxazolidinone thiosialoside donor.

group's electron-withdrawing characteristic, oxazolidinone protection of thiosialosides have also been investigated (Rajender and Crich, 2013). However, activation using NIS/TfOH was only effective at higher temperature (-50°C) and α -sialylation results did not fare better than previously reported *N*-acetyl (Crich and Li, *O*-Sialylation, 2007; Crich and Li, α -Selective, 2007) and *N*-acetoxycetimide oxazolidinone thiosialosides (Crich and Wu, 2008).

On the other hand, the isothiocyanate **27** by-product in the oxazolidinone-protected sialoside synthesis proved to be an excellent donor. Using various acceptors, $\alpha(2,3)$, $\alpha(2,6)$ and $\alpha(2,9)$ sialylations were effected in moderate to high yields with perfect α -selectivity. Most notable was the $\alpha(2,3)$ sialylation with the usually low reactive 4-*O*-benzyl-galactopyranoside acceptor which afforded disaccharide **28** only as the α -anomer in 87% yield (Figure 8). Further diversification after coupling was also possible

by modifying the isothiocyanate moiety. This gave the deamino disaccharide **29** in 78%, protected glycolyl amide **30** in 55%, **31** in 50%, thiourea **32** in 90%, isothiourea **33** in 80% and guanidine **34** in 49% yield (Mandhapati *et al.*, 2015).

Other electron-withdrawing groups have also been employed for C5 protection. Attachment of *N,N*-acetyl, benzoyl group at C5 of a perbenzoylated (Bz protection at C4, 7, 8 and 9) thiosialoside activated using NIS/TfOH or $\text{Ph}_2\text{SO}/\text{Tf}_2\text{O}$, however, have resulted primarily in β -sialosides (Wang and Ye, 2009). This surprising result was suggested to be a consequence of the strong β -directing effects of the per-*O*-benzoylation in the donor. In particular, bulky groups such as *tert*-butyldimethylsilyl (TBDMS) and Bz attached at C4 and C7, respectively, were found to significantly influence the resulting stereoselectivity of the sialylation reaction (Premathilake *et al.*, 2012).

Figure 7. Sialylation using thiosialoside donor double-locked by silylene and oxazolidinone groups.

Figure 8. α -Sialylation using isothiocyante-protected adamantanyl thiosialoside and subsequent diversification of the resulting disaccharide.

A sialyl donor with a modified ureido group in C5 have also been introduced recently (Table 2). Activation of **35** using iodine monobromide/silver trifluoromethanesulfonate (IBr/AgOTf) afforded (2,6)-linked sialosides **36** and **37** in 80% yield and good α -selectivity. Utilizing an excess amount of **35** in (2,3) sialylation resulted in disaccharide **38** with 94% yield and α/β ratio of 24.6:1. To ease the purification process, 1,5-lactamization involving C1 and the nitrogen atom of the ureido group was performed using 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in *N,N*-dimethylformamide (DMF) at 120°C . After the incorporation of Boc on the lactam ring and treatment with sodium methoxide in methanol, the α -sialosides can be obtained in excellent yields (Tanase *et al.*, 2016).

CONCLUSION

Progress in chemical sialylation has led to the development of various promoters, solvent systems, donors and acceptors. All of which are aimed toward better yield and α -selectivity. While excellent yields were already seen in past syntheses, achieving perfect α -selectivity remains a challenge. This is because the inherent characteristics of sialic acids mostly favour the production of β -sialosides, which are not common in nature. Sialic acids in humans and animals are usually found to exist in α -linkages with glycoconjugates. Thus, the need for structural modifications in the sialyl donor. Of these, attachment of oxazolidinone group at C4 and C5 has been very promising in improving both yield and α -selectivity, even without the assistance of nitrile solvents. Oxazolidinone-protection has afforded the synthesis of $\alpha(2,3)$, $\alpha(2,6)$, $\alpha(2,8)$, $\alpha(2,9)$ -linked sialic acids and even non-natural sialosides

Table 2. Sialylation of 5-Ureido Modified Donor 35 with 3- and 6-OH Acceptors.

Acceptor	Disaccharide	%Yield (α/β)
		80 (10.3/1)
		80 (14.3/1)
		94 (24.6/1)

with $\alpha(2,2)$ and $\alpha(2,4)$ linkages. It has also allowed the assembly of dodecasialic acids at impressive yields and selectivity notwithstanding the length of the chain. Other C5 modifications such as the attachment of a modified ureido group has also facilitated easier purification of the α -sialosides through 1,5-lactamization.

However, limited mechanistic work has been undertaken to explain many of these results and reactions are still carried out as small-scale experiments. Furthermore, the number of steps in the overall synthesis and ease of purification are also issues that must be addressed if large-scale synthesis is to be done for the production of vaccines and/or therapeutic agents. Future synthetic work may also include structural modifications on 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid (KDN) and N-glycolyl-neuraminic acid (Neu5Gc) as these sialic acid derivatives have as well been implicated in tumorigenesis.

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